SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: Restylane® Contour

Device Procode: LMH

Applicant's Name and Address: Q-Med AB, a Galderma affiliate
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SE-752 28 Uppsala, Sweden

Galderma Research & Development, LLC
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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140029/S032

Date of FDA Notice of Approval: June 28, 2021

The original PMA (P140029) for Restylane Refyne and Restylane Defyne was approved on December 9, 2016. Restylane Refyne is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21 and Restylane Defyne is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21. The PMA Supplement for Restylane Kysse (P140029/S021) was approved on March 26, 2020, for injection into the lips for lip augmentation and for correction of upper perioral rhytids in patients over the age of 21. The SSEDs to support these indications are available on the CDRH website and are incorporated by reference herein.

Restylane Contour, which is branded as Restylane Volyme outside of the US, is being submitted as a Panel-Track supplement (P140029/S032) to the Restylane Refyne and Restylane Defyne PMA (P140029). The study was performed in the US under IDE G180114 to establish a reasonable assurance of safety and effectiveness for the use of Restylane Contour for injection into the supraperiostic zone or subcutis to augment the volume of the cheeks in patients over the age of 21.

II. INDICATIONS FOR USE

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

III. 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Restylane Contour physician labeling.

V. DEVICE DESCRIPTION

Restylane Contour is a sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless, flexible and homogeneous gel composed of hyaluronic acid of bacterial origin, with a moderate 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.

The gel is supplied in a prefilled plastic syringe and the contents of the syringe are steam sterilized. The syringe is packaged individually in a blister pack, with two sterile 27 G x ½" Ultra-Thin Wall (UTW) needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other approved procedures in the United States for cheek augmentation, such as fat grafting and implants. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Restylane Volyme *(*Restylane Contour in the U.S.), previously named Emervel® Volume Lidocaine*,* was approved in the European Union in 2010 and is today approved for marketing in Argentina, Australia, Azerbaijan, Bahrain, Belarus, Brazil, Canada, Chile, Colombia, Ecuador, Egypt, El Salvador, EU/EEA/EFTA, Georgia, Guatemala, Hong Kong, India, Indonesia, Israel, Jordan, Kazakhstan, Kuwait, Lebanon, Macedonia, Malaysia, Mauritius, Mexico, Moldova, Morocco, New Zealand, Nicaragua, Philippines, Qatar, Saudi Arabia, Serbia, Singapore, South Africa, South Korea, Taiwan, Thailand, Tunisia, Turkey, Ukraine, United Arab Emirates and Vietnam.

The device has not been withdrawn from marketing in any country for any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

Injection related events (IRE) such as bruising, erythema, itching, swelling, pain and tenderness are anticipated and expected to generally resolve spontaneously within 1-2 weeks after injection.

For the specific adverse effects that occurred in the clinical study, please see SECTION X.d1 below.

Post-marketing surveillance

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

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

- mass formation/induration
- pain/tenderness
- papules/nodules
- erythema
- inflammation
- short duration of effect
- presumptive bacterial infections and abscess formation
- bruising/hematoma
- ischemia/necrosis including pallor, due to unintentional intravascular injection or embolisation

- injection site reactions including warmth, burning sensation and exfoliation
- hypersensitivity/angioedema
- neurological symptoms including hypoaesthesia and paraesthesia
- granuloma/foreign body reaction
- device dislocation
- deformity/assymetry
- discoloration
- eye disorders including eye pain and eyelid oedema
- symptoms of reactivation of herpes infection
- pruritus
- blisters/vesicles
- rash
- atrophy/scarring
- acne
- dermatitis
- encapsulation
- extrusion of device
- urticaria,
- non-dermatological events including headache, discomfort, 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 are rare. The most commonly reported serious adverse events with 3 or more reports 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 outcome of ischemia/necrosis cases was 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 local vascular compression by the implant. This may manifest as blanching, discoloration, 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 and brain have led to vision loss and cerebral infarction following facial aesthetic treatments with dermal fillers have been reported. Reported treatments include anticoagulants, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, antibiotics, local wound care, drainage, surgery and hyperbaric oxygen.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory studies

Restylane Contour has been tested and characterized through physical and chemical analyses according to ISO 10993-18, see Table 1.

To ensure that Restylane Contour degrades naturally during its clinical lifespan, degradation assays have also been performed.

