SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: JUVÉDERM VOLLURE™ XC

Device Procode: LMH

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110033/S020

Date of FDA Notice of Approval: March 17, 2017

Priority Review: No

Expedited Access Pathway (EAP): No

The original PMA for JUVÉDERM VOLUMA XC (P110033) was approved on 10/22/2013 and 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 the indication is available on the CDRH website and is incorporated by reference here. JUVÉDERM VOLLURE™ XC is being submitted as a panel-track supplement (P110033/S020) to the JUVÉDERM VOLUMA XC PMA, P110033, to request changes in design or performance of the device, and a new indication for use of the device. The current supplement was submitted for JUVÉDERM VOLLURE™ XC for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

II. INDICATIONS FOR USE

JUVÉDERM VOLLURE™ XC is indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) in adults over the age of 21.

III. CONTRAINDICATIONS

- JUVÉDERM VOLLURE™ XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies

- JUVÉDERM VOLLURE™ XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material
- JUVÉDERM VOLLURE™ 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 VOLLURE™ XC labeling.

V. DEVICE DESCRIPTION

JUVÉDERM VOLLURE™ XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of crosslinked hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, formulated to a concentration of 17.5 mg/mL and 0.3% w/w lidocaine in a physiologic buffer. Each box of JUVÉDERM VOLLURE™ 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. Expiration dating has been established and approved at 24 months. JUVÉDERM VOLLURE™ XC is delivered by an injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for correction of facial wrinkles and folds, including: various minimally invasive injectable procedures (e.g., autologous fat grafting, and other soft tissue fillers approved by FDA) as well as surgical correction. 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 VOLLURE™ XC received the CE Mark on October 7, 2011, under the name JUVÉDERM VOLIFT® with Lidocaine. In addition to being marketed throughout Europe, JUVÉDERM VOLIFT® with Lidocaine is currently marketed globally, including in Australia, Canada, Brazil, Russia, Ukraine, Mexico, Korea, Taiwan, South Africa and Singapore. JUVÉDERM VOLLURE™ XC has not been marketed in the United States.

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, include tenderness, swelling, firmness (induration), lumps/bumps (mass), bruising, pain, redness, discoloration, and itching. Rare, but serious, adverse events associated with the intravascular injection of soft-tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

Post-Market Surveillance

The following reported adverse events were received from post-market surveillance of the use of JUVÉDERM VOLLURE™ XC outside the United States and were not observed in the clinical study. These adverse events, with a frequency of 5 or more events, are listed in order of prevalence: inflammatory reaction, skin nodule, loss/lack of correction, hematoma, allergic reaction, necrosis, infection, flu-like symptoms, paresthesia, migration of device, abscess, drainage, herpes, malaise, headache, and anxiety.

In many cases the symptoms resolved without any treatment. Reported treatments for these events included the use of (in alphabetical order): analgesics, anesthetics, antibiotics, anti-allergy medications, antifungal, antihistamines, anti-inflammatory medications, antiviral, arnica, aspiration, drainage, hyaluronidase, ice, massage, nitrates, oral and topical corticosteroids, and warm compress.

Vision abnormalities have been reported following injection of JUVÉDERM VOLLURE™ XC, with a time to onset ranging from immediate to 1 week following injection. This included one report of blurry vision after injection in an unspecified area, and one report of blurry vision after injection in the highly vascularized periorbital area (outside the device indications for use). In addition, one report of stroke after injections in an unspecified area with multiple dermal fillers was reported. However, no additional details regarding patient outcomes were reported beyond vision abnormalities and stroke.

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Physical and Chemical Characterization

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

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

Test	Purpose	Results
NaHA Concentration (mg/g)	Ensures HA concentration meets specification	Passed
Lidocaine Concentration (%w/w)	Ensures lidocaine concentration meets specification	Passed
pH	Ensures pH meets specification	Passed
Osmolarity (mOsmol/Kg)	Ensures osmolarity meets specification	Passed

Extrusion Force (N)	Ensures extrusion force meets specification	Passed
Residual Crosslinker (ppm)	Ensures residual crosslinker meets specifications	Passed
Endotoxin (EU/Syringe)	Ensures endotoxin meets specification	Passed

Filled syringes are sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle is validated according to 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 36 months at 25°C/60% relative humidity, through 12 months at 30°C/65% relative humidity, and through 6 months at 40°C/75% relative humidity. At each time point, product was evaluated for conformance with microbiological, physical and chemical properties including lidocaine HCl potency and lidocaine-related degradants. Conformance with all specifications was confirmed.

Biocompatibility Testing

JUVÉDERM VOLLURE™ 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 § 58), ISO 10993 and FDA's Blue Book memorandum G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing."

Table 2: Summary of Biocompatibility Testing on JUVÉDERM VOLLURE™ XC

Test	Method	ISO standard	Results
Cytotoxicity	Agar overlay	10993-5	Non-cytotoxic
Sensitization	Guinea pig maximization test	10993-10	Non-sensitizing
Intracutaneous reactivity	72 hour exposure and 14-day exposure, in rabbits	10993-10	Irritant at 3-days Non-irritant at 14-days
Acute Systemic Toxicity	Intraperitoneal injection in mice	10993-11	Not systemically toxic
Subchronic Toxicity (13 Weeks)	Intradermal injection in rats	10993-11	Non-toxic
Muscle Implantation (4 and 12 Weeks)	In rabbits	10993-6	Non-irritant
Subcutaneous Implantation (4 and 12 weeks)	In rats	10993-6	Not causing local skin reaction macroscopically; slight irritant microscopically

Pyrogenicity	Rabbit pyrogen study	USP <151>	Non-pyrogenic
Genotoxicity	Bacterial Reverse Mutation, Micronucleus, and Chromosomal Aberration	10993-3	Non-genotoxic Non-mutagenic

Carcinogenicity risks: The excess cancer risks for JUVÉDERM VOLLURE™ 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 VOLLURE™ XC are in the same range of acceptable cancer risks as other previously approved dermal filler products.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for JUVÉDERM VOLLURE™ XC for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) in adults over the age of 18 in the US under IDE # G120228. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between October 29, 2013 and September 28, 2015. The database for this Panel-Track Supplement reflected data collected through November 09, 2016 and included 123 subjects who were randomized and underwent treatment with either JUVÉDERM VOLLURE™ XC in the right or left nasolabial fold (NLF) and with the control in the other NLF at the outset of the study. An FDA-approved cross-linked hyaluronic acid dermal filler which is legally marketed with similar indications for use was used as a control. There were six investigational sites.

The study was a prospective, double-blind, randomized, within-subject controlled, multicenter clinical study of subjects seeking correction of moderate to severe NLFs. Subjects meeting inclusion/exclusion criteria were randomized to treatment with JUVÉDERM VOLLURE™ XC in either the right or left NLF and with the control product in the other NLF.

1. Key Clinical Inclusion and Exclusion Criteria

Inclusion criteria:

- 18 years of age or older
- Had a severity score of 2 for both NLFs or a score of 3 for both NLFs on the 5-point photographic Nasolabial Fold Severity Scale (range 0-4), as judged live by the Evaluating Investigator

Exclusion criteria:

- Had undergone facial tissue augmentation with dermal fillers in the lower two thirds of the face within 12 months before enrollment
- Had undergone facial tissue augmentation with fat injections, botulinum toxin injections in the lower two-thirds of the face (below the orbital rim), mesotherapy, or cosmetic facial procedures in the face or neck (e.g., face-lift, laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures) within 6 months before enrollment or was planning to undergo any such treatment during the study
- Had ever received semi-permanent fillers or permanent facial implants (e.g., calcium hydroxylapatite, poly-L-lactic acid, polymethylmethacrylate, silicone, expanded polytetrafluoroethylene) anywhere in the lower face (below the orbital rim), or was planning to be implanted with any of these products at any time during the study
- Had a tendency to develop hypertrophic scarring
- Had a history of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), HA products, or Streptococcal protein, or was planning to undergo desensitization therapy during the term of the study
- Had porphyria
- Had any uncontrolled disease
- Had an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound in the NLF area
- Had current cutaneous inflammatory and/or infectious processes (e.g., acne, herpes) in the NLF area
- Was on a concurrent regimen of lidocaine or structurally related local anesthetics (e.g., bupivacaine)
- Had impaired cardiac conduction, severely impaired hepatic function or severe renal dysfunction
- Was on an ongoing regimen of anti-coagulation therapy (e.g., warfarin) or NSAIDs (e.g., aspirin, 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 treatment was able to be delayed as necessary to accommodate this 10-day washout period)
- Females who were pregnant, nursing, or planning a pregnancy

2. Follow-up Schedule

   In the pivotal study, subjects were randomized and underwent treatment with JUVÉDERM VOLLURE™ XC in the right or left NLF and the control product in the other NLF at the outset of the study. An optional touch-up treatment was performed approximately 1 month after the initial treatment, if deemed necessary to achieve optimal correction. Subjects completed a safety diary for 30 days after each treatment and attended safety follow-up visits at 3 and 14 days after each treatment.

