JUVÉDERM® VOLUMA™ XC

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION

JUVÉDERM® VOLUMA™ XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, which is crosslinked with BDDE. It is formulated to a concentration of 20 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

2. INTENDED USE/INDICATIONS

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

3. 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.

4. WARNINGS

- The product must not be injected into blood vessels. Introduction of JUVÉDERM® VOLUMA™ XC into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur (see Health Care Professional Instructions#14).
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process

has been controlled.

- Treatment site reactions consist mainly of short-term inflammatory symptoms and generally resolve within 2 to 4 weeks. Refer to the ADVERSE EVENTS section for details.

5. PRECAUTIONS

- JUVÉDERM® VOLUMA™ XC is packaged for single-patient use. Do not resterilize. Do not use if package is open or damaged.
- In order to minimize the risks of potential complications, this product should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care professionals are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- Based on preclinical studies and a toxicological risk assessment, patients should be limited to 20 mL of any JUVÉDERM® injectable gel per 60 kg (130 lbs) body mass per year. The safety of injecting greater amounts has not been established.
- The safety and effectiveness for the treatment of anatomic regions other than the mid-face, chin, and pre-jowl sulcus regions have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- JUVÉDERM® VOLUMA™ XC is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product.
- The safety for use during pregnancy, in breastfeeding females, and in patients with very thin skin in the mid-face region has not been established.
- The safety has been established for use in patients between 35 and 65 years of age for cheek augmentation and patients between 22 and 80 years of age for chin augmentation.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- JUVÉDERM® VOLUMA™ XC should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at treatment sites.
- Patients who experience skin injury near the site of JUVÉDERM® VOLUMA™ XC implantation may be at a higher risk for adverse events.
- Patients may experience late onset nodules with use of dermal fillers, including JUVÉDERM® VOLUMA™ XC. Refer to ADVERSE EVENTS section for details.
- The safety and effectiveness of cannula injection of JUVÉDERM® VOLUMA™ XC has only been clinically evaluated with the TSK STERiGLIDE™ 25G 1 ½" cannula.
- The safety of JUVÉDERM® VOLUMA™ XC with cannula for cheek augmentation has not been established in patients with Fitzpatrick Skin Types V and VI.
- After use, treatment syringes and needles may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal

requirements.

- JUVÉDERM® VOLUMA™ XC injectable gel is a clear, colorless gel without visible particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; notify Allergan Product Surveillance at (877) 345-5372.
- JUVÉDERM® VOLUMA™ XC should only be used by health care professionals who have appropriate experience and who are knowledgeable about the anatomy and the product for use in deep (subcutaneous and/or supraperiosteal) injection for cheek and chin augmentation.
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the LUER-LOK® and needle hub connection.
- Skin laxity of the chin, neck or jaw could obscure the effects of JUVÉDERM® VOLUMA™ XC treatment in the chin region. Therefore, in the chin study, the device was not evaluated in subjects with significant skin laxity of the chin, neck or jaw.
- The effect of JUVÉDERM® VOLUMA™ XC injection into the chin on facial hair growth has not been studied.

6. ADVERSE EVENTS

A. Clinical Evaluation of JUVÉDERM® VOLUMA™ XC for Cheek Augmentation

In the randomized, controlled clinical trial to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA™ XC, there were 238 subjects 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; 32 control subjects were treated in the study. 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 also underwent repeat treatment following completion of the extended follow-up phase of the study, with 162 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 mild (21.5%) or moderate (59.2%) in severity with a duration of 2 to 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 data from 167 subjects who received repeat treatment, treatment site responses following repeat treatment were less severe, with reduced incidence and duration compared to initial treatment.

Treatment site responses reported by > 5% of subjects after initial treatments are summarized by severity in Table 1 and by duration in Table 2.

Table 1: Treatment Site Responses by Maximum Severity Occurring in > 5% of Subjects After Initial Treatment for Cheek Augmentation (N = 265)

	Severity[a]			
Treatment Site Response	**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.

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.

Table 2: Duration of Treatment Site Responses After Initial Treatment

	Duration[a]					
Treatment Site Response	**Total**	**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 in subject diaries that lasted longer than 30 days were considered adverse events (AEs). AEs were also reported by the Treating Investigator at all follow-up visits where applicable. Table 3 summarizes device/injection-related AEs that occurred with a frequency of > 1%. 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/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. Fewer AEs occurred after repeat treatment than after initial/touch-up treatment.

Table 3: Device/Injection-Related Adverse Events Occurring in > 1% of Treated Subjects for Cheek Augmentation (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/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.

B. 1-Year Post Approval Study of JUVÉDERM® VOLUMA™ XC for Cheek Augmentation

The post-approval study was a statistical evaluation of safety data collected in the JUVÉDERM® VOLUMA™ XC pivotal study. Safety data were analyzed from subjects who elected to undergo repeat treatment with JUVÉDERM® VOLUMA™ XC as part of the pivotal study. Pre-printed diary forms were used by subjects to record specific signs and symptoms experienced during each of the first 30 days after repeat treatment.

Treatment site responses reported by subjects in their diaries after repeat treatment are summarized by severity in Table 4 and by duration in Table 5. The incidence of treatment site responses after repeat treatment was lower than the incidence after initial/touch-up treatment, and treatment site responses were generally less severe and shorter in duration after repeat treatment compared to initial/touch-up treatment. The majority of treatment site responses after repeat treatment resolved within 2 weeks, while treatment site responses after initial/touch-up treatment typically resolved within 2 to 4 weeks.

Table 4: Treatment Site Responses by Maximum Severity Occurring in >5% of Subjects After Repeat Treatment for Cheek Augmentation (N=167)

Treatment Site Responses	Severity[a]			
	Total	Mild	Moderate	Severe
	% (n/N[b])	% (n/N[b])	% (n/N[b])	% (n/N[b])
Any Treatment Site Response	90.1% (146/162)	30.8% (45/146)	54.8% (80/146)	14.4% (21/146)
Tenderness	76.5% (124/162)	52.4% (65/124)	42.7% (53/124)	4.8% (6/124)
Swelling	67.9% (110/162)	42.7% (47/110)	54.5% (60/110)	2.7% (3/110)
Firmness	66.0% (107/162)	40.2% (43/107)	57.0% (61/107)	2.8% (3/107)
Bruising	62.3% (101/162)	49.5% (50/101)	37.6% (38/101)	12.9% (12/101)
Lumps/Bumps	58.0% (94/162)	46.8% (44/94)	47.9% (35/94)	5.3% (5/94)
Redness	56.8% (92/162)	59.8% (55/92)	38.0% (35/92)	2.2% (2/92)
Pain	54.9% (89/162)	65.2% (58/89)	30.3% (27/89)	4.5% (4/89)
Itching	32.7% (53/162)	79.2% (42/53)	20.8% (11/53)	0% (0/53)
Discoloration	26.5% (43/162)	72.1% (31/43)	27.9% (12/43)	0% (0/43)

[a] Maximum severity reported in the diary. The denominator for percentages by severity is the number of subjects with corresponding treatment site response.

