SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: JUVÉDERM VOLUMA™ XC

Device Procode: LMH

Applicant's Name and Address: Allergan
71 S. Los Carneros Rd.
Goleta, CA 93117

Date of Panel Recommendation: May 2, 2013

Premarket Approval Application (PMA) Number: P110033

Date of FDA Notice of Approval: October 22, 2013

Expedited*:* not applicable

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

JUVÉDERM VOLUMA™ XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized gel implant. The gel consists of crosslinked hyaluronic

acid (HA) produced by *Streptococcus equi* bacteria, formulated to a concentration of 20 mg/mL and 0.3% w/w lidocaine in a physiologic buffer. The HA gel is made primarily of crosslinked HA with some remaining lightly crosslinked and uncrosslinked HA. Each box of JUVÉDERM VOLUMA™ XC contains 2 pre-filled disposable syringes each containing 1 mL of hyaluronic gel implant. Each syringe is fitted with a luer lock adaptor, a plunger rod, a rubber stopper tip cap, and a finger grip. Each syringe is labeled with the name of the product, batch number, and expiration date. JUVÉDERM VOLUMA™ XC is delivered by an injection into the mid-face to restore volume.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of age-related volume deficit in the mid-face: surgical implants, autologous fat injections, face-lift surgery, off-label use of soft tissue fillers. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

JUVÉDERM VOLUMA™ XC in a 2 mL glass syringe received the CE Mark in December, 2009 in accordance with the Medical Device Directive (93/42/EEC). The 1 mL plastic syringe configuration received the CE Mark in December, 2010 and the formulation, branded as JUVÉDERM VOLUMA™ with lidocaine in foreign markets, is commercially available in multiple countries globally, including the European Union, Australia, Canada, Brazil, Russia, Ukraine, Mexico, Hong Kong, Korea, Taiwan, and Singapore. JUVÉDERM VOLUMA™ 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, as reported in the clinical study include tenderness, swelling, firmness (induration), lumps/bumps (mass), bruising, pain, redness, discoloration, and itching. Other adverse effects reported less frequently (in less than 5% of study subjects) include injection site reaction, injection site hypertrophy, nodule, inflammation, injection site anesthesia, injection site dryness, injection site erosion, contusion, and syncope.

Post-Market Surveillance

Potential adverse effects associated with the use of the device known from published or unpublished sources outside of the PMA clinical studies are discussed below.

JUVÉDERM VOLUMA™ without lidocaine has been marketed outside the US since 2005, and JUVÉDERM VOLUMA™ with lidocaine has been marketed outside the US since 2009. As of December 31, 2012, the following AEs were received from post-market surveillance for JUVÉDERM VOLUMA™ with and without lidocaine with a

frequency ≥ 5 and were not observed in the clinical study; this includes reports received globally from all sources including scientific journals and voluntary reports. All AEs obtained through post-market surveillance are listed in order of number of reports received: inflammatory reaction, lack of correction, infection, migration, granuloma, allergic reaction, abscess, necrosis, numbness, and vision abnormalities. Reported treatments include: antibiotics, steroids, hyaluronidase, anti-inflammatories, anti-histamines, aspiration, radio frequency therapy, laser treatment, ice, massage, warm compress, analgesics, anti-viral, ultrasound, excision, drainage, and surgery.

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

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Physical and Chemical Characterization

JUVÉDERM VOLUMA™ XC has been extensively tested and characterized through physical and chemical analyses (Table 1). Degradation assays were also performed to ensure that JUVÉDERM VOLUMA™ XC naturally degrades in the body during its clinical lifespan. Based on the chemical and physical testing, there was sufficient data to demonstrate the JUVÉDERM VOLUMA™ XC product were appropriate for evaluation in clinical studies as dermal fillers.

Table 1: Summary of key bench testing

Test	Description	Result
pH	Testing ensures pH meets specifications	passed
Hyaluronic acid concentration	Testing ensures hyaluronic acid concentration meets specifications	passed
Lidocaine concentration	Testing ensures lidocaine concentration meets specifications	passed
Extrusion force	Testing ensures extrusion force meets specifications	passed
Residual cross linker	Testing ensures residual	passed

	cross-linker meets specifications	
Rheological properties	Testing ensures rheological properties meets specifications	passed
Free Hyaluronic acid	Testing ensures free hyaluronic acid meets specifications	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 24 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, chemical, lidocaine HCl potency, and lidocaine-related degradants. Conformance with all specifications was confirmed.

Biocompatibility Testing

JUVÉDERM VOLUMA™ 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), ISO10993 and FDA's Blue Book memorandum G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." The preclinical testing provides a reasonable assurance that the JUVÉDERM VOLUMA™ XC product will be biocompatible when used as intended, and that all known toxicity risks have been adequately mitigated.

