# 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
Seminariegatan 21
SE-752 28 Uppsala, Sweden

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140029/S054

Date of FDA Notice of Approval: 3/20/2026

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 PMA supplement for Restylane Contour (P140024/S032) was approved on June 28, 2021, and is indicated for cheek augmentation and correction of midface contour deficiencies 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.

The current supplement was submitted to expand the indication for *Restylane Contour.* The study was performed in the US under IDE G220259 to establish a reasonable assurance of safety and effectiveness for the use of *Restylane Contour* for correction of temple hollowing 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.

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

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the *Restylane Contour* package insert (Warnings and Precautions*)*.

## V. DEVICE DESCRIPTION

*Restylane Contour* is a sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless, flexible and homogeneous gel composed of hyaluronic acid (HA) 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 several alternative treatments to improve temple hollowing including: fat grafting, surgical implants, and soft tissue fillers such as HA, poly-L-lactic acid, and calcium hydroxylapatite. Each alternative has its own advantages and disadvantages. Patients should fully discuss these alternatives with their physician to select the method that best meets expectations and lifestyle.

## VII. MARKETING HISTORY

*Restylane® Contour (Restylane Volyme* in the EU), previously named *Emervel® Volume Lidocaine,* was approved in the European Union in 2010. In June 2021, Restylane Contour received US marketing approval (P140024/S032) for cheek augmentation and correction of midface contour deficiencies in patients over the age of 21. In addition to being marketed throughout EU and affiliated countries, *Restylane Contour* is currently marketed in countries in the following regions: North America, Latin America, South America, Eastern Europe, Middle-East, Africa, Asia, and Australia/New Zealand under the trade name *Restylane Volume.*

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.

Common treatment site responses that can occur with the use of *Restylane® Contour* include pain, swelling, itching, redness, bruising, tenderness, lumps/bumps. Other adverse events reported less frequently (>1 subject) include nasopharyngitis, actinic keratosis, back pain, dry eye, visual acuity reduced, hypercholesterolaemia, anxiety, depression, and constipation.

For the specific adverse events that occurred in the clinical study, please see Section X below.

Post-marketing surveillance

The adverse event reports received from post-marketing surveillance (voluntary reporting and published literature) for the use of *Restylane Contour (Restylane Volyme* in the EU) with and without lidocaine from worldwide sources mostly report 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
- 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* 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.

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.

## IX. SUMMARY OF NON-CLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for correction of temple hollowing in patients over the age of 21. There was no change in product manufacturing or specifications or shelf-life (24 months). Therefore, the

data previously presented in support of PMA P140029 are incorporated here by reference.

## 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 the correction of temple hollowing in patients over the age of 21 years in the US under IDE # G220259. 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

Patients 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. There were 15 investigational sites.

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.

The statistical analysis followed a Frequentist approach. The primary effectiveness endpoint was the responder rate based on the Blinded Evaluator's assessment of the Galderma Temple Volume Deficit Scale (GTVDS) at 3 months after baseline. The primary analysis compared responder rates between the Restylane Contour and no-treatment groups using a two-sided statistical test with

a significance level of 0.025 for the needle and cannula treatment groups separately to account for multiplicity. The null hypothesis assumed that the probability of response was independent of treatment group. A total sample size of approximately 225 subjects (approximately 180 treatment and 45 control) was planned to provide approximately 90% power, assuming responder rates of 70% in the treatment group and 35% in the control group, with an estimated 15% dropout rate. Effectiveness analyses were conducted primarily on the intention-to-treat population, and missing data for the primary endpoint were handled using multiple imputations under a missing-at-random assumption

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the clinical study was limited to subjects who met the following 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 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.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 3, 6, 9, 12, and 18 months after baseline post-operatively. 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.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards 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 regards to effectiveness, the primary endpoint was the Galderma Temple Volume Deficit Scale (GTVDS, Table 1) 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.

The secondary effectiveness endpoints were as follows:

- 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.

| Score | Grade | Description |
|---|---|---|
| 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. |

**Table 1. Galderma Temple Volume Deficit Scale (GTVDS)**

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 touchup treatment versus those who did not receive the 1-month touch-up treatment.

