# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: JUVÉDERM® VOLUMA™ XC

Device Procode: LMH

Applicant's Name and Address: Allergan
2525 Dupont Drive
Irvine, CA 92612

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110033/S047

Date of FDA Notice of Approval: June 12, 2020

The original JUVÉDERM® VOLUMA™ XC PMA (PMA #P110033) was approved on October 22, 2013 and is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over the age of 21. The SSED to support the indication for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for JUVÉDERM® VOLUMA™ XC for deep (subcutaneous and/or supraperiosteal) injection for augmentation of the chin region to improve the chin profile in adults over the age of 21.

## II. INDICATIONS FOR USE

JUVÉDERM® VOLUMA™ XC is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face and for augmentation of the chin region to improve the chin profile in adults over the age of 21.

## III. CONTRAINDICATIONS

- JUVÉDERM® VOLUMA™ XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- JUVÉDERM® VOLUMA™ XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- JUVÉDERM® VOLUMA™ XC contains lidocaine and is contraindicated for patients with a history of allergies to such material.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the JUVÉDERM® VOLUMA™ XC labeling.

## V. DEVICE DESCRIPTION

JUVÉDERM® VOLUMA™ XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. The gel consists of hyaluronic acid (HA) produced by the *Streptococcus* species of bacteria, which is crosslinked with BDDE. It is formulated to a concentration of 20 mg/mL and 0.3% w/w lidocaine in a physiologic buffer. The HA gel is made primarily of crosslinked HA with some remaining lightly crosslinked and uncrosslinked HA. Each box of JUVÉDERM® VOLUMA™ XC contains 2 pre-filled disposable syringes each containing 1 mL of hyaluronic gel implant. Each syringe is fitted with a Luer lock adaptor, a plunger rod, a rubber stopper tip cap, and a finger grip. Each syringe is labeled with the name of the product, batch number, and expiration date. JUVÉDERM® VOLUMA™ XC is delivered by an injection into the chin region for chin augmentation.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for chin augmentation including: surgically with permanent alloplastic chin implants and genioplasty, and non-surgically with injection of fat. 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

JUVÉDERM® VOLUMA™ XC received the CE Mark in December 2009 for restoration of facial volume and received FDA approval on October 22, 2013 for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over the age of 21. In addition to being marketed throughout EU and affiliated countries, JUVÉDERM® VOLUMA™ XC is currently marketed in countries in the following regions: North America, Latin America, South America, Eastern Europe, Middle-East, Africa, Asia-Pacific, and Australia/New Zealand under the tradename JUVÉDERM® VOLUMA™ XC with Lidocaine.

JUVÉDERM® VOLUMA™ XC has not been withdrawn from any marketplace for any reason.

## 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 which can occur with the use of JUVÉDERM® VOLUMA™ XC, and other dermal fillers, include tenderness, firmness (induration), swelling, pain, lumps/bumps (mass), bruising, redness, itching, and discoloration. Other adverse effects reported less frequently (in less than 1% of the study subjects) include injection site inflammation, injection site abscess, injection site cellulitis, gingival pain, and acne cyst.

Post-Market Surveillance

JUVÉDERM® VOLUMA™ XC without lidocaine has been marketed outside the US since 2005, and JUVÉDERM® VOLUMA™ XC (also known as JUVÉDERM® VOLUMA™ with lidocaine) has been marketed outside the US since 2009 and in the US since 2013.

The following AEs were received from postmarket surveillance for JUVÉDERM® VOLUMA™ XC with and without lidocaine with a frequency of 5 events or more and were not observed in the clinical study (during the 6-13 months that subjects were monitored in this study); this includes reports received globally from all sources including scientific journals and voluntary reports. All AEs obtained through postmarket surveillance are listed in order of number of reports received: inflammatory reaction, lack of correction, infection, migration, allergic reaction, abscess, paresthesia, vascular occlusion, drainage, necrosis, vision abnormalities, malaise, scarring, nausea, granuloma, deeper wrinkle, and dyspnea. Reported treatments include: antibiotics, steroids, antiseptic creams, hyaluronidase, anti-inflammatories, antihistamines, needle aspiration, eye drops, radio frequency therapy, hyperbaric oxygen treatment, laser treatment, ice, massage, warm compress, analgesics, anti-virals, ultrasound therapy, excision, drainage, and surgery.

Vision abnormalities have been reported following injection of JUVÉDERM® VOLUMA™ XC, with and without lidocaine, into the nose, glabella, periorbital area, and/or cheek, with a time to onset ranging from immediate to 1 week following injection. Reported treatments include anticoagulants, sympathomimetics, steroids, and surgery. Outcomes ranged from resolved to ongoing at the time of last contact. Events requiring medical intervention, and events where resolution information is not available, were reported after injection of JUVÉDERM® VOLUMA™ XC with and without lidocaine in the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use (see Warnings section).

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

## IX. SUMMARY OF NONCLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for deep (subcutaneous and/or supraperiosteal) injection for augmentation of the chin region to improve the chin profile in adults 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 P110033 are incorporated here by reference.

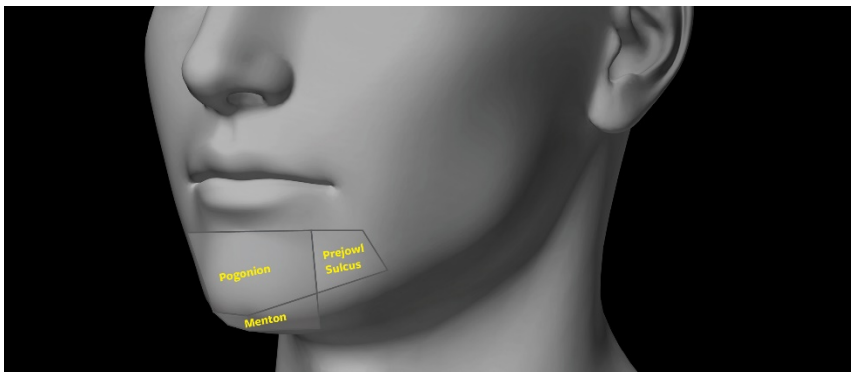
# X. SUMMARY OF PRIMARY CLINICAL STUDY

## A. STUDY DESIGN

Subjects were treated between June 28, 2016 and August 23, 2018. The database for this PMA reflected data collected through February 11, 2019 and included 221 subjects. There were 14 investigational sites.

A multi-center, single-blind, randomized, no-treatment controlled pivotal clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA™ XC for chin augmentation. Subjects were randomized to treatment or no-treatment control in a 3:1 ratio. Treatment group subjects underwent treatment with JUVÉDERM® VOLUMA™ XC at the outset of the study. The Treating Investigator (TI) determined the appropriate volume of JUVÉDERM® VOLUMA™ XC to be injected in the chin area (did not exceed 4 mL for initial and touch-up treatment combined and another 4 mL for repeat treatment): pogonion, mentum, and pre-jowl sulci, as depicted in Figure 1. Injection in the pogonion was only permitted with a 27G ½" needle; a TSK 25 G 1 1/2" Steriglide™ cannula was permitted for injection in the other treatment areas. The no-treatment control subjects had treatment delayed for 6 months.