Table 1: Summary of Key Bench Testing on Restylane Contour

Test	Purpose	Results
Extrusion force (N)	Ensures extrusion force meets specification	Passed
pH	Ensures pH meets specification	Passed
Rheology (tan δ)	Ensures rheological properties meet specification	Passed
HA concentration (mg/mL)	Ensures HA concentration meets specification	Passed
Gel content (%)	Ensures gel content meets specification	Passed
Lidocaine concentration (mg/mL)	Ensures lidocaine concentration meets specification	Passed
Residual crosslinker (ppm)	Ensures residual crosslinker meets specification	Passed
Endotoxin (EU/mL)	Ensures endotoxin meets specification	Passed
Sterility	Ensures device is sterile	Passed

B. Biocompatibility Studies

A biological evaluation was performed on Restylane Contour according to ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.

In the evaluation of Restylane Contour, data from a similar product, Restylane Defyne was also used to assess the biological safety. Restylane Contour and Restylane Defyne are manufactured with the same raw materials, the same manufacturing process, the same primary packaging and the same sterilization process. According to ISO 10993-1, both

Restylane Contour and Restylane Defyne are categorized as implant devices in contact with tissue where the contact duration is more than 30 days.

All tests were performed according to GLP and the requirements of each test were met. The conclusion from the biological testing is that Restylane Contour is safe for the intended use.

Table 1 Biological tests performed on Restylane Contour and Restylane Defyne

Biological endpoint/test method		Test standard/guideline	Test product	Test result
Cytotoxicity		ISO 10993-5	Restylane Contour	Not cytotoxic
Sensitization		ISO 10993-10	Restylane Contour	Not sensitizing
Intradermal reactivity		ISO 10993-10	Restylane Contour	No irritation
Implantation 26 weeks intradermal in rabbits		ISO 10993-6	Restylane Contour	Not causing local skin reaction macroscopically; slight irritant microscopically
Systemic toxicity	**Acute systemic toxicity**	ISO 10993-11 USP <88>	Restylane Contour	No systemic toxicity
	Sub-chronic systemic toxicity, 13 weeks	ISO 10993-11	Restylane Defyne	No systemic toxicity
	Material-mediated pyrogenicity study	ISO 10993-11 <USP 151>	Restylane Contour	No pyrogenic reaction

Genotoxicity	**Ames test**	ISO 10993-3 OECD 471	Restylane Defyne	No mutagenic response
	Mouse lymphoma	ISO 10993-3 OECD 476	Restylane Defyne	No mutagenic response or chromosomal aberration
	Mouse micronucleus	OECD 474	Restylane Defyne	No induction of micronuclei was induced in mice

Carcinogenicity risks: A thorough cancer risk assessment of BDDE was previously performed on Restylane products. Both a linear extrapolation method and a dose-response model were used and the conclusion from both approaches was that the potential cancer risk from BDDE was minimal. The BDDE concentration limit in products was set to ≤ 2 µg/mL (same limit for all Restylane products). A calculation, based on an exposure to 6 mL gel containing ≤ 2 µg/mL every year for 15 years was made; 6 mL x 15 years x ≤ 2 µg/mL, which gives a maximum of ≤ 180 µg BDDE. It was concluded that the risk from exposure to such low levels would be minimal.

C. Additional Studies

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

Stability studies on three batches of Restylane Contour have been performed. Based on the available stability data, a shelf-life of 24 months is proposed for Restylane Contour when stored up to 25°C. The shelf life is based on stability data collected through 24 months at 25°C/40% and 30°C/35% relative humidity, and through 6 months at 40°C/25% relative humidity. At each time point, product was characterized via microbiological, physical, chemical, lidocaine hydrochloride content, and lidocaine-related degradant parameters. Conformance of real-time aged product with all specifications was confirmed.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for the use of Restylane Contour for cheek augmentation and correction of midface contour deficiencies in patients over the age of 21 in the US under IDE G180114. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. 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).

1. 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.

2. 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.

3. 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 3). Responders were defined as having at least 1 point improvement from baseline (as assessed by the blinded evaluator) at 12 weeks after last injection.

Table 2. 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).

[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.

B. 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 4, 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 4 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.

C. 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 5.

Table 5 Subject Demographics and Baseline Characteristics (Intent to Treat Population)

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

Characteristic		Statistic	Treatment Group			
			Group A			Group B
			Restylane Contour	Control	Group A Overall	Restylane Contour
	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.

