SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: JUVÉDERM® VOLUX™ 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/S065

Date of FDA Notice of Approval: July 29, 2022

The original PMA for JUVÉDERM® VOLUMA® XC (P110033) was approved on October 22, 2013. JUVÉDERM® VOLUMA® XC is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the midface in adults over the age of 21. The SSED to support this indication is available on the CDRH website and is incorporated by reference here. JUVÉDERM® VOLUX™ XC is being submitted as a Panel-Track Supplement (P110033/S065) to the JUVÉDERM® VOLUMA™ XC PMA (P110033) to request changes in design or performance of the device, and a new indication for the device. The current supplement was submitted for JUVÉDERM® VOLUX™ XC for improvement of jawline definition in adults over the age of 21.

II. INDICATIONS FOR USE

JUVÉDERM® VOLUX™ XC injectable gel is indicated for subcutaneous and/or supraperiosteal injection for improvement of jawline definition in adults over the age of 21 with moderate to severe loss of jawline definition.

III. CONTRAINDICATIONS

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

- JUVÉDERM® VOLUX™ 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® VOLUX™ XC labeling.

V. DEVICE DESCRIPTION

JUVÉDERM® VOLUX™ XC injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. The device consists of 25 mg/mL hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, crosslinked with 1,4-Butanediol diglycidyl ether (BDDE), and contains 0.3% w/w lidocaine in a physiologic buffer.

Each box of JUVÉDERM® VOLUX™ XC contains 2 thermoformed trays. Each thermoformed tray contains one pre-filled, sterilized, disposable cyclic olefin copolymer (COC) syringes containing 1 mL of JUVÉDERM® VOLUX™ XC gel implant and two 27 G ½" sterile needles. 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.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the improvement of jawline definition. Current treatment options for the improvement of jawline definition include the use of soft tissue fillers, plastic surgery (i.e., facelift), autologous fat injection, and radiofrequency/ultrasound skin tightening. Both HA- and non-HA-based (carboxymethylcellulose) soft tissue fillers have been used to improve jawline definition. 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® VOLUX™ XC received CE Mark in December 2018 for restoration and creation of facial volume, under the name JUVÉDERM® VOLUX™. JUVÉDERM® VOLUX™ XC is currently marketed in the European Union and in over 60 countries. JUVÉDERM® VOLUX™ XC has not been removed from the marketplace for any reasons related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with the use of the device as well as for other devices in the same category, as reported in the clinical study include tenderness, lumps/bumps, pain, swelling, firmness, bruising, redness, itching, and discoloration.

Treatment-related adverse events (AEs) were reported in the US clinical study by the Treating Investigator at follow-up visits. Among the 198 participants who received an initial treatment with JUVÉDERM® VOLUX™ XC, 16 participants (8.1%, 16/198) had 20 treatment-related AEs. These AEs included mastication disorder (2.0%, 4/198), injection site nodule (1.5%, 3/198), injection site bruising (1.0%, 2/198), injection site hypersensitivity (0.5%, 1/198), injection site mass (0.5%, 1/198), injection site pain (0.5%, 1/198), injection site swelling (0.5%, 1/198), injection site infection (0.5%, 1/198), oral herpes (0.5%, 1/198), temporomandibular joint syndrome (0.5%, 1/198), muscle tightness (0.5%, 1/198), muscle twitching (0.5%, 1/198), and headache (0.5%, 1/198).

The product must not be injected into blood vessels. Introduction of JUVÉDERM® VOLUX™ XC injectable gel into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Rare but serious AEs associated with the intravascular injection of injectable gels in the face have been reported and included temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

Post-Market Surveillance

The following AEs were received from postmarket surveillance on the use of JUVÉDERM® VOLUX™ XC outside the United States; this includes reports received globally from all sources including scientific journals and voluntary reports. These AEs, with a frequency of 5 events or more, are listed in order of prevalence: swelling, inflammatory reaction, non-inflammatory nodule, pain, inflammatory nodule, abscess, infection, redness, hematoma, neurological symptom, migration, allergic reaction, loss/lack of correction, vascular occlusion, discoloration, minor inflammatory reaction, autoimmune disorder exacerbation, necrosis, itching, scar, cyst, and bleeding.

In many cases, AEs resolved without any treatment. Reported treatments for these events included (in alphabetical order): Antibiotics, anti-inflammatory drugs, analgesics, antiseptic, antihistamines, anti-bacterial drugs, anti-stress and sleeplessness drugs, anti-edema drugs, antithrombotics, anticoagulants, calcium supplements, cold compress, drainage, hyaluronidase, hair growth stimulators, immunosuppressive drugs, immunotherapy, massage, muscle relaxants, NSAID (non-steroid anti-inflammatory), opioids, proton-pump inhibitors, rectal ointment, steroids, surgery, sedatives, ultrasound, and Vitamin B.

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Physical and Chemical Characterization

JUVÉDERM® VOLUX™ XC has been characterized through physical and chemical analyses (Table 1). Degradation assays were also performed to confirm that JUVÉDERM® VOLUX™ XC degrades via hydrolysis in the body during its clinical lifespan.

Table 1: Summary of Key Bench Testing on JUVÉDERM® VOLUX™ XC

Test	Purpose	Results
NaHA Concentration	Ensures HA concentration meets specification	Passed
Lidocaine HCl Concentration	Ensure lidocaine concentration meets specification	Passed
Characterization of pH	Ensures pH meets specification	Passed
Osmolarity	Ensures osmolarity meets specification	Passed
Extrusion Force	Ensures extrusion force meets specification	Passed
Residual Crosslinker	Ensure residual crosslinker meets specification	Passed
Bacterial Endotoxin	Ensures endotoxin meets specification	Passed
Sterility	Ensures product is sterile	Passed
Rheology	Ensure rheology meets specification	Passed

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

Stability data have been collected through 24 months under ICH Q1A(R) storage conditions. At each timepoint, product was evaluated for conformance with microbiological, physical, and chemical properties including lidocaine hydrochloride potency and lidocaine-related degradants. Conformance with all specifications was confirmed.

Biocompatibility Testing

JUVÉDERM® VOLUX™ XC was evaluated with *in vitro* and *in vivo* biocompatibility studies appropriate for devices in contact with tissue for greater than 30 days. The results of the tests are summarized in Table 2 below. The biocompatibility studies were performed in accordance with the Federal Good Laboratory Practices Regulations (21 CFR Part 58), ISO 10993, and the FDA guidance document Use of International Standard ISO 10993-1 "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process."