   The follow-up period consisted of safety and effectiveness follow-up visits at 1, 3, 6, 9, 12, 15, and 18 months after the last treatment. After the Month 9, 12, and 15 visits, subjects could request a single, unilateral treatment to correct

clinically significant asymmetry (defined as at least a 1-point difference in NLF severity between NLFs, based on the Evaluating Investigator's assessment). The Treating Investigator treated asymmetry using JUVÉDERM VOLLURE™ XC in the more severe NLF only, regardless of which treatment was originally used in that NLF. After the asymmetry correction, subjects completed a safety diary for 30 days and continued with any remaining study follow-up visits. After the Month 12 or 15 visit, subjects could request a repeat treatment in one or both of their NLFs if their NLF severity had returned to baseline or worse, based on the Evaluating Investigator's assessment. Any subject not receiving repeat treatment before the Month 18 visit was eligible to receive a repeat treatment at that time regardless of NLF severity score. Subjects completed another safety diary for 30 days and were followed for 1 month after the repeat treatment, at which time all subjects completed the study. All repeat treatments were performed with JUVÉDERM VOLLURE™ XC.

The Treating Investigator determined the appropriate volume of VOLLURE™ XC or control to inject at initial, touch-up, asymmetry correction, and repeat treatments based on his/her clinical experience. The maximum volume allowed for each NLF was 4.0 mL at initial and touch-up treatments combined. Up to 4.0 mL in one NLF was allowed for asymmetry correction and up to 4.0 mL per NLF was allowed for repeat treatment.

3. Clinical Endpoints

With regards to safety: the safety of JUVÉDERM VOLLURE™ XC in the nasolabial folds was evaluated by the presence, location, frequency, severity, and duration of injection site responses (ISRs) after each treatment (initial, touch-up, asymmetry correction, and repeat) and any adverse events (AEs) throughout the study. ISRs were assessed by a subject safety diary for 30 days after each treatment. ISRs lasting beyond the 30-day diaries were considered adverse events (AEs). AEs were also reported by the Evaluating Investigator at follow-up visits.

With regards to effectiveness: the primary effectiveness endpoint was the analysis of 1) non-inferiority of JUVÉDERM VOLLURE™ XC relative to control in terms of change from baseline to month 6 in mean NLF severity based on the NLF Severity Scale (NLFSS, Table 3, Figure 1) and 2) the analysis of the effectiveness of JUVÉDERM VOLLURE™ XC based on the number and percent of responders on the NLFSS (defined as NLFs demonstrating ≥ 1-point improvement from baseline). Secondary endpoints included analysis at Month 12 of the number and percent of responders on the NLFSS and subject assessment of facial appearance using the Appraisal of Nasolabial Folds module of the FACE-Q questionnaire.

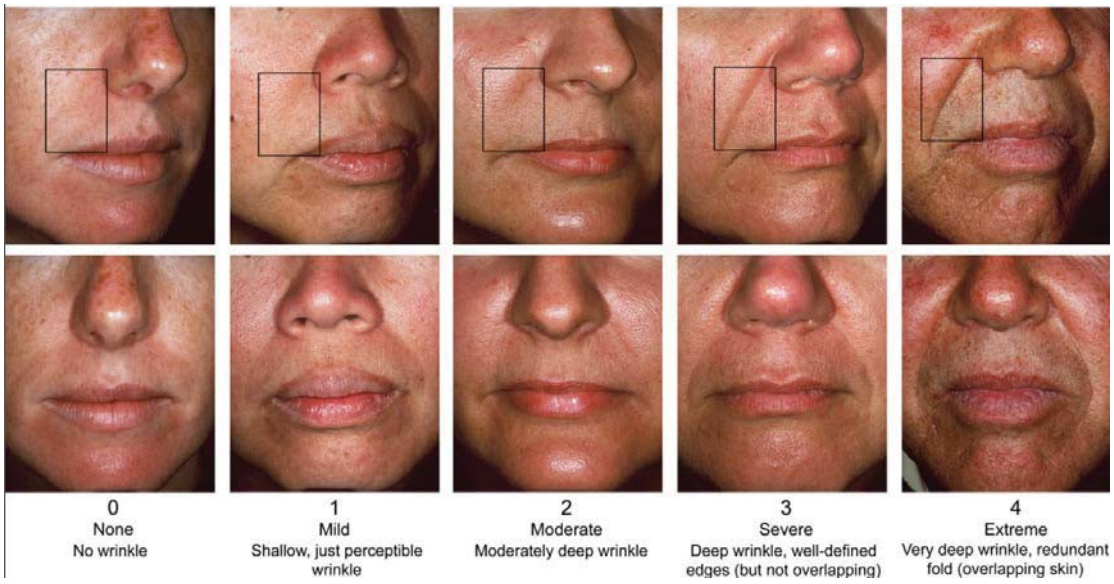
With regard to success/failure criteria of the study, the effectiveness of JUVÉDERM VOLLURE™ XC was demonstrated as non-inferior to control if the lower limit of the 95% confidence interval for the difference in mean change in NLFSS from baseline to month 6 (JUVÉDERM VOLLURE™ XC minus control) was above the

pre-specified non-inferiority margin of -0.5. The effectiveness of JUVÉDERM VOLLURE™ XC was also demonstrated if the responder rate for JUVÉDERM VOLLURE™ XC at Month 6 was statistically greater than 50% based on a 1-sided exact binomial test at 5% level.

Table 3: Allergan 5-point photonumeric Nasolabial Fold Severity Scale

Score	Severity	Description
0	None	No wrinkle
1	Mild	Shallow, just perceptible wrinkle
2	Moderate	Moderately deep wrinkle
3	Severe	Deep wrinkle, well-defined edges (but not overlapping)
4	Extreme	Very deep wrinkle, redundant fold (overlapping skin)

Figure 1: Allergan 5-point photonumeric Nasolabial Fold Severity Scale



B. Accountability of PMA Cohort

The subject disposition is depicted in Table 4 and Figure 2. A total of 126 subjects were enrolled in the study. After enrollment, 3 subjects (2.4%) were screen failures, resulting in 123 (97.6%) subjects randomized and treated, who compose the modified intent-to-treat (mITT) and safety populations. Of the 123 mITT subjects, the primary effectiveness of the product was assessed in 117 (95%) subjects at 6 months post treatment. Within the mITT population, 4 subjects discontinued prior to completing the extended follow-up period leaving 119/123 (96.7%) that completed the extended follow-up.

During the extended follow-up period, asymmetry correction with JUVÉDERM VOLLURE™ XC was administered at months 9, 12, or 15 to a total of 45 subjects (36.6%).

At the end of the extended follow-up period (*i.e.* Month 12, 15 or 18 depending on subject eligibility for repeat treatment), 119 subjects were offered a repeat treatment; 34 (27.6%) subjects discontinued due to not electing to receive repeat treatment and 85 (69.1%) subjects received repeat treatment. One subject discontinued after receiving repeat treatment resulting in a total of 95.9% (118/123) of the treated subjects that either completed the study or completed the extended follow-up period after initial treatment.

The majority of subjects (87.2%, 34/39) who discontinued early exited the study because they refused repeat treatment. The most common rationale provided by the subjects (17 subjects) for refusing repeat treatment was satisfaction with their results.

Review of baseline demographics, adverse events, and device effectiveness data indicate that the loss of subjects did not appear to introduce bias in the assessment of device safety and performance.