**Figure 1: Chin Area Treated**




1. Clinical Inclusion and Exclusion Criteria

Enrollment in the VOLUMA-006 study was limited to patients who met the following inclusion criteria:

- Age 22 or over and in good general health
- Had "Moderate" or "Severe" chin retrusion (grades 2 or 3 on the Allergan Chin Retrusion Scale (ACRS)) as assessed and agreed to a single grade by both the Evaluating Investigator (EI) and TI
- TI considered the subject's chin retrusion to be amenable to temporary correction
- Ability to follow study instructions and likely to complete all required visits
- Written informed consent had been obtained

Patients were not permitted to enroll in the VOLUMA-006 study if they met any of the following exclusion criteria:

- Had ever received permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or was planning to be implanted with any of these products during the study
- Had ever undergone fat injections below the subnasale or was planning to undergo this procedure during the study
- Had tattoos, piercings, facial hair (i.e., beard, mustache), or scars below and including the subnasale that would have interfered with visual assessment of the chin, jowls, or jawline
- Had undergone semi-permanent dermal filler treatment (e.g., calcium hydroxyapatite, poly-L-lactic acid) in the chin or jaw within 36 months before enrollment or was planning to undergo such treatment during the study
- Had undergone dermal filler injections, or had undergone any surgery in the chin or jaw area (including marionette lines, pre-jowl sulci, mandibular body, or masseter muscles) within 24 months before enrollment or was planning to undergo any of these procedures during the study
- Had undergone dermal filler injection in the lips or perioral area within 12 months before enrollment or was planning to undergo such treatment during the study
- Had, in the opinion of the TI, significant skin laxity in the chin, jaw, or neck
- Had clinically significant malocclusion (severe overbite) in the TI's judgment
- Had dentures or any device covering all or part of the palate or was planning to undergo any dental procedure (other than prophylaxis and dental fillings) during the study
- Had undergone mesotherapy or cosmetic treatment (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, liposuction, lipolysis, or other ablative procedures) anywhere in the face or neck, or botulinum toxin treatment below the subnasale (including injections to the masseter muscles) within 6 months before enrollment or was planning to undergo any of these procedures during the study
- Had experienced trauma to the chin and jaw area within 6 months before enrollment or had residual deficiencies, deformities, or scarring
- Had a tendency to develop hypertrophic scarring
- Had a history of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), hyaluronic acid products, or *Streptococcal* protein, or was planning to undergo desensitization therapy during the term of the study
- Had porphyria or untreated epilepsy
- Had active autoimmune disease
- Had current cutaneous or mucosal inflammatory or infectious processes (e.g., acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, below the subnasale (study device injection may have been delayed for subjects with a history of recurrent oral herpes lesions who take prophylactic doses of antiviral/herpes medication for at least 2 days before study treatment administration)
- Was on a concurrent regimen of lidocaine or structurally-related local anesthetics (e.g., bupivacaine) or was on a concurrent regimen of drugs that reduce or inhibit hepatic metabolism (eg, cimetidine, beta-blockers)
- Was on a regimen of anti-coagulation therapy (e.g., warfarin, clopidogrel)

- Was on a regimen of medications (e.g., aspirin or ibuprofen) or other substances known to increase coagulation time (e.g., herbal supplements with garlic or gingko biloba) within 10 days of undergoing study device injection (study device injection may have been delayed as necessary to accommodate this 10-day washout period)
- Had received any investigational product within 30 days prior to study enrollment or was planning to participate in another investigation during the course of this study
- Had begun using any new over-the-counter or prescription oral or topical, anti-wrinkle products below the subnasale within 30 days before enrollment or was planning to begin using such products during the study (subjects who had been on a regimen of such products for at least 30 days were eligible for the study if they intended to continue their regimen throughout the study)
- Females who were pregnant, nursing, or planning a pregnancy
- Was an employee (or a relative of an employee) of the TI, EI, or Allergan, or a representative of Allergan
- Had a condition or was in a situation which in the TI's opinion may have put the subject at significant risk, may have confounded the study results, or may have interfered significantly with the subject's participation in the study

2. Follow-up Schedule

Up to 2 treatments approximately 1 month apart (initial treatment and up to 1 touch-up treatment) were allowed. All subjects returned for routine safety and effectiveness follow-up visits at 1, 3, and 6 months after the last treatment during the primary safety and effectiveness phase. During the extended follow-up period, treatment group subjects returned for safety and effectiveness evaluations at 9 and 12 months after last treatment. An optional repeat treatment was offered to all treatment group subjects after completion of the extended follow-up period, with 1 month of follow-up after repeat treatment. Control subjects followed a similar effectiveness evaluation schedule through Month 6. After Month 6, control subjects received treatment and were followed for an additional 6 months with the same treatment and follow-up schedule as the treatment group.

Pre- and post-procedure, the objective parameters measured during the study included the evaluating investigators' (EIs') assessment of subjects' overall chin volume deficit live and via 2-dimensional (2D) profile images of the left side of the chin, which were rendered by image analysis software from 3-dimensional (3D) photos, using the validated 5-point photonumeric Allergan Chin Retrusion Scale (ACRS). EIs also assessed subjects' improvement on the 5-point Global Aesthetic Improvement Scale (GAIS). Subjects performed self-assessments on the GAIS, the *Satisfaction with Chin* module of the validated FACE-Q questionnaire, the Psychological Well-Being module of the validated FACE-Q questionnaire, and the natural look and natural feel of the chin area on an 11-point scale. Further, 3D facial photography was performed to quantify volume changes. In addition to subject diaries and TI assessment of AEs, safety of the treatment was assessed via facial sensation and facial function assessments conducted by the EI.

Sensation in the chin area was assessed using a 2-point discrimination test and a light touch test. Two-point discrimination was tested at 3 locations on the chin (the pogonion and halfway between the pogonion and each prejowl sulcus). Using the Dellon Disk-Criminator, the EI lightly touched the set of prongs to each location on the chin, while the subject reports whether s/he felt "1" or "2" objects touching his/her skin.

The light touch test was performed at the same 3 locations on the chin. The EI pressed Semmes-Weinstein monofilaments of different diameters against the subject's skin and record the smallest filament size that elicits a response at each assessed location.

The EI tested facial function using the Facial Nerve Grading Scale 2.0 (FNGS 2.0). The EI assessed the subject's face at rest and then requested that the subject make a standardized series of facial movements while the EI rated the movement in each of 4 facial areas: brow, eye, nasolabial fold, and oral commissure. A score was assigned to each facial area, and a score for synkinesis is attributed across the entire face.

3. Clinical Endpoints

With regards to safety, preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments. Subjects were instructed to rate each treatment site response listed on the diary as "Mild (easily tolerated)," "Moderate (affecting daily activity)," "Severe (unable to do daily activity)," or "None." Adverse Events were reported by the TI at all follow-up visits where applicable.

With regards to effectiveness, the primary effectiveness measure was the single blinded EI's assessment of the subject's chin volume deficit in 2D images using the validated 5-point photonumeric ACRS (Table 1, Figure 2).

The ACRS scale was validated in a 61-subject study where three reviewers were shown photographs of the subjects at two different time points. The average weighted kappa for the intra-rater agreement was 0.87, meaning the reviewers' evaluations of the same subjects were consistent between the two time points. The weighted kappa for the inter-rater agreement for two of the three reviewers was 0.84. The agreement between those two reviewers and the third reviewer was lower than 0.6 (0.59 and 0.53), but the balance of evidence suggested that the scale could be used consistently.