Table 2: Summary of Biocompatibility Testing on JUVÉDERM® VOLUX™ XC

Test	Method	Standard	Results
Cytotoxicity	Indirect contact Direct contact Colony assay	ISO 10993-5	Non-cytotoxic
Sensitization	Guinea pig maximization test	ISO 10993-10	Non-sensitizing
Intracutaneous Reactivity	72-hour, 14-day, and 21-day exposure in rabbits	ISO 10993-11	Non-irritant when compared to other approved soft-tissue filler; Irritant when compared to saline.
Acute Systemic Toxicity	Intraperitoneal injection in mice	ISO 10993-11	Non-toxic
Subchronic Toxicity	Intradermal and subcutaneous injection in rats	ISO 10993-6 ISO 10993-11	Non-irritant Non-toxic
Chronic Toxicity	Subcutaneous and deep dermis injection in rats	ISO 10993-6 ISO 10993-11	Non-irritant Non-toxic
Genotoxicity	Bacterial reverse mutation Micronucleus Chromosomal Aberration	ISO 10993-3	Non-genotoxic
Tissue Implantation (4 and 12 Weeks)	Subcutaneous and deep dermis injection in rats	ISO 10993-6	Non-irritant
Pyrogenicity	Rabbit pyrogen study	USP <151>	Non-pyrogenic

Irritation Risks: At day 3 in the Intracutaneous Reactivity Assay, JUVÉDERM® VOLUX™ XC was determined to be a non-irritant relative to a space-occupying control but an irritant compared to saline. Based on intracutaneous reactivity and implantation studies, JUVÉDERM® VOLUX™ XC was considered to be a non-irritant.

Carcinogenicity Risks: The excess cancer risks for JUVÉDERM® VOLUX™ XC range from 6.1×10^{-5} to 1.6×10^{-8} from lifetime exposure to residual BDDE based on a linear extrapolation method and a dose-response model. The excess cancer risks for JUVÉDERM® VOLUX™ XC are in the same range of acceptable cancer risks as other previously approved dermal filler products.

X. SUMMARY OF PRIMARY CLINICAL STUDY

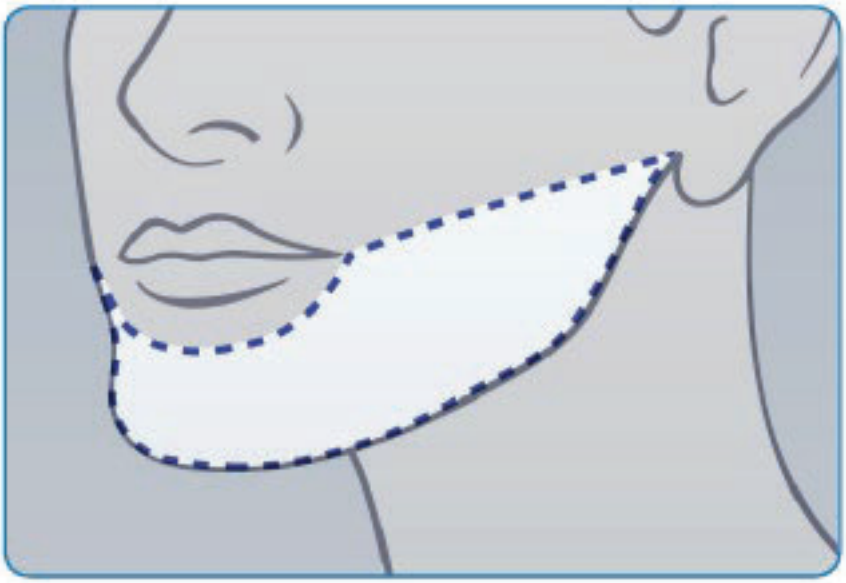
The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness subcutaneous and/or supraperiosteal injection with the treatment of JUVÉDERM® VOLUX™ XC for improvement of jawline definition in adults over the age of 21 with moderate to severe loss of jawline definition in the US under IDE G170209.

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

Participants were treated between November 12, 2018 and January 26, 2021 in a randomized, multicenter, evaluator-blind, controlled pivotal clinical study (V25L-002) conducted to evaluate the safety and effectiveness of JUVÉDERM® VOLUX™ XC to improve jawline definition in patients over the age of 21 with moderate to severe loss of jawline definition. The database for this Panel-Track Supplement reflected data collected through March 9, 2021 and included 157 participants randomized to treatment and 49 participants randomized to delayed-treatment control (3:1 randomization ratio). There were 19 investigational sites. The treatment area is depicted in Figure 1.

Figure 1: Treatment Area for Jawline Definition



Injections were performed in the prejowl sulci, body of the mandible/postjowl sulci, marionette lines, chin, and angle of the mandible to help restore jawline definition and provide for a pleasing overall aesthetic appearance. Injection techniques used were tunnelling, serial puncture, fanning and bolus techniques.

Treatment group participants underwent treatment with JUVÉDERM® VOLUX™ XC, followed by an optional touch-up treatment 1 month after initial treatment, if deemed necessary to achieve optimal improvement, with follow-up visits at 1, 3, 6, 9, and 12 months after the last treatment. Maintenance treatment was offered to treatment group participants at 12 months, with follow-up visits 1 and 3 months after treatment. Control group participants attended a follow-up visit at 1, 3, and 6 months during the "no treatment" control period. Thereafter, control participants were offered study

treatment and optional touch-up with post-treatment follow-up visits at 1, 3, 6, 9, and 12 months after last treatment.

Statistical Analysis Plan

The sample size was determined to provide adequate power to demonstrate effectiveness and safety of the product. The sample size calculation was based on a 1-sided Fisher's exact test assuming a treatment group responder rate of at least 80% and the control group is assumed to have at most 40% responder rate.

The primary analysis of the treatment group and no-treatment control group responder rates was performed on the mITT population using multiple imputation method to handle missing data, where a responder is defined as a participant with ≥ 1-point improvement in jawline definition compared with the pretreatment score on the ALJDS for both sides of the jawline. The statistical hypotheses are as follows:

$$Ho: Pv < 50\%$$

$$Ha: Pv \geq 50\%$$

and

$$Ho: Pv \leq Pc$$

$$Ha: Pv > Pc$$

where Pv and Pc denote the responder rates for the treatment group at Month 6 after the last treatment (initial or touch-up) and for the control group at Month 6 after randomization. Furthermore, the statistical analysis plan provided detailed elaboration on the statistical methods implemented to analyze the effectiveness and safety endpoints considered in the study.