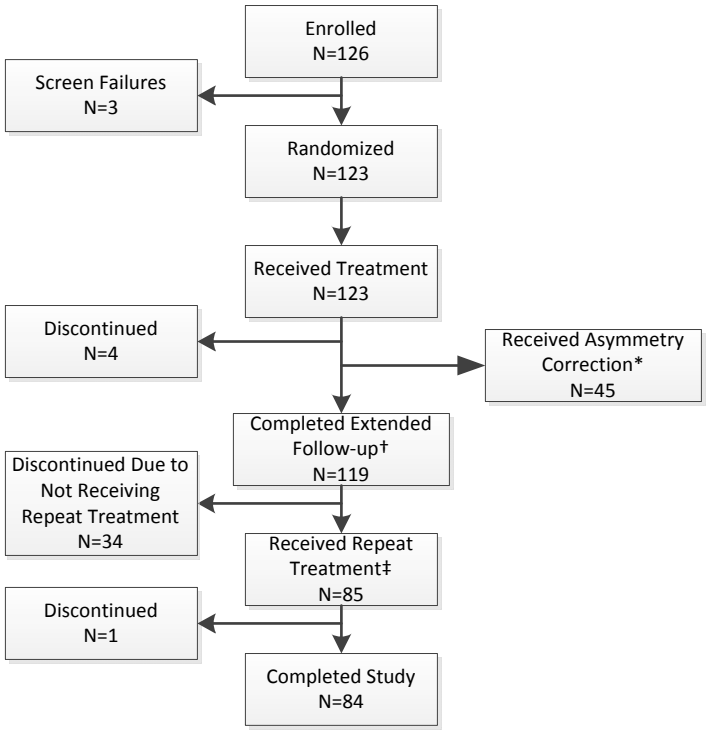
Table 4: Subject Disposition

	Total
Enrolled[a]	**126**
Screen Failures	3
Randomized	**123**
Safety Population[b]	**123**
mITT Population[c]	**123**
Received Asymmetry Correction[d]	45
Discontinued Before Repeat Treatment	4
Completed Month 6 Visit	117
Completed Extended Follow-up[e]	119
Repeat Treatment	
Discontinued Due to Not Receiving Repeat Treatment	34
Received Repeat Treatment[f]	85
Discontinued After Repeat Treatment	1
Completed Study[g]	84
Per-Protocol Population[h]	**114**

[a] The enrolled population consists of all subjects who signed the consent form.
[b] The safety population consists of all subjects who received at least 1 study treatment.
[c] The modified intent-to-treat (mITT) population consists of all subjects who were randomized and received at least 1 study treatment.
[d] Asymmetry correction offered at Months 9, 12, or 15
[e] Includes visits after initial/touch-up treatment prior to repeat treatment. Two subjects from this group missed the 6 month visit, but remained in the study.
[f] Repeat treatment offered at Months 12, 15, or 18

[g] A completed subject received (at a minimum) an initial treatment and a repeat treatment, was never withdrawn from participation, and was reported as having completed the study by the principal investigator on the electronic case report form.
[h] The per-protocol population consists of all mITT subjects who provided primary effectiveness assessment data at Month 6 and did not have any significant protocol deviations that affected the primary effectiveness endpoint.

Figure 2: Subject Disposition Flowchart



* Asymmetry correction offered at Months 9, 12, or 15
† Includes visits after initial/touch-up treatment prior to repeat treatment
‡ Repeat treatment offered at Months 12, 15, or 18

C. Study Population Demographics and Baseline Parameters

Subject demographics and pretreatment characteristics of the JUVÉDERM VOLLURE™ XC and control groups are presented in Table 5.

Table 5: Subject Demographics and Pretreatment Characteristics (N = 123*)

	JUVÉDERM VOLLURE™ XC	Control
	(N = 123) % (n/N)	
Gender		
Female	95.1% (117/123)	
Male	4.9% (6/123)	
Age		
Median	54	
Range	33-83	
Race		
Caucasian	74.0% (91/123)	
African-American	21.1% (26/123)	
Asian	2.4% (3/123)	
American Indian or Alaska Native	1.6% (2/123)	
Other	0.8% (1/123)	
Ethnicity		
Not Hispanic or Latino	76.4% (94/123)	
Hispanic or Latino	23.6% (29/123)	
Fitzpatrick Skin Type		
I	11.4% (14/123)	
II	22.0% (27/123)	
III	25.2% (31/123)	
IV	16.3% (20/123)	
V	14.6% (18/123)	
VI	10.6% (13/123)	
Baseline Nasolabial Fold Severity Scale (NLFSS) Score		
Extreme	0% (0/123)	0% (0/123)
Severe	61.0% (75/123)	61.8% (76/123)
Moderate	39.0% (48/123)	38.2% (47/123)
Mild	0% (0/123)	0% (0/123)
None	0% (0/123)	0% (0/123)

*Information based on the 123 mITT subjects

The median volume for initial and touch-up treatments combined was 1.7 mL (range 0.1 to 3.0 mL) for both JUVÉDERM VOLLURE™ XC and control. After the initial/touch-up treatments, 45 subjects received an additional injection of JUVÉDERM VOLLURE™ XC for asymmetry correction. The median volume for asymmetry correction was 0.5 mL (range 0.0 to 1.0 mL) in the NLF originally treated with JUVÉDERM VOLLURE™ XC, and 0.7 mL (range 0.3 to 1.5 mL) in the NLF originally treated with the control. After the month 12 follow-up, 85 subjects received a repeat treatment with JUVÉDERM VOLLURE™ XC in one or both of their NLFs. The median volume for repeat treatment with was 0.6 mL (range 0.0 to 1.6 mL).

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 123 patients. The side effects reported by the subjects in the study are presented below in Tables 6 to 8. Adverse effects reported by study investigators are presented in Tables 9 to 13.

Injection Site Responses

Injection site responses (ISRs) were assessed by a subject safety diary for 30 days after initial treatment, touch-up treatment (if performed), asymmetry correction (if performed), and repeat treatment. The severity and duration of all ISRs reported by > 5% of subjects who completed post-treatment diary forms after initial treatment are summarized in Table 6 and Table 7, respectively. Table 8 shows the severity and duration of all ISRs after asymmetry correction/repeat treatment with Juvéderm VOLLURE™ XC reported by > 5% of subjects in the NLF originally treated with Juvéderm VOLLURE™ XC.

Subjects reported at least 1 ISR (95.1%, 116/122 after initial treatment and 79.1%, 72/91 after asymmetry correction/repeat treatment) in most NLFs randomized for treatment with JUVÉDERM VOLLURE™ XC. The most frequently reported ISRs after initial treatment and asymmetry correction/repeat treatment with JUVÉDERM VOLLURE™ XC were firmness [88.5% (108/122) and 69.2% (63/91)], swelling [86.1% (105/122) and 67.0% (61/91)], and tenderness [84.4% (103/122) and 64.8% (59/91)]. Other common ISRs after initial treatment were lumps/bumps [82.0% (100/122) and 58.2% (53/91)], redness [73.8% (90/122) and 62.6% (57/91)], and pain [72.1% (88/122) and 52.7% (48/91)]. As seen in Table 6 and Table 8, subjects reported the severity of their individual ISRs as mild, moderate, or severe in the NLFs treated with JUVÉDERM VOLLURE™ XC after initial treatment and asymmetry correction/repeat treatment.

Most of the individual ISRs lasted less than 1 week after initial treatment, asymmetry correction, and repeat treatment, but some of the ISRs lasted between 8-30 days. The most common ISRs that lasted for 8-30 days after initial treatment were: firmness (42.6%, 46/108), lumps/bumps (36.0%, 36/100), and discoloration (24.2%, 8/33).

For most of the individual ISR types, subjects reported significantly fewer severe ISRs for JUVÉDERM VOLLURE™ XC than for the control product. The incidence of ISRs reported after the asymmetry correction/repeat treatment (79.1%, 72/91) was generally lower than that reported after initial treatment (95.1%, 116/122) with JUVÉDERM VOLLURE™ XC. The severity and duration of the reported ISRs were generally similar among the initial and asymmetry correction/repeat treatments.