## B. 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 2. 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 1. 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.

## C. 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 3. 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 2. 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 4.

**Table 3. 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 5.

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 4. 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), 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), 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), m/n (%) | | | |
| Co-packed 27G × ½" UTW needle | 89/181 (49.2) | 51/97 (52.6) | 15/40 (37.5) |
| Cannula size (subdermal), 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.

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of safety was based on the cohort of 224 patients, etc. available for the 3-month evaluation. The key safety outcomes for this study are presented below in Table 6. Adverse effects are reported in Tables 7 to 10.

**Adverse effects that occurred in the PMA clinical study:**

A total of 61 (33.7%) Restylane® Contour subjects and 10 (25.0%) no-treatment subjects who received optional treatment at Month 3 experienced at least one adverse event during the study. Adverse events that occurred in

>2.0% of the study population consisted of headache (17/181 [9.4%] Restylane® Contour subjects and 2/40 [5.0%] no-treatment subjects), implant site pain (12/181 [6.6%] Restylane® Contour subjects and 2/40 [5.0%] no-treatment subjects), and COVID-19 (5/181 [2.8%] Restylane® Contour subjects and 3/40 [7.5%] no-treatment subjects). Additional adverse events reported in more than 1 subject in either group included nasopharyngitis and actinic keratosis (3/181 [1.7%] Restylane® Contour subjects each), and back pain, dry eye, visual acuity reduced, hypercholesterolaemia, anxiety, depression, and constipation (2/181 [1.1%] Restylane® Contour subjects each). The majority of subjects who experienced unrelated AEs had events that were mild or moderate in intensity. Seven (3.9%) Restylane® Contour subjects and 1 (2.5%) no-treatment subject experienced serious adverse events (SAEs) that were considered unrelated to study product or injection procedure. One (0.6%) Restylane® Contour subject experienced AEs leading to study discontinuation that were SAEs and considered unrelated to study product or injection procedure.

Nineteen (10.5%) Restylane® Contour subjects and 2 (5.0%) no-treatment subjects experienced an AE that was considered related to study product or injection procedure. The most common AEs related to study product or injection procedure were implant site pain (12/181 [6.6%] Restylane® Contour subjects and 2/40 [5.0%] no-treatment subjects) and headache (10/181 [5.5%] Restylane® Contour subjects and no no-treatment subjects). All AEs considered related to study product or injection procedure were mild or moderate in intensity. No subject died, and no subject experienced a treatment-related SAE during the study. Four (2.2%) Restylane® Contour subjects and 1 (2.5%) no-treatment subject experienced an adverse event of special interest (AESI); all AESIs were considered unrelated to study product or injection procedure.

A complete summary of investigator-reported adverse events by preferred term is provided in Table 8. All adverse events related to study product or injection procedure reported in the Restylane® Contour and no-treatment groups were mild or moderate in intensity.

**Pre-identified events:** Subjects who received treatment were asked to record pre-identified events in a diary over the first 28 days after each treatment. The events that were experienced are summarized in Table 6. 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 events 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 events (lumps/bumps) after initial treatment; no disabling events were reported after touch-up treatment.

Among subjects randomized to no treatment at baseline, the majority of subjects reported events 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 events.

In both the *Restylane Contour* and the no-treatment groups, the majority of subjects with pre-defined diary events had resolution of their events within the first 7 days after treatment. Overall, 62.7% of events resolved within 7 days after initial treatment and 67.9% after touch-up treatment in the Restylane Contour group, and 48.4% in the no-treatment group that received optional treatment.

**Table 5. Summary of Subject Diary Events by Injection Timepoint and Maximum Intensity (Safety Population)**

| Characteristic | *Restylane Contour* Tolerable n (%) | *Restylane Contour* Affects Daily Activities n (%) | *Restylane Contour* Disabling n (%) | *Restylane Contour* Total n (%) | No Treatment at Baseline Tolerable n (%) | No Treatment at Baseline Affects Daily Activities n (%) | No Treatment at Baseline Disabling n (%) | No Treatment at Baseline 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 7. 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 6. 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 8. 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 7. 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 9. 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.