1. Clinical Inclusion and Exclusion Criteria

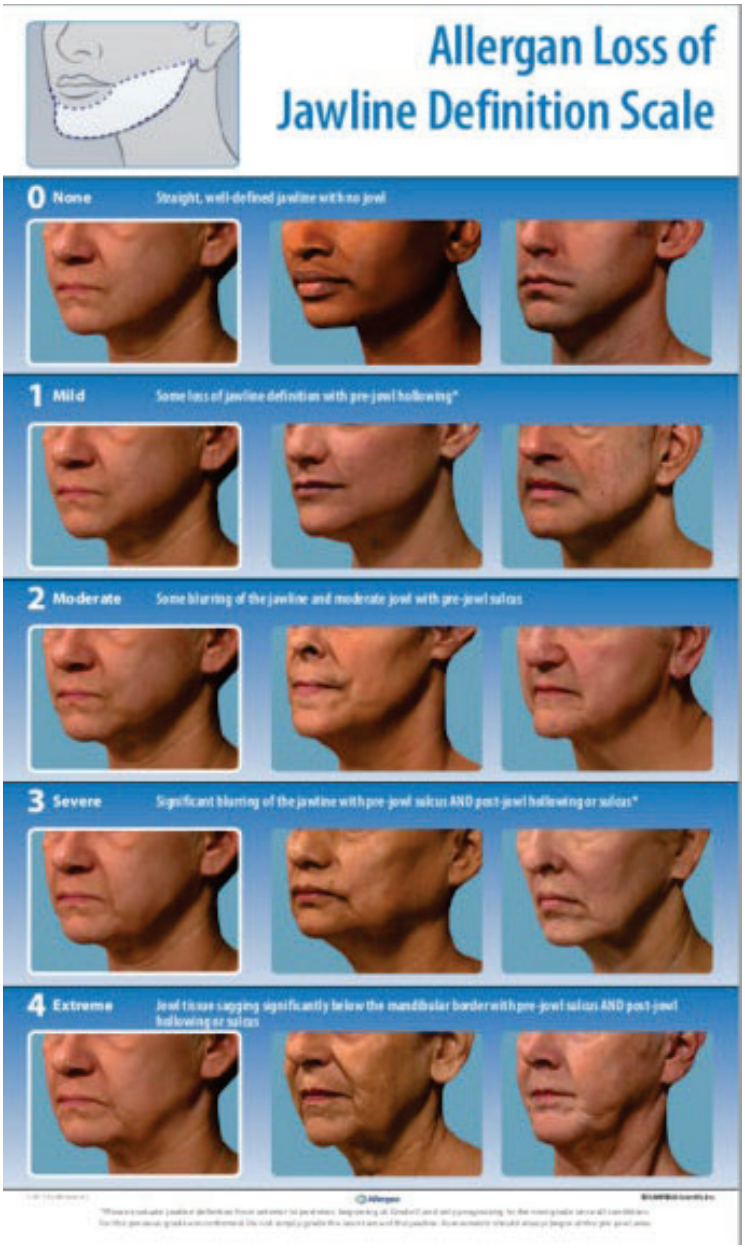
   Enrollment in the V25L-002 study was limited to participants who met the following inclusion criteria:

   1. Age 22 or over and in good general health
   2. Has "Moderate" or "Severe" loss of jawline definition as determined by the Evaluating Investigator (EI) using the Allergan Loss of Jawline Definition Scale (ALJDS) (Grade 2 or 3 on the ALJDS) on both sides. The grade does not have to be the same on both sides, but must be Grade 2 or 3. Scale descriptions were created for each of the five numerical grades of the ALJDS (Table 3 and Figure 2).

Table 3: Allergan Loss of Jawline Definition Scale

Score	Grade	Description
0	None	Jawline: Straight, well defined Pre-Jowl Area: No hollowing or pre-jowl sulcus Post-Jowl Area: Do Not Assess
1	Mild	Jawline: Some loss of jawline definition Pre-Jowl Area: Hollowing only, no jowl formation or pre-jowl sulcus Post-Jowl Area: Do Not Assess
2	Moderate	Jawline: Some blurring of jawline Pre-Jowl Area: Moderate jowl formation and pre-jowl sulcus Post-Jowl Area: No hollowing or post-jowl sulcus
3	Severe	Jawline: Significant blurring of jawline Pre-Jowl Area: Pre-jowl sulcus Post-Jowl Area: Post-jowl hollowing or post-jowl sulcus
4	Extreme	Jawline: Jowl tissue sagging significantly below jawline Pre-Jowl Area: Pre-jowl sulcus Post-Jowl Area: Post-jowl hollowing or post-jowl sulcus

Figure 2: Allergan Jawline Definition Scale



3. Treating Investigator (TI) considers the participant's jaw amenable to an improvement of at least 1 grade on the scale for the jawline definition
4. Ability to follow study instructions and likely to complete all required visits
5. Written Informed Consent (IC) has been obtained

Participants were not permitted to enroll in the V25L-002 study if they met any of the following exclusion criteria:

1. Has ever received permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
2. Has ever undergone fat injections in the malar, chin or jawline area or is planning to undergo this procedure during the study
3. Has facial tattoos, piercings, hair (ie, beard, mustache), or scars below the subnasale that would interfere with visual assessment of the chin or jaw area
4. Has undergone semipermanent dermal filler treatment (eg, calcium hydroxyapatite, poly-L-lactic acid) below the subnasale within 36 months before enrollment or is planning to undergo such treatment during the study
5. Has undergone dermal filler injections in the malar, chin or jawline area within 12 months before enrollment or is planning to undergo this procedure during the study
6. Has 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 injections in the chin, masseter, perioral area, or platysmal bands within 6 months before enrollment or is planning to undergo any of these procedures during the study
7. Has received deoxycholic acid treatment in the submental region in the last 6 months.
8. Has severe midface volume deficit such that restoration of the lower face volume would have an aesthetically unpleasant outcome, as determined by the TI
9. Has severe submental fat, as determined by TI
10. Has severe skin laxity that can interfere with visual assessment of the chin or jaw area, as determined by TI
11. Has a significant facial asymmetry, including but not limited to asymmetry due to trauma, as determined by TI
12. Has experienced trauma to the chin and jaw area within 6 months before enrollment or has residual deficiencies, deformities, or scarring, as determined by TI
13. Has a tendency to develop hypertrophic scarring
14. Has active autoimmune disease
15. Has current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, in chin or masseter

16. Has a history of severe reactions (anaphylaxis) or allergy to lidocaine, HA products, or Streptococcal protein
17. Is on a regimen of anti-coagulation therapy (eg, warfarin, clopidogrel)
18. Is on a regimen of medications (eg, aspirin or ibuprofen) or other substances known to increase coagulation time (eg, herbal supplements with garlic or gingko biloba) within 10 days of undergoing study device injection (study device injection may be delayed as necessary to accommodate this 10-day washout period)
19. Has received any investigational product within 30 days prior to study enrollment or is planning to participate in another investigation during the course of this study
20. Has begun using any new over-the-counter or prescription oral or topical, anti-wrinkle products below the subnasale within 30 days before enrollment or is planning to begin using such products during the study (participants who have been on a regimen of such products for at least 30 days are eligible for the study if they intend to continue their regimen throughout the study)
21. Is planning to undergo orthodontic treatment (eg, removal of braces, jaw surgery, headgear) during the study, with the exclusion of prophylaxis and dental filling. Dentures are acceptable if stable.
22. Females who are pregnant, nursing, or planning a pregnancy during the course of the study.
23. Is an employee (or a relative of an employee) of the TI, EI, Allergan, or a representative of Allergan
24. Has a condition or is in a situation which in the TI's opinion may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study

2. Follow-up Schedule

The follow-up period consisted of safety and effectiveness follow-up visits at 1, 3, 6, 9, and 12 months after the last treatment (initial or touch-up). Participants were eligible for a touch-up treatment with JUVÉDERM® VOLUX™ XC 30 days after initial treatment. An optional maintenance treatment was offered to all treatment group participants after completion of the 12-month follow-up visit, with 3 months of follow-up after maintenance treatment. Control participants followed a similar effectiveness evaluation schedule through 6 months. After 6 months, control participants were offered treatment and followed for an additional 12 months.