Table 6: Severity of Injection Site Responses after Initial Treatment[a] Occurring in > 5% of Treated Subjects

Injection Site Response	JUVÉDERM VOLLURE™ XC				Control			
	Incidence (n/N[b])	Severity[c]			Incidence (n/N[a])	Severity[c]		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Firmness	88.5% (108/122)	30.6% (33/108)	50.0% (54/108)	19.4% (21/108)	92.6% (113/122)	14.2% (16/113)	43.4% (49/113)	42.5% (48/113)
Swelling	86.1% (105/122)	42.9% (45/105)	40.0% (42/105)	17.1% (18/105)	92.6% (113/122)	17.7% (20/113)	38.9% (44/113)	43.4% (49/113)
Tenderness to Touch	84.4% (103/122)	52.4% (54/103)	31.1% (32/103)	16.5% (17/103)	94.3% (115/122)	28.7% (33/115)	37.4% (43/115)	33.9% (39/115)
Lumps/Bumps	82.0% (100/122)	47.0% (47/100)	39.0% (39/100)	14.0% (14/100)	90.2% (110/122)	27.3% (30/110)	33.6% (37/110)	39.1% (43/110)
Redness	73.8% (90/122)	43.3% (39/90)	41.1% (37/90)	15.6% (14/90)	86.9% (106/122)	34.0% (36/106)	44.3% (47/106)	21.7% (23/106)
Pain After Injection	72.1% (88/122)	51.1% (45/88)	33.0% (29/88)	15.9% (14/88)	79.5% (97/122)	32.0% (31/97)	35.1% (34/97)	33.0% (32/97)
Bruising	56.6% (69/122)	43.5% (30/69)	31.9% (22/69)	24.6% (17/69)	59.0% (72/122)	30.6% (22/72)	38.9% (28/72)	30.6% (22/72)
Itching	31.1% (38/122)	73.7% (28/38)	7.9% (3/38)	18.4% (7/38)	45.1% (55/122)	61.8% (34/55)	23.6% (13/55)	14.5% (8/55)
Discoloration	27.0% (33/122)	54.5% (18/33)	30.3% (10/33)	15.2% (5/33)	29.5% (36/122)	44.4% (16/36)	36.1% (13/36)	19.4% (7/36)

[a] Does not include data after touch-up treatment

[b] N denotes the number of mITT subjects who recorded in the diaries after initial treatment

[c] Maximum severity reported in the diary. Denominator for percentages by severity is the number of subjects with corresponding ISR

Table 7: Duration of Injection Site Responses after Initial Treatment[a] Occurring in > 5% of Treated Subjects

Injection Site Response	JUVÉDERM VOLLURE™ XC					Control				
	Incidence (n/N[b])	Duration[c]				Incidence (n/N[a])	Duration[c]			
		1-3 Days	4-7 Days	8-14 Days	15-30 Days		1-3 Days	4-7 Days	8-14 Days	15-30 Days
Firmness	88.5% (108/122)	29.6% (32/108)	27.8% (30/108)	20.4% (22/108)	22.2% (24/108)	92.6% (113/122)	21.2% (24/113)	30.1% (34/113)	23.0% (26/113)	25.7% (29/113)
Swelling	86.1% (105/122)	55.2% (58/105)	23.8% (25/105)	19.0% (20/105)	1.9% (2/105)	92.6% (113/122)	39.8% (45/113)	34.5% (39/113)	18.6% (21/113)	7.1% (8/113)
Tenderness to Touch	84.4% (103/122)	62.1% (64/103)	23.3% (24/103)	10.7% (11/103)	3.9% (4/103)	94.3% (115/122)	45.2% (52/115)	33.9% (39/115)	15.7% (18/115)	5.2% (6/115)
Lumps/Bumps	82.0% (100/122)	40.0% (40/100)	24.0% (24/100)	19.0% (19/100)	17.0% (17/100)	90.2% (110/122)	32.7% (36/110)	26.4% (29/110)	17.3% (19/110)	23.6% (26/110)
Redness	73.8% (90/122)	58.9% (53/90)	26.7% (24/90)	10.0% (9/90)	4.4% (4/90)	86.9% (106/122)	57.5% (61/106)	28.3% (30/106)	9.4% (10/106)	4.7% (5/106)
Pain After Injection	72.1% (88/122)	80.7% (71/88)	8.0% (7/88)	10.2% (9/88)	1.1% (1/88)	79.5% (97/122)	71.1% (69/97)	19.6% (19/97)	6.2% (6/97)	3.1% (3/97)
Bruising	56.6% (69/122)	55.1% (38/69)	31.9% (22/69)	8.7% (6/69)	4.3% (3/69)	59.0% (72/122)	47.2% (34/72)	34.7% (25/72)	9.7% (7/72)	8.3% (6/72)
Itching	31.1% (38/122)	71.1% (27/38)	15.8% (6/38)	10.5% (4/38)	2.6% (1/38)	45.1% (55/122)	63.6% (35/55)	21.8% (12/55)	10.9% (6/55)	3.6% (2/55)
Discoloration	27.0% (33/122)	72.7% (24/33)	3.0% (1/33)	15.2% (5/33)	9.1% (3/33)	29.5% (36/122)	61.1% (22/36)	19.4% (7/36)	13.9% (5/36)	5.6% (2/36)

[a] Does not include data after touch-up treatment

[b] N denotes the number of mITT subjects who recorded in the diaries after initial treatment

[c] Maximum reported successive occurrence of an ISR. Denominator for percentages by duration is the number of subjects with corresponding ISR

Table 8: Severity and Duration of Injection Site Responses after Asymmetry Correction /Repeat Treatment Occurring in >5% of Subjects in the JUVÉDERM VOLLURE™ XC Group

Injection Site Response	Incidence (n/N[a])	Severity[b]			Duration[c]			
		Mild	Moderate	Severe	1-3 Days	4-7 Days	8-14 Days	15-30 Days
Firmness	69.2% (63/91)	22.2% (14/63)	47.6% (30/63)	30.2% (19/63)	11.1% (7/63)	28.6% (18/63)	22.2% (14/63)	38.1% (24/63)
Swelling	67.0% (61/91)	36.1% (22/61)	47.5% (29/61)	16.4% (10/61)	29.5% (18/61)	41.0% (28/61)	13.1% (8/61)	16.4% (10/61)
Tenderness to touch	64.8% (59/91)	39.0% (23/59)	44.1% (26/59)	16.9% (10/59)	40.7% (24/59)	33.9% (20/59)	10.2% (6/59)	15.3% (9/59)
Redness	62.6% (57/91)	45.6% (26/57)	42.1% (24/57)	12.3% (7/57)	42.1% (24/57)	33.3% (19/57)	10.5% (6/57)	14.0% (8/57)
Lumps/Bumps	58.2% (53/91)	28.3% (15/53)	52.8% (28/53)	18.9% (10/53)	20.8% (11/53)	34.0% (18/53)	3.8% (2/53)	41.5% (22/53)
Pain after injection	52.7% (48/91)	39.6% (19/48)	50.0% (24/48)	10.4% (5/48)	54.2% (26/48)	29.2% (14/48)	6.3% (3/48)	10.4% (5/48)
Bruising	44.0% (40/91)	45.0% (18/40)	32.5% (13/40)	22.5% (9/40)	22.5% (9/40)	45.0% (18/40)	15.0% (6/40)	17.5% (7/40)
Itching	20.9% (19/91)	68.4% (13/19)	26.3% (5/19)	5.3% (1/19)	63.2% (12/19)	15.8% (3/19)	10.5% (2/19)	10.5% (2/19)
Discoloration	20.9% (19/91)	63.2% (12/19)	31.6% (6/19)	5.3% (1/19)	47.4% (9/19)	21.1% (4/19)	5.3% (1/19)	26.3% (5/19)

[a] N denotes the number of subjects who recorded in the diaries after asymmetry correction/repeat treatment (offered at months 9, 12, 15, or 18) with JUVÉDERM VOLLURE™ XC group
[b] Maximum severity reported in the diary. Denominator for percentages by severity is the number of subjects with corresponding ISR
[c] Maximum reported successive occurrence of an ISR. Denominator for percentages by duration is the number of subjects with corresponding ISR

Adverse Events

Adverse events (AEs) were reported by Evaluating Investigators throughout the study. ISRs that lasted beyond the 30-day diaries were also considered as AEs. After initial/touch-up treatment, 23.6% (29/123) of the NLFs treated with JUVÉDERM VOLLURE™ XC and 22.0% (27/123) of the NLFs treated with the control experienced at least 1 adverse event, and most were considered treatment-related. A summary of AEs at NLFs after initial/touch-up treatment is provided in Table 9. The severity and duration of AEs reported in >5% of NLFs after initial/touch-up treatment are listed in Tables 10, 11, and 12.