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, injections were made in the subcutaneous region and the supraperiosteal zone. The suprapeiosteal zone was the most common injection depth (99.3% [Restylane Contour]; 97.1–98.5% [Control]). Injection techniques used were linear anterograde, linear retrograde, fanning, depot, serial puncture and fern pattern techniques. Depot was the most common injection method (70.2% [Restylane Contour]; 69.1% [Control]) followed by serial puncture (62.4% [Restylane Contour]; 61.8% [Control]) for the initial treatment.

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

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

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

Injection Characteristics for initial treatment are described in Table 6 below.

Table 6 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

D. Safety and Effectiveness Results

1. 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 7 through Table 15. Subject-reported injection related events are presented in Table 7 – Table 12. Physician-reported adverse events (AEs) are presented in Table 13 – Table 15.

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 7 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 8 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 9 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 10 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 11 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 12 Duration of Pre-defined Injection Related Events Occurring in Subjects After Re-treatment (Safety Population)

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

Tenderness	24 (70.6)	14 (58.3)	7 (29.2)	2 (8.3)	1 (4.2)	27 (84.4)	15 (55.6)	7 (25.9)	4 (14.8)	1 (3.7)
Redness	14 (41.2)	10 (71.4)	4 (28.6)	0	0	13 (40.6)	11 (84.6)	1 (7.7)	1 (7.7)	0
Bruising	7 (20.6)	3 (42.9)	4 (57.1)	0	0	11 (34.4)	4 (36.4)	1 (9.1)	6 (54.5)	0
Swelling	20 (58.8)	11 (55.0)	5 (25.0)	4 (20.0)	0	20 (62.5)	13 (65.0)	4 (20.0)	3 (15.0)	0
Itching	1 (2.9)	0	0	1 (100)	0	2 (6.3)	1 (50.0)	0	1 (50.0)	0

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

Device and Injection Related Events: AEs were evaluated by Investigators throughout entirety of the study. An overall summary of AEs following initial and touch-up treatment is presented in Table 13.

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 Restylane Contour in Group A, 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 14 - 15. 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 vast 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 13 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 14 Treatment Related Adverse Events Occurring ≥ 2% of Subjects by Maximum Severity after treatment, Group A (Safety Population)

		Group A					
		Initial Treatment with Restylane Contour (N=141)		Re-treatment with Restylane Contour (N=92)		Initial Treatment wit Control (N=68)	
System Organ Class/ *Preferred Term*	**Severity**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**
Any Related AE	Total	21(14.9%)	57	6 (6.5%)	10	13(19.1%)	79
	Mild	18(12.8%)	53	6 (6.5%)	10	8 (11.8%)	72
	Moderate	3 (2.1%)	4	0	0	4 (5.9%)	6
	Severe	0	0	0	0	1 (1.5%)	1
Eye disorders	Total	1 (0.7%)	1	1 (1.1%)	1	0	0
	Mild	1 (0.7%)	1	1 (1.1%)	1	0	0
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Blepharospasm	Total	0	0	1 (1.1%)	1	0	0
	Mild	0	0	1 (1.1%)	1	0	0
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Swelling of eyelid	Total	1 (0.7%)	1	0	0	0	0
	Mild	1 (0.7%)	1	0	0	0	0
	Moderate	0	0	0	0	0	0
	Severe	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
	Mild	15(10.6%)	47	4 (4.3%)	7	7 (10.3%)	70
	Moderate	3 (2.1%)	4	0	0	4 (5.9%)	6
	Severe	0	0	0	0	1 (1.5%)	1

		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**
Implant site pain	Total	6 (4.3%)	16	0	0	9 (13.2%)	36	4 (8.9%)	13
	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

		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	2 (1.4%)	4	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
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 15 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.

2. 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 17 through 18.

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

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

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

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

Group A							
Population (Imputation)	**Group 1: Restylane Contour**		**Group 2: Control**		**Difference (Group 1 – Group 2)**		
	LS Mean	**95% CI**	**LS Mean**	**95% CI**	**LS Mean**	**SE**	**95% CI**
ITT (Hot deck*)	-1.4	-1.48, -1.32	-1.3	-1.44, -1.20	-0.1	0.07	-0.22, 0.06
PP (Observed)	-1.4	-1.51, -1.35	-1.3	-1.44, -1.20	-0.1	0.07	-0.26, 0.03
Group B							
Change from Baseline to Visit 5 (Week 12)	**Restylane Contour Cannula**		**Restylane Contour Needle**		**Difference**	**95% CI**	
n	60		60		60		
Mean (SD)	-1.3 (0.75)		-1.3 (0.74)		-0.1 (0.39)	(-0.15, 0.05)	
Median	-1.0		-1.0		0		
Min, Max	(-3, 1)		(-3, 1)		(-1, 1)		