[b] N denotes number of subjects who recorded responses in the diaries after the repeat treatment.

Table 5: Duration of Treatment Site Responses After Repeat Treatment

Treatment Site Responses	Duration[a]					
	Total	1-3 Days	4-7 Days	8-14 Days	15-30 Days	>30 Days
	% (n/N[b])	% (n/N[b])	% (n/N[b])	% (n/N[b])	% (n/N[b])	% (n/N[b])
Any Treatment Site Response	90.1% (146/162)	18.5% (27/146)	30.1% (44/146)	24.0% (35/146)	19.2% (28/146)	8.2% (12/146)
Tenderness	76.5% (124/162)	42.7% (53/124)	32.3% (40/124)	13.7% (17/124)	10.5% (13/124)	0.8% (1/124)
Swelling	67.9% (110/162)	61.8% (68/110)	23.6% (26/110)	7.3% (8/110)	6.4% (7/110)	0.9% (1/110)
Firmness	66.0% (107/162)	26.2% (28/107)	33.6% (36/107)	19.6% (21/107)	14.0% (15/107)	6.5% (7/107)
Bruising	62.3% (101/162)	33.7% (34/101)	33.7% (34/101)	23.8% (24/101)	7.9% (8/101)	1.0% (1/101)
Lumps/Bumps	58.0% (94/162)	37.2% (35/94)	28.7% (27/94)	16.0% (15/94)	10.6% (10/94)	7.4% (7/94)
Redness	56.8% (92/162)	58.7% (54/92)	29.3% (27/92)	7.6% (7/92)	4.3% (4/92)	0% (0/92)
Pain	54.9% (89/162)	65.2% (58/89)	20.2% (18/89)	11.2% (10/89)	3.4% (3/89)	0% (0/89)
Itching	32.7% (53/162)	81.1% (43/53)	13.2% (7/53)	5.7% (3/53)	0% (0/53)	0% (0/53)
Discoloration	26.5% (43/162)	76.7% (33/43)	7.0% (3/43)	7.0% (3/43)	7.0% (3/43)	2.3% (1/43)

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

Among the 167 subjects who received repeat treatment, 8.4% (14/167) experienced device/injection-related AEs following treatment. All AEs after repeat treatment occurred within 1 month of repeat treatment. The rate of device/injection-related AEs was lower after repeat treatment compared to initial/touch-up treatment. The most common AEs were injection site mass and induration (Table 6).

Table 6: Device/Injection-Related AEs after Repeat Treatment Occurring in > 1% of Treated Subjects for Cheek Augmentation (N = 167)

Adverse Event	Treated Subjects % (n/N)
Injection Site Mass	4.2% (7/167)
Injection Site Induration	4.2% (7/167)
Injection Site Bruising	1.2% (2/167)

All device/injection-related AEs after repeat treatment were mild to moderate, required no action, and resolved without sequelae. Generally, device/injection-related AEs were less severe after repeat treatment compared to initial/touch-up treatment, and most resolved within 3 months. Similar to the initial/touch-up treatment, 3 subjects experienced a device/injection-related AE that lasted more than 180 days, but all resolved without requiring any treatment. Device/injection-related adverse events occurring in ≤ 1% of subjects included injection site swelling (0.6%), injection site pain (0.6%), and injection site papule (0.6%).

Of the 121 subjects who completed the 12 months of follow-up after repeat treatment, none experienced any late onset device/injection-related AEs (those occurring more than 1 month after repeat treatment). There were no device/injection-related serious adverse events after repeat treatment.

C. Other Safety Data JUVÉDERM® VOLUMA™ XC Cannula Study

In the randomized, within-subject controlled clinical trial to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA™ XC using cannula in subjects seeking correction of age-related mid-face volume deficit, 60 subjects received treatment using a TSK STERiGLIDE™ 25G 1 ½" cannula in one cheek and a needle in the other cheek. To achieve optimal correction, the use of a needle was also permitted in the zygomaticomalar region in the cheek randomized to cannula. Preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after treatment. Of the 60 subjects who underwent treatment, 60 completed the diary forms. 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 treatment with JUVÉDERM® VOLUMA™ XC, all subjects reported experiencing a local treatment site response. Subjects rated treatment site responses as being mostly mild or moderate in severity (91.7%), with 60% of subjects having responses resolved within 2 weeks.

Treatment site responses reported by > 5% of subjects after initial treatments are summarized by severity in Table 7 and by duration in Table 8.

AEs were also reported by the Treating Investigator at all follow-up visits, when applicable. Among the 60 mITT subjects, 2 subjects experienced 3 treatment-related AEs (injection site mass on the needle cheek in one subject and injection site plaque on both the needle and cannula cheeks in another subject).

Table 7: Severity of ISRs Occurring in >5% of Subjects (Safety Population)

	Cannula Severity				Needle Severity			
Treatment Site Response	Total % (n/N [b])	Mild % (n/N [b])	Moderate % (n/N [b])	Severe % (n/N [b])	Total % (n/N [b])	Mild % (n/N [b])	Moderate % (n/N [b])	Severe % (n/N [b])
Any Treatment Site Response	100.0% (60/60)	50.0% (30/60)	41.7% (25/60)	8.3% (5/60)	100.0% (60/60)	43.3% (26/60)	45.0% (27/60)	11.7% (7/60)
Tenderness to touch	91.7% (55/60)	60.0% (36/60)	28.3% (17/60)	3.3% (2/60)	96.7% (58/60)	53.3% (32/60)	38.3% (23/60)	5.0% (3/60)
Firmness	83.3% (50/60)	53.3% (32/60)	28.3% (17/60)	1.7% (1/60)	90.0% (54/60)	53.3% (32/60)	31.7% (19/60)	5.0% (3/60)
Swelling	81.7% (49/60)	60.0% (36/60)	20.0% (12/60)	1.7% (1/60)	85.0% (51/60)	55.0% (33/60)	28.3% (17/60)	1.7% (1/60)
Lumps or bumps	70.0% (42/60)	51.7% (31/60)	16.7% (10/60)	1.7% (1/60)	83.3% (50/60)	56.7% (34/60)	25.0% (15/60)	1.7% (1/60)
Pain after injection	66.7% (40/60)	45.0% (27/60)	18.3% (11/60)	3.3% (2/60)	83.3% (50/60)	56.7% (34/60)	26.7% (16/60)	0% (0/60)
Bruising	60.0% (36/60)	40.0% (24/60)	16.7% (10/60)	3.3% (2/60)	71.7% (43/60)	41.7% (25/60)	30.0% (18/60)	0% (0/60)
Redness	55.0% (33/60)	46.7% (28/60)	8.3% (5/60)	0% (0/60)	61.7% (37/60)	45.0% (27/60)	16.7% (10/60)	0% (0/60)
Discoloration	36.7% (22/60)	28.3% (17/60)	8.3% (5/60)	0% (0/60)	43.3% (26/60)	28.3% (17/60)	15.0% (9/60)	0% (0/60)
Itching	18.3% (11/60)	16.7% (10/60)	1.7% (1/60)	0% (0/60)	20.0% (12/60)	20.0% (12/60)	0% (0/60)	0% (0/60)