After initial/touch-up treatment of NLFs treated with JUVÉDERM VOLLURE™ XC, 29 subjects experienced 55 AEs that were considered severe (21.8% [12/55]), moderate (29.1% [16/55]) and mild (49.1% [27/55]). Similar results were observed at the NLFs treated with the control: 27 subjects experienced 53 AEs that were considered severe (30.2% [16/53]), moderate (15.1% [8/53]), and mild (54.7% [29/53]). Regardless of treatment group, the AEs at the NLFs generally required no action for treatments with

JUVÉDERM VOLLURE™ XC (94.5% [52/55]) and the control (90.6% [48/53]) and resolved without sequelae (98.2% [54/55] for JUVÉDERM VOLLURE™ XC and 100% (53/53) for control). Two AEs not at the NLFs were reported to be related to treatment: a subject was reported to have a broken eye vessel of mild severity which resolved without requiring treatment and another subject was reported to experience a severe headache which resolved after the subject took oral acetaminophen/hydrocodone and oral prednisone.

For NLFs treated with JUVÉDERM VOLLURE™ XC, 5.5% (3/55) of AEs resolved within 7 days, 12.7% (7/55) resolved between 8-14 days, 12.7% (7/55) resolved between 15-30 days, and 30.9% (17/55) resolved between 31-60 days (Table 9). AEs with a duration of more than 60 days included: injection site induration (9.1%, 5/55), injection site mass (7.3%, 4/55), injection site swelling (7.3%, 4/55), injection site erythema (3.6%, 2/55), injection site discoloration, injection site pain, injection site pruritus, and skin mass (each 1.8%, 1/55). There was one ongoing event of mild injection site swelling at a JUVÉDERM VOLLURE™ XC-treated NLF. This AE did not require any treatment, and no further information was available on the resolution of this AE.

For NLFs treated with control, 18.9% (10/53) resolved within 7 days, 3.8% (2/53) resolved between 8-14 days, 15.1% (8/53) resolved between 15-30 days, and 18.9% (10/53) resolved between 31-60 days (Table 9). AEs with a duration of more than 60 days included: injection site induration (9.4%, 5/53), injection site mass (11.3%, 6/53), injection site swelling (11.3%, 6/53), injection site erythema (3.8%, 2/53), injection site discoloration (3.8%, 2/53), injection site pain (1.9%, 1/53), and injection site pruritus (1.9%, 1/53).

Table 9: Summary of Treatment-Related Adverse Events after Initial/Touch-up Treatment (N = 123)

	JUVÉDERM VOLLURE™ XC		Control	
	NLFs (N = 123) n (%)	Events (N = 55) n (%)	NLFs (N = 123) n (%)	Events (N = 53) n (%)
Overall	29 (23.6)	55 (100.0)	27 (22.0)	53 (100.0)
Duration				
≤ 7 Days	3 (2.4)	3 (5.5)	10 (8.1)	10 (18.9)
8 - 14 Days	6 (4.9)	7 (12.7)	2 (1.6)	2 (3.8)
15 - 30 Days	5 (4.1)	7 (12.7)	5 (4.1)	8 (15.1)
31 - 60 Days	12 (9.8)	17 (30.9)	7 (5.7)	10 (18.9)
> 60 Days	13 (10.6)	20 (36.4)	14 (11.4)	23 (43.4)
Severity				
Mild	14 (11.4)	27 (49.1)	14 (11.4)	29 (54.7)

Moderate	9 (7.3)	16 (29.1)	3 (2.4)	8 (15.1)
Severe	6 (4.9)	12 (21.8)	10 (8.1)	16 (30.2)
Causality				
Treatment-related	29 (23.6)	55 (100.0)	26 (21.1)	52 (98.1)
Not treatment-related	0	0	1 (0.8)	1 (1.9)
Outcome				
Resolved without sequelae	29 (23.6)	54 (98.2)	27 (22.0)	53 (100.0)
Ongoing	1 (0.8)	1 (1.8)	0	0
Death	0	0	0	0
Treatment Required				
No	26 (21.1)	51 (92.7)	22 (17.9)	48 (90.6)
Medication	3 (2.4)	3 (5.5)	5 (4.1)	5 (9.4)
Procedure	1 (0.8)	1 (1.8)	0	0

Table 10: AEs After Initial/Touch-up Treatment Occurring in > 5% of NLFs (N = 123)

Adverse Event	JUVÉDERM VOLLURE™ XC	Control
	% (n/N)	% (n/N)
Injection Site Induration	10.6% (13/123)	8.9% (11/123)
Injection Site Mass	8.1% (10/123)	7.3% (9/123)
Injection Site Swelling	7.3% (9/123)	9.8% (12/123)

Table 11: Severity of Adverse Events after Initial/Touch-Up Treatment Occurring in > 5% of Subjects

	JUVÉDERM VOLLURE™ XC				Control			
Adverse Event	Events % (n/N[a])	Mild % (n/N[b])	Moderate % (n/N[b])	Severe % (n/N[b])	Events % (n/N[a])	Mild % (n/N[b])	Moderate % (n/N[b])	Severe % (n/N[b])
Injection Site Induration	25.5% (14/55)	42.9% (6/14)	28.6% (4/14)	28.6% (4/14)	22.6% (12/53)	50.0% (6/12)	16.7% (2/12)	33.3% (4/12)
Injection Site Mass	20.0% (11/55)	54.5% (6/11)	9.1% (1/11)	36.4% (4/11)	18.9% (10/53)	60.0% (6/10)	0% (0/10)	40.0% (4/10)
Injection Site Swelling	18.2% (10/55)	60.0% (6/10)	20.0% (2/10)	20.0% (2/10)	24.5% (13/53)	46.2% (6/13)	23.1% (3/13)	30.8% (4/13)

[a] Denominator is the number of adverse events reported after initial/touch-up treatment of the 123 mITT subjects.
[b] Denominator for percentages by severity is the number of subjects with corresponding treatment-related adverse events.

Table 12: Duration of Adverse Events after Initial Treatment/Touch-Up Occurring in > 5% of Subjects

Adverse Event	JUVÉDERM VOLLURE™ XC						Control					
	Events % (n/N[a])	≤ 7 Days[b] %	8-14 Days[b] %	15-30 Days[b] %	31-60 Days[b] %	> 60 Days[b] %	Events % (n/N[a])	≤ 7 Days[b] %	8-14 Days[b] %	15-30 Days[b] %	31-60 Days[b] %	> 60 Days[b] %
Injection Site Induration	25.5% (14/55)	0% (0/14)	0% (0/14)	7.1% (1/14)	57.1% (8/14)	35.7% (5/14)	22.6% (12/53)	8.3% (1/12)	0% (0/12)	8.3% (1/12)	41.7% (5/12)	41.7% (5/12)
Injection Site Mass	20.0% (11/55)	0% (0/11)	0% (0/11)	9.1% (1/11)	45.5% (5/11)	45.5% (5/11)	18.9% (10/53)	0% (0/10)	0% (0/10)	20.0% (2/10)	20.0% (2/10)	60.0% (6/10)
Injection Site Swelling[c]	18.2% (10/55)	10.0% (1/10)	20.0% (2/10)	0% (0/10)	20.0% (2/10)	40.0% (4/10)	24.5% (13/53)	23.1% (3/13)	7.7% (1/13)	15.4% (2/13)	7.7% (1/13)	46.2% (6/13)

[a] Denominator is the number of adverse events reported after initial/touch-up treatment of the 123 mITT subjects.
[a] The percentages by duration are based on the number of subjects with the corresponding treatment-related adverse event.
[c] There was one ongoing AE of mild injection site swelling.

There were 20 AEs after initial/touch-up treatment with JUVÉDERM VOLLURE™ XC that occurred in ≤5% of NLFs, including injection site bruising, erythema, pain, discoloration, pruritus, reaction, facial asymmetry, and needle track marks.

After initial/touch-up treatment with JUVÉDERM VOLLURE™ XC, 3 AEs occurred weeks to months after the injection procedure. These events included mild swelling, moderate skin mass, and severe itching. Swelling was treated with fexofenadine hydrochloride and ibuprofen, the skin mass was treated with triamcinolone, and the itching did not require any treatment. All 3 events resolved without sequelae.