Secondary measures included the statistical superiority, at Month 6 compared to baseline, of the mean overall score on the *Satisfaction with Chin* module of the validated FACE-Q questionnaire (0 to 100, where higher scores reflect a better outcome) as assessed by the subjects, and the level of improvement on the GAIS as assessed by the blinded EIs and the subjects. Other effectiveness endpoints included the responder rate and ACRS score based on the EI's live assessment at baseline and Month 6.

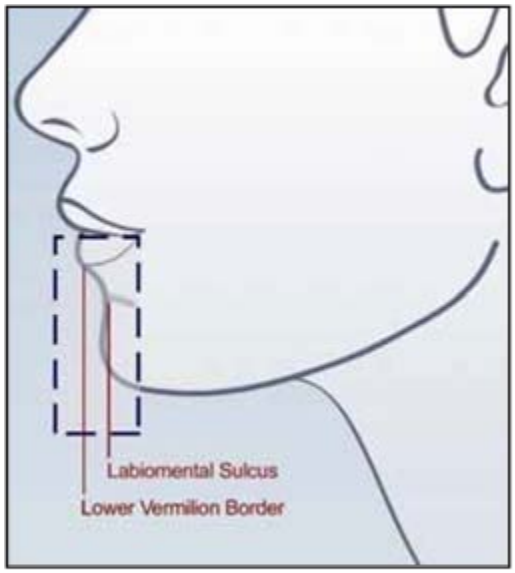
With regards to success/failure criteria, a responder was defined as a subject with ≥ 1-point improvement in the ACRS score compared to the baseline score. Effectiveness of JUVÉDERM® VOLUMA™ XC was demonstrated if at least 50% of subjects treated with JUVÉDERM® VOLUMA™ XC were responders (≥ 1-point improvement) at Month 6, and if the responder rate for the treatment group was statistically superior to that of the no-treatment control group at Month 6.

**Table 1: Allergan Chin Retrusion Scale**

| Score | Grade | Description |
|---|---|---|
| 0 | None | No chin retrusion; Chin midpoint* at or in front of the lower vermilion border vertical line |
| 1 | Minimal | Minimal chin retrusion; Chin midpoint* is between the labiomental sulcus vertical line and lower vermilion border vertical line |
| 2 | Moderate | Moderate chin retrusion; Chin midpoint* at labiomental sulcus vertical line |
| 3 | Severe | Severe chin retrusion; Chin midpoint* slightly behind labiomental sulcus vertical line |
| 4 | Extreme | Extreme chin retrusion; Chin midpoint* significantly behind labiomental sulcus vertical line |

* Chin midpoint: the midpoint between the labiomental sulcus and the inferior point of the chin

**Figure 2: Lines Used in the ACRS Descriptors**




## B. ACCOUNTABILITY OF PMA COHORT

At the time of database lock, data from all 221 enrolled subjects were available for analysis (Table 2). Of the 221 subjects, 29 were screen failures primarily due to ineligibility, and 192 were randomized per protocol, with 144 in the treatment group and

48 in the control group. Of the 192 randomized subjects, 169 (88.0%; 128 treatment and 41 control) completed the Month 6 primary endpoint visit, and 38 of the 48 control group subjects (79.2%) opted to receive study treatment after the completion of the 6-month control period. A total of 167 (87.0%; 127 treatment and 40 control) completed the study.

At baseline, 7.8% (15/192) of subjects had mild, 40.6% (78/192) had moderate, 43.2% (83/192) had severe, and 8.3% (16/192) had extreme chin volume deficit based on EI photo assessments on the ACRS.

**Table 2: Participant Disposition**

| Population | Number of Participants | | |
|---|---|---|---|
| | Treatment Group | Control Group | Total |
| **Enrolled** | **N/A** | | **221** |
| Screen failures | N/A | | 29 |
| **Randomized** | **144** | **48** | **192** |
| **Modified Intent-to-Treat (mITT) Population** | **144** | **48** | **192** |
| Number of Participants Treated | 144 | 38 | 182 |
| Completed Month 6 visit (primary endpoint) | 128 | 41 | 169 |
| Completed Month 12 visit | 128 | N/A | 128 |
| Received Repeat Treatment at Month 12 | 74 | N/A | 74 |
| Completed Study | 127 | 40 | 167 |
| Discontinued from the Study | 17 | 8 | 25 |
| Adverse Event* | 1 | 2 | 3 |
| Lost to follow-up | 10 | 1 | 11 |
| Personal Reasons | 6 | 4 | 10 |
| Protocol Deviation** | 0 | 1 | 1 |
| **Per-Protocol (PP) Population** | **139** | **48** | **187** |
| **Safety Population** | **144** | **48** | **192** |

* The one treatment group participant was discontinued from the study due to a treatment-related serious adverse event, as detailed in Section D.1. The two control group participants discontinued due to adverse events prior to receiving any study treatment.

** The one control group participant discontinued from the study due to protocol deviation of unable to comply with the study visit schedule.

## C. STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS

The demographics of the study population are typical for a study performed in the US. Subject demographics and pre-treatment characteristics are presented in Table 3.

**Table 3: Demographics and Pretreatment Characteristics (N = 192)**

| Characteristic | | Treatment Group (N = 144) % (n) | Control Group (N = 48) % (n) |
|---|---|---|---|
| Gender | Female | 90% (129) | 85% (41) |
| | Male | 10% (15) | 15% (7) |
| Age (years) | Median | 51.5 | 52.5 |
| | Range (min, max) | (23-80) | (22-72) |
| Race | White | 58% (137) | 60% (28) |
| | Black or African-American | 15% (35) | 9% (4) |
| | Asian | 19% (44) | 26% (12) |
| | American-Indian or Alaska Native | 4% (9) | 6% (3) |
| | Multiple | 4% (10) | 0% (0) |
| Ethnicity | Hispanic or Latino | 19% (27) | 13% (6) |
| | Not Hispanic or Latino | 81% (117) | 87% (42) |
| Fitzpatrick Skin Type | I | 5% (7) | 2% (1) |
| | II | 31% (44) | 31% (15) |
| | III | 37% (54) | 33% (16) |
| | IV | 15% (22) | 17% (8) |
| | V | 7% (10) | 13% (6) |
| | VI | 5% (7) | 4% (2) |

## D. SAFETY AND EFFECTIVENESS RESULTS

1. Safety Results

The analysis of safety was based on the cohort of subjects available at each follow-up time point (1, 3, 6, 9, and 12 months after the initial/touch-up treatment and 1 month after the repeat treatment). The key safety outcomes for this study are presented below.

Preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments. Of the 182 subjects who underwent treatment (from both the treatment and control groups), 181 subjects completed the diary forms, and of the 74 subjects who received repeat treatment, 73 completed the diary forms. Subjects were instructed to rate each treatment site response listed on the diary as "Mild (easily tolerated)," "Moderate (affecting daily activity)," "Severe (unable to do daily activity)," or "None."

After initial treatment with JUVÉDERM® VOLUMA™ XC, 92% of subjects reported experiencing a local treatment site response (TSR). Subjects rated TSRs as predominantly mild in severity with a majority (64.7%, 108/167) resolving within 2 weeks. The incidence, severity, and duration of TSRs following repeat treatment were similar to that following initial treatment.

TSRs reported by > 5% of subjects after initial treatments are summarized by severity in Table 4 and by duration in Table 5.

