SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: Juvéderm® Ultra XC

Device Procode: LMH

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

Date(s) of Panel Recommendation: Not Applicable

Premarket Approval Application (PMA) Number: P050047/s044

Date of FDA Notice of Approval: September 30, 2015

Priority Review: No

The original Juvéderm® PMA (P050047) was approved on June 2, 2006 for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds). Juvéderm Ultra XC received FDA approval on January 7, 2010 for incorporation of 0.3% lidocaine hydrochloride into the formulation. The SSED to support the indication for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for Juvéderm Ultra XC to include injection into the lips and perioral area for lip augmentation in adults over the age of 21.

II. INDICATIONS FOR USE

- Juvéderm Ultra 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).
- Juvéderm Ultra XC is indicated for injection into the lips and perioral area for lip augmentation in adults over the age of 21.

III. CONTRAINDICATIONS

- Juvéderm Ultra XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- Juvéderm Ultra XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- Juvéderm Ultra 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 Ultra XC labeling.

V. DEVICE DESCRIPTION

Juvéderm Ultra XC is a sterile, biodegradable, nonpyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of crosslinked hyaluronic acid (HA) produced by Streptococcus species of bacteria, formulated to a concentration of 24 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies include autologous fat grafting, surgical facelift, and other soft tissue fillers approved by FDA for lip augmentation.

Fat grafting is similar in result and usually requires multiple sessions. Fat grafting requires an invasive procedure to remove fat from the body (such as lipoplasty). Risks of fat grafting include donor site morbidity, graft resorption, fat necrosis, oil cyst, and uneven result.

Surgical face lift is not directly comparable, but can decrease an aged look without providing additional volume. Face lift is a surgical procedure and carries the risks typically associated with a surgical procedure requiring general anesthesia and a prolonged recovery with scarring.

VII. MARKETING HISTORY

Juvéderm Ultra XC was approved by FDA on January 7, 2010, under Supplement 5 to P050047 and is also indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds). This product received CE Mark on April 17, 2008, under the name Juvéderm Ultra with Lidocaine. It is approved in multiple countries globally, including the European Union, Argentina, Australia, Brazil, Canada, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Hong Kong, India, Indonesia, Korea, Macau, Malaysia, Mexico, New Zealand, Panama, Peru, Philippines, Singapore, Taiwan, Thailand, and Vietnam.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of Juvéderm Ultra XC for lip augmentation was evaluated in a premarket study. Potential adverse effects associated with the use of the device include: swelling, bruising, firmness, lumps/bumps, tenderness, redness, pain, discoloration, and itching. Infrequent adverse events (AEs) included angioedema, injection site mass, severe pain, bruising, swelling, erythema, and hypertrophy.

The following AEs were received from post-market surveillance for JUVÉDERM Ultra, with and without lidocaine, with a frequency of 5 events or more 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: lack or loss of correction, inflammatory reaction, allergic reaction, necrosis, infection, migration, paresthesia, dry skin, abscess, headache, malaise, flu like symptoms, vision abnormalities, scarring, nausea, drainage, dyspnea, syncope, dizziness, anxiety, granuloma.

Vascular occlusion of vessels resulting in necrosis and vision abnormalities, have been reported following injection of JUVÉDERM Ultra, with and without lidocaine, with a time to onset ranging from immediate to within one week following injection. These reported events likely resulted from inadvertent vascular injection. In many of these cases, the product was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use

IX. SUMMARY OF PRECLINICAL STUDIES

No new preclinical studies were presented in this PMA Supplement. JUVÉDERM Ultra XC has previously been tested and characterized through bench and animal studies submitted in P050047 and P050047/s005. Please refer to the SSED for P050047 for more information.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The sponsor performed a clinical study to establish a reasonable assurance of safety and effectiveness for JUVÉDERM Ultra XC for injection into the lips and perioral area for lip augmentation in adults over the age of 21.

A. Study Design

Subjects were treated between August 30, 2010 and December 27, 2013. The database for this PMA supplement reflected data collected through September 12, 2014 and included 213 subjects randomized to either treatment with Juvéderm Ultra XC (N = 157) or to delayed-treatment control (N = 56). There were 9 investigational sites.

The pivotal clinical study was a prospective, randomized, multicenter, evaluator blind study of subjects seeking lip augmentation. Subjects meeting inclusion/exclusion criteria were randomized 3:1 into the treatment group or a non-treated control group. The control group was crossed over at 3 months.

1. Key Clinical Inclusion and Exclusion Criteria

   Enrollment in the pivotal study was limited to subjects who met the following inclusion criteria:

   - Was male or female, 18 years of age or older
   - Desired augmentation of his/her lips, i.e., vermilion (body of the lip).
   - Signed the IRB-approved Informed Consent Form and the Authorization for Use and Release of Health and Research Study Information (HIPAA) form prior to any study- related procedures being performed
   - Had an overall pre-treatment score of Minimal or Mild, as assessed by the Treating Investigator (TI) according to the 5-point Allergan Lip Fullness

Scale (Minimal, Mild, Moderate, Marked, Very Marked). For subjects with Fitzpatrick skin phototype IV, V, or VI, only 1 lip was required to have a pretreatment score of Minimal or Mild
- Was able to follow study instructions and likely to complete all required visits, as assessed by the Treating Investigator
- 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 treatment, used contraception for at least 1 month prior to treatment, and agreed to use contraception for the duration of the study

Subjects were not permitted to enroll in the pivotal study if they met any of the following exclusion criteria:

- Had lip tattoos, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments
- Had dentures or any device covering all or part of the upper palate, and/or severe malocclusion, dentofacial or maxillofacial deformities, or significant asymmetry of the lips and perioral area, as judged by the Treating Investigator
- Had undergone oral surgery or other dental procedures (e.g. tooth extraction, orthodontia, or implantation) within 30 days prior to enrollment or was planning to undergo any of these procedures during the study
- Had ever undergone facial plastic surgery or received semi-permanent fillers or permanent facial implants (e.g. calcium hydroxyapatite, L-polylactic acid, polymethylmethacrylate, silicone, expanded polytetrafluoroethylene) anywhere in the face or neck, or was planning to be implanted with any of these products at any time during the study.
- Had undergone temporary dermal filler treatment within 24 months prior to study entry or was planning to undergo any of these procedures at any time during the study
- Had undergone cosmetic facial procedures, e.g., resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) or mesotherapy anywhere in the face or neck, or BOTOX® Cosmetic injections in the lower face (below the orbital rim), within 6 months prior to entry in the study or was planning to undergo any of these procedures at any time during the study
- Began use of any new over-the-counter or prescription, oral or topical, antiwrinkle products for the lips or around the mouth within 3 months (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 cosmeceuticals [e.g., alpha hydroxy acids, glycolic acids, retinol, or retinoic acids] was allowed if the regimen was established $\geq$ 3 months [90 days] prior to enrollment and the regimen remained unchanged during the study)

- Had a history of anaphylaxis, multiple severe allergies, atopy, allergy to lidocaine, hyaluronic acid products, or Streptococcal protein, or was planning to undergo desensitization therapy during the term of the study
- Had an active inflammation, infection, cancerous or pre-cancerous lesion, or unhealed wound in the mouth area
- Was on an ongoing regimen of anti-coagulation therapy (e.g., warfarin) or had taken nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen) or other substances known to increase coagulation time (e.g., herbal supplements with garlic or gingko) within 10 days of undergoing study device injections (Study device injections were permitted to be delayed as necessary to accommodate this 10-day washout period)
- 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 immediate relative of an employee) of the Treating Investigator, Evaluating Investigator, Sponsor or representative of the Sponsor
- Had a condition or was in a situation that, in the Treating Investigator's opinion, might have put the subject at significant risk, may have confounded the study results, or may have interfered significantly with the subject's participation in the study

2. Follow-up Schedule

The follow-up schedule is described in table 1.

Table 1A: Treatment Group: Schedule of Study Periods, Visits, and Procedures

	Treatment (Initial and Touch-up[a])		Primary F/U	Extended F/U	Repeat Treatment and F/U	
	Day -30 to -14 (± 5 days) or Day 0 (If No Touch-up)	Day 0 (If Touch-up Performed)	Months 1, 3 (± 5 days)	Months 6, 7.5, 9, 10.5, 12 (± 10 days)	Repeat Treatment[b]	Months 1, 3, 6[c] (± 5 days)
Urine pregnancy test[d]	X	X			X	
Pronunciation video	X	X	X		X	X
Vital signs[e]	X	X			X	X
3D imaging[f]	X	X	X	X	X	X
OFF assessment	X	X	X	X	X	X
Subject –FAS	X	X	X	X	X	X
Treatment	X	X			X	
Treatment characteristics[g]	X	X			X	
Phone call/email[h]	X	X			X	
EI assessments						
LFS2			X	X		X
POL			X	X		X
OCS			X	X		X
OAF			X	X		X
Lip sensitivity			X			X
Guess randomization assignment[i]			X			
Subject self-assessments						
LFS2			X	X		
Lip fullness treatment goal			X[j]			
POL						
OCS						
LAF			X	X		X
WUTA			X[k]	X[k]		
30-day safety diary[l]	X	X			X	
Adverse events	Continuous monitoring					
Concomitant medications/procedures[m]	Continuous monitoring					

3D = 3 dimensional, EI = Evaluating Investigator, FAS = Function and Sensation of the Lips and Mouth, F/U = follow-up ISRs = Injection Site Responses, LAF = Look and Feel of Lips and Mouth questionnaire, LFS2 = Lip Fullness Scale 2, OAF = Other Aesthetic Features assessment, OCS = Oral Commissures Severity Scale, OFF = Other Functional Features assessment, POL = Perioral Lines Severity Scale, TI = Treating Investigator, WUTA = Willingness to Undergo Treatment Again. At every study visit the TI, study coordinator, and the subject were to strive to assure that the EI did not discover that the control subjects did not undergo Ultra XC treatment or that the treated subjects had been treated. The EI was not to discuss the randomization assignments nor assessments with the subject.