After asymmetry correction/repeat treatment with JUVÉDERM VOLLURE™ XC, 20 AEs were reported in 10.8% (10/93) of NLFs initially treated with JUVÉDERM VOLLURE™ XC and 31 AEs in 15.1% (14/93) of NLFs initially treated with the control. A summary of AEs at the NLFs after asymmetry correction/repeat treatment with JUVÉDERM VOLLURE™ XC by randomization group is provided in Table 13. The AEs were similar between the two groups after asymmetry correction/repeat treatment. Similar types of AEs were reported after asymmetry correction/repeat treatment, but with a lower incidence rate compared to the initial/touch-up treatment.

AEs reported in >5% of NLFs after asymmetry correction/repeat treatment are listed in Table 14. AEs at the NLFs after asymmetry correction/repeat treatment occurring in ≤5% of subjects included injection site pain, discoloration, erythema, swelling, exfoliation, and pruritus.

There were no treatment-related serious adverse events or unanticipated adverse device effects reported in the study.

Table 13: Summary of Treatment-Related Adverse Events after Asymmetry Correction/Repeat Treatment (Offered at Months 9, 12, 15, or 18)

	JUVÉDERM VOLLURE™ XC		Control[a]	
	NLFs (N = 93) n (%)	Events (N = 20) n (%)	NLFs (N = 93) n (%)	Events (N = 31) n (%)
Overall	10 (10.8)	20 (100.0)	14 (15.1)	31 (100.0)
Duration				
≤ 7 Days	0	0	3 (3.2)	3 (9.7)
8 - 14 Days	0	0	0	0
15 - 30 Days	2 (2.2)	3 (15.0)	2 (2.2)	2 (6.5)
31-60 Days	5 (5.4)	7 (35.0)	3 (3.2)	8 (25.8)
> 60 Days	3 (3.2)	3 (15.0)	5 (5.4)	12 (38.7)
Severity				
Mild	2 (2.2)	4 (20.0)	7 (7.5)	12 (38.7)
Moderate	4 (4.3)	9 (45.0)	3 (3.2)	7 (22.6)
Severe	4 (4.3)	7 (35.0)	4 (4.3)	12 (38.7)
Causality				
Treatment-related	9 (9.7)	19 (95.0)	12 (12.9)	29 (93.5)
Not treatment-related	1 (1.1)	1 (5)	2 (2.2)	2 (6.5)
Outcome				
Resolved without sequelae	7 (7.5)	13 (65)	12 (12.9)	25 (80.6)
Ongoing[b]	4 (4.3)	7 (35.0)	4 (4.3)	6 (19.4)
Death	0	0	0	0
Treatment Required				
No	10 (10.8)	20 (100.0)	13 (13.9)	30 (96.8)
Medication	0	0	0	0
Procedure	0	0	1 (1.1)	1 (3.2)

[a] Denotes NLFs which received initial treatment with the control but asymmetry correction/repeat treatment with JUVÉDERM VOLLURE™ XC

[b] At the end of the study, 4 NLFs originally treated with JUVÉDERM VOLLURE XC had 7 ongoing AEs, which included injection site induration, mass, swelling, bruising, and discoloration. These AEs did not require treatment. No additional information is available on the resolution of these AEs.

Table 14: AEs after Asymmetry Correction/Repeat Treatment Occurring in > 5% of NLFs

Adverse Event	JUVÉDERM VOLLURE™ XC	Control*
	% (n/N)	% (n/N)
Injection Site Induration	7.5% (7/93)	6.5% (6/93)
Injection Site Mass	3.2% (3/93)	7.5% (7/93)
Injection Site Bruising	1.1% (1/93)	5.4% (5/93)

* Denotes NLFs which received initial treatment with the control but asymmetry correction/repeat treatment with JUVÉDERM VOLLURE™ XC

Subgroup analyses

Subgroup analyses of ISRs and device-related AEs at the NLFs (Table 15) were performed by Fitzpatrick skin phototype (grouped as I/II, III/IV, and V/VI), volume injected (≤ or > the median injected volume), and investigational site. The overall ISR incidence results suggested that skin phototype has no impact on the safety of the product, but, for pain after injection, Fitzpatrick skin phototypes I/II reported a significantly lower incidence rate as compared to Fitzpatrick skin phototypes III/IV and V/VI in NLFs treated with JUVÉDERM VOLLURE™ XC. In NLFs treated with the control, Fitzpatrick skin phototypes I/II reported a significantly lower incidence rate for pain after injection and itching as compared to Fitzpatrick skin phototypes III/IV and V/VI. Analyses of ISR incidence rates by injected volume and investigational site showed similar results between the compared subgroups.

For AEs at the NLFs after initial/touch-up treatment, no significant differences in overall AE incidence rates were observed between the treatment and control groups for Fitzpatrick skin phototype subgroups. Overall AE rates were lower for NLFs treated with less than or equal to the median injection volume compared with NLFs treated with greater than the median injection volume for both treatment and control groups. The percentages of NLFs for which AEs were reported after initial/touch-up treatment varied across the study sites, from 5.0% (1/20) at one site to 40.0% (8/20) at another site.

Other safety analyses

Other safety assessments in the study included:

- Subject assessment of procedural pain (pain during injection) for the right and left NLF on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable). The mean score following initial treatment was 2.3 points for both products.
- Subject responses to the 17 items on the Recovery Early Symptoms module of the FACE-Q questionnaire were assessed for each NLF. For both JUVÉDERM VOLLURE™ XC and control, a majority of subjects reported feeling not at all or a little bothered by the 17 symptoms on Day 3. The proportion of subjects reporting the least symptoms (not at all or a little bothered) was ≥ 15 percentage points higher for JUVÉDERM VOLLURE™ XC compared with the control for 4 of the 17 questions: discomfort (90.1% JUVÉDERM VOLLURE™ XC vs 74.4% control), tenderness (88.4% vs 69.4%), feeling sore (89.3% vs 71.1%), and swelling (84.9% vs 60.0%). The magnitude of difference in percentage of the Recovery Early Symptoms module that is considered clinically significant has not been established.

Table 15: Incidence of Device-Related Adverse Events after Initial/Touch-up Treatment by Subgroup

	JUVÉDERM VOLLURE™ XC NLFs % (n/N)	Control NLFs % (n/N)
Fitzpatrick Skin Phototype[a]		
I/II	22.0% (9/41)	14.6% (6/41)
III/IV	29.4% (15/51)	23.5% (12/51)
V/VI	16.1% (5/31)	29.0% (9/31)
Median Volume[b] (1.7 mL for JUVÉDERM VOLLURE™ XC and 1.65 mL for the control)		
≤ Median Volume	15.9% (10/63)	11.3% (7/62)
> Median Volume	31.7% (19/60)	32.8% (20/61)
Investigational Site[c]		
Site 10001	22.7% (5/22)	31.8% (7/22)
Site 10002	23.8% (5/21)	19.0% (4/21)
Site 10003	5.0% (1/20)	5.0% (1/20)
Site 10004	40.0% (8/20)	40.0% (8/20)
Site 10005	20.0% (4/20)	10.0% (2/20)
Site 10006	30.0% (6/20)	25.0% (5/20)

[a] Denominators based on number of mITT subjects within each subgroup, as outlined in Table 5.
[b] Denominators based on the number of mITT subjects (N = 123) receiving ≤ or > the median volume.
[c] Denominators based on the number of mITT subjects (N = 123) at each investigational site.

2. Effectiveness Results

The analysis of primary effectiveness was based on the 117 evaluable patients at the 6-month time point. Key effectiveness outcomes are presented in Tables 16 and 17.

Co-Primary Endpoints

The co-primary effectiveness endpoints of this study were met (Table 16 and Table 17). The mean NLFSS score at baseline for the subjects was 2.6, and the score improved by 1.4 for JUVÉDERM VOLLURE™ XC and 1.3 for the control as assessed by the Evaluating Investigator at Month 6. The observed responder rate (percentage of NLFs with 1-point improvement on the NLFSS scale since baseline) at Month 6 for the NLFs treated with JUVÉDERM VOLLURE™ XC was 93.2% (109/117), which was greater than 50% ($p<0.001$).