**Table 4: Treatment Site Responses by Maximum Severity Occurring in > 5% of Subjects After Initial Treatment for Chin Augmentation (N=181)**

| | Severity[a] | | | |
|---|---|---|---|---|
| **Treatment Site Response** | **Total** | **Mild** | **Moderate** | **Severe** |
| | **% (n/N[b])** | **% (n/N)** | **% (n/N)** | **% (n/N)** |
| Any Treatment Site Response | 92.3% (167/181) | 44.9% (75/167) | 43.1% (72/167) | 12.0% (20/167) |
| Tenderness | 81.8% (148/181) | 56.8% (84/148) | 35.8% (53/148) | 7.4% (11/148) |
| Firmness | 75.1% (136/181) | 58.8% (80/136) | 36.0% (49/136) | 5.1% (7/136) |
| Swelling | 68.5% (124/181) | 64.5% (80/124) | 30.6% (38/124) | 4.8% (6/124) |
| Pain | 63.0% (114/181) | 67.5% (77/114) | 26.3% (30/114) | 6.1% (7/114) |
| Lumps/Bumps | 60.2% (109/181) | 67.9% (74/109) | 25.7% (28/109) | 6.4% (7/109) |
| Bruising | 59.1% (107/181) | 59.8% (64/107) | 31.8% (34/107) | 8.4% (9/107) |
| Redness | 48.6% (88/181) | 69.3% (61/88) | 28.4% (25/88) | 2.3% (2/88) |
| Itching | 27.6% (50/181) | 86.0% (43/50) | 14.0% (7/50) | 0% (0/50) |
| Discoloration | 14.9% (27/181) | 74.1% (20/27) | 18.5% (5/27) | 7.4% (2/27) |

[a] Maximum severity reported in the diary. The denominator for percentages by severity is the number of subjects with the corresponding treatment site response.
[b] N denotes number of subjects who recorded responses in the diaries after the initial treatment.

**Table 5: Duration of Treatment Site Responses After Initial Treatment for Chin Augmentation (N = 181)**

| | Duration[a] | | | | |
|---|---|---|---|---|---|
| **Treatment Site Response** | **Total** | **1-3 Days** | **4-7 Days** | **8-14 Days** | **15-30 Days** |
| | **% (n/N[b])** | **% (n/N)** | **% (n/N)** | **% (n/N)** | **% (n/N)** |
| Any Treatment Site Response | 92.3% (167/181) | 13.2% (22/167) | 24.0% (40/167) | 27.5% (46/167) | 35.3% (59/167) |
| Tenderness | 81.8% (148/181) | 31.8% (47/148) | 43.2% (64/148) | 18.2% (27/148) | 6.8% (10/148) |
| Firmness | 75.1% (136/181) | 35.3% (48/136) | 27.2% (37/136) | 20.6% (28/136) | 16.9% (23/136) |
| Swelling | 68.5% (124/181) | 53.2% (66/124) | 31.5% (39/124) | 8.9% (11/124) | 6.5% (8/124) |
| Pain | 63.0% (114/181) | 69.3% (79/114) | 21.9% (25/114) | 6.1% (7/114) | 2.6% (3/114) |
| Lumps/Bumps | 60.2% (109/181) | 23.9% (26/109) | 21.1% (23/109) | 21.1% (23/109) | 33.9% (37/109) |
| Bruising | 59.1% (107/181) | 18.7% (20/107) | 46.7% (50/107) | 31.8% (34/107) | 2.8% (3/107) |
| Redness | 48.6% (88/181) | 61.4% (54/88) | 22.7% (20/88) | 11.4% (10/88) | 4.5% (4/88) |
| Itching | 27.6% (50/181) | 70.0% (35/50) | 20.0% (10/50) | 8.0% (4/50) | 2.0% (1/50) |
| Discoloration | 14.9% (27/181) | 63.0% (17/27) | 22.2% (6/27) | 3.7% (1/27) | 11.1% (3/27) |

[a] Maximum duration reported in the diary. The denominator for percentages by duration is the number of subjects with the corresponding treatment site response.
[b] N denotes number of subjects who recorded responses in the diaries after the initial treatment.

Overall, 167 treated participants (92.3%) reported at least 1 TSR after initial treatment, 86 (82.7%) reported at least 1 TSR after touch-up treatment, and 55 (75.3%) participants reported TSRs after repeat treatment.

TSRs reported by ≤ 5% of subjects included pimples, flakiness, numbness, throbbing, tightness, and tingling.TSRs were reported by subjects in their diary for 30 days after treatment. TSRs were considered severe in 12.0% of subjects and lasted 15-30 days in 35.3% of subjects.

Adverse events (AEs) were reported by the TI at all follow-up visits, where applicable. An AE was defined in accordance with ISO 14155 as "*any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device*." A treatment-emergent AE (TEAE) was defined as an AE that initially occurred or increased in severity on or after the treatment start date for the treatment group and on or after the randomization date for the control group, and was reported by the treating investigator.

Among the 182 treated subjects, 7.7% (14/182) experienced 20 treatment-related TEAEs following initial and touch-up treatment. Most of the treatment-related TEAEs occurred

within 7 days after treatment, were mild or moderate in severity, and resolved without sequelae within 14 days.

Table 6 summarizes treatment-related TEAEs that occurred with a frequency of > 1%. Treatment-related TEAEs occurring in ≤ 1% of subjects included injection site bruising, indentation, induration, inflammation, mass, edema, abscess, cellulitis, gingival pain, and cystic acne, all occurring in 0.5% (1/182) of subjects.

**Table 6: Treatment-Related TEAEs Occurring in > 1% of Treated Subjects for Chin Augmentation (N = 182)**

| Adverse Event | Treated Subjects % (n/N) |
|---|---|
| Treatment site erythema | 1.6% (3/182) |
| Treatment site pain | 1.6% (3/182) |

Fewer AEs occurred after repeat treatment than after initial/touch-up treatment (Table 7). Among the 74 subjects who received repeat treatment, 4.1% (3/74) experienced TEAEs following treatment. The most common TEAE occurring after repeat treatment was injection site mass (2.7%; 2/74). All TEAEs after repeat treatment were mild or moderate in severity, did not require any intervention and most resolved within 30 days without sequelae. There were no serious TEAEs after repeat treatment.

**Table 7: Summary of TEAEs for Repeat Treatment (Safety Population)**

| | Number (%) | | | |
|---|---|---|---|---|
| | Repeat Treatment | | Initial Treatment[a] | |
| | Participants (N = 74) | Events (N = 12) | Participants (N = 74) | Events (N = 26) |
| All TEAEs | 8 ( 10.8%) | 12 | 21 ( 28.4%) | 26 |
| Treatment-related TEAEs | 3 ( 4.1%) | 7 | 12 ( 16.2%) | 14 |
| At Injection Site | 2 ( 2.7%) | 5 | 10 ( 13.5%) | 11 |
| Not at Injection Site | 1 ( 1.4%) | 2 | 2 ( 2.7%) | 3 |
| All SAEs | 0 | 0 | 2 ( 2.7%) | 2 |
| Treatment-related SAEs | 0 | 0 | 0 | 0 |
| Discontinued due to TEAE | 0 | 0 | 0 | 0 |
| Deaths | 0 | 0 | 0 | 0 |

[a] AEs with onset within 30 days of initial treatment are included for participants who received repeat treatment.

For initial/touch-up treatment, 63 treated participants (34.6%) had 111 TEAEs, and 14 treated participants (7.7%) had 20 treatment-related TEAEs. For repeat treatment, 8 treated participants (10.8%) had 12 TEAEs, and 3 treated participants (4.1%) had 7 treatment-related TEAEs.