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

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

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

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

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

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

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

	95% CI	(47.73, 74.59)	(51.42, 77.76)

Subject and Treating Investigator GAIS: Independently of each other, the investigator and the subject evaluated the degree of improvement from baseline in the appearance of the subject's midface area using the GAIS at each post-baseline visit. The majority of subjects (76.9–94.9%) in Group A who were treated with Restylane Contour reported aesthetic improvements (improved, much improved or very much improved) in the midface area across the Week 12, Week 24, Week 36 and Week 48 assessments using the GAIS. Similarly, across the same time points, Treating Investigators scored 86.9–97.8% of subjects in the Restylane Contour group as improved, using the GAIS.

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

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

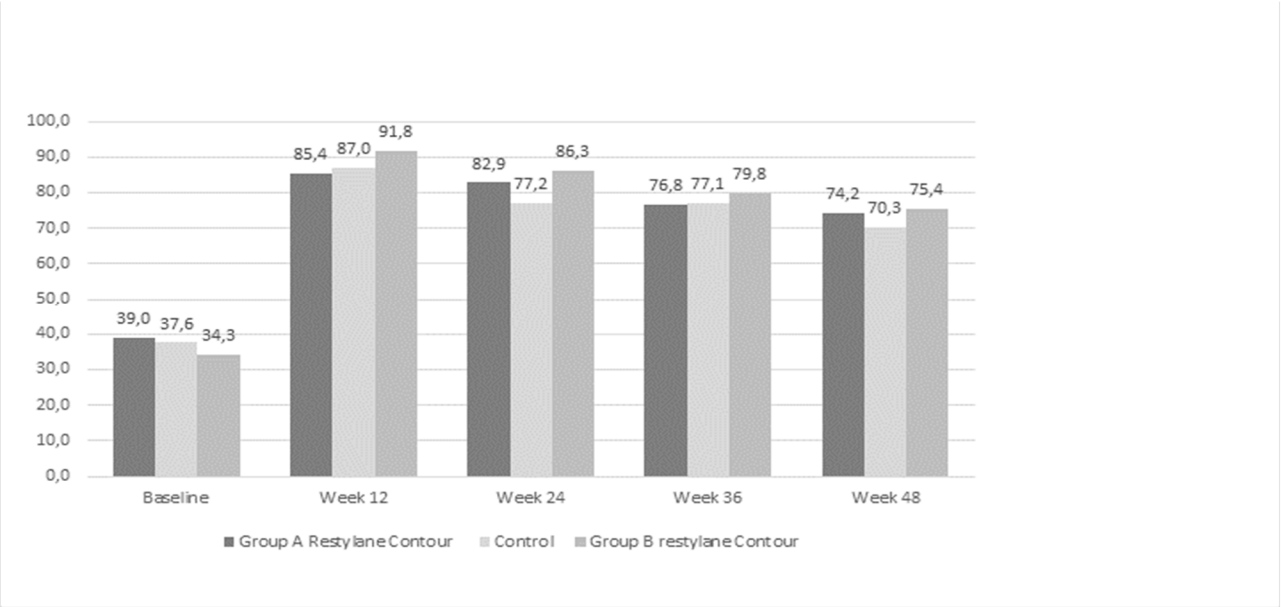
Likewise, for Group B, the IPR (blinded to study treatment and visit name/date) considered similar proportions of cheek augmentations by cannula (58.6–74.1%) and needle (56.9–68.5%) to reflect an improvement across all timepoints, based on comparison of random pairings of baseline and post-baseline photographs.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

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

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

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

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



3. 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.

Examination of ad-hoc analysis, out of window protocol deviations: During the study, some subject visits occurred out of window. The Sponsor conducted an ad hoc analysis to evaluate the number of days these visits were out of window. The overall percentage of out of window visits in Group A ranged from 0% to 28.6%. The overall percentage of

out of window visits in Group B was similar to Group A, ranging from 0% to 25%. There was no scheduled study visit with a significant proportion of out of window deviations for either Group A or Group B. In addition, there were no notable differences between the Restylane Contour and Control group within Group A in terms of percentages of out of window visits at any visit. The range of out of window visits in Group A for Restylane Contour was 0% to 28.9% and the Control group was 0% to 27.9%. One subject in Group A (Restylane Contour) had an out of visit window at the Week 12 primary endpoint visit of more than 30 days; data from this visit was excluded from the per protocol analysis, as it occurred 56 days outside of the permitted window. The ad-hoc analysis on the out of window protocol deviations concluded the effectiveness data was not biased, as both groups had similar proportions of out of window visits.