Table 16: Co-Primary Effectiveness Endpoint: Change from Baseline to Month 6 in NLF Severity (Modified Intent-to-treat Population)

	JUVÉDERM VOLLURETM XC (N = 123)	Control (N = 123)	P-value	Difference (Lower Limit of 1-Sided 95% Confidence Interval)
N	117	117		
Mean	1.4	1.3	0.097	0.1
SD	0.67	0.72		(-0.02)
Median	1.0	1.0		
Min, Max	0, 3	0, 3		
95% CI	(1.28, 1.52)	(1.17, 1.44)		

Table 17: Co-Primary Effectiveness Endpoint: Responder Rate at Month 6

	JUVÉDERM VOLLURE™ XC (N = 123)
Responder rate	109/117 (93.2%)
95% CI	(87.0%, 97.0%)
P-value	< 0.001

Throughout the follow-up period, JUVÉDERM VOLLURE™ XC continued to provide a clinically significant improvement in NLF severity (≥ 1-point mean improvement on the NLFSS), with a majority of subjects treated with JUVÉDERM VOLLURE™ XC demonstrating improvement through 18 months (Table 18).

Table 18: Effectiveness Results Beyond Primary Endpoint (>6 Months)

Time point	**JUVÉDERM VOLLURE™ XC**
	% (n/N*)
9 Months	84.6% (99/117)
12 Months	57.5% (65/113)
15 Months	61.7% (50/81)
18 Months	59.4% (57/96)

*N denotes the number of NLFs assessed within the analysis window. NLFs that received asymmetry correction or repeat treatment were considered non-responders at subsequent time points.

Secondary Endpoints

Secondary measures included observed responder rate at Month 12 based on Evaluating Investigators' assessment of subjects' NLF severity using NLFSS and subject assessment of facial appearance using the Appraisal of Nasolabial Folds module of the FACE-Q questionnaire.

Clinically meaningful improvement (i.e. ≥ 1-point mean improvement on the NLFSS) in NLF severity through 12 months was demonstrated, with 57.5%

(65/113) of the NLFs treated with JUVÉDERM VOLLURE™ XC still showing ≥ 1-point improvement in NLF severity from baseline.

At 6 months, 95.7% (112/117) of subjects reported improvement in their JUVÉDERM VOLLURE™ XC-treated NLFs, based on the *Appraisal of Nasolabial Folds* module of the FACE-Q questionnaire, with a mean score increasing from 32.1 at baseline to 72.8. At 18 months, 61.8% (55/89) of subjects reported improvement in their JUVÉDERM VOLLURE™ XC-treated NLFs over baseline, with a mean score of 50.3. These mean scores indicate that subjects treated with JUVÉDERM VOLLURE™ XC reported being less bothered with the depth of their NLF, with the look of their NLF when relaxed and when smiling, with how old their NLF makes them look, and with how their NLF looks compared with other people their age, when compared with their pretreatment assessments of these questions in the FACE-Q module.

Other Effectiveness Assessments

Additional effectiveness measures included:

- Subject satisfaction with treatment for the right and left NLF on an 11-point scale, where 0 is completely dissatisfied and 10 is completely satisfied
- Subject evaluation of NLF preference for overall treatment outcome (Right, Left, or No preference)

Subjects reported a high level of satisfaction with JUVÉDERM VOLLURE™ XC-treated NLFs throughout the study, with 75.2% (91/121) of the subjects very satisfied (score of 7-10 on a 0 to 10 scale) with JUVÉDERM VOLLURE™ XC at Day 3 compared to 61.2% (74/121) for the control. A majority of the subjects (67.8%, 40/59) continued to be very satisfied with the results of the JUVÉDERM VOLLURE™ XC-treated NLF at the Month 18 visit. At Month 1 after repeat treatment with JUVÉDERM VOLLURE™ XC, 94.0% (79/84) of subjects were very satisfied with the results of the NLFs that were originally treated with JUVÉDERM VOLLURE™ XC.

Of the subjects who expressed a preference for overall treatment outcome between the 2 NLFs on the blinded subject evaluation of NLF preference questionnaire, more preferred JUVÉDERM VOLLURE™ XC at every visit through Month 18.

3. Subgroup Analyses

   Subgroup analyses of the primary effectiveness endpoint were performed by baseline NLFSS score, Fitzpatrick skin phototype (I/II, III/IV, and V/VI), volume injected (≤ or > the median total injected volume), and investigational site. Similar results were observed in the JUVÉDERM VOLLURE™ XC and control groups within each subgroup (Table 19).

Table 19: Subgroup Effectiveness Analyses of Mean (± Standard Deviation) Change from Baseline in NLFSS at Month 6 (mITT Population)

	JUVÉDERM VOLLURE™ XC		Control	
Subgroup	**Subgroup N**	**Result**	**Subgroup N**	**Result**
Baseline NLFSS score				
Moderate	45	1.1 (0.50)	44	1.0 (0.71)
Severe	72	1.6 (0.68)	73	1.5 (0.69)
Volume injected at initial and touch-up treatment combined				
≤ median	60	1.3 (0.63)	59	1.4 (0.72)
> median	57	1.5 (0.71)	58	1.2 (0.73)
Fitzpatrick skin phototype				
I/II	40	1.4 (0.68)	40	1.4 (0.74)
III/IV	49	1.4 (0.64)	49	1.3 (0.73)
V/VI	28	1.4 (0.73)	28	1.3 (0.72)
Investigational site				
10001	22	1.2 (0.66)	22	1.1 (0.83)
10002	18	1.0 (0.49)	18	0.9 (0.42)
10003	19	1.4 (0.83)	19	1.3 (0.95)
10004	20	1.6 (0.60)	20	1.5 (0.60)
10005	19	1.7 (0.67)	19	1.5 (0.70)
10006	19	1.6 (0.51)	19	1.5 (0.61)

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

5. Treatment Characteristics
   Multiple injection techniques were used to achieve optimal results, with the most common being serial puncture, tunneling, and fanning. Most of the injections were in the intradermal plane. Subjects received a median volume of 1.7 mL for both JUVÉDERM VOLLURE™ XC and control for initial and touch-up treatments combined. The median volume for repeat treatment with JUVÉDERM VOLLURE™ XC was 0.6 mL in the NLF originally treated with JUVÉDERM VOLLURE™ XC.

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 pivotal clinical study included 13 investigators. One clinical investigator had a financial arrangement with Allergan to be disclosed under 21 CFR 54.2 (b), not

affecting the outcome of the S17L-001 clinical study. None of the other clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

European Clinical Study

In this prospective, randomized, multicenter study, 70 subjects were treated with JUVÉDERM VOLLURE™ XC for correction of moderate to severe nasolabial folds. Enrolled subjects exhibited moderate to severe NLF severity scores on the validated 5-point photonumeric NLFSS, the same scale as that used for the US pivotal study discussed above. Subjects received treatment with JUVÉDERM VOLLURE™ XC in both NLFs and received a touch-up treatment at Day 14 if optimal correction was not achieved after the initial treatment. Subjects were followed for up to 12 months after the last treatment, returning to the investigational site at regular intervals (Months 1, 9, and 12) throughout the study for safety and effectiveness evaluations. All subjects in the study had the option to receive a repeat treatment at the Month 12 visit; the subjects were followed for up to 1 month after the repeat treatment.

Subjects were monitored throughout the study for any adverse events (AEs) by the investigator. AEs that were related to the study device/procedure were recorded. Expected AEs, listed in the directions for use (DFU), were only reported as AEs if the events were assessed to be more severe or more prolonged than routinely observed. After repeat treatment, subjects completed a 30-day safety diary to record the severity and duration of any injection site responses (ISRs).

No device/procedure-related AE was observed after the initial/touch-up treatment. Forty- one subjects completed the 30-day safety diary after repeat treatment. The most frequently reported ISRs in the diaries were swelling 87.8% (36/41), firmness 80.5% (33/41), and tenderness to touch 78.0% (32/41). Severity of ISRs was mild, moderate, or severe and most resolved within 3 days (Table 20). One device/procedure-related AE was observed after repeat treatment. The subject experienced redness around the mouth, swelling, and lower sensibility requiring treatment with corticoid ointment; the AE symptoms resolved in 51 days.