Carcinogenicity risks: The excess cancer risks for JUVÉDERM VOLUMA™ 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 VOLUMA™ XC are in the same range of acceptable cancer risks as other previously approved dermal filler products, and are supported by the negative genotoxicity results obtained in an appropriate panel of genotoxicity studies and residual BDDE specifications.

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

TEST	RESULT
Cytotoxicity	Negligible cytotoxicity
Dermal Sensitization	Non-sensitizing
Intracutaneous Reactivity including Histological Assessment	Irritant at 3-days Non-irritant at 14-days
Acute Systemic Toxicity	Not systemically toxic
Subchronic Toxicity 13-weeks	Non-toxic
Genotoxicity (bacterial reverse mutation assay (Ames), chromosomal aberration assay, and mouse peripheral blood micronucleus assay.	Non-mutagenic and non-genotoxic
Muscle Implantation (4 and 13 week)	Non-irritant
Pyrogenicity	Non-pyrogenic
Bacterial Endotoxin	Meets specification

B. Additional Studies

Twenty-one biopsies from subdermal depot injections in either the forearm or behind the ear were evaluated by a board-certified dermatopathologist. At least one biopsy was obtained from each of the nine study follow-up visit time points. The dermis and subcutaneous tissue were evaluated for fibrosis, inflammation, and implant material. The implant material stained blue in the hematoxylin and eosin sections and was positive for colloidal iron. These qualities were utilized to determine the presence or absence of implant material. The implant was absent in two-thirds of the samples

(66.7%, 14/21). Lymphocytes and histiocytes were observed in all of the samples. Scant or mild inflammation was present in nearly all samples (95.2%, 20/21), and mild to moderate fibrosis was present in three-fourths of the samples (76.2%, 16/21).

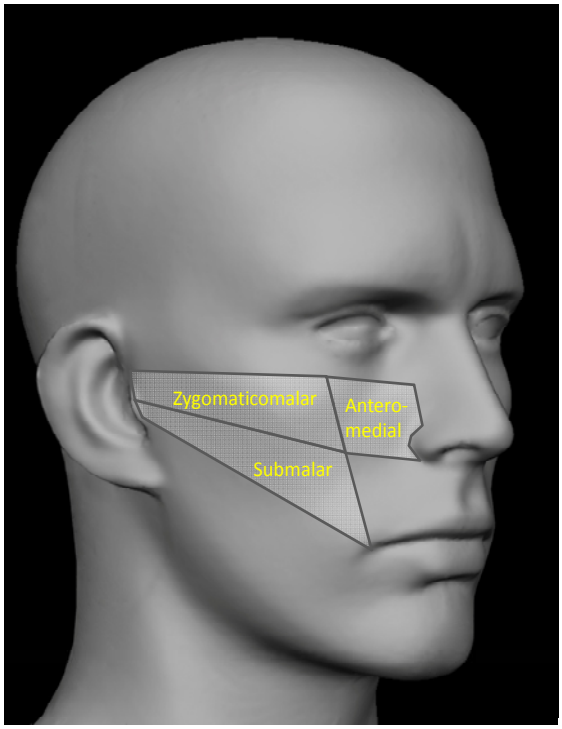
X. SUMMARY OF PRIMARY CLINICAL STUDY

A. Study Design

Patients were treated between August 26, 2009 and June 17, 2010. The database for this PMA reflected data collected through June 17, 2013 and included 345 patients. There were 15 investigational sites.

The study was a multi-center, single-blind, randomized, no-treatment controlled pivotal clinical study conducted to evaluate the safety and effectiveness of JUVÉDERM VOLUMA™ XC for cheek augmentation to correct age-related volume deficit in the mid-face. Subjects were randomized to treatment or no-treatment control in a 5.3:1 ratio. Treatment group subjects underwent treatment with JUVÉDERM VOLUMA™ XC at the outset of the study. Up to 2 treatments approximately 1 month apart (initial treatment and up to 1 touch-up treatment) were allowed. The Treating Investigator (TI) determined the appropriate volume of JUVÉDERM VOLUMA™ XC to be injected in the 3 sub-regions of the mid-face: zygomaticomalar region, anteromedial cheek region, and submalar region, which are depicted in Figure 1. Treatment of the nasolabial folds and periorbital region was prohibited. The no-treatment control subjects had treatment delayed for 6 months.