The majority of the treatment-related TEAEs were mild or moderate in severity. For initial/touch-up treatment, 2.7% of participants had mild TEAEs, 4.4% had moderate TEAEs, and 1.1% had severe TEAEs. For repeat treatment, 4.1% of participants had mild TEAEs, 1.4% had moderate TEAEs, and 0% had severe TEAEs (Table 8).

Fifty percent (7/14) of the participants who experienced treatment-related TEAEs resolved within 1 week (Table 8). For initial/touch-up treatment, 3 participants (1.6%) had 4 treatment-related TEAEs that lasted longer than 30 days, including injection site inflammation that lasted 153 days and injection site cellulitis that lasted 36 days, injection site erythema that lasted 264 days, and acne cyst that lasted 134 days. For repeat treatment, 1 participant (1.4%) had 1 treatment-related TEAE that lasted longer than 30 days: injection site mass that lasted 42 days.

For both initial/touch-up treatments and repeat treatment, most treatment-related TEAEs began within 7 days of treatment. For initial/touch-up treatment, 1 participant had 3 treatment-related TEAEs that began > 30 days after treatment: injection site edema that began 173 days, 248 days, and 252 days after treatment. There were no treatment related TEAEs that began > 30 days after repeat treatment. All treatment-related TEAEs resolved without sequelae during the study period. For initial/touch-up treatment, 4 participants had 5 treatment-related TEAEs that required treatment with medication or procedure. One subject had 3 treatment-related adverse events that began more than 30 days after initial/touch-up treatment: injection site edema that began 173 days, 248 days, and 252 days after treatment. These were resolved within 3 days with medication.

**Table 8: Summary of Treatment-related TEAEs for All Treated Participants (Safety Population)**

| | Number (%) | | | |
|---|---|---|---|---|
| | Initial and Touch-up Participants | Treatment Events | Repeat Treatment | |
| | | | Participants | Events |
| | (N = 182) | (N = 20) | (N = 74) | (N = 7) |
| Overall Duration | 14 (7.7%) | 20 | 3 (4.1%) | 7 |
| ≤ 7 days | 7 (3.8%) | 11 | 1 (1.4%) | 2 |
| 8-14 days | 2 (1.1%) | 3 | 0 | 0 |
| 15-30 days | 2 (1.1%) | 2 | 1 (1.4%) | 4 |
| > 30 days | 3 (1.6%) | 4 | 1 (1.4%) | 1 |
| Not yet resolved | 0 | 0 | 0 | 0 |
| Time to Onset on/after Treatment | | | | |
| ≤ 7 days | 12 (6.6%) | 15 | 3 (4.1%) | 7 |
| 8-14 days | 1 (0.5%) | 2 | 0 | 0 |
| 15-30 days | 0 | 0 | 0 | 0 |
| > 30 days | 1 (0.5%) | 3 | 0 | 0 |
| Severity | | | | |
| Mild | 5 (2.7%) | 6 | 3 (4.1%) | 6 |
| Moderate | 8 (4.4%) | 11 | 1 (1.4%) | 1 |
| Severe | 2 (1.1%) | 3 | 0 | 0 |
| Outcome | | | | |
| Recovered/Resolved | 14 (7.7%) | 20 | 3 (4.1%) | 7 |
| Treatment Required | | | | |
| No | 12 (6.6%) | 15 | 3 (4.1%) | 7 |
| Medication | 4 (2.2%) | 5 | 0 | 0 |
| Procedure | 1 (0.5%) | 1 | 0 | 0 |

Needles were used for 100% of subjects, and cannulas were used for 25.0% of subjects at initial treatment.

Only needle treatment was allowed in the pogonion whereas all participants in the cannula treatment subgroup had some treatment with the needle. Results (Table 9) showed lower incidence of TSRs for injections with cannula than without cannula after each treatment (initial, touch-up, and repeat).

**Table 9: Incidence of TSRs After Initial Treatment With and Without Cannula (Safety Population)**

| TSR | All Treated With Cannula (N = 44) n (%)[a] | All Treated Without Cannula (N = 137) n (%)[a] |
|---|---|---|
| Any TSR | 34 (77.3%) | 133 (97.1%) |
| Tenderness to touch | 30 (68.2%) | 118 (86.1%) |
| Firmness | 28 (63.6%) | 108 (78.8%) |
| Swelling | 24 (54.5%) | 100 (73.0%) |
| Bruising | 24 (54.5%) | 83 (60.6%) |
| Pain after injection | 23 (52.3%) | 91 (66.4%) |
| Lumps/Bumps | 21 (47.7%) | 88 (64.2%) |
| Redness | 16 (36.4%) | 72 (52.6%) |
| Itching | 10 (22.7%) | 40 (29.2%) |
| Discoloration | 5 (11.4%) | 22 (16.1%) |
| Other | 3 (6.8%) | 25 (18.2%) |

For the Treated Control group, data after receiving initial treatment at Month 6 are included.
a Number of participants who recorded in the diaries after the treatment

For initial/touch-up treatment with cannula, 2 treated participants (4.3%) had 2 treatment-related TEAEs, and without cannula 12 treated participants (8.8%) had 18 treatment-related TEAEs (Table 10). For repeat treatment with cannula, there were no treatment related TEAEs; without cannula 3 treated participants (5.4%) had 7 treatment-related TEAEs.

**Table 10: Comparison of Rate of Treatment-related TEAEs in Participants Treated with and without Cannula**

| Treatment | AEs in Participants Treated with Cannula and Needle % (n/N) | AEs in Participants Treated Only with Needle % (n/N) |
|---|---|---|
| Initial/touch-up treatment | 4.3% (2/46) | 8.8% (12/136) |
| Repeat treatment | 0 (0/18) | 5.4% (3/56) |

A total of 11 subjects experienced 14 serious adverse events (SAEs) with onset after the study treatment in the VOLUMA-006 study (Table 11). One subject (0.5%; 1/182) reported 2 SAEs, injection site inflammation and injection site cellulitis, that were considered to be related to the device. These events began 7 days after touch-up treatment and were treated with hyaluronidase, antibiotics, steroid, analgesics/narcotics, sedative, anticoagulant, antacid, electrolyte solutions, antihistamine, and anti-inflammatory medicines. Both events resolved without sequelae, in 36 days for the cellulitis and 153 days for the inflammation, and the participant was discontinued from the study due to these events (the SAE of cellulitis required hospitalization). SAEs that were considered to be not treatment-related were non-cardia chest pain, invasive papillary breast carcinoma, appendicitis, pneumonia, uterin hemorrhage, keratoacanthoma, squamous cell carcinoma,

diverticulitis, atypical pneumonia, intraductal proliferative breast lesion, osteoarthritis, and cholecystitis.

Subjects above the median age (51.5 years and older), experienced more total SAEs (9.9%) than subjects younger than 51.5 years old (2.2%) (Table 14).

**Table 11: Summary of Treatment-Related SAEs**

| # | SAE Type | Relationship to Treatment | Duration | Treatment |
|---|---|---|---|---|
| 1 | Injection Site Inflammation | Treatment-related | 153 days | Hyaluronidase, Bactrim, Biaxin, hydromorphone, diphenhydramine, vancomycin, clindamycin, prednisone, oxycodone, hydrocodone acetaminophen, ibuprofen, heparin, proton pump inhibitors, electrolyte solutions, triamcinolone acetonide sulfamethoxazole+trimethoprim, and valium |
| 2 | Injection Site Cellulitis | Treatment-related | 36 days | |

**Procedural Pain**

Participants assessed procedural pain (pain during injection) immediately after completion of each treatment on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable). Pain rated after treatment was minimal, with a mean score of 2.3 for the treatment group at each treatment (initial, touch-up, and repeat) and ranged from 0.0 to 8.0, 0.0 to 7.0, and 0.0 to 6.0 for initial, touch-up, and repeat treatments, respectively. Procedural pain was similar for the treated control participants.