[a] Touch-up treatment, if performed, was to occur approximately 14 to 30 days ± 5 days after the initial treatment if the TI and subject determined that augmentation of the subject's lips had not been optimized, if the subject's allotment of Ultra XC had not been depleted, and if the TI believed that additional Ultra XC would improve lip augmentation. If no touch-up was performed, then the subject entered the Primary Follow-up Period.

[b] Subjects were to undergo repeat treatment within 10 days of the month-12 follow-up visit or within 6 weeks of the follow-up visit at which the subject's overall lip fullness score returned to or was lower than the baseline score.

[c] The post-repeat treatment follow-up visit at month 6 applied only to subjects who were enrolled under Protocol Amendment 10 and also received repeat treatment at month 6, 7.5, or 9

[d] For female subjects of childbearing potential. Urine pregnancy testing was to be performed within 10 days prior to any treatment administration and at the final study visit.

[e] Vital signs include blood pressure, heart rate, respiratory rate, and temperature, were to be measured prior to initial, touch-up, and repeat treatments and at the final visit.

[f] 3D images were to be captured before and after treatment at all treatment visits and once at each follow-up visit.

[g] Treatment characteristics included injection sites, injection plane, volume injected, and injection techniques

[h] Three days after treatment, the subject was contacted by phone or email for safety inquiry.

[i] At month 3, the EI was to guess the subject's randomization assignment (treatment or control).

[j] At month 3, subjects assessed whether their lip fullness treatment goal, as recorded prior to treatment, had been attained.

[k] At month 3 and prior to repeat treatment, the subject indicated willingness to undergo repeat treatment.

[l] The subject recorded ISRs in the safety diary for 30 days following study treatment, or until touch-up if performed. At each visit, the TI and/or study coordinator elicited information from the subject regarding any new or ongoing ISRs or adverse events (unrelated events, related events, or ISRs lasting longer than 30 days), including symptom, sign or diagnosis, location, severity, onset and resolution dates, causality, any action taken, and outcome.

[m] At every study visit, the TI and/or study coordinator was to inquire whether the subject had used any prescription or over-the-counter medications or anti-wrinkle products or procedures since the previous visit.

Table 1B: Control Group: Schedule of Study Periods, Visits, and Procedures

	Primary F/U	Treatment (Initial and Touch-up[a])		Extended F/U	Repeat Treatment and F/U	
	Months 1, 3 (±5 days)	Day -30 to -14 (±5 days) or Day 0 (If No Touch-up)	Day 0 (If Touch-up Performed)	Months 1T, 3T, 6T, 7.5T, 9T, 10.5T, 12T (±10 days)	Repeat Treatment[b]	Months 1, 3, 6[c] (±5 days)
Urine pregnancy test[d]		X	X		X	
Pronunciation video	X[e]	X	X	X[e]	X	X[e]
Vital signs[f]		X	X		X	X
3D imaging[g]	X	X	X	X	X	X
OFF assessment	X	X	X	X	X	X
Subject –FAS	X	X	X	X	X	X
Treatment		X	X		X	
Treatment characteristics[h]		X	X		X	
Phone call/email[i]		X	X		X	
EI assessments						
LFS2	X			X		X
POL	X			X		X
OCS	X			X		X
OAF	X			X		X
Lip sensitivity	X[e]			X[e]		X[e]
Guess randomization assignment[j]	X					
Subject self-assessments						
LFS2				X		
Lip fullness treatment goal				X[k]		
POL						
OCS						
LAF				X		X
WUTA				X[l]		
30-day safety diary[m]		X	X		X	
Adverse events		Continuous monitoring				
Concomitant medications/procedures[n]		Continuous monitoring				

3D = 3 dimensional, EI = Evaluating Investigator, FAS = Function and Sensation of the Lips and Mouth, F/U = follow-up,ISRs = Injection Site Responses, LAF = Look and Feel of Lips and Mouth questionnaire, LFS2 = Lip Fullness Scale 2, OAF = Other Aesthetic Features assessment, OCS = Oral Commissures Severity Scale, OFF = Other Functional Features assessment, POL = Perioral Lines Severity Scale, TI = Treating Investigator, WUTA = Willingness to Undergo Treatment Again.

At every study visit the TI, study coordinator, and the subject were to strive to assure that the EI did not discover that the control subjects did not undergo Ultra XC treatment or that treated subjects had been treated. The EI was not to discuss the randomization assignments nor assessments with the subject.

[a] A touch-up treatment, if performed, was to occur approximately 14 to 30 days ± 5 days after the initial treatment if the TI and subject determined that augmentation of the subject's lips had not been optimized, if the subject's allotment of Ultra XC had not been depleted, and if the TI believed that additional Ultra XC would improve lip augmentation. If no touch-up was performed, then the subject entered the Primary Follow-up Period.

[b] Subjects were to undergo repeat treatment within 10 days of the month-12 follow-up visit or within 6 weeks of the follow-up visit at which the subject's overall lip fullness score returned to or was lower than the baseline score.

[c] The post-repeat treatment follow-up visit at month 6 applied only to subjects who were enrolled under Protocol Amendment 10 and also received repeat treatment at month 6, 7.5, or 9

[d] For female subjects of childbearing potential. Urine pregnancy testing was to be performed within 10 days prior to any treatment administration and at the final study visit.

[e] At months 1 and 3 during primary follow-up, 1T and 3T during extended follow-up, at months 1 and 3 after repeat treatment.

[f] Vital signs include blood pressure, heart rate, respiratory rate, and temperature, were to be measured prior to initial, touch-up, and repeat treatments and at the final visit.

[g] 3D images were to be captured before and after treatment at all treatment visits and once at each follow-up visit.
[h] Treatment characteristics included injection sites, injection plane, volume injected, and injection techniques
[i] Three days after treatment, the subject was contacted by phone or email for safety inquiry.
[j] At month 3, the EI was to guess the subject's randomization assignment (treatment or control).
[k] At month 3T, subjects assessed whether their lip fullness treatment goal, as recorded prior to treatment, had been attained.
[l] At month 3T and prior to repeat treatment, the subject indicated willingness to undergo repeat treatment.
[m] The subject recorded ISRs in the safety diary for 30 days following study treatment, or until touch-up if performed. At each visit, the TI and/or study coordinator elicited information from the subject regarding any new or ongoing ISRs or adverse events (unrelated events, related events, or ISRs lasting longer than 30 days), including symptom, sign or diagnosis, location, severity, onset and resolution dates, causality, any action taken, and outcome.
[n] At every study visit, the TI and/or study coordinator was to inquire whether the subject had used any prescription or other-the-counter medications or anti-wrinkle products or procedures since the previous visit.

With regards to safety, pre-printed diaries were used by subjects to record observations of symptoms experienced 30 days after initial, touch-up, and repeat treatments. AEs were assessed by the investigator at each follow up period after treatment.

In the 30-day diaries, subjects indicated the occurrence of ISRs as well as their location and severity (none, mild, moderate, severe). Subjects were contacted by telephone or email 3 days after each treatment (initial, touch-up, and repeat) and attended office visits at 14 days and 1 month after initial treatment and touch-up (if performed) and then at 3, 6, 7.5, 9, 10.5, and 12 months after the later of these 2 treatment sessions. After repeat treatment, the subject attended office visits at 14 days and at 1 and 3 months, with an additional follow-up visit at 6 months for subjects who were enrolled under Protocol Amendment 10 and received repeat treatment before the month 10.5 follow-up visit. Lip sensation testing, lip function testing, and discussion of the subject's observations and the investigator's personal observations of the subject were also part of the safety assessment.

After each treatment, the subject assessed the level of procedural pain. To monitor potential effects on lip function, the subject read a series of words and phrases while being video recorded. These recordings were assessed by a blinded speech and language professional who evaluated the subject's ability to pronounce words and phrases with sounds such as B, F, and P that require normal lip function. These included (1) speech articulation screening, (2) an assessment of labial sounds in connected speech, (3) an assessment of speed and precision of lip closure, and (4) an assessment of overall speech naturalness.

At follow-up visits, the subject completed a self-assessment related to function and sensation of the lips and mouth area using a questionnaire.