Figure 1. Mid-Face Regions Treated



Treated subjects returned for routine safety visits with the TI at 1, 3, and 6 months after the last treatment during the primary safety and effectiveness phase. All subjects returned for effectiveness follow-up visits with 2 independent Evaluating Investigators (EI) at 1, 3, and 6 months after the last treatment. The control group were no-treatment control subjects that had treatment delayed for 6 months.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the VOLUMA-002 study was limited to patients who met the following inclusion criteria:

   - Male or female, 35-65 years of age
   - Signed the IRB-approved Informed Consent form and the HIPAA form prior to any study-related procedures performed
   - Had zygomaticomalar region, anteromedial cheek, submalar region, and/or overall mid-facial volume deficit assessed by the TI as grade 3, 4, or 5 on the photometric Mid-Face Volume Deficit Scale (MFVDS)
   - Desired cheek augmentation to correct age-related volume deficit in the mid-face, i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region, as recommended by the TI
   - Accepted the obligation not to receive any other facial procedures or treatments affecting facial volume deficit at any time during the study
   - Was able to follow study instructions and likely to complete all required visits, as assessed by the TI

- If the subject was a female of childbearing potential (sexually active and not sterile nor postmenopausal for at least 1 year), had a urine pregnancy test evaluated as negative within 10 days prior to enrollment, had used contraception for at least 30 days prior to enrollment, and agreed to use a reliable method of contraception for the duration of the study

Patients were <u>not</u> permitted to enroll in the VOLUMA-002 study if they met any of the following exclusion criteria:

- Had received (or was planning to receive) anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (oral/injectable corticosteroids or non-steroid anti-inflammatory drugs, e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., Vitamin E, garlic, gingko), from 10 days pre- to 3 days post-injection [Study device injections were delayed as necessary to accommodate this 10-day wash-out period.]
- Had undergone cosmetic facial plastic surgery (with the exception of rhinoplasty more than 2 years prior to enrollment), tissue grafting, or tissue augmentation with silicone, fat, or other permanent, or semi-permanent dermal fillers or was planning to undergo any of these procedures at any time during the study
- Had undergone temporary facial dermal filler injections with HA-based fillers within 12 months, porcine-based collagen fillers within 24 months, or neuromodulator injections, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) within 6 months prior to entry in the study or was planning to undergo any of these procedures at any time during the study
- Had begun use of any new over-the-counter or prescription, oral or topical, anti-wrinkle products in the treatment area within 90 days prior to enrollment or was planning to begin use of such products at any time during the study. [NOTE: Use of sunscreens and continued therapy with some topical treatments (e.g., alpha hydroxyl acids, glycolic acids, retinol, or retinoic acids) was allowed if the regimen was established ≥ 90 days prior to enrollment]
- Had very thin skin in the mid-facial region, tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, i.e., significant convexity or projection from the infraorbital fat pads
- Had mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or HIV-related disease
- Had a history of anaphylaxis, multiple severe allergies, atopy, or allergy to lidocaine (or any amide-based anesthetic), HA products, or *Streptococcal* protein, or had plans to undergo desensitization therapy during the term of the study
- Had noticeable acne scarring, an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound or had undergone radiation treatment in the area to be treated

- Was pregnant, lactating, or planning to become pregnant at any time during the study
- Had received any investigational product within 30 days prior to study enrollment or was planning to participate in another investigation during the course of this study
- Was an employee (or a relative of an employee) of the EIs, TI, Sponsor, or representative of the Sponsor
- Had a condition or was in a situation that, in the TI's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

2. Follow-up Schedule

In the randomized, controlled clinical trial to evaluate the safety and effectiveness of JUVÉDERM VOLUMA™ XC, subjects were treated with JUVÉDERM VOLUMA™ XC in the mid-face (zygomaticomalar region, anteromedial cheek, and/or submalar region, see Figure 1) during the primary phase of the study. Touch-up treatments occurred approximately 30 days after initial injection. After the 6-month blinded "no treatment" control period, control subjects were allowed to receive treatment.

All treated subjects returned for routine safety visits with the Treating Investigator at 1, 3, and 6 months after the last treatment during the primary safety and effectiveness phase.

During the extended follow-up period, subjects returned for safety and effectiveness evaluations at quarterly intervals up to 24 months or until any visit at or after Month 12 when the average of the EIs' live assessments of the MFVDS returned to, or was worse than, the pre-treatment level. Control subjects followed a similar effectiveness evaluation schedule through Month 6 but were not treated and not required to undergo safety evaluations or self-assessments of effectiveness. After Month 6, control subjects received treatment and followed the same treatment and follow-up schedule as the treatment group. An optional repeat treatment was offered to all subjects after completion of the extended follow-up period, with continued follow-up through 12 months after repeat treatment.

