SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: JUVÉDERM® VOLBELLA® XC

Device Procode: LMH

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

Date(s) of Panel Recommendation: March 23, 2021

Premarket Approval Application (PMA) Number: P110033/S053

Date of FDA Notice of Approval: May 28, 2021

Priority Review: No

Breakthrough Device: N/A

The original PMA P110033/S018 was approved on May 31, 2016 and is indicated for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the device.

II. INDICATIONS FOR USE

JUVÉDERM® VOLBELLA® XC injectable gel is indicated for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21.

JUVÉDERM® VOLBELLA® XC is indicated for the improvement of infraorbital hollowing in adults over the age of 21.

III. CONTRAINDICATIONS

- JUVÉDERM® VOLBELLA® XC is contraindicated for participants with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies
- JUVÉDERM® VOLBELLA® XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for participants with a history of allergies to such material
- JUVÉDERM® VOLBELLA® XC contains lidocaine and is contraindicated for participants with a history of allergies to such material

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the JUVÉDERM® VOLBELLA® XC labeling.

V. DEVICE DESCRIPTION

JUVÉDERM® VOLBELLA® XC injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. The gel is comprised of 15 mg/mL HA crosslinked with BDDE and contains 0.3% w/w lidocaine in a physiologic buffer. VOLBELLA® XC is supplied in a 1 mL cyclic olefin copolymer syringe. One sterilized syringe is packaged in a sealed thermoformed tray with two sterile needles, and two trays are placed together in a cardboard box.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies to treat infraorbital hollowing include autologous fat injection or transposition, plasma gel injection, and acellular dermal graft treatment. Each alternative has its own advantages and disadvantages. A patient should fully discuss these

alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

JUVÉDERM® VOLBELLA® XC received CE Mark on October 7, 2011, under the name JUVÉDERM VOLBELLA with Lidocaine for treatment of fine lines and medium-sized skin depressions due to conditions such as premature or normal aging or scars as well as for enhancement and pout of the lips or to correct structure defect such as asymmetry, contour deformities, and volume loss. JUVÉDERM® VOLBELLA® XC received PMA approval under P110033/S018 on May 31, 2016 for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21. In addition to being marketed throughout Europe and affiliated countries, JUVÉDERM® VOLBELLA® XC is currently marketed globally, including Australia, Canada, Brazil, Russia, Ukraine, Mexico, Japan, South Korea, Taiwan, and Singapore under the tradename JUVEDERM® VOLBELLA® with Lidocaine.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with the use of the device as well as for other devices in the same category, as reported in the clinical study include injection site bruising and injection site swelling. Other adverse effects reported less frequently (in less than 5% of the study participants) include dizziness, injection site pain, injection site edemas, headache, and syncope.

JUVÉDERM® VOLBELLA® with lidocaine has been marketed outside the US since 2011, and JUVÉDERM® VOLBELLA® XC (also known as JUVÉDERM® VOLBELLA® with lidocaine) has been marketed in the US since 2016.

The following AEs were received from postmarket surveillance with a frequency of 5 events or more and were not observed in the clinical study. All AEs obtained through postmarket surveillance are listed in order of number of reports received: inflammatory reaction, loss/lack of correction, unsatisfactory result, allergic reaction, hematoma, infection, neurological symptoms such as increase or decrease of sensation, vascular

occlusion, migration, abscess, varied injuries, anxiety, flulike symptoms, herpes, overcorrection, headache, malaise, angioedema, vision abnormalities, bleeding, cyst, scarring, necrosis, autoimmune disorder exacerbation, dyspnea, extrusion, calcification, depression, vision loss, and extrusion.

In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, antifungals, antihistamines, antiviral, arnica, drainage, eye drops, hyaluronidase, ice, laser treatment, massage, NSAIDs, petroleum jelly, steroids, ultrasound therapy, vasodilators, and warm compress. Outcomes for these reported events ranged from resolved to ongoing at the time of last contact.

Vision abnormalities have been reported following injection of JUVÉDERM® VOLBELLA® XC into the glabella, lip, cheek and/or periorbital area, with a time to onset ranging from immediate to 2 months following injection. Reported treatments include antibiotics, anti-inflammatories, hyaluronidase, NSAIDs, and steroids. Outcomes ranged from resolved to ongoing at the time of last contact.

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

IX. SUMMARY OF NONCLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for the improvement of infraorbital hollowing in adults over the age of 21. There was no change in product manufacturing or specifications. Therefore, the data was previously presented in support of PMA P110033/S018.

A. Laboratory Studies

There were no manufacturing or specification changes due to this supplement.

B. Animal Studies

This supplement presented clinical data to support approval of a new indication for use. Because no change in product manufacture or specification was proposed, the

biocompatibility studies previously submitted in PMA P110033/S018 and supplements support the new proposed indications for use.