**Table 8. 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 10.

**Table 9. 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.

**Implant site pain events:** 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.

**Device deficiencies:** One subject in the *Restylane Contour* group experienced a device deficiency (i.e., syringe failure, needle attachment, etc.) 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.

2. Effectiveness Results

The analysis of primary effectiveness was based on the 181 evaluable subjects in the Treatment group and 44 evaluable subjects in Control group at 3months after baseline. Key effectiveness outcomes are presented in Table 11.

**Primary Effectiveness Results**

The primary effectiveness endpoint was the responder rate based on the Blinded Evaluators' live assessment of the 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 11 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 10. 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, n (%)[1] | 181 (91.2) | 44 (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, n (%)[1] | 97 (87.6) | 44 (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, n (%)[1] | 94 (95.7) | 44 (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 Effectiveness Results

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 1.

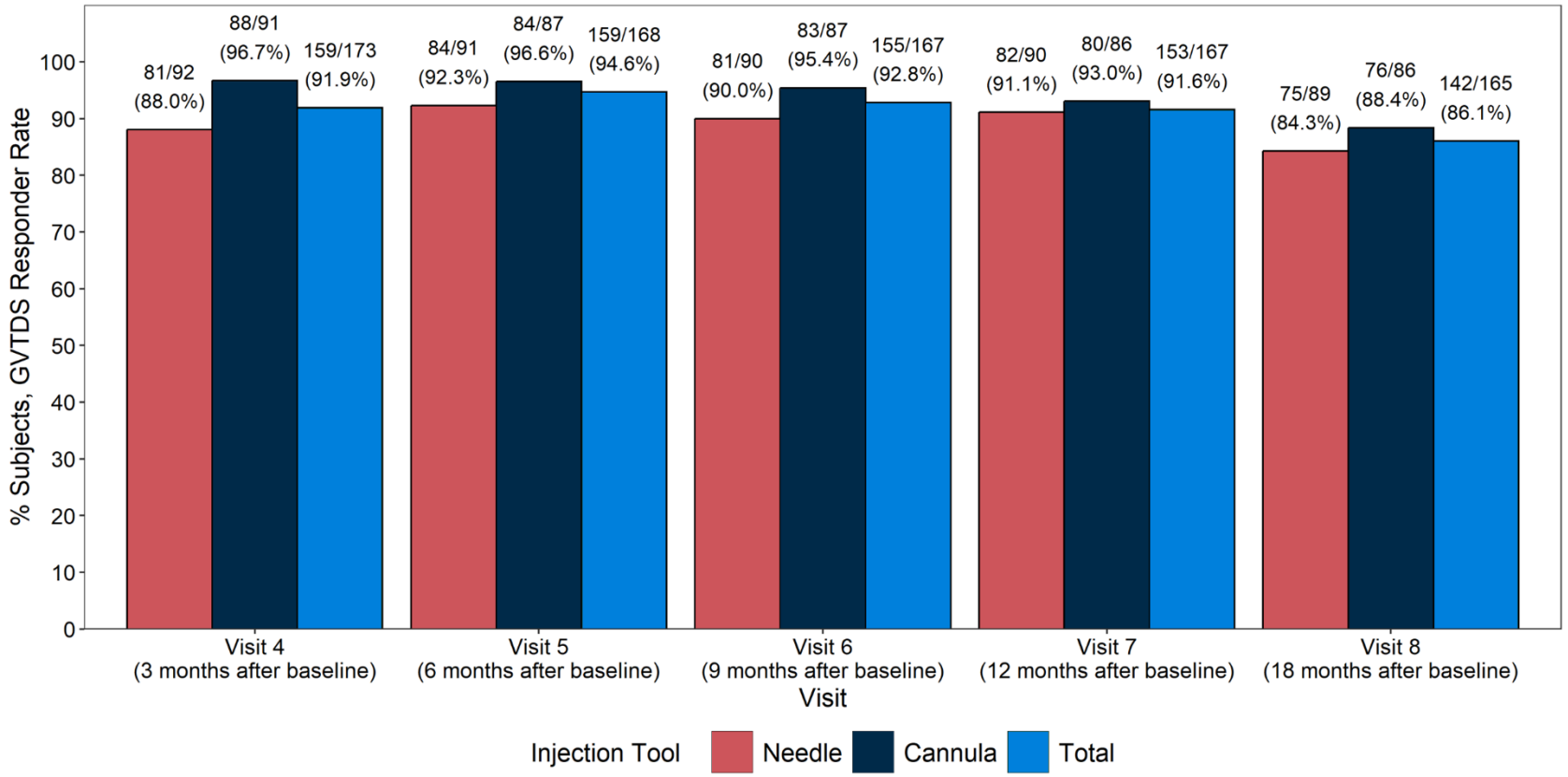


**Figure 1. Responder Rate Based on the Galderma Temple Volume Deficit Scale by Visit (Blinded Evaluator) – Treatment Group (Observed Cases – Intention-to-Treat Population)**

**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.

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: study site, race, ethnicity, sex at birth, age category (above or below median age), FST (I-III versus IV-VI), injection volume (above or below median volume), and injection tool for subdermal (superficial) injections (needle or cannula).

The study was not specifically powered for study site, race, ethnicity, sex at birth, age, FST, injection volume, or injection tool subgroups.

**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]).

The subgroup analyses of subjects in the Restylane Contour group with treatment-related AEs are presented in Table 12.

**Table 11. Subgroup Analyses of Subjects with Treatment-Related AEs by Preferred Term - Initial Treatment + Touch-up (*Restylane Contour* group)**

| Subgroup | Any related AE | Implant site pain | Headache |
|---|---|---|---|
| Injection volume ≤ median (n=91 subjects) | 2.8% | 1.1% | 2.8% |
| Injection volume > median (n=90 subjects) | 7.7% | 5.5% | 6.6% |