Pre- and post-procedure, the objective parameters measured during the study included Evaluating Investigator's (EI) assessment of subjects' overall mid-face volume deficit on the validated 6-point photometric MFVDS as well as volume deficit for each of the 3 facial sub-regions. EIs also assessed subjects' improvement on the 5-point photometric Nasolabial Fold Photo Severity Scale (NLFSS) and the 11-point Other Aesthetic Features of the Mid-Face (OAFM) questionnaire. Subjects performed self-assessments on MFVDS, NLFSS, treatment goal achievement, satisfaction with mid-facial regions, self-perception

of age, look and feel of the face, and satisfaction with facial appearance. Further, 3D facial photography was performed, and volume changes were calculated. Post-procedure, both EIs and subjects assessed improvement using the 5-point Global Aesthetic Improvement Scale (GAIS).

3. Clinical Endpoints

With regards to safety, preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments in each region of the mid-face. Subjects were instructed to rate each treatment site response listed on the diary as "Mild (barely noticeable)," "Moderate (uncomfortable)," "Severe (severe discomfort)," or "None." Treatment site responses reported in subject diaries that were ongoing at the end of the 30 day-diary were considered adverse events (AEs). AEs were also reported by the TI at all follow-up visits where applicable.

With regards to effectiveness, the primary effectiveness measure was the average of the 2 blinded EIs' live assessments of the subject's overall mid-face volume deficit on the validated 6-point photometric MFVDS.

Secondary measures included the level of improvement on the GAIS and MFVDS assessments for each region of the mid-face as assessed by the blinded EIs.

With regard to success/failure criteria, a responder was defined as a subject with ≥1 grade improvement in the average MFVDS score since baseline. Effectiveness of JUVÉDERM VOLUMA™ XC was demonstrated if at least 70% of subjects treated with JUVÉDERM VOLUMA™ XC were responders at Month 6, and if the responder rate for the treatment group was statistically superior to that of the no-treatment control group at Month 6.

B. Accountability of PMA Cohort

At the time of database lock, a total of 345 subjects were enrolled in the study: 16 were screen failures primarily due to ineligibility, 30 were run-in subjects, and 299 were randomized per protocol, 17 of whom discontinued prior to treatment. Of the remaining 282 subjects, 235 were randomized to the treatment group, and 47 were randomized to the control group. Three-fourths (74.0%, 174/235) of the treatment group completed the extended follow-up period. Sixty-one subjects (26.0%) discontinued the study primarily due to loss to follow-up (34.4%, 21/61) or withdrawal of consent (36.1%, 22/61). At baseline, the majority of subjects in the treatment group (93.6%, 220/235) and all subjects in the control group (100%, 46/46) had moderate, significant, or severe volume deficit (encompassing scores of 2.5 through 5 on the MFVDS scale) in their mid-face according to the average of EI assessments; 32 control subjects were treated in the study after completion of 6 months of follow-up with no treatment.

C. Study Population Demographics and Baseline Parameters

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

Table 3: Demographics and Pretreatment Characteristics (N = 282)

		Treatment Group	Control Group
		(N = 235)	(N = 47)
Characteristic		% (n)	% (N)
Gender			
	Female	80% (189)	79% (37)
	Male	20% (46)	21% (10)
Age (years)			
	Median	56	55
	Range (Min, Max)	(35-65)	(36-65)
Race			
	Caucasian	58% (137)	60% (28)
	Hispanic	15% (35)	9% (4)
	African-American	19% (44)	26% (12)
	Asian	4% (9)	6% (3)
	Other	4% (10)	0% (0)
Fitzpatrick Skin Type			
	I	3% (6)	4% (2)
	II	26% (62)	21% (10)
	III	29% (67)	23% (11)
	IV	18% (43)	30% (14)
	V	19% (44)	19% (9)
	VI	6% (13)	2% (1)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of subjects available at each followup time point (1, 3, and 6 months after the last treatment during the primary safety and effectiveness phase and at quarterly intervals up to 24 months). The key safety outcomes for this study are presented below in Tables 4-5. Adverse effects are reported in Table 6. Preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments in each region of the mid-face. Of the 270 subjects who underwent treatment (from both the treatment and control groups), 265 completed the diary forms. A subset of subjects has also

undergone repeat treatment following completion of the extended follow-up phase of the study, with 120 subjects completing diary forms after repeat treatment. Subjects were instructed to rate each treatment site response listed on the diary as "Mild (barely noticeable)," "Moderate (uncomfortable)," "Severe (severe discomfort)," or "None." After initial treatment with JUVÉDERM VOLUMA™ XC, 98% of subjects reported experiencing a local treatment site response. Subjects rated treatment site responses as predominantly moderate (59.2%) in severity with a duration of 2-4 weeks. For those treatment site responses evaluated as moderate or severe, the median duration as moderate or severe was 2 days, and the median time to complete resolution was 6 days. Based on available data from 120 subjects, the severity of CTRs following repeat treatment is similar, with a reduced incidence and duration compared to initial treatment.