[a] Maximum reported severity in the diary

[b] Denominator for percentages is the number of subjects who recorded in the diaries after the treatment.

Table 8: Total Duration of ISRs (Safety Population)

Treatment Site Responses	Cannula Duration[a]					Needle Duration[a]				
	Total % (n/N[b])	1 -3 Days % (n/N[b])	4 – 7 Days % (n/N[b])	8 – 14 Days % (n/N[b])	15 – 30 Days % (n/N[b])	Total % (n/N[b])	1 -3 Days % (n/N[b])	4 – 7 Days % (n/N[b])	8 – 14 Days % (n/N[b])	15 – 30 Days % (n/N[b])
Any Treatment Site Response	100.0% (60/60)	16.7% (10/60)	21.7% (13/60)	21.7% (13/60)	40.0% (24/60)	100.0% (60/60)	8.3% (5/60)	25.0% (15/60)	25.0% (15/60)	41.7% (25/60)
Tenderness to touch	91.7% (55/60)	25.0% (15/60)	26.7% (16/60)	23.3% (14/60)	16.7% (10/60)	96.7% (58/60)	23.3% (14/60)	31.7% (19/60)	26.7% (16/60)	15.0% (9/60)
Firmness	83.3% (50/60)	25.0% (15/60)	21.7% (13/60)	21.7% (13/60)	15.0% (9/60)	90.0% (54/60)	26.7% (16/60)	26.7% (16/60)	21.7% (13/60)	15.0% (9/60)
Swelling	81.7% (49/60)	33.3% (20/60)	30.0% (18/60)	6.7% (4/60)	11.7% (7/60)	85.0% (51/60)	28.3% (17/60)	35.0% (21/60)	15.0% (9/60)	6.7% (4/60)
Lumps or bumps	70.0% (42/60)	20.0% (12/60)	13.3% (8/60)	16.7% (10/60)	20.0% (12/60)	83.3% (50/60)	23.3% (14/60)	23.3% (14/60)	20.0% (12/60)	16.7% (10/60)
Pain after injection	66.7% (40/60)	53.3% (32/60)	5.0% (3/60)	5.0% (3/60)	3.3% (2/60)	83.3% (50/60)	53.3% (32/60)	16.7% (10/60)	11.7% (7/60)	1.7% (1/60)
Bruising	60.0% (36/60)	20.0% (12/60)	18.3% (11/60)	16.7% (10/60)	5.0% (3/60)	71.7% (43/60)	20.0% (12/60)	18.3% (11/60)	20.0% (12/60)	13.3% (8/60)
Redness	55.0% (33/60)	36.7% (22/60)	13.3% (8/60)	5.0% (3/60)	0% (0/60)	61.7% (37/60)	41.7% (25/60)	16.7% (10/60)	3.3% (2/60)	0% (0/60)
Discoloration	36.7% (22/60)	11.7% (7/60)	11.7% (7/60)	8.3% (5/60)	5.0% (3/60)	43.3% (26/60)	11.7% (7/60)	13.3% (8/60)	11.7% (7/60)	6.7% (4/60)
Itching	18.3% (11/60)	13.3% (8/60)	0% (0/60)	5.0% (3/60)	0% (0/60)	20.0% (12/60)	10.0% (6/60)	5.0% (3/60)	3.3% (2/60)	1.7% (1/60)

[a] Total calendar days from first to last occurrence of ISR in the diary

[b] Denominator for percentages is the number of subjects who recorded in the diaries after the treatment.

D. JUVÉDERM® VOLUMA™ XC Chin Augmentation Study

In a randomized, controlled clinical trial to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA™ XC for chin augmentation, there were 144 subjects treated with JUVÉDERM® VOLUMA™ XC in the chin area (pogonion, menton, and pre-jowl sulci, see Figure 2) 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 could receive treatment; 38 control subjects elected to receive treatment. Subjects were offered repeat treatment 12 months after the last treatment. A total of 74 subjects opted for the repeat treatment. Preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments. Of the 182 subjects who underwent treatment (from both the treatment and control groups), 181 subjects completed the diary forms, and of the 74 subjects who received repeat treatment, 73 completed the diary forms. Subjects were instructed to rate each treatment site response listed on the diary as "Mild (easily tolerated)," "Moderate (affecting daily activity)," "Severe (unable to do daily activity)," or "None."

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

TSRs reported by > 5% of subjects after initial treatments are summarized by severity in Table 9 and by duration in Table 10.

Table 9: Treatment Site Responses by Maximum Severity Occurring in > 5% of Subjects After Initial Treatment for Chin Augmentation (N=181)

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

[a] Maximum severity reported in the diary. The denominator for percentages by severity is the number of subjects with the corresponding treatment site response.

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

Table 10: Duration of Treatment Site Responses After Initial Treatment for Chin Augmentation (N = 181)

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

[a] Maximum duration reported in the diary. The denominator for percentages by duration is the number of subjects with the corresponding treatment site response.

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

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

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

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

Among the 182 treated subjects, 63 treated participants (34.6%) had 111 TEAEs, and 14 treated participants (7.7%, 14/182) had 20 treatment-related TEAEs following initial and touch-up treatment.

Table 11 summarizes treatment-related TEAEs that occurred with a frequency of > 1%. Treatment-related TEAEs occurring in ≤ 1% of subjects included injection site bruising, indentation, induration, inflammation, mass, edema, abscess, cellulitis, gingival pain, and cystic acne, all occurring in 0.5% (1/182) of subjects.

Table 11: Treatment-Related TEAEs Occurring in > 1% of Treated Subjects for Chin Augmentation (N = 182)

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

The majority of the treatment-related TEAEs after initial/touch-up treatment were mild or moderate in severity. For initial/touch-up treatment, 2.7% of participants had mild TEAEs, 4.4% had moderate TEAEs, and 1.1% had severe TEAEs.