| | | | |
| FST I/II/III (n=126 subjects) | 9.9% | 6.6% | 7.2% |
| FST IV (n=36 subjects) | 0.0% | 0.0% | 0.6% |
| FST V/VI (n=19 subjects) | 0.6% | 0.0% | 1.7% |
| | | | |
| Female (n=173 subjects) | 9.4% | 5.5% | 8.3% |
| Male (n=8 subjects) | 1.1% | 1.1% | 1.1% |
| | | | |
| Age ≤ median (n=104 subjects) | 7.2% | 4.4% | 6.1% |
| Age > median (n=77 subjects) | 3.3% | 2.2% | 3.3% |
| | | | |
| Cannula (n=84 subjects) | 2.2% | 1.7% | 1.7% |
| Needle (n=87 subjects) | 7.7% | 4.4% | 7.2% |
| Needle and cannula (n=10 subjects) | 0.6% | 0.6% | 0.6% |

FST=Fitzpatrick Skin Type

## 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 (data now shown).

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).

4. Pediatric Extrapolation

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

## XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 15 principal investigators and 6 sub-investigators, of which none were full-time or part-time employees of the sponsor, and two investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f).

Enrollment at each study site was limited to minimize the impact of any single site on the study results.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

## 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 43USTH2201 conducted to support PMA approval as described above. Conclusions drawn from the clinical study provide a reasonable assurance that the device is effective to correct temple hollowing in subjects over the age of 21 years.

Conclusions from this study are:

- The primary effectiveness objective was met, as the responder rate based on the Blinded Evaluators' live assessment of the GTVDS 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).

- Subgroup analysis of the primary effectiveness endpoint demonstrated that the treatment difference in Month 3 responder rates favored *Restylane Contour* treatment, regardless of injection tool (needle or cannula) used for subdermal injections. Statistical significance was reached for all subgroups (race, ethnicity, sex at birth, age category, FST category and injection volume category) except for Black/African American race. Due to relatively small sample sizes across the study sites, no meaningful conclusions could be made.

- The responder rate in the treatment group, based on the Blinded Evaluator GTVDS, was, overall, 94.6% at Month 6, 92.8% at Month 9, 91.6% at Month 12, and 86.1% at Month 18. The responder rates were similar between needle and cannula for subdermal injections at all assessment timepoints.