Examination of ad-hoc analysis, concomitant procedures and treatments: During the study, some subjects received concomitant procedures and treatments outside the area of treatment as dictated by the clinical study protocol. The Sponsor conducted an ad hoc analysis excluding all subjects who had concomitant procedures and treatments during the study (specifically botulinum toxin treatments in the face). The revised per protocol (PP) analysis concluded the primary endpoint for Group A was met. Non-inferiority between Restylane Contour and Control for cheek augmentation and correction of midface contour deficiencies was still demonstrated (LS Mean Difference -0.2; SE 0.08; 95% CI: -0.31, -0.01) based on change from baseline to Week 12 in MMVS, as assessed by the Blinded Evaluator. Sensitivity analysis using a mixed model that included treatment group, side of face and a treatment-by-side interaction term showed that the non-inferiority of Restylane Contour to Control remained valid (LS Mean Difference -0.1; SE 0.08; 95% CI: -0.26, 0.06 for the left side of the face, and LS Mean Difference -0.2; SE 0.08; 95% CI: -0.38, -0.05 for the right side). Non-inferiority was demonstrated between Restylane Contour injected by cannula and needle (Mean Difference -0.1[SD: 0.37]; 95% CI: -0.17, 0.03), based on change from baseline to Week 12 in MMVS, as assessed by the Blinded Evaluator. Given that the results from this additional sensitivity analysis were similar to the results presented in **Section D2**, it was concluded the aesthetic cosmetic procedures administered outside of the investigational treatment area during the study period did not produce any bias in the results.

4. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by clinical investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation.

Clinical study 43USV1704 included 17 investigators, three (3) of whom had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). These three investigators had disclosable financial interests/arrangements described as significant payment of other sorts. The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data. No other Clinical Investigators who participated in a Covered Clinical disclosed to the Sponsor significant payments of other sorts received from the Sponsor as defined in 21 CFR §54.2 (a), (b), (c), and (f).

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of the U.S. pivotal study 43USV1704 conducted to support PMA approval as described above. Conclusions drawn from the clinical study provide a reasonable assurance that the device is effective when used for cheek augmentation in subjects over the age of 21.

Conclusions from this study are:

- The study met its primary endpoint, demonstrating non-inferiority between Restylane Contour and Control for cheek augmentation and correction of midface contour deficiencies (LS Mean Difference -0.1; SE 0.07; 95% CI: -0.22, 0.06) based on change from baseline to Week 12 in MMVS, as assessed by the Blinded Evaluator. Sensitivity and subgroup analyses confirmed the robustness of the primary analysis.

- In Group A subjects treated with Restylane Contour, 91.2%, 88.5%, 72.1%, and 62.8% achieved a 1-grade or greater improvement (responders) from baseline in

MMVS on both sides of the face concurrently, as assessed by the Blinded Evaluator, at Weeks 12, 24, 36 and 48, respectively.

- There was no notable difference in the proportion of MMVS responders following Restylane Contour injected by cannula vs. needle at any visit.

- The proportion of subjects who reported aesthetic improvements (responders - improved, much improved or very much improved) in the midface across all assessment timepoints using the GAIS for the Restylane Contour group ranged from 76.9- 94.9%, with similar results based also on the Treating Investigator assessments.

- At all visits, the responder rates based on subject GAIS scores in Group B were similar for Restylane Contour injected by cannula and Restylane Contour injected by needle; Treating Investigators scored 92.6–100% of subjects as improved using the GAIS, with no differences between the injection tools.

- Subject satisfaction with appearance of their cheeks and satisfaction with treatment outcome, based on Rasch transformed FACE-Q total scores, was similar for all groups across all timepoints.

- The proportion of Restylane Contour subjects that achieved an improvement in cheek augmentation based on IPR assessment (blinded to study treatment and visit name/date) ranged from 59.5-69.6% across all timepoints and for both sides of the face.

- There were no notable differences between Restylane Contour injected by cannula and Restylane Contour injected by needle (Group B), for any of the IPR assessments.

- Across all timepoints, the mean increases in total midface volume from baseline in Restylane Contour subjects, as measured by digital 3D photography, ranged from 3.3-2.7 mL for left side and 3.2-2.6 mL for right side of the face.