**Facial Function Assessments**

On the Facial Nerve Grading Scale 2.0, participants were assigned an overall facial function score ranging from I to VI based on the score for individual items (movement in each of 4 facial areas [brow, eye, nasolabial fold, and oral commissure] plus overall facial synkinesis). At baseline and all posttreatment timepoints, over 90% of treated participants were scored as I, indicating the best possible facial function. Only 2 scores of III were given (1 at baseline and 1 at Month 1), both in the treatment group. No scores of IV, V, or VI were given at any point in the study.

**Facial Sensation Assessments**

Responses for the 2-point discrimination test were the distances for which participants indicated they felt 2 distinct points of pressure at the pogonion and halfway between the pogonion and each pre-jowl sulcus, with possible distances of 1 to 10 mm. Results were similar for baseline and all posttreatment follow-up visits.

The light touch assessment determined the smallest filament number for which participants felt the presence of the filament at the pogonion and halfway between the pogonion and each pre-jowl sulcus, where filaments ranged in diameter from 1.65 to 3.61

mm. The majority of responses at baseline and all posttreatment timepoints occurred with the smallest filament: 1.65 mm.

These facial sensation assessments suggest that treatment did not reduce chin area sensitivity at any timepoint throughout the study.

2. Effectiveness Results

The analysis of primary effectiveness was based on the 126 treatment group and 40 control group evaluable subjects at the 6-month time point. Key effectiveness outcomes are presented below.

Primary effectiveness results: JUVÉDERM® VOLUMA™ XC provided a clinically and statistically significant improvement in chin volume deficit compared to the no-treatment control group. The primary effectiveness endpoint was met in that greater than 50% of subjects in the treatment group were responders (56.3% improved by ≥ 1 point compared with their pre-treatment assessment), and the responder rate for the treatment group was significantly greater ($p = 0.0019$) than the responder rate for the control group (a difference of 28.8%) at Month 6 (Table 12). The primary effectiveness endpoint was below 50% in the following subgroups: older subjects (aged 51.5 years and older), darker skin types (FST V/VI), and males. However, the satisfaction rates were high and secondary endpoints were met for these subgroups.

At initial treatment, 99.3% of treatment group subjects were treated in the pogonion, 77.8% in the menton, and 87.5% in the pre-jowl sulci. The median total volume used to achieve optimal correction was 2.4 mL (range, 0.7-4.0 mL), with 1.0 mL in the pogonion, 0.5 mL in the menton, and 1.0 mL in the pre-jowl sulci (right and left combined). The median volume at initial treatment was 2.0 mL. A touch-up treatment was performed for 45.8% (88/192) of subjects with a median total volume of 1.0 mL. The repeat treatment was performed for 45.8% (88/192) of subjects and the median volume injected for repeat treatment was 2.0 mL.

**Table 12: Effectiveness Summary Responder Rate at 6 Months Based on Evaluating Investigators' Assessments of Images**

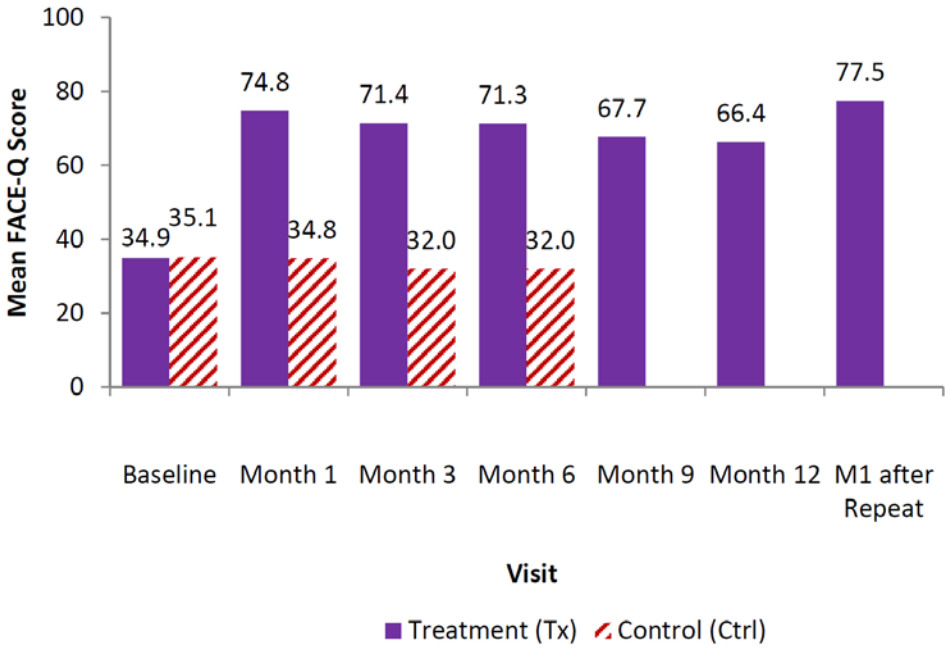
| | **Responder Rate at Month 6** | **p-value** |
|---|---|---|
| **Treatment Group** | 56.3% (71/126) | N/A |
| **Control Group** | 27.5% (11/40) | |
| **Difference in Responder Rates (Treatment rate - Control rate)** | 28.8% | 0.0019 |

The responder rate at the 12-month follow up visit was 57.6% (72/125) and 73.9% (51/69) at 1 month after repeat treatment based on the blinded EI's assessment of 2D images.

The responder rate based on the live assessment of subjects at Month 6 was 91.8% (89/97) for the treatment group and 23.3% (7/30) for the control group.

Secondary effectiveness results: The FACE-Q *Satisfaction with Chin* overall mean score was 34.9 at baseline and improved to 71.3 at Month 6 with the improvement being statistically significant ($p < 0.0001$) (Figure 2). Most of the subjects (91.8%) reported satisfaction with their chin 1 month after treatment. Among other questions, this FACE-Q questionnaire included questions on satisfaction with chin look in profile view and width of the chin. At Month 1, 88.8% of treatment group subjects were satisfied with how their chin looks in profile view and 95.5% were satisfied with the width of their chin.

**Figure 2: FACE-Q Satisfaction with Chin Mean Scores by Visit**




The EI and subject GAIS responder rates at Month 6 for the treatment group were 91.2% (114/125) and 87.3% (110/126), respectively, where the responder rate was the percent of subjects with a score of improved or much improved on the GAIS. The EI GAIS responder rate at Month 6 for the untreated control group was 19.5% (8/41) for EI.

An independent, blinded assessment was conducted on full-face 3D images collected at randomization (baseline) and at follow-up visits, including the primary timepoint (Month 6). Three independent raters used the ACRS to assess the severity of chin retrusion in each 3D image. At Month 6 the mean change in ACRS score for the treatment group was statistically superior to that for the untreated control group ($p < 0.0001$). However, at Month 6 the ACRS responder rate for the treatment group was less than 50%, though it was greater than that for the untreated control group (43.0% versus 12.5%).