3. Clinical Endpoints

With regards to safety, participants used electronic diaries to record specific signs and symptoms of injection site responses (ISRs) experienced during the 30 days after the

initial, touch-up, and maintenance treatments. Adverse Events (AEs) were reported by the Treating Investigator (TI) at follow-up visits.

With regards to effectiveness, the primary effectiveness measure for the study was the blinded Evaluating Investigator's photo assessment of the participant's jawline using the validated 5-point Allergan Loss of Jawline Definition Scale (ALJDS).

A responder was defined as a participant with ≥ 1-point improvement in jawline definition compared with the pretreatment score on the ALJDS for both sides of the jawline. Effectiveness of JUVÉDERM® VOLUX™ XC was demonstrated if the responder rate at 6 months for treatment group participants was significantly greater than that for the control group participants, and the treatment group responder rate was statistically greater than or equal to 50%.

Secondary measures included Evaluating Investigator and participant assessments using the Global Aesthetic Improvement Scale (GAIS) (Table 4) and participant assessment of satisfaction using the validated *Satisfaction with Lower Face and Jawline* module of the FACE-Q questionnaire.

Table 4: 5-Point Global Aesthetic Improvement Scale

Score	Grade
2	Much Improved
1	Improved
0	No Change
-1	Worse
-2	Much Worse

Other effectiveness measures included participant assessments using the validated *Appraisal of Lines – Marionette* module of the FACE-Q questionnaire, 3D facial digital imaging analyses for linear depth and volumetric changes of the jawline profile.

With regard to the success/failure criteria, the primary endpoint would be met if at least 50% of participants in the treatment group were responders at Month 6 and if the responder rate for the treatment group was statistically significantly greater than that for the untreated control group at Month 6. A responder was defined as a participant who showed at least 1-point improvement from baseline on the ALJDS on both sides of the jaw. The multiple imputation method was used for primary effectiveness analysis and missing data handling.

4. Development and Validation of Allergan Loss of Jawline Definition Scale (ALJDS)

In the ALJDS validation study, 5 trained clinicians (raters) independently evaluated 150 digital images (75 left side of jawline, 75 right side of jawline) and assigned each an ALJDS score. The same raters re-evaluated the same images at least 2 weeks later. The validation study demonstrated almost perfect inter-rater agreement (intra class correlation coefficient > 0.80) and intra-rater agreement (mean weighted kappa > 0.80) for both sides of the jawline, indicating that the scale is valid for its intended purpose.

To assess clinical significance, prior to performing scale validation assessments the same 5 clinicians reviewed 36 pairs of images representing varying degrees of differences in jawline definition. The clinicians assessed whether each pair represented a clinically significant difference. Based on this assessment, a 1-point difference on the ALJDS was shown to be clinically meaningful.

The validation results described above confirm that the ALJDS is a robust and reliable scale, which was appropriate for use as the primary effectiveness measure in the pivotal study.

B. Accountability of PMA Cohort

At the time of database lock, of 271 patients enrolled in the PMA study, 86.9% (179) patients are available for analysis at the completion of the study, the 01/21 final follow-up visit. The participant disposition is shown in Table 5.

Table 5: Participant Disposition

Disposition		Number of Participants		
		Treatment	Control	Total
Enrolled		**N/A**	**N/A**	**271**
Screen Failures		**N/A**	**N/A**	**65**
Randomized Participants		**157**	**49**	**206**
Completed Control Period (Month 6 Primary Endpoint)		**149**	**47**	**196**
Continued After Control Period		**149**	**42**	**191**
Reason for Discontinuation	Withdrawal by Participant	3	4	7
	Lost to Follow-up	5	1	6
	Protocol Deviation	0	1	1
	Adverse Event	0	1	1
Completed Follow-up Period Through 12 Months After Treatment		**141**	**35**	**176**
Treatment Group – Did Not Receive Optional Maintenance Treatment (Completed Study)		**54**	**N/A**	**54**
Treatment Group – Received Optional Maintenance Treatment (VMT Population)		**87**	**N/A**	**87**
Reason for Discontinuation	Withdrawal by Participant	1	N/A	1
	Adverse Event	1	N/A	1
Treatment Group – Completed Follow-up Period Through 3 Months After Maintenance Treatment (Completed Study)		**85**	**N/A**	**85**

The analysis populations in the study were as follows:

- The modified intent-to-treat (mITT) Population included all randomized participants who had a baseline assessment on the ALJDS
- The Observed Primary Endpoint Population included all participants who had an ALJDS assessment at the 6-month primary endpoint

- The Safety Population included treatment group participants who were randomized and received study intervention as well as all randomized control group participants (including control group participants who did not opt for optional treatment JUVÉDERM® VOLUX™ XC)
- The VOLUX Treated Population included all participants who received treatment with JUVÉDERM® VOLUX™ XC
- The VOLUX Maintenance Treatment Population included participants who received repeat treatment with JUVÉDERM® VOLUX™ XC

The analysis populations are summarized in Table 6.

Table 6: Summary of Analysis Populations

Population	Treatment	Control	Total
Modified Intent-to-Treat (mITT) Population	157	49	206
Observed Primary Endpoint Population	146	46	192
Safety Population	156	50	206
VOLUX Treated Population	156	42	198
VOLUX Maintenance Treatment Population	87	N/A	87

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. Participant demographics and pretreatment characteristics of the treatment and control groups are presented in Table 7.