- There was no notable difference in the volume increase, as measured by digital 3D photography, between each injection tool (injection vs cannula) at any visit.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical study 43USV1704 conducted to support PMA approval as described above. Conclusions from this study are:

- The majority of Group A and Group B subjects reported pre-defined IREs in subject diaries.

- 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 most common IREs following treatment with Restylane Contour was tenderness and swelling at initial and touch-up treatment and tenderness, swelling and pain following re-treatment.

  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).

- Out of the 141 Group A subjects randomized to receive Restylane Contour treatment, 23 (16.3%) subjects reported 1 or more AEs considered related to the investigational treatment or injection procedure. Out of the 68 Group A subjects randomized to receive Control treatment, 17 (25.0%) subjects reported 1 or more related AEs.

- The majority of related AEs, overall, were classified as mild: 63/67 events in Restylane Contour subjects and 88/101 events in Control subjects.

- The mean duration of related AEs reported after initial treatment in Restylane Contour subjects was 7.2 days (range: 1 to 80 days) and after re-treatment was 18.5 days (range: 3 to 46 days). The mean duration of related AEs after initial treatment for Control subjects was 4.5 days (range: 1 to 36 days) and after re-treatment was 4.7 days (range: 1 to 17 days).

- Three related AEs in Restylane Contour subjects lasted more than 40 days and included one event each of blepharospasm, swelling of eyelid and intravascular embolic injury. All events were resolved without sequelae.

- The median onset time for related AEs overall was on the day of injection for both Restylane Contour and Control subjects.

- The majority of Group B subjects (46/59 [78.0%]) did not experience AEs.

- Subgroup analysis revealed that:
  - There were no obvious reporting trends for related AEs amongst Group A sites; 10 out of 13 sites had subjects who experienced related AEs.
  - Reporting rates for related AEs were highest in the FST IV subjects
  - There was insufficient data to assess any reporting trends by site, FST, or injection volume for Group B subjects, as only 2 subjects experienced related AEs during the study.

- There were four SAEs reported in the study (in 2 Group A subjects and 1 Group B subject). All four SAEs were assessed as unrelated to investigational treatment or injection procedure.

- There were no instances of visual acuity worsening assessed as related to the investigational treatment or injection procedure.

- There were no notable findings following subjects' other safety assessments of pain: midface firmness, symmetry, function, sensation; device palpability; and mass formation.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The primary probable benefit of the device is a perceived improvement in the visual appearance of cheek augmentation and contour as assessed by the investigator using the MMVS, improved global aesthetic appearance according to investigator and subject GAIS assessments, and subject satisfaction with treatment per the FACE-Q questionnaire.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The majority of subjects who reported pre-defined IREs classified them as tolerable in severity at all injections (post-initial injection, touch-up, and at re-treatment). Most of the pre-defined, expected post-treatment events resolved in 2 weeks or less. The Group A Restylane Contour subjects had less adverse events and fewer subjects reporting investigational treatment or injection-procedure related AEs after treatment with Restylane Contour (67 events in 16.3% subjects) than in the Control group (101 events in 25.0% of subjects). Only 2 Group B subjects (3.4%) reported related AEs. Of the 170 related AEs across both groups, 85% were of mild severity. Summary of safety conclusions is provided above.

Additional factors to be considered in determining probable risks and benefits of Restylane Contour included:

1. **Patient Perspective**

Patient perspectives considered during the review included:

- FACE-Q Questionnaires to assess satisfaction with the aesthetic outcome and cheek area. Results for FACE-Q are discussed in Section X.D.2.
- GAIS assess by the patients at weeks 12, 24, 36, and 48 weeks after treatment. Results for GAIS are discussed in Section X.D.2.
- Adverse events were obtained from signs and symptoms reported by patients during visits. Adverse Events are discussed in Section X.D.1.

- Patient Diaries were used to collect information about predefined, injection related events at the treated area. Diary Information is discussed in Section X.D.1. Despite the frequency of IREs, patients are willing to accept the risk of these events as shown through patient-reported outcomes and the willingness to receive additional treatments during the study.

In conclusion, given the available information above, the data support that for cheek augmentation and correction of midface contour deficiencies in patients over the age of 21, the probable benefits outweigh the probable risks.

D. Overall Conclusions

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

XIV. CDRH DECISION

CDRH issued an approval order on June 28, 2021.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.