3. Clinical Endpoints

Safety

The safety of Ultra XC in the lips and perioral area was evaluated by the presence, location, frequency, severity, and duration of injection site responses (ISRs) after each treatment (initial, touch-up, and repeat) as reported by subjects and any AEs throughout the study. ISRs were assessed by a subject safety diary for 30 days after each treatment. Adverse events were assessed by the TI throughout the study. If an

ISR was determined to be ongoing at the end of the 30-day diary, the TI followed the ISR to resolution and documented the entire course of the ISR as an adverse event (AE). If an ISR was ongoing on the last diary page, the investigator followed the ISR to resolution and documented the entire course of the ISR, including severity, on an AE CRF. Additionally, AEs could be reported at any time during the study. Investigators assessed AE severity according to the following criteria:

Mild: Awareness of sign or symptom, but easily tolerated
Moderate: Discomfort enough to cause interference with usual activity
Severe: Incapacitating with inability to work or do usual activity

Effectiveness

The primary effectiveness measure was the blinded EI's live assessment at 3 months of the subject's overall lip fullness or lip fullness of the eligible lip, for subjects with Fitzpatrick skin type IV, V, or VI who had only 1 eligible lip, on the validated 5-point Allergan Lip Fullness Scale (Table 2, Figure 1).

The primary effectiveness endpoint for the study was the blinded Evaluating Investigator's assessment of the subject's overall Lip Fullness on the validated 5-point Allergan Lip Fullness Scale. A responder was defined as a subject with ≥1 point improvement in overall lip fullness score (or lip fullness of the eligible lip, for subjects with Fitzpatrick skin type IV, V, or VI who had only 1 eligible lip) compared with the pre-treatment score on the Allergan Lip Fullness Scale. Effectiveness was demonstrated if at least 60% of subjects treated with Juvéderm Lip XC were observed to be responders and if the responder rate for treated subjects was statistically superior to the responder rate for the no-treatment control group at 3 months after treatment. Responder rates (with 95% exact CIs) were calculated for the treatment group and control group at month 3.

The secondary effectiveness analyses included the responder rates (with 95% CIs) at month 3 in the treatment group based on the blinded EI's assessments of the following:

- Lip fullness of upper and lower lips, using the Allergan Lip Fullness Scale
- Perioral lines severity for upper lip, using the validated Perioral Lines Severity Scale (POL)
- Oral commissures using the validated Oral Commissures Severity Scale (OCS)
- Subject's assessment of lip fullness goals
- Duration of effect

Additional prespecified effectiveness analyses:

- Overall, upper, and lower lip fullness based on the EI's assessment and subject's self-assessment, using the Allergan Lip Fullness Scale
- Severity of perioral lines of the upper lip based on the EI's assessment and subject's self-assessment, using the POL

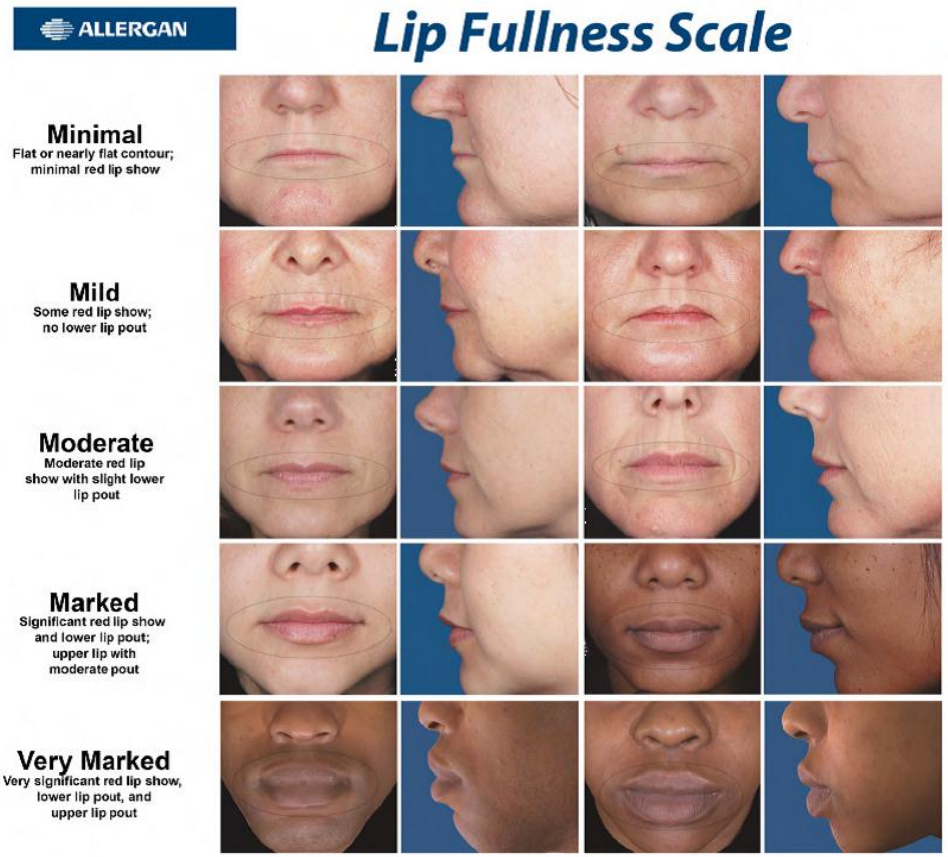
- Severity of oral commissures based on the EI's assessment and subject's self-assessment, using the OCS
- OAF assessment of the subject's lips and mouth area based on the EI's assessment
- Look and feel of lips based on the subject's assessment
- Willingness to undergo treatment again assessment at month 3 of the primary follow-up period and at the end of the extended follow-up period (before repeat treatment, if performed)
- Lip measurements obtained from 3D digital images included:

    - change in lip surface area
    - change in lip volume
    - vertical red lip heights
    - anterior lip projection

Table 2: Allergan Lip Fullness Scale

Grade	Description
5- Very Marked	Very significant red lip show, lower lip pout, upper lip pout
4- Marked	Significant red lip show and lower lip pout
3- Moderate	Moderate red lip show and lower lip pout
2- Mild	Some red lip show, no lower lip pout
1- Minimal	Flat or nearly flat contour, minimal red lip show