Table 7: Participant Demographics and Pretreatment Characteristics

	JUVÉDERM® VOLUX™ XC (N = 157) % (n/N)	Control (N = 49) % (n/N)
Sex		
Female	89.8% (141/157)	79.6% (39/49)
Male	10.2% (16/157)	20.4% (10/49)
Age		
Median	60	57
Range	26-79	37-81
Race		
White	84.1% (132/157)	85.7% (42/49)
Black or African American	13.4% (21/157)	12.2% (6/49)
American Indian or Alaska Native	0.6% (1/157)	0%
Multiple	1.9% (3/157)	2.0% (1/49)
Ethnicity		
Hispanic or Latino	19.7% (31/157)	22.4% (11/49)
Not Hispanic or Latino	80.3% (126/157)	77.6% (38/49)
Fitzpatrick Skin Type		
I/II	34.4% (54/157)	28.6% (14/49)
III/IV	51.6% (81/157)	59.2% (29/49)
V/VI	14.0% (22/157)	12.2% (6/49)

Study subject age ranged from 26 – 81 years, with a median age of 59 yrs. 22% subjects were in age range of 45-54. Allergan 2021 Market research showed that 16% of this age group received filler treatment in the jawline. Therefore, the study population was representative of the real-world patients who get this treatment. The percentage of birth male participants (12.6%, 26/206), the percentage of Fitzpatrick skin type (FST) V/VI participants (13.6%, 28/206), and the percentage of Black or African American participants (13.1%, 27/206) and Hispanic (20.4%, 42/206) participants included in this study are all reflective of clinical practice, based on the 2019 Cosmetic Surgery National Data Bank Statistics[1] and the 2020 Plastics Surgery Statistics Report[2]. The enrolled numbers of specific demographics groups in the V25L-002 study were consistent with previous filler studies conducted by Allergan and other sponsors for a variety of indications.

Injections were administered using 27 G ½" needles and 25 G 1½" cannulas. The TSK STERiGLIDE™ 25- G 1½" cannula was used in the clinical trial and is the only cannula recommended for use with JUVÉDERM® VOLUX™ XC. The most common

[1] The American Society for Aesthetic Plastic Surgery – Cosmetic (Aesthetic) Surgery National Data Bank Statistics. Available at: www.surgery.org/sites/default/files/ASAPS-Stats2018.pdf

[2] American Society of Plastic Surgeons – 2020 Plastics Surgery Statistics Report. Available at: https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf

injection techniques to achieve optimal results were tunneling, serial puncture, and bolus injections. In the treatment group, the median total injection volume was 4.35 mL at initial treatment, 2.0 mL at touch-up treatment, and 3.0 mL at maintenance treatment. The amount used ranged from 1.0 to 9.3 mL for initial and touch-up treatment combined.

Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on the treated population comprising of 42 participants in the control and 156 participants in the treatment group. The key safety outcomes for this study are presented below in Table 8 to Table 12. Participants used electronic diaries to record specific signs and symptoms of injection site responses (ISRs) experienced during the 30 days after the initial, touch-up, and maintenance treatments. Participants were instructed to rate each ISR listed on the diary as Mild, Moderate, Severe, or None.

   - Mild ISRs were defined as symptoms causing little, if any, discomfort leading to little, if any, effect on daily activities.
   - Moderate ISRs were defined as symptoms causing some discomfort leading to some effect on daily activities.
   - Severe ISRs were defined as symptoms causing great discomfort leading to compromised performance of daily activities.

   The severity and duration of all ISRs reported by > 5% of participants after initial treatment (from both the treatment and control groups) are summarized in Table 8. Most ISRs were mild or moderate, and their duration was short lasting (14 days or less). The incidence, severity, and duration of ISRs reported after the touch-up and repeat treatments were similar to those reported after initial treatment. ISRs manifests after receiving an injection, examples of ISRs are redness, pain after injection, tenderness to touch, firmness, swelling, lumps/bumps, bruising, itching and discoloration (not redness or bruising).

Table 8: Injection Site Responses by Severity and Duration After Initial Treatment with JUVÉDERM® VOLUX™ XC Occurring in > 5% of Treated Participants

Injection Site Response	Total % (n/N[a])	Severity[b]			Duration[c]			
		Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])	1-3 Days % (n/N[a])	4-7 Days % (n/N[a])	8-14 Days % (n/N[a])	15-30 Days % (n/N[a])
Any ISR	85.2% (167/196)	32.7% (64/196)	42.3% (83/196)	10.2% (20/196)	20.4% (40/196)	14.3% (28/196)	15.3% (30/196)	35.2% (69/196)
Tenderness	80.1% (157/196)	42.3% (83/196)	36.2% (71/196)	1.5% (3/196)	29.1% (57/196)	21.4% (42/196)	18.4% (36/196)	11.2% (22/196)
Lumps/Bumps	79.1% (155/196)	40.3% (79/196)	32.7% (64/196)	6.1% (12/196)	20.9% (41/196)	12.8% (25/196)	12.8% (25/196)	32.7% (64/196)
Pain	78.1% (153/196)	44.9% (88/196)	31.1% (61/196)	2.0% (4/196)	41.3% (81/196)	21.4% (42/196)	10.2% (20/196)	5.1% (10/196)
Swelling	77.6% (152/196)	42.9% (84/196)	31.1% (61/196)	3.6% (7/196)	37.2% (73/196)	23.5% (46/196)	11.7% (23/196)	5.1% (10/196)
Firmness	73.5% (144/196)	41.8% (82/196)	29.1% (57/196)	2.6% (5/196)	33.7% (66/196)	15.3% (30/196)	12.2% (24/196)	12.2% (24/196)
Bruising	69.4% (136/196)	38.8% (76/196)	25.0% (49/196)	5.6% (11/196)	24.5% (48/196)	18.9% (37/196)	19.4% (38/196)	6.6% (13/196)
Redness	67.9% (133/196)	41.8% (82/196)	24.5% (48/196)	1.5% (3/196)	44.9% (88/196)	13.8% (27/196)	7.1% (14/196)	2.0% (4/196)
Itching	33.2% (65/196)	27.0% (53/196)	6.1% (12/196)	0%	21.4% (42/196)	4.6% (9/196)	5.1% (10/196)	2.0% (4/196)
Discoloration	32.7% (64/196)	23.5% (46/196)	8.2% (16/196)	1.0% (2/196)	20.9% (41/196)	4.6% (9/196)	5.6% (11/196)	1.5% (3/196)

[a] N denotes the number of participants who recorded responses in the diaries after initial treatment
[b] Maximum severity reported in the diary
[c] Duration is calculated based on the difference between the first and last date of occurrence

Adverse Events (AEs) were 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." This definition includes events related to the investigational medical device and events related to the procedures involved except for events in users or other persons, which only included events related to investigational medical devices.

Disease signs and symptoms that existed prior to the study treatment are not considered AEs unless the condition recurs after the subject has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study. AEs were to be monitored throughout the study beginning with signing of the ICF.

AEs were reported by the Treating Investigator at follow-up visits. Among the 198 participants who received an initial treatment with JUVÉDERM® VOLUX™ XC, 16 participants (8.1%, 16/198) had 20 treatment-related AEs (Table 9). These AEs included mastication disorder (2.0%, 4/198), injection site nodule (1.5%, 3/198), injection site bruising (1.0%, 2/198), injection site hypersensitivity (0.5%, 1/198), injection site mass (0.5%, 1/198), injection site pain (0.5%,

1/198), injection site swelling (0.5%, 1/198), injection site infection (0.5%, 1/198), oral herpes (0.5%, 1/198), temporomandibular joint syndrome (0.5%, 1/198), muscle tightness (0.5%, 1/198), muscle twitching (0.5%, 1/198), and headache (0.5%, 1/198). An AE is considered a treatment-related AE if the AE is deemed related to the procedure or the study device by the Treating Investigator.