3. Subgroup Analyses

The following characteristics were evaluated for potential association with outcomes: Fitzpatrick Skin Type (FST) (Table 13), age (Table 14), gender (Table 15), baseline ACRS, injection volume, cannula usage (Table 9 and 10), and investigational site.

**Table 13: Effectiveness and Safety Results at 6 Months by FST Subgroups**

| Assessment | Group | Fitzpatrick Skin Type Subgroup | | |
|---|---|---|---|---|
| | | I/II | III/IV | V/VI |
| **EFFECTIVENESS*** | | | | |
| **2D ACRS Responder Rate, % (n/N)** | **Treatment** | 63.0% (29/46) | 57.6% (38/66) | 28.6% (4/14) |
| | **Control** | 12.5% (2/16) | 33.3% (6/18) | 50.0% (3/6) |
| **EI GAIS Responder Rate, % (n/N)** | **Treatment** | 93.5% (43/46) | 89.4% (59/66) | 92.3% (12/13) |
| | **Control** | 18.8% (3/16) | 15.8% (3/19) | 33.3% (2/6) |
| **Subject GAIS Responder Rate, % (n/N)** | **Treatment** | 87.0% (40/46) | 89.4% (59/66) | 78.6% (11/14) |
| **FACE-Q Satisfaction with Chin Mean Score (n)** | **Treatment** | 71.0 (46) | 71.7 (66) | 70.0 (14) |
| | **Control** | 30.9 (16) | 30.5 (19) | 41.0 (6) |
| **FACE-Q Satisfaction with Chin Mean Change from Baseline (n)** | **Treatment** | 35.0 (46) | 35.8 (66) | 36.2 (14) |
| | **Control** | -2.7 (16) | -2.9 (18) | -6.2 (6) |
| **Live ACRS Responder Rate, % (n/N)** | **Treatment** | 97.1% (33/34) | 90.7% (49/54) | 77.8% (7/9) |
| | **Control** | 11.1% (1/9) | 27.8% (5/18) | 33.3% (1/3) |
| **Mean Change in Volume in cc using 3D Image Analysis (n)**** | **Treatment** | 2.0 (46) | 2.9 (66) | 1.6 (14) |
| | **Control** | -0.03 (16) | 0.53 (18) | -0.6 (6) |
| **SAFETY*** | | | | |
| **Total TEAEs** | **Treatment** | 33.0% (22/66) | 36.6% (34/93) | 30.4% (7/23) |
| **Treatment-related TEAEs** | | 7.6% (5/66) | 6.5% (6/93) | 13.0% (3/23) |
| **All SAEs** | | 7.6% (5/66) | 4.3% (4/93) | 8.7% (2/23) |
| **Injection Site Responses after Initial Treatment** | | 98.5% (65/66) | 90.2% (83/92) | 82.6% (19/23) |

* The N for the effectiveness data is only the treatment group and the N for the safety data includes all treated subjects.
** Median injection volume for the treatment group was 2.0 mL, 2.5 mL, and 2.0 mL in FST I/II, III/IV, and V/VI groups, respectively.

For subjects with darker skin (FST V/VI) (Table 13), the device did not meet the primary effectiveness endpoint (28.6% responder rate in the treatment group) and performed worse than the no-treatment control (50.0% responder rate, where a responder is a subject with at least a 1-point improvement in the 2D ACRS score at 6 months from baseline).

**Table 14: Effectiveness and Safety Results at 6 Months by Age Subgroups**

| Assessment | Group | Age Subgroup | |
|---|---|---|---|
| | | **< 51.5 years** | **≥ 51.5 years** |
| EFFECTIVENESS* | | | |
| **2D ACRS Responder Rate, % (n/N)** | **Treatment** | 67.8% (40/59) | 46.3% (31/67) |
| | **Control** | 26.3% (5/19) | 28.6% (6/21) |
| **EI GAIS Responder Rate, % (n/N)** | **Treatment** | 91.5% (54/59) | 90.9% (60/66) |
| | **Control** | 42.1% (8/19) | 0 (0/22) |
| **Subject GAIS Responder Rate, % (n/N)** | **Treatment** | 93.2% (55/59) | 82.1% (55/67) |
| **FACE-Q Satisfaction with Chin Mean Score (n)** | **Treatment** | 72.1 (59) | 70.5 (67) |
| | **Control** | 32.7 (19) | 31.7 (22) |
| **FACE-Q Satisfaction with Chin Mean Change from Baseline (n)** | **Treatment** | 37.4 (59) | 33.9 (67) |
| | **Control** | -4.2 (18) | -2.6 (22) |
| **Live ACRS Responder Rate, % (n/N)** | **Treatment** | 97.9% (46/47) | 86.0% (43/50) |
| | **Control** | 30.8% (4/13) | 17.6% (3/17) |
| **Mean Change in Volume in cc using 3D Image Analysis (n)**** | **Treatment** | 2.8 (59) | 2.1 (67) |
| | **Control** | 0.02 (19) | 0.25 (21) |
| SAFETY* | | | |
| **Total TEAEs** | **Treatment** | 29.7% (27/91) | 39.6% (36/91) |
| **Treatment-related TEAEs** | **Treatment** | 7.7% (7/91) | 7.7% (7/91) |
| **All SAEs** | **Treatment** | 2.2% (2/91) | 9.9% (9/91) |
| **Injection Site Responses after Initial Treatment** | **Treatment** | 97.8% (88/90) | 86.8% (79/91) |

* The N for the effectiveness data is only the treatment group and the N for the safety data includes all treated subjects.
** Median injection volume for the treatment group was 2.5 mL and 2.1 mL in < 51.5 and ≥ 51.5, respectively.

The median age of subjects was 51.5 years. For subjects aged 51.5 years and older (Table 14), the device did not meet the primary effectiveness endpoint (46.3% responder rate in the treatment group). The responder rate for subjects aged 51.5 years or older is statitistically higher than the no-treatment control group (28.6%).

**Table 15: Effectiveness and Safety Results at 6 Months by Gender Subgroups**

| Assessment | Group | Gender Subgroup | |
|---|---|---|---|
| | | Female | Male |
| EFFECTIVENESS* | | | |
| **2D ACRS Responder Rate, % (n/N)** | **Treatment** | 57.7% (64/111) | 46.7% (7/15) |
| | **Control** | 32.4% (11/34) | 0% (0/6) |
| **EI GAIS Responder Rate, % (n/N)** | **Treatment** | 91.9 (102/111) | 85.7% (12/14) |
| | **Control** | 20.0% (7/35) | 16.7% (1/6) |
| **Subject GAIS Responder Rate, % (n/N)** | **Treatment** | 86.5% (96/111) | 93.3% (14/15) |
| **FACE-Q Satisfaction with Chin Mean Score (n)** | **Treatment** | 71.3 (111) | 71.0 (15) |
| | **Control** | 31.5 (34) | 35.0 (6) |
| **FACE-Q Satisfaction with Chin Mean Change from Baseline (n)** | **Treatment** | 35.0 (111) | 39.5 (15) |
| | **Control** | -3.9 (34) | 0.2 (6) |
| **Live ACRS Responder Rate, % (n/N)** | **Treatment** | 92.9% (79/85) | 83.3% (10/12) |
| | **Control** | 26.9% (7/26) | 0 (0/4) |
| **Mean Change in Volume in cc using 3D Image Analysis (n)**** | **Treatment** | 2.44 (111) | 2.39 (15) |
| | **Control** | 0.01 (34) | 0.85 (6) |
| SAFETY* | | | |
| **Total TEAEs** | **Treatment** | 35.8% (58/162) | 25.0% (5/20) |
| **Treatment-related TEAEs** | **Treatment** | 8.0% (13/162) | 5.0% (1/20) |
| **All SAEs** | **Treatment** | 6.8% (11/162) | 0 (0/20) |
| **Injection Site Responses after Initial Treatment** | **Treatment** | 93.8% (151/161) | 80.0% (16/20) |

* The N for the effectiveness data is only the treatment group and the N for the safety data includes all treated subjects.
** Median injection volume for the treatment group was 2.0 mL and 3.7 mL in females and males, respectively.