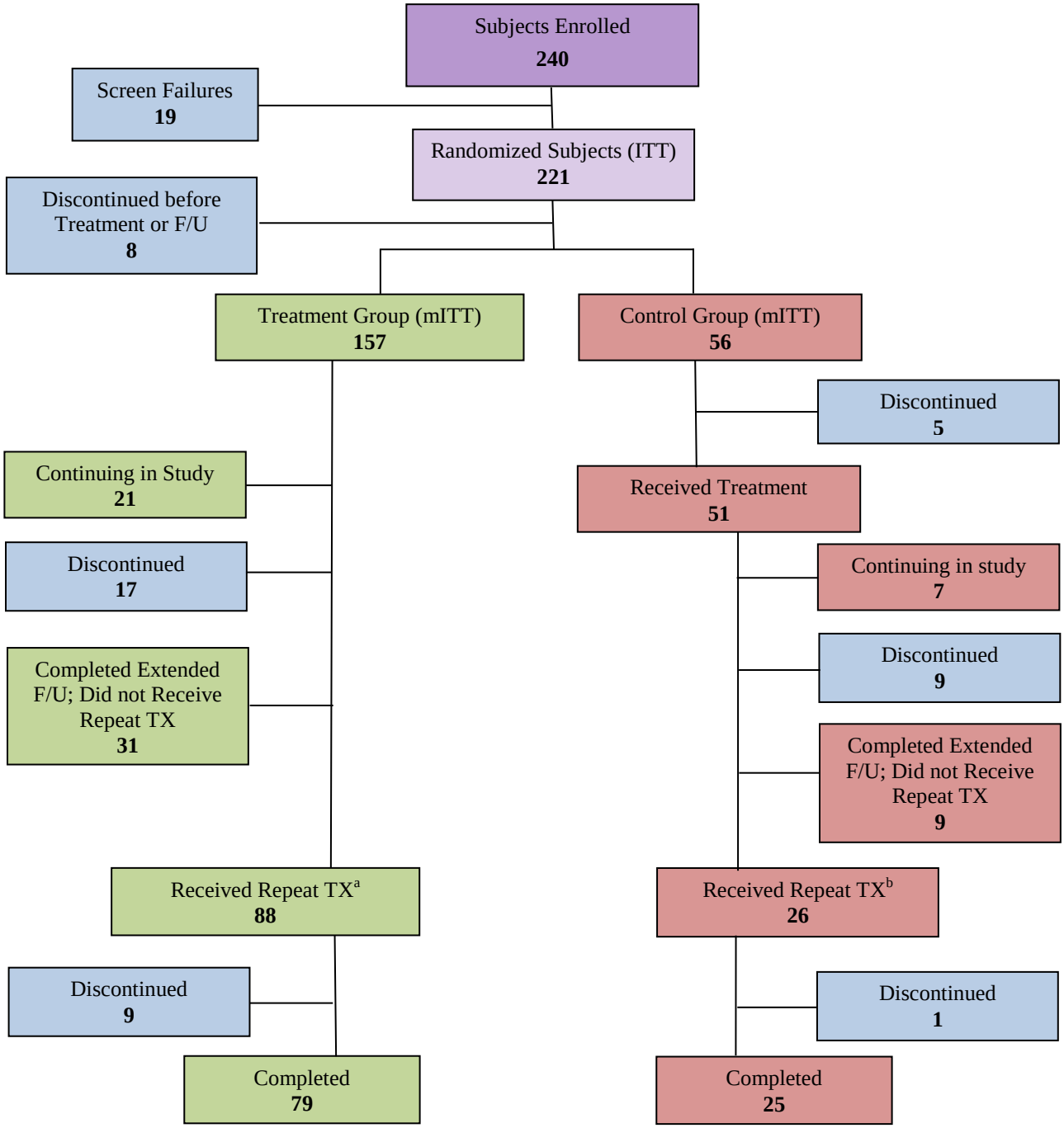
Figure 1: Allergan Lip Fullness Scale



B. Accountability of PMA Cohort

At the time of database lock, of 240 subjects were enrolled in the PMA study, and 89% (213) subjects were available for analysis (Figure 2, Table 3). After enrollment, 19 subjects were deemed screen failures, and the remaining 221 subjects were randomized 3:1 to either the treatment group (164 subjects) or the control group (57 subjects). Prior to treatment or follow-up, 8 randomized subjects (7 treatment, and 1 control) discontinued, resulting in 213 subjects (157 treatment and 56 control) in the modified intent-to-treat (mITT) population. Of the 157 treatment group subjects, 114 completed the extended follow-up period, and 21 are currently active in the study, having completed follow-up through Month 6. In the control group, 52 of the 56 subjects completed the primary follow-up period, with 51 receiving treatment. Among the 51 control subjects who received treatment, 32 completed the extended follow-up period, and 7 are currently active in the study having recently completed follow-up through Month 3 post-treatment. A total of 114 mITT subjects (88 treatment and 26 control) received repeat treatment and 104 (79 treatment and 25 control) completed the follow-up after repeat treatment. One subject withdrew following a serious AE. Repeat treatment was offered to all subjects within 10 days after Month 12 or within 6 weeks after any follow-up visit between Month 6 and Month 12 if, during that time, the evaluating investigator (EI)'s assessment of the subject's overall lip fullness score (or score of the eligible lip in Fitzpatrick skin type IV-VI subjects) returned to or was lower than the baseline score.

Figure 2: Disposition of subjects



F/U = follow-up, ITT = Intent-to-Treat, mITT = modified Intent-to-Treat, TX = treatment

[a] 5 subjects in the treatment group did not complete the extended follow-up but received repeat treatment

[b] 3 subjects in the control group did not complete the extended follow-up but received repeat treatment

Table 3: Subject disposition

Population	N
Enrolled	**240**
Screen Failures	**19**
Randomized Subjects (ITT)	**221**
Randomized to treatment, but discontinued before treatment	7
Randomized to control, but failed to complete a follow-up visit	1
mITT	**213**
Treatment Group	**157**
Control Group	**56**
Major Protocol Deviations	13
Per-Protocol (PP)	**200**
PP Treatment Group	**147**
PP Control Group	**53**
Treatment Group	**157**
Completed extended follow-up period	114
Did not complete extended follow-up period	22
Received repeat treatment	88
Completed follow-up after repeat treatment	79
Did not complete follow-up after repeat treatment	9
Did not receive repeat treatment	48
Continuing in the study	21
Control Group	**56**
Completed primary follow-up period	52
Discontinued before completing primary follow-up period	4
Received treatment after primary follow-up period	51
Did not receive treatment after primary follow-up period	1
Completed extended follow-up period	32
Did not complete extended follow-up period	12
Received repeat treatment	26
Completed follow-up after repeat treatment	25
Did not complete follow-up after repeat treatment	1
Did not receive repeat treatment	18
Continuing in the study	7

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US (table 4). The mean age of subjects in the mITT population was 48.8. The median age was 49.0 and the standard deviation was 11.01. Patients ranged from 20 to 79 years of age.

Table 4: Study Demographics

	Treatment Group (N = 157) % (n/N)	Control Group (N = 56) % (n/N)
Gender		
Female	95.5% (150/157)	96.4% (54/56)
Male	4.5% (7/157)	3.6% (2/56)
Ethnicity		
Caucasian	84.7% (133/157)	85.7% (48/56)
Hispanic	5.1% (8/157)	3.6% (2/56)
African-American	8.3% (13/157)	5.4% (3/56)
Asian	0.6% (1/157)	3.6% (2/56)
Other	1.3% (2/157)	1.8% (1/56)
Fitzpatrick Skin Type		
I	1.3% (2/157)	5.4% (3/56)
II	36.9% (58/157)	32.1% (18/56)
III	45.9% (72/157)	44.6% (25/56)
IV	3.8% (6/157)	7.1% (4/56)
V	10.2% (16/157)	8.9% (5/56)
VI	1.9% (3/157)	1.8% (1/56)
Baseline Overall Lip Fullness (Allergan Lip Fullness Scale) Score		
Minimal	30.6% (48/157)	33.9% (19/56)
Mild	59.9% (94/157)	53.6% (30/56)
Baseline Perioral lines		
None-Mild	54.8% (86/157)	58.9% (33/56)
Moderate-Severe	45.2% (71/157))	41.1% (23/56)
Baseline Oral Commissures*	**N=314**	**N=112**
None-Mild	43.3% (136/314)	32.1% (36/112)
Moderate-Severe	56.7% (178/314)	67.9% (76/112)

* The number of OCs treated can exceed the number of subjects treated since each person can have up to 2 OCs treated (right and left)

Nearly all subjects in the treatment group received initial treatment for augmentation of both the upper and lower lips (96% [151/157] and 93% [146/157], respectively). Perioral lines of the upper and lower lip were treated in 65/157 (41%) and 33/57 (21%), respectively. Oral commissures were injected in 128/157 subjects, 82%. Injection site locations for the touch-up and repeat treatments were similar to those for initial treatment.

A variety of injection planes were utilized in combination to obtain optimal results. Subdermal injections were the most frequently used for initial treatment. Intradermal injections were used mainly in perioral lines (45%, 30/67) and oral commissures (52%, 67/128). Intramuscular injections were used oral commissures (27%, 34/128). Injection planes for the touch-up and repeat treatments were similar to those for the initial treatment.

Multiple injection techniques were used in combination. Tunneling was used most frequently during initial treatment. Serial puncture was used mainly perioral lines (27%, 18/66), and oral commissures (55%, 70/128). Fanning and cross-hatching were mainly used in the oral commissures (41% [52/128] and 45% [57/128], respectively).

Injection techniques for the touch-up and repeat treatments were similar to those for the initial treatment.

The median total volume injected at the initial and touch-up treatments were 1.7 mL and 0.7 mL, respectively (Table 5). Most subjects received initial treatment in the upper lip (n = 205) with a median volume of 0.8 mL and in the lower lip (n = 201) with a median volume of 0.7 mL. The median volumes after touch-up treatment in the upper lip (n = 84) and lower lip (n = 63) were 0.2 mL and 0.3 mL, respectively.

Perioral lines of the upper lip were treated in 82 subjects at initial treatment and 15 subjects at touch-up treatment with a median volume of 0.1 mL at each treatment. Perioral lines of the lower lip were treated in 42 subjects at initial treatment with a median volume of 0.1 mL and 11 subjects at touch-up treatment with a median volume of 0.2 mL.

Oral commissures were treated in 173 subjects at initial treatment and 55 subjects at touch-up treatment with a median volume of 0.4 mL at each treatment.

Table 5: Median volume injected mITT population

Treatment Area	Combined initial and touch up (N=208)	Initial Treatment (N=208)	Touch-up Treatment (n=94)	Repeat Treatment N=114
Total volume Injected				
n	208	208	94	114
Median	2.125	1.675	0.675	1.450
Range (min, max)	0.30, 4.80	0.30, 4.00	0.10, 2.40	0.45, 3.70
Total upper lip				
n	206	205	84	113
Median	0.900	0.800	0.210	0.550
Range (min, max)	0.10, 2.50	0.10, 2.50	0.03, 1.20	0.15, 2.25
Total lower lip				
n	201	201	63	111
Median	0.700	0.700	0.250	0.500
Range (min, max)	0.08, 2.60	0.08, 1.50	0.02, 1.30	0.10, 1.65
Upper lip perioral lines				
n	83	82	15	32
Median	0.150	0.115	0.100	0.175
Range (min, max)	0.01, 1.05	0.01, 1.05	0.03, 0.90	0.02, 0.40
Lower lip Perioral lines				
N	45	42	11	17
Median	0.100	0.100	0.150	0.100
Range (min, max)	0.01, 1.95	0.01, 0.70	0.05, 1.30	0.05, 1.30
Total Oral Commissures				
n	176	173	55	87
Median	0.400	0.400	0.400	0.400
Range (min, max)	0.02, 2.15	0.02, 1.30	0.10, 1.15	0.10, 1.20

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of subjects available at each follow-up timepoint. The key safety outcomes for this study are presented below in tables 6 to 16. Adverse effects are reported in tables 7-8, 10, and 12-15.