Table 9: V25L-002 Participants with Treatment-Related AEs after Initial/Touch-up Treatment (JUVÉDERM® VOLUX™ XC Treated Population)

AE		Severity		
	Participants % (n/N[a])	Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])
Mastication Disorder	2.0% (4/198)	1.5% (3/198)	0.5% (1/198)	0%
Injection Site Nodule	1.5% (3/198)	1.0% (2/198)	0.5% (1/198)	0%
Injection Site Bruising	1.0% (2/198)	0.5% (1/198)	0.5% (1/198)	0%
Injection Site Hypersensitivity	0.5% (1/198)	0%	0.5% (1/198)	0%
Injection Site Infection	0.5% (1/198)	0.5% (1/198)	0%	0%
Injection Site Mass	0.5% (1/198)	0.5% (1/198)	0%	0%
Injection Site Pain	0.5% (1/198)	0%	0.5% (1/198)	0%
Injection Site Swelling	0.5% (1/198)	0.5% (1/198)	0%	0%
Oral Herpes	0.5% (1/198)	0.5% (1/198)	0%	0%
Temporomandibular Joint Syndrome	0.5% (1/198)	0.5% (1/198)	0%	0%
Muscle Tightness	0.5% (1/198)	0.5% (1/198)	0%	0%
Muscle Twitching	0.5% (1/198)	0.5% (1/198)	0%	0%
Headache	0.5% (1/198)	0.5% (1/198)	0%	0%

[a] N denotes the number of participants who received initial treatment with JUVÉDERM® VOLUX™ XC

There were 15 mild and 5 moderate AEs. The severity and duration of all treatment-related AEs (from both the treatment and control groups) are summarized in Table 10. Among the 87 participants who received maintenance treatment, 3 participants (3.4%, 3/87) had 4 treatment-related AEs, which included injection site nodule (2.3%, 2/87) and mastication disorder (1.1%, 1/87). Most AEs were mild and resolved within 7 days without sequelae. There were 3 participants that required medical intervention, which may have included antibiotics, oral and intralesional steroids, antihistamines, diuretics, or hyaluronidase to resolve the adverse events. The treatment-related AEs lasting longer than 30 days and with a delayed onset (> 30 days) are summarized in Table 11 and Table 12. All 7 treatment-related AEs lasting longer than 30 days were mild or moderate in severity and resolved within 180 days without sequelae.

Table 10: Severity and Duration of Treatment-Related AEs in the Treated Period (JUVÉDERM® VOLUX™ XC Treated Population)

	Participants (N=198) n (%)	Treatment-Related AEs
Severity		
Total	16 (8.1%)	20
Mild	12 (6.1%)	15
Moderate	4 (2.0%)	5
Severe	0 (0.0%)	0
Duration		
Total	16 (8.1%)	20
≤ 7 Days	10 (5.1%)	13
8-14 Days	0 (0.0%)	0
15-30 days	0 (0.0%)	0
> 30 days	7 (3.5%)	7
Ongoing	0 (0.0%)	0

n: number of participants with at least one treatment-related AE

Table 11: Treatment-Related AEs with Duration Greater than 30 Days in the Treated Period (JUVÉDERM® VOLUX™ XC Treated Population)

AE	Severity	Time to Onset (Days after last treatment)	Duration (Days)	Outcome
Injection site nodule	Mild	4	176	Recovered/Resolved
Injection site mass	Mild	1	163	Recovered/Resolved
Injection site nodule	Mild	13	48	Recovered/Resolved
Injection site hypersensitivity reaction	Moderate	17	118	Recovered/Resolved
Injection site nodule	Mild	2	106	Recovered/Resolved
Injection site nodule	Moderate	76	80	Recovered/Resolved
Muscle twitching	Mild	8	33	Recovered/Resolved

Table 12: Treatment-Related AEs with Onset Days Greater than 30 Days After Last Treatment (JUVÉDERM® VOLUX™ XC Treated Population)

AE	Severity	Time to Onset (Days after last treatment)	Duration (Days)	Outcome
Injection site swelling	Mild	251	6	Recovered/Resolved
Injection Site nodule	Moderate	76	80	Recovered/Resolved

The incidence of treatment-related AEs in different subgroups is summarized in Table 13. The differences observed in the percentages of participants who experienced treatment-related AEs within the different subgroups were not statistically significant.

Table 13: Treatment-Related AEs by Different Subgroups

Subgroup	Participants (%)	Events
Total Treatment-related AE (N=198)	16 (8.1%)	20
≤ Median Volume (N=103	12 (11.7%)	15
> Median Volume (N=95)	4 (4.2%)	5
Fitzpatrick Skin Phototype I/II (N=67)	3 (4.5%)	4
Fitzpatrick Skin Phototype III/IV (N=104)	8 (7.7%)	11
Fitzpatrick Skin Phototype V/VI (N=27)	5 (18.5%)	5
Needle Only (N=106)	10 (9.4%)	11
Cannula (N=92)	6 (6.5%)	9
Male (N=22)	1 (4.5%)	1
Female (N=176)	15 (8.5%)	19
≤ Median Age (59) (N=99)	7 (7.1%)	9
> Median Age (59) (N=99)	9 (9.1%)	11

N: number of participants in each group

Other Safety Assessments

Jaw Functional Limitation Scale

Participant assessments on the Jaw Functional Limitation Scale[3] in the JUVÉDERM® VOLUX™ XC Treated and Maintenance Treatment populations showed a median score of zero at baseline and all postbaseline timepoints in overall score and scores for the 3 subscales of mastication, mobility, and verbal and nonverbal communication, indicating that treatment did not affect jaw function.

EI Assessment of Facial Sensation

To determine facial sensitivity, 2-point discrimination and light-touch tests were performed by the Evaluating Investigator. The 2-point discrimination test assessed the distances for which participants indicated they felt 2 distinct points of pressure in the left and right prejowl and postjowl areas. The light touch assessment determined the smallest filament number for which participants felt the presence of the filament in the left and right prejowl and postjowl areas. For both the JUVÉDERM® VOLUX™ XC Treated and Maintenance Treatment populations, the assessments showed that the treatment did not affect facial sensation.

Pronunciation Video Recordings

The pronunciation video recordings comprised of 5 assessments: pronunciation of individual words, pronunciation of words in a sentence, the number and preciseness of "tuh" iterations performed in 10 seconds, and the naturalness of a spoken paragraph. Participants were video recorded reading a script of words and sentences, and the videos were then assessed by an independent speech and language pathologist. The results showed that JUVÉDERM® VOLUX™ XC treatment did not affect the pronunciation for both the Treated and Maintenance Treatment populations.