Fifty percent (7/14) of the participants who experienced treatment-related TEAEs resolved within 1 week (Table 12). For initial/touch-up treatment, 3 participants (1.6%) had 4 treatment-related TEAEs that lasted longer than 30 days, including injection site inflammation that lasted 153 days and injection site cellulitis that lasted 36 days, injection site erythema that lasted 264 days, and acne cyst that lasted 134 days.

Fewer AEs occurred after repeat treatment than after initial/touch-up treatment (Table 12). Among the 74 subjects who received repeat treatment, 8 treated participants (10.8%; 8/74) had 12 TEAEs, and 3 treated participants (4.1%; 3/74) had 7 treatment-related TEAEs. The most common TEAE occurring after repeat treatment was injection site mass (2.7%; 2/74). For repeat treatment, 4.1% of participants had mild TEAEs, 1.4% had moderate TEAEs, and 0% had severe TEAEs (Table 13). All TEAEs after repeat treatment did not require any intervention and most resolved within 30 days without sequelae. After repeat treatment, 1 participant (1.4%) had 1 treatment-related TEAE that lasted longer than 30 days: injection site mass that lasted 42 days. There were no serious TEAEs after repeat treatment.

Table 12: Summary of TEAEs after Repeat Treatment (Safety Population)

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

[a] AEs with onset within 30 days of initial treatment are included for participants who received repeat treatment to compare the AE rate within the same subset of subjects.

For both initial/touch-up treatments and repeat treatment, most treatment-related TEAEs began within 7 days of treatment. For initial/touch-up treatment, 1 participant had 3 treatment-related TEAEs that began > 30 days after treatment: injection site edema that began 173 days, 248 days, and 252 days after treatment. These were resolved within 3 days with medication.

There were no treatment related TEAEs that began > 30 days after repeat treatment. All treatment-related TEAEs resolved without sequelae during the study period (12 months of follow-up after initial treatment or 1 month of follow-up after repeat treatment, if applicable). For initial/touch-up treatment, 4 participants had 5 treatment-related TEAEs that required treatment with medication or procedure.

Table 13: Summary of Treatment-related TEAEs for All Treated Participants (Safety Population)

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

Only needle treatment was allowed in the pogonion whereas all participants in the cannula treatment subgroup had some treatment with the needle. Results (Table 14) showed lower incidence of TSRs for injections with cannula than without cannula after each treatment (initial, touch-up, and repeat).

Table 14: Incidence of TSRs After Initial Treatment With and Without Cannula (Safety Population)

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

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

For initial/touch-up treatment with cannula, 2 treated participants (4.3%; 2/46) had 2 treatment-related TEAEs, and without cannula 12 treated participants (8.8%; 12/136) had 18 treatment-related TEAEs (Table 15). For repeat treatment with cannula, there were no treatment related TEAEs; without cannula 3 treated participants (5.4%; 3/56) had 7 treatment-related TEAEs.

Table 15: Comparison of Rate of Treatment-related TEAEs in Participants Treated with and without Cannula

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

A total of 11 subjects experienced 14 serious adverse events (SAEs) with onset after the study treatment in the VOLUMA-006 study (Table 16). One subject (0.5%; 1/182) reported 2 SAEs, injection site inflammation and injection site cellulitis, that were considered to be related to the device. These events began 7 days after touch-up treatment and were treated with hyaluronidase, antibiotics, steroid, analgesics/narcotics, sedative, anticoagulant, antacid, electrolyte solutions, antihistamine, and anti-inflammatory medicines. Both events resolved without sequelae, in 36 days for the cellulitis and 153 days for the inflammation, and the participant was discontinued from the study due to these events (the SAE of cellulitis required hospitalization). SAEs that were considered to be not treatment-related were non-cardiac chest pain, invasive papillary breast carcinoma, appendicitis, pneumonia, uterine hemorrhage, keratoacanthoma, squamous cell carcinoma, diverticulitis, atypical pneumonia, intraductal proliferative breast lesion, osteoarthritis, and cholecystitis.

Subjects above the median age (51.5 years and older), experienced more total SAEs (9.9%) than subjects younger than 51.5 years old (2.2%) (Table 27).

Table 16: Summary of Treatment-Related SAEs

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

Procedural Pain

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

Facial Function Assessments

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

Facial Sensation Assessments

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

The light touch assessment determined the smallest filament number for which participants felt the presence of the filament at the pogonion and halfway between the pogonion and each pre-jowl sulcus, where filaments ranged in diameter from 1.65 to 3.61 mm. The majority of responses at baseline and all posttreatment timepoints occurred with the smallest filament: 1.65 mm.

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

D. Other Safety Data

Postmarket Surveillance

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

The following AEs were received from postmarket surveillance for JUVÉDERM® VOLUMA™ XC with and without lidocaine with a frequency of 5 events or more and were not observed in the clinical study (during the 6-13 months that subjects were monitored in this study); this includes reports received globally from all sources including scientific journals and voluntary reports. All AEs obtained through postmarket surveillance are listed in order of number of reports received: inflammatory reaction, lack of correction, infection, migration, allergic reaction, abscess, paresthesia, vascular occlusion, drainage, necrosis, vision abnormalities, malaise, scarring, nausea, granuloma, deeper wrinkle, and dyspnea.

Reported treatments include: antibiotics, steroids, antiseptic creams, hyaluronidase, anti-inflammatories, antihistamines, needle aspiration, eye drops, radio frequency therapy, hyperbaric oxygen treatment, laser treatment, ice, massage, warm compress, analgesics, anti-virals, ultrasound therapy, excision, drainage, and surgery.

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

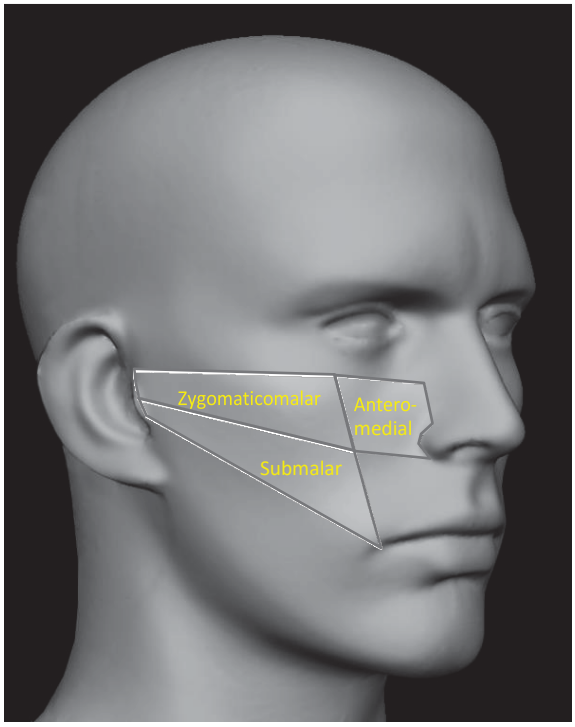
Adverse reactions should be reported to Allergan Product Surveillance Department at (877) 345-5372.