Injection Site Responses after Initial Treatment

A total of 193 treated mITT subjects completed safety diaries after initial treatment, and 103 subjects completed the diaries after repeat treatment. Nearly all subjects (99.5%, 192/193 after initial treatment and 97.1%, 100/103 after repeat treatment) reported at least 1 ISR (table 6). The most frequently reported ISRs after initial and repeat treatment were swelling (95.9%, 185/193, and 94.2%, 97/103, respectively), bruising (93.3%, 180/193 and 91.3%, 94/103, respectively)

and firmness (89.6%, 173/193 and 88.3%, 91/103, respectively). Other common ISRs were lumps/bumps (87.6%, 169/193), tenderness (85.5%, 165/193), redness (78.2%, 151/193), and pain (74.1%, 143/193). Notably, a large portion of subjects reported the severity of their ISR after initial treatment as moderate (48.4%, 93/192) or severe 38.5% (74/192).

Most ISRs lasted less than 2 weeks after initial (64.1%, 123/192) and repeat treatment (61.0%, 61/100), but 35.9% of the ISRs lasted between 15 and 30 days of duration. The most common ISRs that lasted for 15 to 30 days after initial treatment were lumps/bumps (30.8%, 52/169), firmness (21.4%, 37/173), and swelling (10.8%, 20/185). Similarly after repeat treatment, the most common ISRs lasting 15 to 30 days were firmness (29.7%, 27/91), lumps/bumps (27.3%, 24/88), and swelling (12.4%, 12/97).

Table 6: Injection Site Responses after Initial Treatment Occurring in > 5% of Treated Subjects after Lip Augmentation by Severity and Duration

Injection Site Responses	Subjects N=193[c]	Severity			Duration			
		Mild	Moderate	Severe	<3 Days	4-7 Days	8-14 Days	15-30 Days
	n %	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]
Swelling	185 96%	45 24%	94 51%	46 25%	51 28%	63 34%	51 28%	20 11%
Bruising	180 93%	35 19%	84 47%	61 34%	31 17%	91 51%	46 26%	12 7%
Firmness	173 90%	53 31%	91 53%	29 17%	38 22%	43 25%	55 32%	37 21%
Lumps/Bumps	169 88%	59 35%	81 48%	29 17%	41 24%	32 19%	44 26%	52 31%
Tenderness	165 86%	75 46%	64 39%	26 16%	56 34%	41 25%	53 32%	15 9%
Redness	151 78%	55 36%	69 46%	27 18%	69 46%	49 33%	27 18%	6 4%
Pain	143 74%	70 49%	60 42%	13 9%	93 65%	28 20%	19 13%	3 2%
Discoloration	70 36%	36 51%	25 36%	9 13%	37 53%	8 11%	21 30%	4 6%
Itching	56 29%	34 61%	18 32%	4 7%	37 66%	11 20%	6 11%	2 4%
Peeling	13 7%	5 39%	7 54%	1 8%	9 69%	1 8%	3 23%	0 0%

Adverse Events after Initial Treatment

The treated mITT population experienced 250 AEs (Table 7). The AEs had the following characteristics:

- mild or moderate in severity 93.6% (234/250),
- severe 6.0% (15/250)
- occurred at the injection site 68.4% (171/250)
- lasted 30 days or more 50% (124/250)
- resolved without sequelae 89.2% (223/250)
- related to device/procedure 67.2% (168/250)
    - related to the injection/procedure 50.8% (127/250)
    - related to the study device 57.2% (143/250)

Table 7A Summary of Device-/Procedure-related Adverse Events Before Repeat Treatment (Treated mITT Population, N = 208)

	Subjects % (n/N)	**95% Confidence Interval (%,%)**	**Events % (n/N)**
One or More Adverse Event	28.8 (60/208)	(22.79, 35.52)	100.0 (168/168)
At Injection Site	28.4 (59/208)	(22.35, 35.01)	99.4 (167/168)
Upper lip	24.5 (51/208)	(18.83, 30.95)	46.4 (78/168)
Upper Perioral Lines	5.3 (11/208)	(2.67, 9.27)	9.5 (16/168)
Lower lip	18.8 (39/208)	(13.69, 24.73)	37.5 (63/168)
Lower Perioral Lines	4.8 (10/208)	(2.33, 8.66)	7.7 (13/168)
Oral Commissures	7.7 (16/208)	(4.46, 12.19)	15.5 (26/168)
Not at Injection Site	0.5 (1/208)	(0.01, 2.65)	0.6 (1/168)
Severity			
Mild	24.5 (51/208)	(18.83, 30.95)	77.4 (130/168)
Moderate	5.8 (12/208)	(3.02, 9.86)	16.1 (27/168)
Severe	1.9 (4/208)	(0.53, 4.85)	6.5 (11/168)

Table 7B Duration of Device-/Procedure-related Adverse Events Before Repeat Treatment (Treated mITT Population, N = 208)

Duration	**Events % (n/N)**
≤ 7 Days	12.5 (21/168)
8-30 Days	17.9 (30/168)
> 30 Days	62.5 (105/168)
Not yet Resolved	2.4 (4/168)

Most AEs were related to the study device or procedure. Before repeat treatment, 60 subjects (28.8%, 60/208) in the treated mITT population experienced 168 device-/procedure-related AEs. These 168 events include AEs that were device-related only (n = 41), those that were device and procedure-related (n = 102), and those that were procedure-related only (n = 25). Of these 168 AEs, 77.4% (130/168) were mild, 16.1% (27/168) were moderate, and 6.5% (11/168) were

severe. The severe AEs included injection site bruising (4 events), injection site pain (2), injection site erythema (1), injection site hypertrophy (1), injection site mass (1), injection site swelling (1), and injection site angioedema (1). All of these events resolved without sequelae and within 1 month. Of these events, only the injection site angioedema required intervention. It was resolved following administration of oral antihistamine, hyaluronidase injection, and oral anti-inflammatory medication. The AE not at the injection site was presyncope. The 3 AEs that had an onset of greater than 30 days were injection site pain, oral herpes, and injection site hypoaesthesia. Of the 168 device-/procedure-related AEs 62.5% lasted more than 30 days. No deaths occurred. No action was taken for 91.1% (153/168), medication was administered for 7.7% (13/168), nondrug therapy for 1.2% (2/168), and other action was taken for 0.6% (1/168) of the AEs. The AEs treated with medication included chapped lips (4 events), injection site reaction (2), herpes simplex (2), injection site bruising (2), oral herpes (1), angioedema (1), and injection site vesicles (1). The AEs treated with nondrug therapy were injection site mass and presyncope. The AE of presyncope was also treated with other action (treated with orange juice). The most common device/procedure related AEs were injection site mass and injection site induration (Table 8).

Table 8: Device/Procedure-Related AEs with Onset Prior to Repeat Treatment Occurring in >1% of Treated mITT Subjects

AE	Subjects % (n/N)
Injection Site Mass	15.9% (33/208)
Injection Site Induration	10.1% (21/208)
Injection Site Discoloration	4.8% (10/208)
Injection Site Pain	4.3% (9/208)
Injection Site Bruising	3.4% (7/208)
Injection Site Swelling	3.4% (7/208)
Injection Site Erythema	1.9% (4/208)
Injection Site Reaction	1.9% (4/208)

All non-device-/procedure-related AEs occurred at incidence rates of < 2.5%. The most common non–device-/procedure-related AEs were sinusitis, nasopharyngitis, acne, actinic keratosis, and procedural pain (related to a procedure other than the study procedure). All other non–device-/procedure-related AEs occurred at incidence rates of < 1%.

Subgroup Analyses

Subgroup analyses were completed to compare rates of AE and ISRs in Fitzpatrick I, II, and III subjects to skin type IV, V, and VI subjects (tables 9, 10). No increased safety risk was observed based on phototype.

Table 9: Severity after Initial Treatment for ISRs Occurring in > 5% of Subjects by Fitzpatrick Skin Type

ISR	Fitzpatrick Skin Types I/II/III			
	% (n/N)	Severity		
		Mild	Moderate	Severe
Any ISR	100% (165/165)	9.1%	48.5%	42.4%
Swelling	98.8% (163/165)	23.3%	50.3%	26.4%
Bruising	97.6% (161/165)	16.8%	46.0%	37.3%
Firmness	92.1% (152/165)	27.6%	53.9%	18.4%
Lumps/Bumps	90.3% (149/165)	31.5%	50.3%	18.1%
Tenderness	88.5% (146/165)	43.2%	40.4%	16.4%
Redness	84.2% (139/165)	36.0%	44.6%	19.4%
Pain	77.6% (128/165)	46.1%	43.8%	10.2%
Discoloration	38.8% (64/165)	50.0%	35.9%	14.1%
Itching	31.5% (52/165)	57.7%	34.6%	7.7%

ISR	Fitzpatrick Skin Types IV/V/VI			
	% (n/N)	Severity		
		Mild	Moderate	Severe
Any ISR	96.4% (27/28)	37.0%	48.1%	14.8%
Swelling	78.6% (22/28)	31.8%	54.5%	13.6%
Bruising	67.9% (19/28)	42.1%	52.6%	5.3%
Firmness	75.0% (21/28)	52.4%	42.9%	4.8%
Lumps/Bumps	71.4% (20/28)	60.0%	30.0%	10.0%
Tenderness	67.9% (19/28)	63.2%	26.3%	10.5%
Redness	42.9% (12/28)	41.7%	58.3%	0%
Pain	53.6% (15/28)	73.3%	26.7%	0%
Discoloration	21.4% (6/28)	66.7%	33.3%	0%
Itching	14.3% (4/28)	100%	0%	0%

Table 10: Device/procedure AE incidence with onset prior to repeat treatment of treated mITT subjects by Fitzpatrick Skin Type

	Fitzpatrick Skin Types I/II/III	Fitzpatrick Skin Types IV/V/VI
Total % (n/N)	32.2% (56/174)	11.8% (4/34)
Severity		
Mild	83.9%	100.0 %
Moderate	21.4%	0.0 %
Severe	7.1%	0.0 %
Mean Duration (Days)	71 (N=53)	57 (N=4)

Subgroup analysis was also completed to analyze ISRs and AEs in relation to age (tables 11, 12). No differences in safety were observed in younger subjects (≤35).