Table 20: Injection Site Responses by Severity and Duration after Repeat Treatment with JUVÉDERM VOLLURE™ XC Occurring in > 5% of Subjects

ISR	Incidence (n/N[a])	Severity[b]			Duration[c]			
		Mild	Moderate	Severe	1-3 Days	4-7 Days	8-14 Days	15-30 Days
Swelling	87.8% (36/41)	55.6% (20/36)	27.8% (10/36)	16.7% (6/36)	86.1% (31/36)	11.1% (4/36)	2.8% (1/36)	0% (0/36)
Firmness	80.5% (33/41)	57.6% (19/33)	30.3% (10/33)	12.1% (4/33)	75.8% (25/33)	15.2% (5/33)	9.1% (3/33)	0% (0/33)
Tenderness	78.0% (32/41)	65.6% (21/32)	25.0% (8/32)	9.4% (3/32)	87.5% (28/32)	12.5% (4/32)	0% (0/32)	0% (0/32)
Redness	58.5% (24/41)	66.7% (16/24)	29.2% (7/24)	4.2% (1/24)	83.3% (20/24)	16.7% (4/24)	0% (0/24)	0% (0/24)
Lumps/Bumps	56.1% (23/41)	47.8% (11/23)	30.4% (7/23)	21.7% (5/23)	56.5% (13/23)	26.1% (6/23)	8.7% (2/23)	8.7% (2/23)
Bruising	53.7% (22/41)	40.9% (9/22)	31.8% (7/22)	27.3% (6/22)	40.9% (9/22)	50.0% (11/22)	9.1% (2/22)	0% (0/22)
Pain	51.2% (21/41)	76.2% (16/21)	14.3% (3/21)	9.5% (2/21)	95.2% (20/21)	4.8% (1/21)	0% (0/21)	0% (0/21)
Itching	12.2% (5/41)	60.0% (3/5)	40.0% (2/5)	0% (0/5)	80.0% (4/5)	0% (0/5)	0% (0/5)	20.0% (1/5)
Discoloration	4.9% (2/41)	100% (2/2)	0% (0/2)	0% (0/2)	50.0% (1/2)	0% (0/2)	0% (0/2)	50.0% (1/2)

[a] N denotes the number of subjects who recorded in the diaries
[b] Maximum severity reported in the diary. Denominator for percentages by severity is the number of subjects with corresponding ISR
[c] Maximum reported successive occurrence of an ISR. Denominator for percentages by duration is the number of subjects with corresponding ISR

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of the U.S. pivotal study. These submitted data provided a reasonable assurance that the device is effective for correction of moderate to severe facial wrinkles and folds. The specific conclusions are:

- Both co-primary endpoints were met: JUVÉDERM VOLLURE™ XC was shown to be non-inferior to the control in NLF improvement, and the NLFSS responder

rate for JUVÉDERM VOLLURE™ XC was statistically greater than 50% at Month 6 after treatment.

- Improvements in NLF severity lasted through 18 months with JUVÉDERM VOLLURE™ XC.
- Subjects reported significant improvement in their NLFs on the Appraisal of Nasolabial Folds module of the FACE-Q questionnaire through 18 months with JUVÉDERM VOLLURE™ XC.
- Of the subjects who expressed a preference for overall treatment outcome between the 2 NLFs, more than 50% preferred JUVÉDERM VOLLURE™ XC on the blinded subject evaluation of NLF preference questionnaire at every visit through 18 months.
- Two-thirds of subjects were still very satisfied at 18 months after JUVÉDERM VOLLURE™ XC treatment.
- Investigators reported that JUVÉDERM VOLLURE™ XC was easier to inject and easier to mold than the control.
- The typical total volume to achieve optimal correction of moderate to severe nasolabial folds was 1.7 mL per treatment site. To maintain optimal correction, approximately one-third of the volume per treatment site was needed at repeat treatment.
- More than 90% of subjects in the JUVÉDERM VOLLURE™ XC treatment group were very satisfied with their NLF at 1 month after repeat treatment.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in the clinical study conducted to support PMA approval as described above. The submitted data provide a reasonable assurance of safety of JUVÉDERM VOLLURE™ XC for correction of moderate to severe facial wrinkles and folds. The specific conclusions are:

- Most subjects [95.1% (116/122) after initial treatment and 79.1% (72/91) after asymmetry correction/repeat treatment] treated with JUVÉDERM VOLLURE™ XC reported at least 1 ISR. The most frequently reported ISRs after initial treatment and asymmetry correction/repeat treatment were firmness [88.5% (108/122) and 69.2% (63/91)], swelling [86.1% (105/122) and 67.0% (61/91)], and tenderness [84.4% (103/122) and 64.8% (59/91)]. Other common ISRs after initial treatment were lumps/bumps [82.0% (100/122) and 58.2% (53/91)], redness [73.8% (90/122) and 62.6% (57/91)], and pain [72.1% (88/122) and 52.7% (48/91)]. Subjects reported the severity of their individual ISRs after initial treatment as mild, moderate, or severe. Individual ISRs generally resolved within 1 week after injection. The overall rates of ISRs and AEs were similar for JUVÉDERM VOLLURE™ XC and the control.
- The most frequent AEs after initial/touch-up treatment with JUVÉDERM VOLLURE™ XC were mild injection site induration, injection site mass, and injection site swelling.
- Severe AEs after initial/touch-up treatment included: injection site induration (3.3%, 4/123), injection site mass (1.6%, 2/123), injection site swelling (1.6%,

2/123), injection site pruritus (1.6%, 2/123), injection site erythema (0.8%, 1/123), and injection site bruising (0.8%, 1/123).

- AEs after initial/touch-up treatment with a duration of more than 60 days included: injection site induration (4.1%, 5/123), injection site mass (3.3%, 4/123), injection site swelling (3.3%, 4/123), injection site erythema (1.6%, 2/123), injection site discoloration, injection site pain, injection site pruritus, and skin mass (each 0.8%, 1/123).
- Subjects reported being less bothered by symptoms such as discomfort, tenderness, feeling sore, and swelling with JUVÉDERM VOLLURE™ XC treatment than with control.
- Individual ISRs were less frequent after asymmetry correction/repeat treatment than after initial treatment.
- There were no treatment-related deaths or serious AEs.

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 study was a prospective, controlled study using a validated scale and blinded, live evaluations. The study investigated the safety and effectiveness of JUVÉDERM VOLLURE™ XC for injection into mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as NLFs). The co-primary effectiveness endpoints were the analysis of non-inferiority of JUVÉDERM VOLLURE™ XC relative to the control in terms of change from baseline to month 6 in mean NLF severity and responder rate (percentage of NLFs with ≥ 1-point improvement since baseline) at Month 6 being statistically greater than 50% based on Evaluating Investigator assessments using the 5-point Nasolabial Fold Severity Scale (NLFSS). The data are considered to be as robust as possible for an aesthetic endpoint. The co-primary endpoints of the study were met. Summary of effectiveness conclusions is provided above.

Additional factors to be considered in determining probable risks and benefits of JUVÉDERM VOLLURE™ XC injection included: A majority of the subjects (95.1%, 116/122 after initial treatment and 79.1%, 72/91 after asymmetry correction/repeat treatment) experienced an injection site response in their JUVÉDERM VOLLURE™ XC-treated NLF. However, a majority of the injection site responses were mild or moderate in severity and resolved within a week. Summary of safety conclusions is provided above.

The probable benefits outweigh the probable risks, as determined by the robustness of the effectiveness results, the lack of any long term sequelae, and the high subject satisfaction. 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 device use.

Patient Perspectives

Patient perspectives considered during the review included:

- Despite the frequency of ISRs, 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, 82.1% (96/117) of subjects treated with JUVÉDERM VOLLURE™ XC reported being very satisfied with their treatment.
- At 6 months, 95.7% (112/117) of subjects reported improvement in their JUVÉDERM VOLLURE™ XC-treated NLFs, based on the Appraisal of Nasolabial Folds module of the FACE-Q questionnaire, with a mean score increasing from 32.1 at baseline to 72.8. The mean score was 50.3 in the JUVÉDERM VOLLURE™ XC group at 18 months.
- A total of 85 subjects received repeat treatment in the study. The most common reason given for refusal of repeat treatment was satisfaction with current results.

In conclusion, given the available information above, the data support the use of JUVÉDERM VOLLURE™ XC for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as NLFs), and the probable benefits outweigh the probable risks.

D. Overall Conclusions

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

XIV. CDRH DECISION

CDRH issued an approval order on March 17, 2017.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: None