7. CLINICAL STUDIES

A. Pivotal Study for JUVÉDERM® VOLUMA™ XC for Cheek Augmentation Pivotal Study Design

A multi-center, single-blind, randomized, no-treatment controlled pivotal clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA™ XC for 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 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 Treating Investigator 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. EIs assessed subjects' overall mid-face volume deficit on the validated 6-point photometric Mid-Face Volume Deficit Scale (MFVDS) as well as volume deficit for each of the 3 facial sub-regions. EIs also assessed subjects' improvement on the 5-point Global Aesthetic Improvement Scale (GAIS), the 5-point photometric Nasolabial Fold Photo Severity Scale (NLFSS), and the 11-point Other Aesthetic Features of the Mid-Face questionnaire. Subjects performed self-assessments on MFVDS, GAIS, 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.

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.

Study Endpoints

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. 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.

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.

Subject Demographics

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%, 61/235) 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. Subject demographics and pre-treatment characteristics are presented in Table 17.

Table 9: Demographics and Pre-treatment Characteristics (N = 282)

Characteristic		Treatment Group (N = 235) % (n)	Control Group (N = 47) % (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)

Treatment Characteristics

Multiple injection techniques were used for 95% of subjects, with the most common being tunneling, fanning, and serial puncture. Subjects were injected equally in the 3 facial sub-regions for a total median volume of 2.0 mL for the zygomaticomalar region, 2.0 mL for the anteromedial cheek, and 2.1 mL for the submalar region. The overall total volume used to achieve optimal correction for all 3 sub-regions ranged from 1.2 mL to 13.9 mL, with a median of 6.6 mL. The median volume at initial treatment was 4.8 mL. A touch-up treatment was performed for 82% (195/238) of subjects. The median total volume used for touch-up treatment was 1.9 mL. The median volume injected for repeat treatment was 2.0 mL. The volume of JUVÉDERM® VOLUMA™ XC varied depending on the subject's volume deficit and treatment goal.

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 18). JUVÉDERM® VOLUMA™ XC was found to be effective in all Fitzpatrick Skin Types, for males and females, and across the studied age range.

Table 108: 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.

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 19 shows the mean MFVDS scores during the extended follow-up period (Months 9 to 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 119 Mean MFVDS Scores after Initial/Touch-up Treatment

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 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.

B. Post-Approval Study for JUVÉDERM® VOLUMA™ XC for Cheek Augmentation

Post-Approval Study Design

The post-approval study was a statistical evaluation of safety data collected from the pivotal study for JUVÉDERM® VOLUMA™ XC. The safety data were analyzed for subjects who elected to undergo repeat treatment with JUVÉDERM® VOLUMA™XC as part of the pivotal study. Treated subjects returned for safety visits with the Treating Investigator at 1, 3, 6, 9, and 12 or 12+ months. There were 14 enrolled study sites and 167 subjects from the pivotal study who received repeat treatment and were included in the post-approval study.

The study objective was to compare device/injection-related AEs before and after repeat treatment for subjects who received both initial/touch-up and repeat treatments.

Subject Accountability

After repeat treatment, 93.4% of subjects (156/167) attended the Month 1 visit. Of the 167 subjects, 127 subjects consented to long-term follow-up. At the end of the study, 95.3% of subjects (121/127) completed the follow-up at 12 or 12+ months.

Subject Demographics

Subject demographics (gender, age, race/ethnicity, and Fitzpatrick Skin Type) for the 167 subjects who received repeat treatment are shown in Table 20. The majority of subjects were female and Caucasian, with a median age of 56. Subjects were distributed across all Fitzpatrick Skin Types, with the majority being Fitzpatrick II, III, and IV.

Table 20: Post-Approval Study Subject Demographics

Characteristic		**% (n/N)** **N = 167**
Gender	Female	77.8% (130/167)
	Male	22.2% (37/167)
Age (years)	Mean	54.8
	Standard Deviation	6.70
	Median	56.0
	Range (Min, Max)	(37, 65)
Race	Caucasian	64.1% (107/167)
	Hispanic	10.8% (18/167)
	African-American	16.2% (27/167)
	Asian	3.6% (6/167)
	Other	5.4% (9/167)
Fitzpatrick Skin Type	I	3.6% (6/167)
	II	27.5% (46/167)
	III	28.1% (47/167)
	IV	21.0% (35/167)
	V	15.6% (26/167)
	VI	4.2% (7/167)

Study Safety Findings

The primary endpoint was met, demonstrating that the safety profile of JUVÉDERM® VOLUMA™ XC after repeat treatment was not worse than the safety profile after initial/touch-up treatment. The rate of AEs after repeat treatment [8.4% (14/167)] was significantly lower than the rate of AEs after initial/touch-up treatment [33.5% (56/167)].

No new safety concerns were identified after repeat treatment. The types of treatment site responses and AEs observed after repeat treatment were similar to those after initial/touch-up treatment, but were generally less severe after repeat treatment. Most treatment site responses after repeat treatment were mild to moderate and resolved within 2 weeks. Device/injection-related AEs after repeat treatment were all mild to moderate, required no action, and resolved without sequelae, with most resolving within 3 months. After repeat treatment, no subjects experienced any late onset device/injection-related AEs (those occurring more than 1 month after repeat treatment) and no device/injection-related SAEs occurred.

The results of a multivariate analysis demonstrated that device/injection-related AE rates were different among clinical sites, increased with higher injection volumes, and were higher in females as compared to males.

Study Strengths/Limitations

The strength of the study is that long-term safety data were collected after repeat treatment, with high subject compliance (95.3%) at the end of the study (12/12+ month visit). A limitation of the study was that the length of follow-up after repeat treatment was approximately one year shorter than after initial/touch-up treatment.

C. JUVÉDERM® VOLUMA™ XC Cannula Study

Study Design

A multi-center, evaluator-blinded, randomized, within-subject controlled clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA™ XC with cannula to correct age-related mid-face volume deficit. Subjects were randomized to undergo treatment with the TSK STERiGLIDE™ 25G 1 ½" cannula in one cheek and a needle in the other cheek. The use of a needle was also permitted in the zygomaticomalar region in the cheek randomized to cannula to achieve optimal correction. At the outset of the study, 60 enrolled subjects underwent treatment with JUVÉDERM® VOLUMA™ XC.