Table 11: ISRs Occurring in > 5% of Subjects by Maximum Severity by Age

ISR	Age ≤ 35 (N = 25)				Age > 35 (N = 218)			
		Severity				Severity		
		Mild	Moderate	Severe		Mild	Moderate	Severe
	% (n/N)	%	%	%	% (n/N)	%	%	%
Any ISR	100% (25/25)	20.0%	24.0%	56.0%	99.5% (217/218)	13.4%	52.5%	34.1%
Swelling	100% (25/25)	40.0%	32.0%	28.0%	95.0% (207/218)	23.2%	54.1%	22.7%
Bruising	92.0% (23/25)	21.7%	26.1%	52.2%	93.1% (203/218)	22.2%	49.8%	28.1%
Firmness	88.0% (22/25)	31.8%	36.4%	31.8%	88.1% (192/218)	31.3%	56.3%	12.5%
Lumps/Bumps	96.0% (24/25)	33.3%	45.8%	20.8%	84.9% (185/218)	38.4%	47.6%	14.1%
Tenderness	96.0% (24/25)	45.8%	29.2%	25.0%	84.9% (185/218)	50.3%	38.4%	11.4%
Redness	72.0% (18/25)	66.7%	5.6%	33.3%	77.5% (169/218)	43.2%	42.8%	13.0%
Pain	72.0% (18/25)	44.4%	27.8%	27.8%	72.5% (158/218)	54.4%	39.9%	5.7%
Discoloration	28.0% (7/25)	42.9%	28.6%	28.6%	35.8% (78/218)	57.7%	33.3%	9.0%
Itching	12.0% (3/25)	0%	33.3%	66.7%	29.4% (64/218)	68.8%	28.1%	3.1%

Table 12: Device/procedure AE incidence with onset prior to repeat treatment of treated mITT subjects by Age

	Age ≤ 35 (N=28)	Age > 35 N=230
Total % of subjects (n/N)	32.1% (9/28)	30.9% (71/230)
Severity		
Mild	88.9%	70.4%
Moderate	33.3%	36.6%
Severe	11.1%	9.9%
Mean Duration (Day)	99 (N=8)	57 (N=69)

AEs and ISRs were analyzed related to investigational site (table 13). While there appears to be disparity between the sites, the results of a poolability analysis conducted using multivariate analyses to determine the impact of investigational site on safety and effectiveness in the presence of other covariates demonstrated that investigational site was not a significant factor.

Table 13: Incidence Rate of Device/Procedure-Related AEs by Site

Site	Incidence Rate	95% Confidence Interval
10002	25.6% (11/43)	13.52%, 41.17%
10003	15.4% (4/26)	4.36%, 34.87%
10005	35.6% (16/45)	21.87%, 51.22%
10006	27.8% (5/18)	9.69%, 53.48%
10007	37.5% (3/8)	8.52%, 75.51%
10008	41.2% (14/34)	24.65%, 59.30%
10010	30.0% (6/20)	11.89%, 54.28%
10012	0% (0/8)	0%, 36.94%
10013	16.7% (1/6)	0.42%, 64.12%

ISRs and AEs after Repeat Treatment

After repeat treatment, 17 subjects (14.9%, 17/114) experienced 59 device-/procedure-related AEs (table 14). Of these, 76.3% (45/59) were mild, 23.7% (14/59) were moderate, and none were severe. All (100.0%, 59/59) occurred at the injection site. The time to onset was ≤ 30 days after repeat treatment for 91.5% (54/59) of AEs. For the remaining 5 events, the time to onset was 31 to 90 days. The AEs with a time to onset of 31 to 90 days were injection site pruritus (3 events), injection site mass (1 event), and injection site induration (1 event). Of the 59 device-/procedure-related AEs, none lasted for 14 days or less, 11.9% (7/59) lasted for 15 to 30 days, 50.8% (30/59) for 31 to 60 days, 23.7% (14/59) for 61 to 90 days, and 11.9% (7/59) for greater than 90 days. The AEs that lasted greater than 90 days were injection site mass (5 events) and injection site induration (2 events). Nearly all AEs had resolved: 98.3% (58/59) resolved without sequelae, and 1.7% (1/59) is ongoing (injection site erythema). No deaths and no unknown outcomes occurred. No action was taken for any of the 59 AEs.

Table 14A: Summary of Device-/Procedure-related AEs After Repeat Treatment

	Subjects % (n/N)	**95% Confidence Interval (%,%)**	**Events % (n/N)**
One or More Adverse Event	14.9 (17/114)	(8.93, 22.80)	100.0 (59/59)
At Injection Site	14.9 (17/114)	(8.93, 22.80)	100.0 (59/59)
Upper lip	13.2 (15/114)	(7.56, 20.77)	47.5 (28/59)
Upper Perioral Lines	6.1 (7/114)	(2.50, 12.24)	16.9 (10/59)
Lower lip	9.6 (11/114)	(4.92, 16.61)	33.9 (20/59)
Lower Perioral Lines	6.1 (7/114)	(2.50, 12.24)	18.6 (11/59)
Oral Commissures	7.0 (8/114)	(3.08, 13.36)	18.6 (11/59)
Severity			
Mild	13.2 (15/114)	(7.56, 20.77)	76.3 (45/59)
Moderate	3.5 (4/114)	(0.96, 8.74)	23.7 (14/59)
Severe	0	(0.00, 3.18)	0

Table 14B: Duration of Device-/Procedure-related AEs after Repeat Treatment

Duration	**Events % (n/N)**
≤ 7 Days	0
8-30 Days	11.9 (7/59)
> 30 Days	86.4 (51/59)
Not yet Resolved	1.7 (1/59)

AEs after repeat treatment were similar to those observed prior to repeat treatment (Table 15).

Table 15: Device/Procedure-Related AEs with Onset after Repeat Treatment Occurring in >1% of Treated mITT Subjects

AE	**Subjects % (n/N)**
Injection Site Mass	9.6% (11/114)
Injection Site Induration	9.6% (11/114)
Injection Site Pain	5.3% (6/114)
Injection Site Swelling	2.6% (3/114)
Injection Site Erythema	2.6% (3/114)

The type and duration of ISRs were also similar after repeat treatment (Table 16).

Table 16: Severity and Duration after Repeat Treatments for ISRs Occurring in > 5% of Subjects

ISR[c]		Severity[a]			Duration[b]			
		Mild	Moderate	Severe	1-3 Days	4-7 Days	8-14 Days	15-30 Days
Repeat Treatment (N[d] = 103)								
Any ISR	97.1%	12.0%	57.0%	31.0%	10.0%	25.0%	26.0%	39.0%
Swelling	94.2%	30.9%	53.6%	15.5%	35.1%	37.1%	15.5%	12.4%
Bruising	91.3%	24.5%	58.5%	17.0%	28.7%	48.9%	20.2%	2.1%
Firmness	88.3%	30.8%	56.0%	13.2%	23.1%	23.1%	24.2%	29.7%
Lumps/Bumps	85.4%	39.8%	51.1%	9.1%	31.8%	18.2%	22.7%	27.3%
Tenderness	82.5%	52.9%	42.4%	4.7%	38.8%	22.4%	29.4%	9.4%
Redness	80.6%	43.4%	51.8%	4.8%	41.0%	43.4%	10.8%	4.8%
Pain	68.9%	54.9%	39.4%	5.6%	57.7%	29.6%	9.9%	2.8%
Itching	33.0%	76.5%	20.6%	2.9%	70.6%	17.6%	8.8%	2.9%
Discoloration	27.2%	46.4%	35.7%	17.9%	50.0%	35.7%	10.7%	3.6%

[a] Maximum severity reported in the diary. Denominator for percentages by severity is the number of subjects with corresponding ISR
[b] Maximum reported successive occurrence of an ISR. Denominator for percentages by duration is the number of subjects with corresponding ISR
[c] ISRs are listed in decreasing order of frequency of occurrence
[d] N denotes the number of subjects who recorded in the diaries after treatment

Other Safety Evaluations

Subjects completed a self-assessment questionnaire related to the function and sensation of the lips and mouth area, which comprises 13 questions asking if functional ability (eg, ability to speak, eat, suck, brush, floss, kiss, whistle, or pucker) or sensation (eg, sensitivity to cold or touch, feeling numb, tingling, or burning) was affected by study treatment. Possible responses for each question ranged from 0 to 10 (0 = not at all, 5 = somewhat, and 10 = very much), and results were grouped in ranges of 0 to 3, 4 to 6, and 7 to 10. For all questions at all timepoints, > 90% of subjects scored 0 to 3 indicating that functional ability or sensation was not affected by study treatment.