Table 4: Treatment Site Responses by Maximum Severity Occurring in > 5% of Subjects after Initial Treatment (N = 265)

		Severity[a]		
Treatment Site Responses	**Total**	**Mild**	**Moderate**	**Severe**
	% (n/N[b])	**% (n/N)**	**% (n/N)**	**% (n/N)**
Any Treatment Site Response	98.1% (260/265)	21.5% (56/260)	59.2% (154/260)	19.2% (50/260)
Tenderness	92.1% (244/265)	46.3% (113/244)	50.0% (122/244)	3.7% (9/244)
Swelling	85.7% (227/265)	46.7% (106/227)	43.6% (99/227)	9.7% (22/227)
Firmness	82.3% (218/265)	37.6% (82/218)	54.6% (119/218)	7.8% (17/218)
Lumps/Bumps	81.1% (215/265)	41.4% (89/215)	48.8% (105/215)	9.8% (21/215)
Bruising	77.7% (206/265)	37.4% (77/206)	51.5% (106/206)	11.2% (23/206)
Pain	66.4% (176/265)	59.1% (104/176)	38.6% (68/176)	2.3% (4/176)
Redness	66.0% (175/265)	60.0% (105/175)	36.0% (63/175)	4.0% (7/175)
Discoloration	41.1% (109/265)	62.4% (68/109)	27.5% (30/109)	10.1% (11/109)
Itching	38.5% (102/265)	70.6% (72/102)	18.6% (19/102)	10.8% (11/102)

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

Table 5: Duration of Treatment Site Responses after Initial Treatment (N = 265)

Treatment Site Response	Total	Duration[a]				
		1-3 Days	4-7 Days	8-14 Days	15-30 Days	>30 Days
	% (n/N[b])	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)
Any Treatment Site Response	98.1% (260/265)	8.1% (21/260)	22.7% (59/260)	24.6% (64/260)	24.6% (64/260)	20.0% (52/260)
Tenderness	92.1% (244/265)	29.9% (73/244)	30.7% (75/244)	27.9% (68/244)	8.6% (21/244)	2.9% (7/244)
Swelling	85.7% (227/265)	41.0% (93/227)	33.0% (75/227)	17.6% (40/227)	5.3% (12/227)	3.1% (7/227)
Firmness	82.3% (218/265)	26.6% (58/218)	29.8% (65/218)	20.2% (44/218)	11.0% (24/218)	12.4% (27/218)
Lumps/Bumps	81.1% (215/265)	21.4% (46/215)	22.3% (48/215)	22.3% (48/215)	18.1% (39/215)	15.8% (34/215)
Bruising	77.7% (206/265)	24.8% (51/206)	30.6% (63/206)	29.6% (61/206)	14.6% (30/206)	0.5% (1/206)
Pain	66.4% (176/265)	56.3% (99/176)	31.3% (55/176)	9.7% (17/176)	2.8% (5/176)	0% (0/176)
Redness	66.0% (175/265)	59.4% (104/175)	28.0% (49/175)	8.6% (15/175)	2.3% (4/175)	1.7% (3/175)
Discoloration	41.1% (109/265)	64.2% (70/109)	19.3% (21/109)	6.4% (7/109)	5.5% (6/109)	4.6% (5/109)
Itching	38.5% (102/265)	81.4% (83/102)	16.7% (17/102)	2.0% (2/102)	0% (0/102)	0% (0/102)

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

Treatment site responses reported by ≤ 5% of subjects included ache, acne, bulge, bumps, cheek larger upon waking up, dry patch, fine wrinkles, injection/needle marks, numbness, pigmentation from treatment, puffiness, rash, scratch near injection point, soreness, tightness, and yellowness

Adverse effects that occurred in the PMA clinical study:

Treatment site responses reported in subject diaries that lasted longer than 30 days were considered adverse events (AEs). AEs were also reported by the TI at all follow-up visits where applicable. Table 6 summarizes device- and injection-related AEs that occurred with a frequency of > 5%. These adverse events were seen more frequently in subjects that received injection volumes greater than 9 mL, and in older subjects (> 60 years). Rarely, adverse events occurred weeks to months after the injection procedure.

Among the 270 treated subjects, 32.6% (88/270) experienced device- and injection-related AEs following initial and touch-up treatment, 99% (624/627) of which were reported at a treatment site. The treatment site AEs were evenly divided across the 3 mid-facial regions. Information on AEs following repeat treatment is being collected as part of the post-approval study.