C. Additional Studies

This supplement presented clinical data to support approval of a new indication for use. Because no change in product manufacture or specification was proposed, the studies previously submitted in PMA P110033/S018 and supplements support the new proposed indications for use.

X. SUMMARY OF PRIMARY CLINICAL STUDY

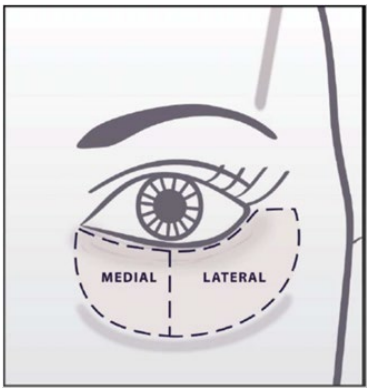
The applicant performed a clinical study (1932-701-008) to establish a reasonable assurance of safety and effectiveness of JUVÉDERM® VOLBELLA® XC for the improvement of infraorbital hollows in the adults over the age of 21 in the US under IDE G170098. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Participants were treated between January 26, 2018 and October 16, 2018. The database for this Panel Track Supplement reflected data collected through August 21, 2019 and included 140 participants who were randomized and underwent treatment with either JUVÉDERM® VOLBELLA® XC (N = 105) or no treatment control (N = 35) at the outset of the study. There were 15 investigational sites.

A multicenter, single-blind, randomized, no treatment controlled clinical study of participants seeking treatment for infraorbital hollowing. Participants were randomized to treatment or no-treatment control in a 3:1 ratio. Treatment group participants underwent treatment with JUVÉDERM® VOLBELLA® XC at the outset of the study. The Treating Investigator (TI) determined the appropriate volume of JUVÉDERM® VOLBELLA® XC to be injected into the orbital rim (see Figure 1). Injection for subcutaneous and/or supraperiosteal injections was permitted with a 32G 1/2" needle or TSK STERiGLIDE 27G 1 1/2" cannula. The no-treatment control participants had treatment delayed for 3 months.

Figure 1: Treatment Area for Infraorbital Hollowing



1. Clinical Inclusion and Exclusion Criteria

Enrollment in the 1932-701-008 study was limited to participants who met the following inclusion criteria:

- Age 22 or older and in good general health
- Had "Moderate" or "Severe" infraorbital hollowing (grade 2 or 3 on the AIHS [Allergan Infraobital Hollows Scale]) for each eye as assessed by the Evaluating Investigator (EI) (ie, both eyes must qualify but did not need to have the same score)
- Treating Investigator (TI) considered the participant's anatomy to be amenable to improvement to an AIHS grade of 0 or 1
- Ability to complete effectiveness self-assessments without the use of glasses
- Ability to follow study instructions and likely to complete all required visits
- Written informed consent had been obtained

Participants were not permitted to enroll in the 1932-701-008 study if they met any of the following exclusion criteria:

- Had atrophic skin in the tear trough region as determined by the TI

- Had large lower lid fat pads that would mask improvement, as determined by TI
- Had hyperpigmentation in the infraorbital area (does not include dark circles under the eyes not due to hyperpigmentation)
- Had significant volume loss in the midface
- Had a cornea that projects farther forward than the most anteriorly projected part of the cheek
- Had ever received permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
- Had ever undergone fat injections above the subnasale or is planning to undergo this procedure during the study
- Had tattoos, piercings, facial hair (ie, beard, mustache), or scars that would interfere with visual assessment of the infraorbital hollows
- Had undergone volume augmentation with semipermanent dermal fillers (eg, calcium hydroxyapatite, poly-L-lactic acid) or temporary dermal fillers in the malar area, temples, or around the eyes within 12 months before enrollment or planned to undergo such treatment during the study
- Had an active or recurrent inflammation or infection in either eye
- Had ever received a blepharoplasty, facelift, browlift, or planned to during the study
- Had undergone mesotherapy or cosmetic treatment (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, liposuction, lipolysis, or other ablative procedures) anywhere in the face or neck or botulinum toxin injections above the subnasale within 6 months before enrollment or is planning to undergo any of these procedures during the study
- Had experienced trauma to the infraorbital area within 6 months before enrollment or has residual deficiencies, deformities, or scarring in the periorbital or cheek areas
- Had a tendency to develop hypertrophic scarring

- Had a history of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), hyaluronic acid products, or Streptococcal protein, or is planning to undergo desensitization therapy during the term of the study
- Had active autoimmune disease
- Had current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, above the subnasale
- Had received any investigational product within 30 days prior to study enrollment or is planning to participate in another investigation during the course of this study
- Had begun using any new over-the-counter or prescription oral or topical, anti-wrinkle products within 30 days before enrollment or is planning to begin using such products during the study (subjects who have been on a regimen of such products for at least 30 days are eligible for the study if they intend to continue their regimen throughout the study)
- Females who are pregnant, nursing, or planning a pregnancy
- Was an employee (or a relative of an employee) of the TI, EI, or Allergan, or a representative of Allergan
- Had a condition or is in a situation which in the TI's opinion may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