The treating investigator also assessed functional features of the lips and mouth. Based on these results, the proportion of responses indicating the subjects were not affected by the treatment was between 95.7% and 100%.

The evaluating investigator also assessed lip sensitivity at all follow up visits. The test evaluated the minimum distance for which subjects indicated they felt 2 points of pressure. Median scores were similar pre and post treatment. The evaluating investigator also used a light touch assessment to determine the smallest filament a subject could feel. The majority of responses at all timepoints occurred with the two smallest filaments.

2. Effectiveness Results

The analysis of effectiveness was based on the blinded live evaluator's assessment of the overall lip fullness or lip fullness of eligible lip at the 3-month

timepoint on the validated Allergan Lip Fullness Scale. Key effectiveness outcomes are presented in tables 17 to 20.

Based on EI assessments at Month 3, the treatment group responder rate (79.1%) was significantly greater ($p < 0.0001$) than the control group responder rate (26.1%) and greater than the 60% responder rate established *a priori* as meaningful clinical effectiveness (table 17).

Table 17: Month 3 Overall Lip Fullness based on EI Assessments (mITT population)

	Responder Rate at Month 3	95% Confidence Interval	P-Value
Treatment Group	79.1% (110/139)	71.43%, 85.56%	
Control Group	26.1% (12/46)	14.27%, 41.13%	
Difference in Responder Rates	53%		<0.0001

The subjects were followed up to 12 months following treatment, and effectiveness was determined at 1, 3, 6, 9, and 12 months (table 18). A majority of the assessed subjects had a treatment effect at 12 months.

Table 18: Lip Fullness Effectiveness through 1 Year

		Treatment Group (N=157)
	N[a]	**Responder Rate % (n)**
Baseline	157	N/A
1 Month	139	79.9% (111)
3 Months	139	79.1% (110)
6 Months	118	80.5% (95)
9 Months	99	63.6% (63)
12 Months	101	56.4% (57)

[a] Number of subjects with data at baseline and the specified timepoint

Repeat treatment was administered to 114 subjects. The effectiveness profile after repeat treatment was similar to that after the initial treatment (table 19)

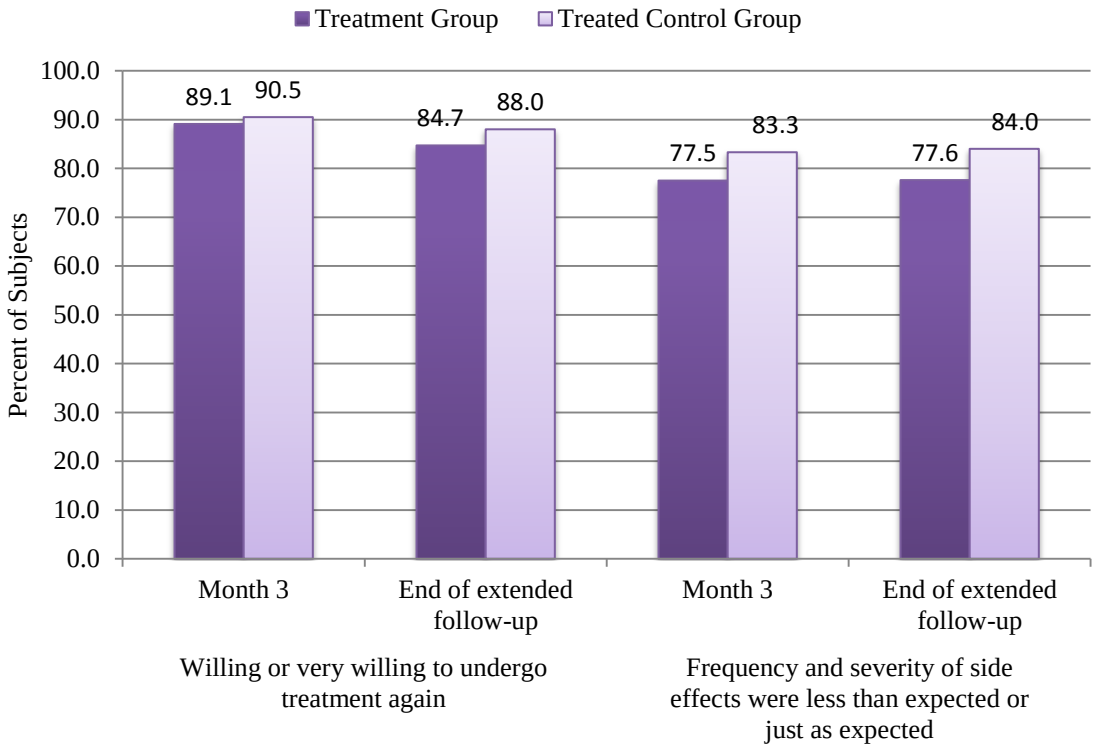
Table 19: Lip Fullness Effectiveness after Repeat Treatment

	n[a]	**Responder Rate % (n)**
Month 1	71	87.3% (62)
Month 3	76	85.5% (65)

[a] Number of subjects with data at baseline and the specified timepoint

Subject self assessments were completed to determine the subject willingness to undergo treatment again (Figure 3).

Figure 3: **Willingness to undergo treatment again by subject self assessments**



Objective lip measurements calculated from the 3D imaging showed an increase in both lip volume and overall lip surface area. At Month 3, treatment group subjects showed a mean increase in lip volume of 0.61 cc and a 25% increase in surface area (N = 130), while control group subjects showed almost no increase in lip volume and an 8% increase in surface area (N = 44). Treatment group subjects showed an increase in these measurements at later timepoints that gradually tapered off to a mean lip volume increase of 0.54 cc and a 19% surface area increase at Month 12 (N = 54). As expected, these measurements increased after repeat treatment, with treatment group subjects showing a 0.73 cc mean lip volume increase and 34% surface area increase at Month 3 post-repeat treatment (N = 69). Similar results were obtained for treated control group subjects.

Secondary endpoints included upper and lower lip fullness as determined by the Allergan Lip Fullness scale, upper lip perioral line and oral commissures improvement, and achievement of treatment goals by subject assessment (Table 20). The perioral lines and oral commissure responder rates at Month 3 (47.5% [29/61] and 47.3% [114/241], respectively) may demonstrate some improvement in severity of upper lip perioral lines and oral commissures; however inadequate information was presented regarding the clinical and statistical significance of this improvement. Subgroup analysis was not conducted for these secondary effectiveness endpoints.

Table 20: Improvement in Lip and Mouth Areas and Treatment Goal Achievement

Month 3 Assessments	Responder Rate[a]	99% CI[b]
	% (n/N)	(%,%)
Improvement since baseline: EI assessment		
Upper lip fullness since baseline	75.4 (104/138)	(64.77, 84.15)
Lower lip fullness since baseline	79.9 (107/134)	(69.56, 87.95)
Upper lip perioral lines since baseline[c]	47.5 (29/61)	(31.01, 64.46)
Oral commissures since baseline[d]	47.3 (114/241)	(38.93, 55.78)
Achievement of treatment goals: Subject assessment[e]	81.8 (112/137)	(71.83, 89.38)

CI = confidence interval, EI = Evaluating Investigator, OCS = Oral Commissures Severity Scale, POL = Perioral Lines Severity Scale

[a] Responder rates are the proportion of subjects who exhibit ≥ 1 point improvement (ie, increase of 1 point in LFS2 score for lips and a decrease in POL and OCS scores for perioral lines and oral commissures, respectively), since baseline

[b] Confidence intervals were adjusted for multiplicity of secondary endpoints using the Bonferroni correction

[c] The denominator is the number of subjects who received treatment in the perioral lines

[d] The denominator is the number of oral commissures that were treated

[e] The denominator is the number of subjects who indicated treatment goal achievement

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: baseline lip fullness, gender, race, site, plane of injection, injection technique, injection volume, and Fitzpatrick skin phototype (table 21). No differences in overall lip fullness responder rates at Month 3 were observed based on the following subgroup analyses: baseline lip fullness, gender, race, investigational site, plane of injection, injection technique, injection volume, injection site, and Fitzpatrick skin phototype.