Treated subjects returned for routine safety visits with the TI at 1 and 3 months after the treatment. At these visits, blinded EIs assessed subjects' overall mid-face volume deficit on the validated 6-point photometric MFVDS. Subjects performed self-assessments on the Satisfaction with Cheeks module of the FACE-Q Questionnaire.

Study Endpoints

The primary effectiveness measure was the blinded EI's assessment at Month 1 of the subject's volume deficit for each cheek on the validated 6-point photometric MFVDS. The primary effectiveness endpoint was to demonstrate non-inferiority of JUVÉDERM® VOLUMA™ XC administered via a TSK *STERiGLIDE*™ 25G 1 ½" cannula versus needle.

Secondary measures included EI-assessed overall MFVDS responder rates and subject-assessed mean overall satisfaction scores on the validated *Satisfaction with Cheeks* module of the FACE-Q Questionnaire at Month 1. A responder was defined as a subject with ≥ 1 grade improvement in the MFVDS score since baseline.

Subject Demographics

A total of 60 subjects received treatment. At baseline, all subjects had moderate, significant, or severe volume deficit (encompassing scores of 3 through 5 on the MFVDS scale) in their mid-face according to the EI's assessments. Subject demographics and pre-treatment characteristics are presented in Table 21.

Table 21: Subject Demographics

Parameter	Total (N = 60)
Gender	
Female	49 (81.7%)
Male	11 (18.3%)
Age	
Median (SD)	54.9 (6.41)
Range (Min, Max)	37, 65
Fitzpatrick Skin Type	
I	2 (3.3%)
II	15 (25.0%)
III	31 (51.7%)
IV	11 (18.3%)
V	0
VI	1 (1.7%)

Primary Effectiveness Results

This study demonstrated non-inferiority of JUVÉDERM® VOLUMA™ XC administered via a TSK *STERiGLIDE*™ 25G 1 ½" cannula versus needle. Based on the blinded EI assessments, the 95% confidence interval for the difference in mean change in MFVDS from baseline to Month 1 (cannula minus needle) was 0.1. The upper confidence limit was < 0.5 and therefore, statistical non-inferiority was concluded.

Secondary Effectiveness Results

The EI-assessed MFVDS responder rates at Month 1 were 93.3% for cannula-treated and 95.0% for needle-treated cheeks, with a paired difference of -1.7 (95% CI: -7.31 to 3.98). The mean score at baseline on the *Satisfaction with Cheeks* module of the FACE-Q questionnaire was 32.1 and at Month 1 increased by 55.5 points; over 85% of subjects had improved satisfaction with the attractiveness, youthful fullness, and contour of their cheeks.

Other Effectiveness Results

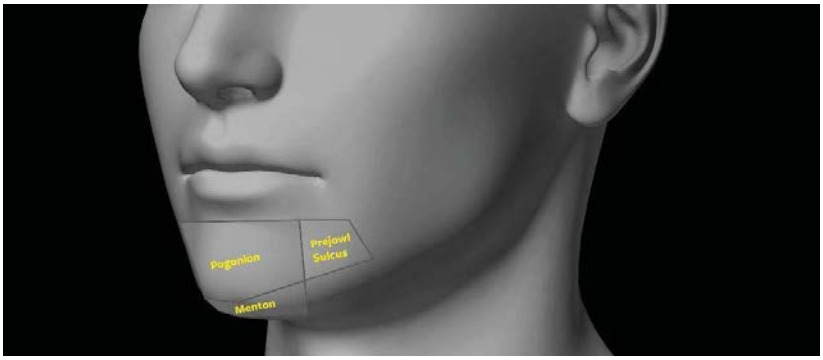
The EI assessed MFVDS responder rates at Month 3 were 93.3% for cannula-treated and 98.3% for needle-treated cheeks, with a paired difference of -5.0 (95% CI: -10.51 to 0.51).

D. Pivotal Study for JUVÉDERM® VOLUMA™ XC for Chin Augmentation

Study Design

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

Figure 2. Chin Area Treated



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

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

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

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

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

Study Endpoints

With regards to safety, preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments. Subjects were instructed to rate each treatment site response listed on the diary as "Mild (easily tolerated)," "Moderate (affecting daily activity)," "Severe (unable to do daily activity)," or "None." Adverse Events were reported by the TI at all follow-up visits where applicable. With regards to effectiveness, the primary effectiveness measure was the single blinded EI's assessment of the subject's chin volume deficit in 2D images using the validated 5-point photonumeric ACRS (Table 22, Figure 3).

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

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

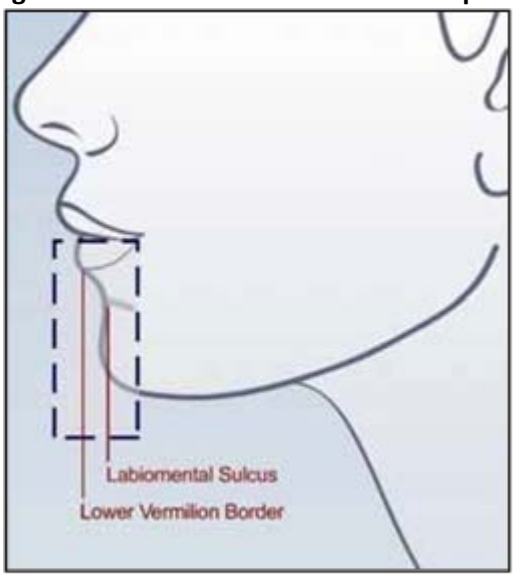
With regards to success/failure criteria, a responder was defined as a subject with ≥ 1-point improvement in the ACRS score compared to the baseline score. Effectiveness of JUVÉDERM® VOLUMA™ XC was demonstrated if at least 50% of subjects treated with JUVÉDERM® VOLUMA™ XC were responders (≥ 1-point improvement)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

Table 22: Allergan Chin Retrusion Scale

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

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

Figure 3: Lines Used in the ACRS Descriptors



Subject Demographics

Data from all 221 enrolled subjects were available for analysis (Table 23). Of the 221 subjects, 29 were screen failures primarily due to ineligibility, and 192 were randomized per protocol, with 144 in the treatment group and 48 in the control group. Of the 192 randomized subjects, 169 (88.0%; 128 treatment and 41 control) completed the Month 6 primary endpoint visit, and 38 of the 48 control group subjects (79.2%) opted to receive study treatment after the completion of the 6-month control period. A total of 167 (87.0%; 127 treatment and 40 control) completed the study.

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

Table 23: Participant Disposition

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

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

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

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 24.