- In the treatment group, aesthetic improvement was reported for most subjects across all assessment timepoints, with GAIS improvement rates ranging from 88.5% to 100% as assessed by the Treating Investigator, and from 80.6% to 96.0% as assessed by subjects.

- In the control group, aesthetic improvement was reported for most subjects who accepted optional treatment across all assessment timepoints, with GAIS improvement rates ranging from 92.1% to 97.4% as assessed by the Treating Investigator, and from 81.6% to 92.3% as assessed by subjects.

- Based on the SSQ, 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 this group were satisfied with how quickly they could go back to social engagements at Month 3.

- Based on the ISQ at Month 3, almost all Treating Investigators agreed or strongly agreed that in the treatment group the results were natural looking (99.4%). They were also satisfied with how the product enabled them to correct temple hollowing (97.7%) and liked how the subjects looked after treatment (99.4%).

- Based on 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 (mean increase from baseline range: 52.1 to 58.6), whereas subjects in the control group had a mean change from baseline at Month 3 of -1.9. Based on this same questionnaire, subjects in the treatment group were also satisfied with their treatment outcome at all post-baseline visits (mean range: 74.1 to 79.6).

- The responder rate, as assessed by IPR, for the treatment and control groups was 74.4% and 24.4%, respectively, at 3 months after baseline.

- The median time to feeling comfortable returning to social engagement for subjects in the treatment group was 5.4 hours after initial treatment and 3.6 hours after optional touch-up treatment.

## B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical study 43USTH2201 conducted to support PMA approval as described above. Conclusions from this study are:

- The percentage of subjects reporting pre-defined, expected post-treatment events (i.e., pain, tenderness, redness, bruising, swelling, itching, or lumps/bumps) at initial treatment was similar between the treatment group and subjects randomized to the control group who had optional treatment at Month 3 (84.7% and 79.5%, respectively). This percentage was lower (58.7%) at the touch-up treatment in the

treatment group. The majority of subjects reported events that were tolerable after treatment (whether initial or touch-up) and had resolution of their events within the first 7 days after treatment.

- Nineteen (10.5%) *Restylane Contour* subjects and 2 (5.0%) no treatment subjects who received optional treatment at Month 3 experienced an AE considered related to study product or injection procedure. All AEs related to study product or injection procedure were mild or moderate in intensity. The only AEs considered related to study product or injection procedure were implant site pain (14 [6.3%]) and headache (10 [4.5%]).

- 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 but related to injection procedure. The duration of events ranged from 1 to 5 days.

- One *Restylane Contour* subject experienced SAEs leading to study discontinuation, which were considered unrelated to study product or injection procedure.

- The percentage of subjects who experienced an AE related to study product or injection procedure was higher among subjects whose subdermal injection tool was needle (15.7%) than among those whose subdermal injection tool was cannula (3.7%), and higher and among subjects with FST I-III (13.2%) than among those with FST IV-VI (1.4%). No clinically meaningful differences were observed in AE incidence for other subgroups.

- One subject experienced a device deficiency during the study. No AE was reported for this subject due to the deficiency.

- 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 study discontinuation of the subject described above. All AESIs were considered not related to study product or injection procedure.

- Seven (3.9%) *Restylane Contour* subjects and 1 (2.5%) subject who received no treatment at baseline but optional treatment at Month 3 experienced at least 1 SAE, none of which was considered related to study product or injection procedure. No subject died during the study.

- Mean left and right temple numeric pain scores post-injection at initial treatment was 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. 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 correction of temple hollowing as assessed by the blinded evaluator/investigator using the GTVDS, improved global aesthetic appearance according to investigator and subject GAIS assessments and increased satisfaction measured with an investigator/subject satisfaction questionnaire and a subject FACE-Q™ satisfaction with temples 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 self-reported events (subject diary data) 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 within the first 7 days after treatment. Nineteen (10.5%) *Restylane Contour* subjects and 2 (5.0%) no treatment subjects who received optional treatment at Month 3 experienced an AE considered related to study product or injection procedure. All AEs related to study product or injection procedure were mild or moderate in intensity. The only AEs considered related to study product or injection procedure were implant site pain (14 [6.3%]) and headache (10 [4.5%]). Summary of safety conclusions is provided above.