Table 21: Subgroup analysis of lip fullness responder rate at month 3- treament group

Subgroup	Treatment Group Responder Rate at 3 Months (%) (n/N)	95% CI (%, %)
Baseline overall lip fullness		
Minimal	86.4 (38/44)	(72.65, 94.83)
Mild	79.5 (66/83)	(69.24, 87.59)
Gender		
Female	78.2 (104/133)	(70.21, 84.88)
Male	100.0 (6/6)	(54.07, 100.00)
Race		
Caucasian	79.7 (94/118)	(71.27, 86.51)
Hispanic	75.0 (6/8)	(34.91, 96.81)
African-American	81.8 (9/11)	(48.22, 97.72)
Asian	N/A	N/A
Other	50.0 (1/2)	(1.26, 98.74)
Fitzpatrick skin phototype		
I/II/III	78.6 (92/117)	(70.09, 85.67)
IV/V/VI	81.8 (18/22)	(59.72, 94.81)
Investigational site		
10002	81.5 (22/27)	(61.92, 93.70)
10003	83.3 (15/18)	(58.58, 96.42)
10005	75.8 (25/33)	(57.74, 88.91)
10006	100.0 (10/10)	(69.15, 100.00)
10007	100.0 (5/5)	(47.82, 100.00)
10008	54.5 (12/22)	(32.21, 75.61)
10010	92.3 (12/13)	(63.97, 99.81)
10012	75.0 (6/8)	(34.91, 96.81)
10013	100.0 (3/3)	(29.24, 100.00)
Plane of injection		
Intra-dermal	80.0 (68/85)	(69.92, 87.90)
Subdermal	81.4 (79/97)	(72.27, 88.62)
Intramuscular	80.4 (45/56)	(67.57, 89.77)
Injection technique		
Tunneling	79.1 (110/139)	(71.43, 85.56)
Serial puncture	83.9 (73/87)	(74.48, 90.91)
Fanning	86.3 (44/51)	(73.74, 94.30)
Cross-hatching	78.9 (45/57)	(66.11, 88.62)
Volume injected (mL)		
≤ 2.15 mL	70.1 (47/67)	(57.73, 80.72)
> 2.15 mL	87.5 (63/72)	(77.59, 94.12)

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 9 investigators. None of the 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. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of the product effectiveness is based on the results of the pivotal study. The submitted data provide a reasonable assurance of effectiveness of Juvéderm Ultra XC for lip augmentation when injected into the lips and perioral area in patients over the age of 21. Specific conclusions are:

- The study met its prespecifed success criteria. The primary effectiveness measure was the blinded evaluating investigator (EI)'s live assessment of the subject's overall lip fullness (for Fitzpatrick skin types I, II or III), or lip fullness of the eligible lip (for subjects with Fitzpatrick skin type IV, V, or VI who had only 1 eligible lip), on the validated 5-point Allergan Lip Fullness Scale. A responder was defined as a subject having a greater than or equal to 1-point improvement on the Allergan Lip Fullness Scale. Based on EI assessments at Month 3, the treatment group responder rate was 79.1% (110/139) with 95% CI (71.4%, 85.6%), and it was significantly greater ($p < 0.0001$) than the control group responder rate of 26.1% (12/46) with 95% CI (14.3%, 41.1%). The treatment group responder rate was also greater than the prespecified 60% to show clinical significance.

- Lip augmentation was consistently effective when evaluating subjects with Fitzpatrick skin types IV, V, and VI and subjects > 21 and ≤ 35 compared to the overall study population.

- A majority of subjects were injected in multiple injection sites. Comparing the injection site, plane, and technique used in the study, the effectiveness of the device was independent of these factors.

- The majority of treatment group subjects (81.8%, 112/137) assessed that their treatment goals at Month 3 were met. In addition, the Month 3 responder rates based on EI assessments for improvement in upper lip fullness (75.4%, 104/138) and lower lip fullness (79.9%, 107/134) were similar to that for overall lip fullness.

- The perioral lines and oral commissure responder rates at Month 3 (47.5% [29/61] and 47.3% [114/241], respectively) may demonstrate some improvement in severity of upper lip perioral lines and oral commissures;

however inadequate information was presented regarding the clinical and statistical significance of this improvement.

- The majority of treatment group subjects (81.8%, 112/137) assessed that their treatment goals at Month 3 were met. Following extended follow-up, 84.7% (72/85) of the treatment group indicated a willingness to undergo treatment again.

- Effectiveness with concomitant therapies or in subjects under the age of 22 was not studied.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The submitted data provide a reasonable assurance of safety of Juvéderm Ultra XC for lip augmentation when injected into the lips and perioral area in patients over the age of 21. The specific conclusions are

- Ninety nine percent of subjects experienced at least one injection site response. The most common injection site responses were swelling, bruising, firmness, lumps/bumps, tenderness, redness, and pain. Many subjects reported the severity of their ISR after initial treatment as moderate (48.4%, 93/192) or severe 38.5% (74/192).

- Most ISRs lasted less than 2 weeks after initial (64.1%, 123/192) and repeat treatment (61.0%, 61/100), but 35.9% of the ISRs lasted between 15 and 30 days of duration. The most common ISRs that lasted for 15 to 30 days after initial treatment were lumps/bumps (30.8%, 52/169), firmness (21.4%, 37/173), and swelling (10.8%, 20/185). Similarly after repeat treatment, the most common ISRs lasting 15 to 30 days were firmness (29.7%, 27/91), lumps/bumps (27.3%, 24/88), and swelling (12.4%, 12/97).

- Twenty-nine percent of subjects experienced 168 investigator-reported AEs. Of these 168 AEs, 77.4% (130/168) were mild, 16.1% (27/168) were moderate, and 6.5% (11/168) were severe. The severe AEs included injection site bruising (4 events), injection site pain (2), injection site erythema (1), injection site hypertrophy (1), injection site mass (1), injection site swelling (1), and injection site angioedema (1). One subject experienced a serious device related AE (angioedema). This event resolved with intervention, but without sequelae.

- A majority of subjects were injected in multiple injection sites. Comparing the injection site, plane, and technique used in the study, the incidence of ISRs and AEs was independent of these factors.

- Lips treated for perioral lines and oral commissures showed a safety profile similar to the overall study population.

- Similar proportions of AEs and ISRs were observed in Fitzpatrick skin types IV, V, and VI and subjects ≤35 years of age compared to the overall population.

- A majority of treatment group subjects (77.6%) at the end of the extended follow-up period reported that side effects were less than or as severe and frequent as expected.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The study was a, prospective, no-treatment controlled study using a validated scale and blinded, live evaluations. The study investigated the safety and effectiveness of Juvéderm Ultra for lip augmentation. The primary effectiveness endpoint was improvement of ≥1 point on the validated Allergan Lip Fullness Scale at 3 months. The data are considered to be as robust as possible for an aesthetic endpoint. At 3 months, 79.1% (110 of 139) of subjects experienced a 1- point or greater increase in lip fullness compared to 26.1% (12/46) of the control group. The treatment effect at 6 months was similar, with 80.5% (95/118) subjects experiencing the same 1-point or greater increase. By 12 months the effectiveness rate decreases to 56.4% (57/101). Effectiveness of repeat treatment was similar to initial treatment. The majority of treatment group subjects (81.8%, 112/137) assessed that their treatment goals at Month 3 were met. Following extended follow-up, 84.7% (72/85) of the treatment group indicated a willingness to undergo treatment again. The perioral lines and oral commissure responder rates at Month 3 (47.5% [29/61] and 47.3% [114/241], respectively) may demonstrate some improvement in severity of upper lip perioral lines and oral commissures; however inadequate information was presented regarding the clinical and statistical significance of this improvement. Thus, the treatment benefit for perioral lines and oral commissures was not determined.

Additional factors to be considered in determining probable risks and benefits for the Juvéderm Ultra XC device included: Nearly all of the treated subjects (99.5%, 192/193) experienced an injection site response. The most frequently reported ISRs after initial and repeat treatment were swelling (95.9%, 185/193, and 94.2%, 97/103, respectively), bruising (93.3%, 180/193 and 91.3%, 94/103, respectively), and firmness (89.6%, 173/193 and 88.3%, 91/103, respectively). Other common ISRs were lumps/bumps (87.6%, 169/193), tenderness (85.5%, 165/193), redness (78.2%, 151/193), and pain (74.1%, 143/193). Notably, a large portion of subjects reported the severity of their ISR after initial treatment as moderate (48.4%, 93/192) or severe 38.5% (74/192). Before repeat treatment, 60 subjects (28.8%, 60/208) in the treated mITT population experienced 168 device-/procedure-related AEs. Of these 168 AEs, 77.4% (130/168) were mild, 16.1% (27/168) were moderate, and 6.5% (11/168) were severe. The severe AEs included injection site bruising (4 events), injection site pain (2), injection site erythema (1), injection site hypertrophy (1), injection site mass (1), injection site swelling (1), and injection site angioedema (1). All of these events resolved without sequelae and within 1 month. Rare risks include infection and vascular occlusion (including ocular) from embolization. Neither was observed in this

pivotal study. A majority of treatment group subjects (77.6%, 66/85) at the end of the extended follow-up period reported that side effects were either less than or as severe as expected. This, combined with 84.7% (72/85) of the treatment group willing to undergo treatment again indicates that the majority of subjects value the treatment benefit when weighted against the adverse effects.

The probable benefits outweigh the probable risks, as determined by the robustness of the effectiveness results, the lack of any long term sequelae, and subject willingness to undergo treatment again. 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.

In conclusion, given the available information above, the data support the use of Juvéderm Ultra XC for lip augmentation in patients over the age of 21, and the probable benefits outweigh the probable risks, as determined by short term adverse outcomes and the rare adverse events seen after injection balanced against the improvement seen in the Allergan Lip Fullness Scale and patient willingness to undergo treatment again.

D. Overall Conclusions

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

XIII. CDRH DECISION

CDRH issued an approval order on September 30, 2015.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.