Vision Assessments

Snellen visual acuity assessments in the Treated and Maintenance Treatment populations showed that over 90% of participant eyes had the same or better visual acuity at all post-treatment assessments.

Only 2 eyes in one participant in the VOLUX Treated population and no eyes in the VOLUX Maintenance Treatment population showed a ≥ 3-line worsening in visual acuity at any assessment. These results were not related to intravascular injection and were deemed not clinically significant by the Treating Investigator.

Confrontational visual fields and ocular motility assessments showed that 100% of eyes were full to confrontation and had full duction and version, with no changes from pre-treatment at all assessments.

[3] Ohrbach, R., et al. (2008). The Jaw Functional Limitation Scale: Development, reliability, and validity of 8-item and 20-item versions. Journal of Orofacial Pain 22: 219-230

Pain Assessment

Treatment group participants reported a median pain score immediately after the injection of 2 on an 11-point scale where 0 is no pain and 10 is worst pain imaginable.

2. Effectiveness Results

The primary analysis of effectiveness was based on the 206 participants in the mITT population (157 participants in the treatment group and 49 participants in the control group) at the Month 6 time point. Key effectiveness outcomes on the observed data are presented in Tables 16 to 18.

Follow-up After Initial Treatment

JUVÉDERM® VOLUX™ XC provided a clinically and statistically significant improvement in jawline definition compared to the no treatment control group at 6 months after treatment among participants with moderate or severe loss of jawline definition.

The primary effectiveness endpoint was met in that the treatment group ALJDS responder rate (69.0%, 108.3/157, 95% CI 61.53 - 76.39%) was significantly greater ($p = 0.0001$) than the control group responder rate (38.0%, 18.6/49, 95% CI 24.25 - 51.80%), and the treatment group responder rate was also statistically greater than 50%. Most treatment group participants maintained a clinically significant improvement in jawline definition (≥ 1 point improvement on the ALJDS) through the 12-month follow-up period (Table 16). The ALJDS responder rates within the subgroups at 6 months were analyzed but were not statistically significant (Table 17 and Table 18).

Table 14: Effectiveness of JUVÉDERM® VOLUX™ XC for Jawline Definition through 12 Months VOLUX

Timepoint After Initial/Touch-up Treatment	Treatment Group Responder Rate % (n/N[a])	Control Group Responder Rate % (n/N[a])
1 Month	78.7% (118/150)	22.7% (10/44)
3 Months	76.0% (111/146)	30.4% (14/46)
6 Months	69.9% (102/146)	39.1% (18/46)
9 Months	64.9% (87/134)	N/A[b]
12 Months	61.3% (84/137)	N/A[b]

[a] Number of participants with data at baseline and the specified timepoint
[b] No control results were available at Month 9 and Month 12 since the control period ended at Month 6. At Month 6, the control participants were given the option to get the treatment.

Table 15: ALJDS Responder Rates at Month 6 by Sex and FST Subgroups (mITT Population)

	Sex		Fitzpatrick Skin Type (FST)		
	Male	Female	I/II	III/IV	V/VI
Treatment Group Responder Rate, % (n/N)	78.6% (11/14)	68.9% (91/132)	62.7% (32/51)	72.0% (54/75)	80.0% (16/20)
95% CI (%)	49.20 - 95.34	60.30 - 76.70	48.08 - 75.87	60.44 - 81.76	56.34 -94.27

Table 16: ALJDS Responder Rates at Month 6 by Route of Administration and Age Subgroups (mITT Population)

	Route of Administration		Age	
	Cannula	Needle Only	<= Median Age	> Median Age
Treatment Group Responder Rate, % (n/N)	73.5% (50/68)	66.7% (52/78)	76.1% (54/71)	64.0% (48/75)
95% CI (%)	61.43 - 83.50	55.08 - 76.94	64.46 - 85.39	52.09 - 74.77

The Evaluating Investigators rated the majority of treatment group participants (89.0%, 130/146) as showing improvement in overall aesthetic appearance at 6 months based on the GAIS, with the majority continuing to show improvement through 12 months (79.9%, 107/134).

At 6 months, 88.4% (129/146) of treatment group participants reported improvement in the overall aesthetic appearance of their skin on the GAIS. Most treatment group participants continued to report improvement on the GAIS at 12 months (74.3%, 104/140).

Per the *Satisfaction with Lower Face and Jawline* module of the FACE-Q questionnaire, the majority of treatment group participants (82.3%, 116/141) were satisfied with the appearance of their lower face and jawline through 12 months following treatment with JUVÉDERM® VOLUX™ XC. Within the *Satisfaction with Lower Face and Jawline* module of the FACE-Q questionnaire, participants reported the following:

- 81.5% (119/146) of participants at 6 months were satisfied with how sculpted (well-defined) their jawline looked compared to 12.2% (19/156) at baseline
- 70.5% (103/146) of participants at 6 months were satisfied with how smooth their lower face looked (i.e., no jowls or folds of fatty skin) compared to 7.7% (12/156) at baseline
- 73.1% (106/145) of participants at 6 months were satisfied with how nice their lower face looked compared to 9.0% (14/156)

The 3D facial digital analyses showed that treatment group participants had an overall mean change of 4.6 mm in linear depth and overall mean volume change of 6.0 cc at 6 months. These changes in the treatment group participants continued to be observed at 12 months, with an overall mean change of 4.4 mm in linear depth and overall volume change of 6.4 cc. The control group participants had an overall mean change of 2.5 mm in linear depth and overall mean volume change of -2.6 cc at 6 months.

Patient reported outcomes only reported by the treatment group:

The following two measures were only performed on the treatment group and were not collected from the control group as they had not received a treatment during the control period.

The majority of treatment group participants (78.8%, 115/146) reported being satisfied or definitely satisfied with the overall result of treatment at 6 months. At 12 months, 68.1% (96/141) of treatment group reported being satisfied or definitely satisfied with the overall result of treatment.

At 6 months, 89.7% (131/146) of treatment group participants were willing torecommend the treatment to a friend, with the majority continuing to recommend treatment at 12 months (87.2%, 123/141).

Follow-up After Maintenance Treatment

Maintenance treatment with JUVÉDERM® VOLUX™ XC was administered to 87 participants. The effectiveness profile after maintenance treatment was similar to that after initial treatment. The ALJDS responder rate after maintenance treatment was 70.3% (45/64) at 1 month and 63.6% (49/77) at 3 months.

3. Pediatric Extrapolation

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

D. Financial Disclosure

[[DISCLOSABLE FINANCIAL ARRANGEMENTS: NO EFFECT ON RELIABILITY OF DATA]

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 42 investigators of which none were full-time or part-time employees of the sponsor and 8 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and 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: 8

Proprietary interest in the product tested held by the investigator: None

Significant equity interest held by investigator in sponsor of covered study: 1

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

Device didn't go to Panel.