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

Patient perspectives considered during the review included:

- FACE-Q Questionnaires to assess satisfaction with the aesthetic outcome and temple area. Results for FACE-Q are discussed in Section X.d2.
- GAIS assessed by the patients after treatment. Results for GAIS are discussed in Section X.d2.
- Adverse events were obtained from signs and symptoms reported by patients during visits. Adverse Events are discussed in Section X.d1.
- Patient Diaries were used to collect information about predefined, injection related events at the treated area. Diary Information is discussed in Section X.d1. Despite the frequency of pre-defined self-reported events, 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 correction of temple hollowing 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 March 20, 2026. The final clinical conditions of approval cited in the approval order are described below.

Conditions of Approval

**Device Tracking**

The device will be tracked as per FDA medical device tracking requirements (21 CFR 821).

**PAS Study Design:**

Per agreement reached March 20, 2026, a post-approval study will be performed

The following elements have been suggested for the post approval study.

- **Study purpose/objectives:** To evaluate the safety of *Restylane Contour* in treatment of temple hollowing 3 months after optional Month 12 retreatment.
- **Study design (specify control, randomization, etc.):** This is a prospective, multicenter study designed to evaluate the safety of retreatment with *Restylane Contour* in correction of temple hollowing.
- **Total number of subjects (including relevant subgroups and targets for ensuring diversity with respect to sex, age, race, and ethnicity, as appropriate):**
  - Will be agreed upon in the protocol

    This study will enroll:

    - Patient who are 22 years and older with moderate to severe temple hollowing
    - Sufficient sample size to assess as will be agreed upon in the final protocol:
      - Approximately 100 subjects will be enrolled in the study
- **Length of follow-up and frequency of assessments**

  PAS Visit Schedule

  - Baseline: Treatment with initial Restylane Contour at day 0
  - Follow-up 72 hours, 2 weeks, 1 Month, and 3 months after each injection
- Physical follow-up visits at Month 1, 3 and 12 after initial treatment and 1 month and 3 months after re-treatment Endpoint(s)

- **Primary endpoints:** Treatment-emergent adverse events (TEAEs) that are related to the device and/or injection procedure after the Month 12 optional retreatment.
- **Secondary endpoints:**
  - Proportion of **(a)** responders (subject has at least 1 grade improvement from baseline in both temples based on the Treating Investigators' live assessment of the Galderma Temple Volume Deficit Scale [GTVDS]), **(b)** 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) as assessed by the Subject and Treating Investigator, separately, **and (c)** subjects in each response category for every question in the Subject Satisfaction Questionnaire with temple hollowing correction on both sides of the face at 3 and 12 months after initial treatment and 3 months after optional retreatment at Month 12.
  - 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.

- **High-level description of the data analysis plan for the primary endpoints (include hypotheses, if applicable)**
  - Adverse event reporting: AE will be obtained from signs and symptoms reported by Subject or detected during examination. Any ongoing AEs related to product or injection procedure will be followed until resolved or chronic/stable through end of study participation
  - Subject Diaries: A subject diary will be dispensed to all subjects for daily completion over the first 4 weeks after each treatment to record the presence of each of the following: bruising, redness, tenderness, swelling, pain, lumps/bumps, itching, and other. Information from the diary will be presented separately from other AEs.
  - Device Deficiencies. Device deficiencies will be assessed at treatment visits.
  - Jaw functionality, temple firmness, symmetry, and sensation, visual function and mass formation according to pre-defined methods, at baseline and at each physical follow-up visit. Palpation tests according to pre-defined methods, at each physical follow-up visit.
- **Reference to protocol (e.g., version number, date of amendment or email in which it was received)**
  - Outlined agreed upon in March 20, 2026 email correspondence. Final protocol pending the Agency's approval.
- Plan for interim data release
  - Pending Agency review and approval.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

## 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.