Table 24: Demographics and Pre-treatment Characteristics (N = 192)

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

Treatment Characteristics

The most common injection techniques at any treatment were bolus and serial puncture. At initial treatment, 99.3% of treatment group subjects were treated in the pogonion, 77.8% in the menton, and 87.5% in the pre-jowl sulci. Needles were used for 100% of subjects, and cannulas were used for 25.0% of subjects at initial treatment. The median total volume used to achieve optimal correction was 2.4 mL (range, 0.7-4.0 mL), with 1.0 mL in the pogonion, 0.5 mL in the menton, and 1.0 mL in the pre-jowl sulci (right and left combined). The median volume at initial treatment was 2.0 mL. A touch-up treatment was performed for 45.8% (88/192) of subjects with a median total volume of 1.0 mL. The repeat treatment was performed for 45.8% (88/192) of subjects and the median volume injected for repeat treatment was 2.0 mL. The volume of JUVÉDERM® VOLUMA®™ XC varied depending on the subject's chin volume deficit and treatment goal.

Primary Effectiveness Results

JUVÉDERM® VOLUMA™ XC provided a clinically and statistically significant improvement in chin volume deficit compared to the no-treatment control group. The analysis of primary effectiveness was based on the 126 treatment group and 40 control group evaluable subjects at the 6-month time point. The primary effectiveness endpoint was met in that greater than 50% of subjects in the treatment group were responders (56.3% improved by ≥ 1 point compared with their pre-treatment assessment), and the responder rate for the treatment group was significantly greater (p = 0.0019) than the responder rate for the control group (a difference of 28.8%) at Month 6 (Table 25). The primary effectiveness endpoint was below 50% in the following subgroups: older subjects (aged 51.5 years and older), darker skin types (FST V/VI), and males. However, the satisfaction rates were high and the secondary endpoints were met for these subgroups.

Table 25: Effectiveness Summary Responder Rate at 6 Months Based on Evaluating Investigators' Assessments of Images

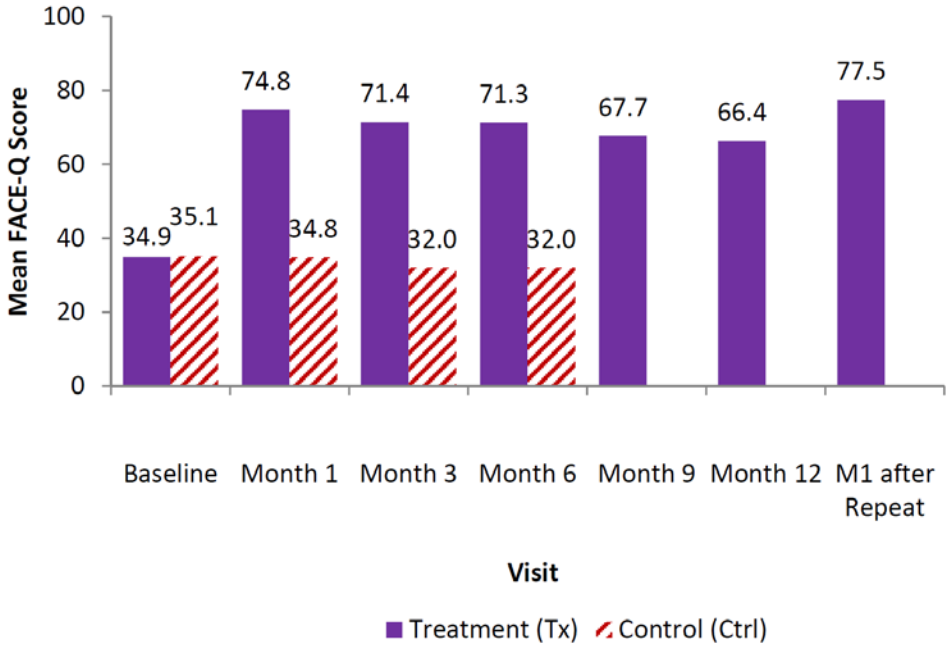
	Responder Rate at Month 6	p-value
Treatment Group	56.3% (71/126)	N/A
Control Group	27.5% (11/40)	
Difference in Responder Rates (Treatment rate - Control rate)	28.8%	0.0019

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

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

Secondary effectiveness results: The FACE-Q *Satisfaction with Chin* overall mean score was 34.9 at baseline and improved to 71.3 at Month 6 with the improvement being statistically significant ($p < 0.0001$) (Figure 4). Most of the subjects (91.8%) reported satisfaction with their chin 1 month after treatment. Among other questions, this FACE-Q questionnaire included questions on satisfaction with chin look in profile view and width of the chin. At Month 1, 88.8% of treatment group subjects were satisfied with how their chin looks in profile view and 95.5% were satisfied with the width of their chin.

Figure 4: FACE-Q Satisfaction with Chin Mean Scores by Visit



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

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

However, at Month 6 the ACRS responder rate for the treatment group was less than 50%, though it was greater than that for the untreated control group (43.0% versus 12.5%).

Subgroup Analyses

The following characteristics were evaluated for potential association with outcomes: Fitzpatrick Skin Type (FST) (Table 26), age (Table 27), gender (Table 28), baseline ACRS, injection volume, cannula usage (Table 9 and 10), and investigational site.

Table 26: Effectiveness and Safety Results at 6 Months by FST Subgroups

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

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

For subjects with darker skin (FST V/VI) (Table 26), the device did not meet the primary effectiveness endpoint (28.6% responder rate in the treatment group) and performed worse than the no-treatment control (50.0% responder rate, where a responder is a subject with at least a 1-point improvement in the 2D ACRS score at 6 months from baseline).

Table 27: Effectiveness and Safety Results at 6 Months by Age Subgroups

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

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

The median age of subjects was 51.5 years. For subjects aged 51.5 years and older (Table 27), the device did not meet the primary effectiveness endpoint (46.3% responder rate in the treatment group). The responder rate for subjects aged 51.5 years or older is statistically higher than the no-treatment control group (28.6%).

Table 28: Effectiveness and Safety Results at 6 Months by Gender Subgroups

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

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

For male subjects (Table 28), the device did not meet the primary effectiveness endpoint (46.7% responder rate in the treatment group). There were no responders in the male control subjects.

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

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

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

8. INSTRUCTIONS FOR USE

E. To Attach Needle to Syringe

STEP 1: Remove tip cap
Hold syringe and pull tip cap off the syringe, as shown in Figure A.

FIGURE A

STEP 2: Insert needle
Hold the syringe body and firmly insert the hub of the needle (provided in the JUVÉDERM® VOLUMA™ XC package) into the LUER-LOK® end of the syringe.

STEP 3: Tighten the needle
Tighten the needle by turning it firmly in a clockwise direction (see Figure B) until it is seated in the proper position, as shown in Figure C.