For male subjects (Table 15), the device did not meet the primary effectiveness endpoint (46.7% responder rate in the treatment group). There were no responders in the male control subjects.

The effectiveness of JUVÉDERM® VOLUMA™ XC for chin augmentation in the VOLUMA-006 study was similar for subjects with:

- Moderate or severe chin retrusion
- Treatment with or without cannula.

By investigational site, the responder rate for the treatment group based on photo assessment was lower at some sites, but the sample sizes were small.

### 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. The VOLUMA-006 study included 33 Treating and Evaluating Investigators in total. Twenty of the 33 investigators have, by way of a signed Financial Disclosure/Certification Form, verified that they have no applicable financial arrangement with Allergan defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

Thirteen of the 33 investigators have financial arrangements with Allergan to be disclosed under 21 CFR 54.2 (b), not affecting the outcome of the VOLUMA-006 clinical study. The nature of these disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) is described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 13
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

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.

## XI. 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.

## XII. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

### A. EFFECTIVENESS CONCLUSIONS

- JUVÉDERM® VOLUMA™ XC met the pre-specified primary endpoint, and the secondary endpoints support product effectiveness. The balance of the data indicate that JUVÉDERM® VOLUMA™ XC is effective in augmenting the chin region to improve the chin profile at the 6-month primary effectiveness time point. The treatment was less effective (less than 50% responder rate) in FST V-VI, subjects aged 51.5 years and older, and males. However, the responder rate in older subjects and males were statistically higher than the control. In addition, most subjects

reported satisfication with the treatment through the subject GAIS and FACE-Q scores.

## B. SAFETY CONCLUSIONS

The potential risks and adverse effects of the device are based on data collected in the clinical study conducted to support the indication expansion as described above as well as evaluation of device use in the Post-Market setting. The data submitted provide a reasonable assurance that the device is safe for deep (subcutaneous and/orsupraperiosteal) injection for augmentation of the chin region to improve the chin profile in adults over the age of 21. The specific conclusions are:

- After initial treatment, 88.0% of subjects experienced TSRs that were mild to moderate in severity, and 37.2% of subjects experienced TSRs that resolved within 7 days.
- After initial treatment, 35.3% (59/167) of subjects with TSRs resolved between Day 15-30, and 12.0% (20/167) of subjects experienced severe TSRs.
- After touch-up treatment, 89.5% of subjects experienced TSRs that were mild to moderate in severity, and 48.8% of subjects experienced TSRs that resolved within 7 days.
- After repeat treatment, 87.2% of subjects experienced TSRs that were mild to moderate in severity, and 41.8% of subjects experienced TSRs that resolved within 7 days.
- The most common TSRs were tenderness to touch, firmness, and swelling.
- Injections with cannula had a lower incidence rate of TSRs than injections without cannula.
- Subjects assessed procedural pain during injection as minimal.
- The most common treatment-related TEAEs after initial/touch-up treatment were injection site erythema, injection site pain, lumps/bumps, swelling, and firmness.
- Most treatment-related AEs were mild (30.0%, 6/20) or moderate (55.0%, 11/20) in severity. A majority of the treatment-related AEs (55%, 11/20) resolved within 1 week.
- The incidence of treatment-related TEAEs was lower after repeat treatment.
- One subject had treatment-related SAEs of injection site inflammation and injection site cellulitis that resolved in 36 days for the cellulitis and 153 days for the inflammation. The patient was hospitalized for cellulitis.
- There were no deaths or unanticipated adverse device effects.
- Treatment with JUVÉDERM® VOLUMA™ XC did not compromise facial function or sensation.

## C. BENEFIT-RISK CONCLUSIONS

The probable benefits of the device are based on data collected in clinical studies conducted to the indication expansion as described above. The study was a prospective, no-treatment controlled study using a validated scale and blinded, photographic evaluations via 2D profile images of the left side of the chin rendered by image analysis software from 3D images. In the JUVÉDERM® VOLUMA™ XC group at Month 6,

56.3% were responders and the effect lasted through 1 year with a majority (57.6%, 72/144) of the subjects still responders at Month 12. The findings of the primary effectiveness assessment were supported by the secondary endpoints. The improvement in the FACE-Q *Satisfaction with Chin* overall mean score from baseline and to Month 6 was statistically significant ($p < 0.0001$). The Month 6 GAIS investigator and subject assessments showed responder rates of 91.2% and 87.3%, respectively. The majority of the patients have elected to undergo retreatment, indicating that they perceive a benefit and that they would like continued benefit.

Additional factors to be considered in determining probable risks and benefits of JUVÉDERM® VOLUMA™ XC injection included: A majority (92%, 167/181) of the subjects experienced common treatment site responses which included tenderness, firmness (induration), swelling, pain, lumps/bumps (mass), bruising, redness, itching, and discoloration. Subjects rated treatment site responses as predominantly mild in severity with a majority resolving within 2 weeks. One subject had swelling which developed more than 4 weeks after treatment. All adverse events resolved either spontaneously or with treatment. Summary of safety conclusions is provided above.

Regarding subgroups, while FST V-VI, males and subjects ≥ 51.5 years of age did not meet the 50% responder rate threshold, subject satisfaction in these subgroups was acceptable and these subjects acceptable rates of AE when compared with subjects who did meet the 50% responder rate threshold.

The probable benefits outweigh the probable risks, as determined by the short-term adverse outcomes and rare late adverse events seen after injection. The risks of short-term adverse outcomes seen after injection and rare adverse events are sufficiently well understood for patients to make informed decisions about the device.

**Patient Perspectives**

Patient perspectives considered during the review included:

- Despite the frequency of TSRs, patients are willing to accept the probable risk of these harmful events as shown through patient-reported outcomes and patient willingness to receive additional repeat treatments.
- At 6 months, 87.3% (110/126) of subjects treated with JUVÉDERM® VOLUMA™ XC reported being very or somewhat satisfied with their treatment based on the subject GAIS.
- At 6 months, 93.7% (118/126) of subjects reported improvement in their JUVÉDERM® VOLUMA™ XC-treated chin, based on the *Satisfaction with Chin* module of the FACE-Q questionnaire, with a mean score increasing from 34.9 at baseline to 71.3. The mean score was 66.4 in the JUVÉDERM® VOLUMA™ XC group at 12 months.
- A total of 74 subjects received repeat treatment in the study. The most common reason given for refusal of repeat treatment was satisfaction with the results at the Month 12 visit (52.9%, 27/51).

In conclusion, given the available information above, the data support that for deep (subcutaneous and/or supraperiosteal) injection for augmentation of the chin region to improve chin profile in adults 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.

## XIII. CDRH DECISION

CDRH issued an approval order on June 12, 2020.

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

## XIV. 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.