Table 6: Device- and Injection-Related Adverse Events Reported by Treating Investigator and Subjects Occurring in > 1% of Treated Subjects (N = 270)

Adverse Event	Treated Subjects % (n/N)
Treatment site mass	18.9% (51/270)
Treatment site induration	14.1% (38/270)
Treatment site swelling	7.0% (19/270)
Treatment site pain	5.9% (16/270)
Treatment site hematoma	3.7% (10/270)
Treatment site discoloration	2.2% (6/270)
Treatment site erythema	1.9% (5/270)
Treatment site reaction	1.5% (4/270)

Device- and injection-related adverse events occurring in ≤ 1% of subjects included injection site hypertrophy (0.7%), nodule (0.7%), inflammation (0.4%), injection site anesthesia (0.4%), injection site dryness (0.4%), injection site

erosion (0.4%), mass (0.4%), contusion (0.4%) and syncope (0.4%).

Two subjects (0.7%; 2/270) reported 3 serious adverse events (SAEs) that were considered to be related to the device. Approximately 6 months after treatment, after being scratched near the treated area by a tree branch, one subject experienced inflammation under the left eye. The subject also experienced nodularity in the right cheek approximately 7 months after treatment. The second subject experienced lumps in the cheeks approximately 7 months after treatment. A couple of days before the onset, the subject experienced myofascial pain and body aches. Treatment of the SAEs included topical steroids, oral antibiotics, intralesional steroids, anti-inflammatory medication, and hyaluronidase. All events resolved.

2. Effectiveness Results

Primary effectiveness results: JUVÉDERM VOLUMA™ XC provided a clinically and statistically significant improvement in mid-face volume deficit compared to the no-treatment control group. Primary effectiveness was met in that significantly greater than 70% of subjects in the treatment group were responders (85.6% improved by ≥ 1 grade compared with their pre-treatment assessment, $p < 0.0001$ against the 70% responder rate threshold), and the responder rate for the treatment group was significantly greater ($p < 0.0001$) than the responder rate for the control group (a difference of 46.7%) at Month 6 (Table 7). JUVÉDERM VOLUMA™ XC was found to be effective in all Fitzpatrick skin phototypes, for males and females, across the studied age range. The median volume injected was 6.6mL.

Table 7: Effectiveness Summary Responder Rate at 6 Months Based on Evaluating Investigators' Assessments

	Responder Rate at Month 6	**p-value**
Treatment Group	85.6% (178/208)	<0.0001
Control Group[a]	38.9% (14/36)	
Difference in Responder Rates (Treatment rate - Control rate)	46.7%	<0.0001

[a] Includes 2 subjects who were treated in error

The treatment group's median MFVDS scores improved by 2 points during the primary follow-up period (Months 1, 3, and 6), whereas the control group's scores remained the same. During the extended follow-up period (Months 9-24), the median MFVDS score improvement of the treatment group reduced to 1.5 points.

The analysis of effectiveness was based on the 244 evaluable subjects at the 6-month time point.

Secondary effectiveness results: The GAIS responder rate for the treatment group was 82.2% (171/208) at Month 6, where the responder rate was the percent of subjects with a score of ≥ 1 (improved or much improved) on the GAIS for overall mid-face volume based on EIs' assessments. At Month 6 the MFVDS responder rate for each of the facial sub-regions was above 75%.

Extended follow-up: Table 8 shows the mean MFVDS scores during the extended follow-up period (Months 9-24). The mean improvement was clinically significant (≥ 1 point), with the majority of subjects demonstrating improvement.

- 86.6% (181/209) at Month 9
- 85.2% (172/203) at Month 12
- 71.5% (128/179) at Month 18
- 67.1% (112/167) at Month 24

Table 8: Mean MFVDS Scores Over 24 Months

Visit	N	Mean MFVDS Score	Mean Change since Baseline
Baseline	235	3.3	N/A
Month 9	209	1.7	1.6
Month 12	203	1.8	1.5
Month 18	179	2.1	1.3
Month 24	167	2.2	1.1

Subject Self-Assessments: Subjects performed numerous self-assessments, including satisfaction with facial appearance, self-perception of age, and NLF severity. At each time point more than three-fourths of the treatment group subjects demonstrated an improvement in the overall satisfaction with facial appearance since baseline. In addition, the majority of treatment group subjects perceived themselves as looking younger than perceived at baseline, from 76.4% at Month 1 to 55.4% at Month 24. Subjects, on average, reported themselves as looking approximately 5 years younger at Month 6 and 3 years younger at Month 24. Lastly, more than half (57%, 236/414) of the treatment group subjects at Month 6 observed a ≥ 1-point improvement in their NLFs.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender, race, age, Fitzpatrick skin phototype, baseline volume deficit, investigational site, plane of injection, injection technique, and injection volume. The subgroup analysis did not identify differences in the incidence of device-related AEs for the different planes of injection (subcutaneous or supraperiosteal), or injection techniques. There is a significant increase in the

incidence of device related AEs with increased injection volume (p=0.0117) and increased age (p=0.0173) based on the results of a multiple logistic regression of incidence of device-related AEs on baseline, demographic, and treatment-related covariates, with a correlation between injection volume and swelling and bruising.