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 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 PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The data submitted provide a reasonable assurance that the device is effective for improving jawline definition in patients with moderate to severe loss of jawline definition. The specific conclusions from the pivotal study are:

- The primary endpoint was met: at Month 6 the ALJDS responder rate for the treatment group was statistically superior to that for the untreated control group and was statistically greater than or equal to 50%.
- Improvements in jawline definition lasted through 1 year after JUVÉDERM® VOLUX™ XC treatment based on ALJDS assessment.
- 89% of participants had overall aesthetic improvement at 6 months and 80% at 1 year after JUVÉDERM® VOLUX™ XC treatment based on EI GAIS assessment of the jawline area.
- 88% of participants had overall aesthetic improvement at 6 months and 74% at 1 year after JUVÉDERM® VOLUX™ XC treatment based on participant GAIS assessment of the jawline area.
- Participant jawline satisfaction showed a clinically relevant and statistically significant improvement from baseline ($p < 0.0001$) at 6 months and a mean improvement of 30.3 points from baseline at 1 year after JUVÉDERM®

VOLUX™ XC treatment based on the FACE-Q *Satisfaction with Lower Face and Jawline* questionnaire.

- Over 80% of participants had improved satisfaction with their jawline for 1 year after JUVÉDERM® VOLUX™ XC treatment based on the FACE-Q *Satisfaction with Lower Face and Jawline* questionnaire.
- Over 80% of participants were satisfied with how prominent and well-defined their jawline looked at 6 months after JUVÉDERM® VOLUX™ XC treatment based on the FACE-Q *Satisfaction with Lower Face and Jawline* questionnaire.
- Objective calculations from 3D imaging showed increases in jawline profile volume through 1 year after JUVÉDERM® VOLUX™ XC treatment.
- Maintenance treatment received 1 year later produced similar results at 3 months with less than half the injection volume.
- Subgroup analyses demonstrated that JUVÉDERM® VOLUX™ XC is effective for moderate and severe loss of jawline definition, ≤ median and > median injection volumes, and both needle and cannula treatments.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The data submitted provide a reasonable assurance that the device is safe for improving jawline definition in adults over the age of 21 with moderate to severe loss of jawline definition. The specific conclusions with regard to safety from the pivotal study are:

- For initial, touch-up, and maintenance treatments, most ISRs were mild or moderate in severity (75%, 147/196 for any ISRs after initial treatment) and resolved within 2 weeks.
- The most common ISRs after initial treatment were tenderness to touch (80.1%, 157/196), lumps/bumps (79.1%, 155/196), and pain after injection (78.1%, 153/196).
- The incidence of any ISRs was lower for touch-up (77.0%, 124/161) and maintenance (71.3%, 62/87) treatments than for initial treatment (85.2%, 167/196).
- Participants assessed procedural pain during injection as minimal.
- The most common treatment-related AE after initial/touch-up treatment was mastication disorder, occurring in 2% (4/198) of participants; most (1.5%, 3/198) were mild severity, and all resolved within 3 days.
- Other AEs included injection site nodule (1.5%, 3/198), injection site bruising (1.0%, 2/198), injection site hypersensitivity (0.5%, 1/198), injection site mass (0.5%, 1/198), injection site pain (0.5%, 1/198), injection site swelling (0.5%, 1/198), injection site infection (0.5%, 1/198), oral herpes (0.5%, 1/198), temporomandibular joint syndrome (0.5%, 1/198), muscle tightness (0.5%,

1/198), muscle twitching (0.5%, 1/198), and headache (0.5%, 1/198). There were 15 mild and 5 moderate adverse events.

- Most treatment-related TEAE began within 1 week of treatment (5.6%, 11/198), were mild in severity (6.1%, 12/198), and resolved within 1 week (5.1%, 10/198).
- There were no deaths, unanticipated adverse device effects, or treatment-related adverse events of special interest.
- 5 participants had treatment-related SAEs (3 injection site nodules, 1 injection site infection, and 1 injection site hypersensitivity) that resolved without sequelae following treatment.
- Treatment with JUVÉDERM® VOLUX™ XC did not compromise jaw function, sensation, or speech articulation.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The results of the V25L-002 study demonstrate the effectiveness of JUVÉDERM® VOLUX™ XC for improvement in jawline definition. The predefined primary endpoint was met in that in that the treatment group ALJDS responder rate at 6 months was statistically superior ($p = 0.0001$) to the control group responder rate, and the treatment group responder rate was statistically greater than or equal to 50%.

The secondary and other effectiveness endpoints further demonstrate that JUVÉDERM® VOLUX™ XC is effective for improvement in jawline definition based on patient-reported outcome measures and other subjective and objective measures. Based on EI and participant GAIS assessments, over 85% of participants had an overall aesthetic improvement at 6 months, with most continuing through 1 year. The improvement versus baseline in overall mean score on the FACE-Q Satisfaction with Lower Face and Jawline questionnaire was statistically significant at 6 months for the treatment group, and participants continued to show improved satisfaction through 1 year. Furthermore, objective measurements from 3D digital images showed increases in jawline profile volume through 1 year.

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 clinical study results demonstrated that the safety profile of JUVÉDERM® VOLUX™ XC injection for improvement in jawline definition is consistent with that of other HA fillers. Most participants in the clinical study experienced common ISRs, such as tenderness to touch and lumps/bumps after treatment, the majority of which were mild to moderate in severity and resolved within 2 weeks of treatment. Most treatment-related AEs were mild in nature, began within 1 week of treatment, and resolved within 1 week, and all resolved without sequelae by study end. Five participants had treatment-related SAEs (3 injection site nodules, 1 injection site infection, and 1 injection site hypersensitivity) that resolved without sequelae following treatment. There were no treatment related AEs of special interest or unanticipated adverse device effects.

1. Patient Perspective

Patient perspectives considered during the review included:

- At 6 months, 88.4% (129/146) of treatment group participants reported improvement in the overall aesthetic appearance of their jawline area on the GAIS. Most treatment group participants continued to report improvement on the GAIS at 12 months (74.3%, 104/140).
- Per the Satisfaction with Lower Face and Jawline module of the FACE-Q® questionnaire, the majority of treatment group participants (82.3%, 116/141) were satisfied with the appearance of their lower face and jawline through 12 months following treatment with JUVÉDERM® VOLUX™ XC.
- Treatment group participants reported a median pain score immediately after the injection of 2 on an 11-point scale where 0 is no pain and 10 is worst pain imaginable.

In conclusion, given the available information above, the data support that for improvement of jawline definition of JUVÉDERM® VOLUX™ XC 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. The data demonstrate the benefits of JUVÉDERM® VOLUX™ XC for improvement of jawline definition outweigh the risks and the intended patient populations will achieve clinically significant results. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XIII. CDRH DECISION

CDRH issued an approval order on July 29, 2022.

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.