NOTE: If the position of the needle cap is as shown in Figure D, it is not attached correctly. Continue to tighten until the needle is seated in the proper position.

FIGURE B

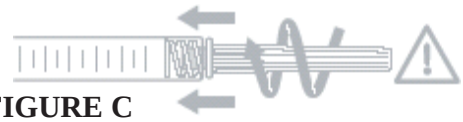
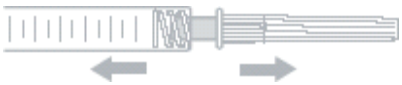


FIGURE C

FIGURE D

STEP 4: Remove the needle cap
Hold the syringe body in one hand and the needle cap in the other. Without twisting, pull in opposite directions to remove the needle cap, as shown in Figure E.

FIGURE E



F. Health Care Professional Instructions

1. JUVÉDERM® VOLUMA™ XC injectable gel is a crosslinked, robust, injectable gel formulation, injected using a 27G ½" or 25G 1" needle or a 25G 1 ½" cannula to volumize and contour the cheek for correction of mid-face volume deficit and to augment the chin region to improve the chin profile.

2. The TSK *STERiGLIDE*™ 25G 1 ½" cannula was used in the clinical trials (cannula study for cheek and chin study) and is recommended for use with JUVÉDERM® VOLUMA™ XC. An entry point was made in the skin with the TSK 23 G introducer needle. In the chin clinical study, JUVÉDERM® VOLUMA™ XC was injected into the pogonion (needle), menton (needle or cannula), and left and right pre-jowl sulci (needle or cannula).

3. JUVÉDERM® VOLUMA™ XC with needle was studied in all Fitzpatrick Skin Types 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. However, the safety of JUVÉDERM® VOLUMA™ XC with cannula for cheek augmentation has not been established in Fitzpatrick Skin Types V and VI.

4. Prior to treatment, the patient's medical history should be obtained, and the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental "touch-up" implantations may be required to achieve and maintain maximum correction.

5. The patient's soft-tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Pre-treatment photographs are recommended.

6. Topical or injectable anesthesia may be used to manage pain during and after injection.

7. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be prepped with alcohol or other antiseptic. Prior to injecting, depress the plunger rod until the product flows out of the needle/cannula.

8. If the needle/cannula is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle/cannula.

9. When using a cannula, an entry point is made in the skin, e.g. with a sharp needle of appropriate size.

10. After insertion of the needle, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify the needle is not intravascular.

11. After the first small amount of material has been injected into the patient, wait a full 3 seconds to allow the lidocaine to take effect before proceeding with the rest of the injection.

12. The injection technique for JUVÉDERM® VOLUMA™ XC with regard to the angle and orientation of the bevel, the depth (subcutaneous and/or submuscular/supraperiosteal) of injection, and the quantity administered may vary depending on the area being treated. Injection of JUVÉDERM® VOLUMA™ XC too superficially (intradermally), or in large volumes over a small area, may result in visible and persistent lumps and/or discoloration.

13. Tunneling, fanning, crosshatching, and ferning techniques may be used with a needle or cannula to deliver JUVÉDERM® VOLUMA™ XC to achieve optimal results. Serial puncture may be used with a needle to deliver JUVÉDERM® VOLUMA™ XC to achieve optimal results. Bolus and serial puncture techniques may be used to achieve optimal results in the chin area. Injection may be administered in an antegrade or retrograde fashion. Inject JUVÉDERM® VOLUMA™ XC while applying even pressure on the plunger rod and slowly moving the needle/cannula in the subcutaneous or submuscular/supraperiosteal plane.

14. JUVÉDERM® VOLUMA™ XC should be distributed in small aliquots (small boluses of 0.1 mL to 0.2 mL) over a large area to reduce the risk of persistent lumpiness.

15. With submuscular/supraperiosteal injection, the number of times the needle passes through the muscle should be minimized to reduce the risk of bruising. It is important to stop injecting before the needle tip reaches the level of the deep dermis to prevent material from being placed too superficially in the skin.

16. Correct to 100% of the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.

17. If immediate blanching occurs, the injection should be stopped, and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.[1]

18. The area of lost facial volume should be lifted by the end of the injection. When injection is completed, the treated site may be gently massaged to mold the product to the contour of the surrounding tissue and assure that it is evenly distributed and conforms to the contour of the surrounding tissues. If overcorrection occurs, massage the area between your fingers or against an underlying superficial bone to obtain optimal results.

19. With patients who have localized swelling, the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to invite the patient back to the office for a touch-up treatment.

20. After the initial treatment, an additional treatment may be necessary to achieve the desired level of correction. The same procedure should be repeated until a satisfactory result is obtained. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as mid-face volume deficit or chin retrusion severity, skin elasticity, and dermal thickness at the treatment site.

21. Patients may experience treatment site responses, which typically resolve within 2 to 4 weeks for treatment in the cheek and the chin. Ice may be applied for a brief period following treatment to minimize swelling and reduce pain.

[1] Alam, M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers *Dermatol Surg.* 2008;34(suppl 1):S115-S148.

22. The health care professional should instruct the patient to promptly report any evidence of problems possibly associated with the use of JUVÉDERM® VOLUMA™ XC.

G. Patient Instructions

It is recommended that the following information be shared with patients:

- Within the first 24 hours, patients should avoid strenuous exercise and extensive sun or heat exposure. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the treatment sites
- If the treated area is swollen, an ice pack may be applied to the site for a short period
- To report an adverse reaction, phone the Allergan Product Surveillance Department at (877) 345-5372

9. HOW SUPPLIED

JUVÉDERM® VOLUMA™ XC injectable gel is supplied in individual treatment syringes with needles as indicated on the carton. JUVÉDERM® VOLUMA™ XC can be injected with either a 27G ½", a 25G 1" needle or a 25G 1 ½" cannula. The TSK STERiGLIDE 25G 1½" cannula is not supplied with JUVEDÉRM® VOLUMA™ XC but is available for purchase through Allergan. The volume in each syringe is as stated on the syringe label and on the carton. The contents of the syringe are sterile and non-pyrogenic. Do not resterilize. Do not use if package is open or damaged.

10. SHELF LIFE AND STORAGE

JUVÉDERM® VOLUMA™ XC injectable gel must be used prior to the expiration date printed on the label. Store at room temperature (up to 25°C/77°F). DO NOT FREEZE.

JUVÉDERM® VOLUMA™ XC injectable gel has a clear appearance. In the event that a syringe contains material that is not clear, do not use the syringe; notify Allergan Product Surveillance immediately at (877) 345-5372.

To place an order, contact Allergan at (800) 377-7790.

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