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 15 Treating Investigators and 30 Evaluating Investigators. Among the 15 TIs and 30 EIs involved in the study, 36 have, by way of a signed Certification of Investigator Financial Interest Form, verified that they have no applicable financial arrangement with Allergan defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

The pivotal clinical study included 9 Investigators that have disclosable financial arrangements with Allergan disclosed under 21 CFR 54.2, not affecting the outcome of the JUVÉDERM VOLUMA™ XC clinical study. The nature of these disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) is described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 9
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Australian Clinical Study: An open label study was conducted in Australia to evaluate the safety and effectiveness of JUVÉDERM VOLUMA™ (without lidocaine) in subjects with moderate to significant mid-face volume deficit. This formulation is identical to JUVÉDERM VOLUMA™ XC (with Lidocaine) with regard to all product specifications, other than the 0.3% lidocaine.

103 subjects were treated with JUVÉDERM VOLUMA™ to treat age-related mid-face volume deficit. JUVÉDERM VOLUMA™ was delivered using either a cannula (53%) or

a needle (47%). Subjects attended follow-up visits at Weeks 4 (with optional touch-up), 8, 52, 78, and 104 from the initial treatment, with an optional retreatment at the Week 78 or 104 visits. The primary effectiveness measure was the improvement in facial fullness, using an unmasked MFVDS. Additional effectiveness measures included subject and Investigator assessments on the GAIS. The incidence and severity of AEs related to JUVÉDERM VOLUMA™ and its administration, as reported by the subject and as documented by the Investigator, were collected. After treatment with JUVÉDERM VOLUMA™, the most common AEs were bruising, swelling, pain/tenderness, and erythema. There were 14 severe AEs, which included bruising (7 events), swelling (5 events), and pain (2 events). Most events resolved spontaneously within 2 weeks. Of the 103 subjects enrolled, 84% had moderate or significant volume deficiency at baseline. At the first post-treatment evaluation (week 8), 96% were documented as MFVDS responders, with 98% and 100% graded as GAIS responders as assessed by the subjects and investigators, respectively. At week 78, 81.7% of subjects were still MFVDS responders, with 73.2% and 78.1% GAIS responders, respectively.

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

A. Panel Meeting Recommendation

At an advisory meeting held on May 2, 2013, the General and Plastic Surgery Devices Panel voted 7-0 that there is reasonable assurance that the device is safe, 7-0 that there is reasonable assurance that the device is effective, and 7-0 that the benefits of the device outweigh the risks in patients who meet the criteria in the proposed indication.

The Advisory Panel agreed the 6-month data supported product effectiveness. The Advisory Panel did not have a consensus opinion on the effectiveness data collected in the absence of a blinded control after the 6-month time point, but agreed the data supporting effectiveness after 6-months was less rigorous. The Advisory Panel recommended the labeling include language that states individual results may vary, and that the extended effectiveness results be presented in the labeling.

The Advisory Panel agreed with the Sponsor's proposed post-approval study to evaluate the safety of JUVÉDERM VOLUMA™ XC following repeat treatment.

The meeting transcript may be accessed at the following webpage:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/UCM354230.pdf

The FDA's Executive Summary may be accessed at the following webpage:
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/generalandplasticsurgerydevicespanel/ucm349459.pdf

B. FDA's Post-Panel Action

After the Panel meeting, FDA completed review of the product labeling and incorporated panel recommendations into the labeling for rare adverse events, vision abnormalities, and the relationship between dose, age and adverse events.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

JUVÉDERM VOLUMA™ XC met the pre-specified primary endpoint, and the secondary endpoints support product effectiveness. The balance of the data indicates that JUVÉDERM VOLUMA™ XC is effective in correcting volume deficit in the mid-face at the 6-month primary effectiveness time point.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the clinical studies conducted to support PMA approval as described above. The adverse effects of the device are based on data collected in the clinical studies conducted to support PMA approval as described above as well as evaluation of device use in the Post Market setting. The submitted data provided a reasonable assurance that the device is safe for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over the age of 21. The specific conclusions are:

- The most frequent CTRs reported by subjects were tenderness, swelling, and firmness. CTRs lasted 15-30 days in 24.6% of subjects, and 78.4% of CTRs were moderate to severe.

- Common treatment site responses continued in 20.0% of subjects beyond 30 days becoming classified as AEs, with the most frequent responses being injection site mass and induration.

- The incidence of CTRs decreased for subjects receiving touch-up and repeat treatments.

- There is a significant increase in the incidence of device related AEs with increased injection volume (p=0.0117) and increased age (p=0.0173) with a correlation between injection volume and swelling and bruising.

- Two subjects (0.7%; 2/270) reported 3 serious adverse events (SAEs) that were considered to be related to the device. Approximately 6 months after treatment, one subject experienced inflammation under the left eye. The subject also experienced nodularity in the right cheek approximately 7 months after treatment. The second subject experienced lumps in the cheeks approximately 7 months after treatment. Treatment of the SAEs included topical steroids, oral antibiotics,

intralesional steroids, anti-inflammatory medication, and hyaluronidase. All events resolved.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. The study was a well-designed prospective, no-treatment controlled study using a validated scale and blinded, live evaluations. The data is considered to be as robust as possible for an aesthetic endpoint. In the JUVÉDERM VOLUMA™ XC group at Month 6, more than 85.6% were responders. The duration of effect was evaluated by responder rate at 6 months to be 86%, at 12 months to be 85%, and at 24 months to be 67% in patients who received a mean injection volume of 6.8mL. The findings of the primary effectiveness assessment were supported by the secondary endpoints. The Month 6 GAIS Investigator assessment was 82%, comparing favorably to the Mid-Face Volume Deficit Scale assessment (85.6%). The Month 6 subject GAIS assessment was 93%. The majority of the patients have elected to undergo retreatment, indicating that they perceive a benefit and that they would like continued benefit.

Almost all (98%) of the patients experienced common treatment responses which included Tenderness, Swelling, Firmness, Lumps/Bumps, Bruising, Pain, Redness, Discoloration, Itching, and Other. 20% of patients had common treatment responses lasting longer than 30 days. 3 patients had swelling, lumps or bumps which developed more than six weeks after treatment. All adverse events resolved either spontaneously or with treatment. Rare risks include vascular occlusion (including ocular) from embolization and infection. Neither was seen in this pivotal study of 270 treated patients. The probable benefits outweigh the probable risks, as determined by the short term adverse outcomes and rare late adverse events seen after injection, balanced against the improvement seen on the Mid-Face Volume Deficit Scale and patient satisfaction.

In conclusion, given the available information above, the data support that for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over the age of 21, the 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 October 22, 2013. The final conditions of approval cited in the approval order are described below.

VOLUMA-003 Repeat Treatment Study: This study will be conducted as per protocol dated August 30, 2013. The post-approval study is a statistical evaluation of data collected in the premarket VOLUMA-002 study. The purpose of the VOLUMA-003 study is to evaluate the safety of repeat treatment with JUVEDERM VOLUMA® XC for correction of mid-facial volume deficit. Safety endpoints include: presence, severity, location, and duration of common treatment site responses (CTRs) and any adverse events (AEs) after repeat treatment.

The primary analysis will be an evaluation of early safety endpoints (those occurring within 1 month) in at least 167 subjects who received repeat treatment and have completed 30-day follow-up in the premarket study. The main study hypothesis is that the incidence of early (within 1 month) device- or injection-related AEs after repeat treatment will not be more than the incidence rate with a 5% margin for the device- or injection-related AEs after initial/touch-up treatment. A 1-sided 95% Unmodified Wald's CI for the difference in the incidence rates of early device- or injection-related AEs (those occurring within 1 month) after initial and repeat treatment will be constructed to test the primary safety hypothesis. As reported in the 24-month clinical study report, the incidence of early device- or injection-related AEs after initial/touch-up treatment and prior to repeat treatment for the 125 subjects was 31%. Assuming that the incidence of early device- or injection-related AEs after repeat treatment will be less than 22%, a sample of 167 subjects will provide 96% power using a 1-sided McNemar test at the 5% level to test that the incidence after repeat treatment will not be more than the incidence with a 5% margin after initial/touch-up treatment. The proportion of discordant pairs is assumed to be 28% for sample size calculation.

The VOLUMA-003 protocol also includes a long-term safety evaluation after repeat treatment. A descriptive summary of safety endpoints will be provided for the 3-, 6-, 9-, and 12-month follow-up visits. At least 80 subjects have consented to the extended 12-month follow-up and a minimum of 64 subjects (80 minus 20% drop-out rate at 1 year) are required for the long-term evaluation. If less than 64 subjects complete the 12-month follow-up, FDA may require you to enroll new patients or consider other regulatory options to reach the required study sample size.

The sponsor was advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.