2. Follow-up Schedule

All participants were scheduled to return for follow-up examinations at 1, 3, 6, 9, and 12 months after the last treatment (initial or touch-up). Participants were eligible for an optional touch-up treatment with JUVÉDERM® VOLBELLA® XC, 30 days after initial treatment. An optional repeat treatment was offered to all treatment group participants after completion of the 12-month follow-up visit, with 1 month of follow-up after repeat treatment. The untreated control group participants had follow-up visits at Months 1 and 3 after randomization. After the completion of the 3-month control period procedures, participants were offered treatment with JUVÉDERM® VOLBELLA® XC (initial

and touch-up) and were followed for 9 months for safety only. Vision assessments (Snellen visual acuity, confrontational visual fields, and ocular motility) were performed on participants at initial and touch-up treatment days before and after treatment, as well as 14 days after treatment.

Pre- and post-procedure, the objective parameters measured during the study included the blinded Evaluating Investigator's (EI) live assessment of participants' infraorbital hollowing using a validated 5-point photo numeric Allegan Infraorbital Hollows Scale (AIHS) which was performed separately for each infraorbital hollow (described in Table 1 and shown in Figure 2). EIs also assessed participants' improvement on the 5-point Global Aesthetic Improvement Scale (GAIS) and the Lower Eyelids module of the FACE-Q questionnaire.

Table 1: Allergan Infraorbital Hollowing Scale

Score	Grade	Description
0	None	No visible hollowing or volume loss medially or laterally
1	Minimal	Presence of hollowing with some volume loss medial to the mid-pupillary line; smooth lateral lid-cheek transition
2	Moderate	Defined hollowing extending laterally beyond the mid-pupillary line with moderate volume loss; smooth lateral lid-cheek transition with mild volume loss
3	Severe	Defined hollowing extending laterally beyond the mid-pupillary line with moderate volume loss creating a defined groove along the lid-cheek junction
4	Extreme	Defined hollowing extends from medial to lateral canthus; severe volume loss creates a marked step along the lid-cheek junction

Figure 2: Allergan Infraorbital Hollows Scale

Participants performed self-assessments on the GAIS, the Lower Eyelids module of the validated FACE-Q questionnaire, and satisfaction of the overall result of

treatment. Further, 3D facial photography was performed, and quantitative volume changes were calculated. Additionally, participant diaries and TI assessment of AEs assessed safety of the treatment. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, preprinted diary forms were used by participants after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments. Participants were instructed to rate each Injection Site Response (ISR) listed on the diary as "Mild, (easily tolerate)," "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 blinded EIs' assessment of the participants' infraorbital hollowing in a live assessment using the validated 5-point photo numeric AIHS, which was performed separately for each infraorbital area. Secondary measures included assessments completed by the blinded EI and the participant of GAIS (Table 2) and participants responses on the validated FACE-Q Appraisal of Lower Eyelids questionnaire.

Table 2: Global Aesthetic Improvement Scale

Score	Grade	Description
2	Much Improved	Marked improvement in appearance
1	Improved	Improvement in appearance, but a touch-up or retreatment is indicated
0	No Change	The appearance is essentially the same as the original condition
-1	Worse	The appearance is worse than the original condition
-2	Much Worse	The appearance is much worse than the original condition

With regard to success/failure criteria, the responder rate was defined as the percent of participants with ≥ 1 grade improvement in the AIHS score from baseline in both infraorbital areas. Effectiveness of JUVEDÉRM® VOLBELLA® XC was demonstrated if the responder rate at Month 3 for the treatment group was statistically significantly greater than that for the no-treatment control group.

B. Accountability of PMA Cohort

Participant disposition for the PMA study is shown in Table 3. At the time of database lock, data from all 163 participants enrolled in the PMA study were available for analysis. Of the 163 participants, 23 were screen failures primarily due to ineligibility, and 140 were randomized per protocol, with 105 in the treatment group and 35 in the control group. Of the 140 randomized participants, 133 (95.0%: 101 treatment and 32 control) completed the Month 3 primary endpoint visit, 37 of 94 treatment group participants (39.4%) opted for repeat treatment, and 29 of the 32 control group participants (90.6%) opted to receive study treatment after the completion of the 3-month control period. A total of 124 participants (88.6%; 94 treatment and 30 control) completed the study.

The mITT population included treatment randomized treatment group participants, received at least 1 treatment, have a baseline and at least 1 post-treatment assessment in addition to the randomized control group participants, baseline and at least 1 follow-up assessment. Of the 135 mITT participants, there were 103 in the treatment group and 32 in the control group. At baseline, 40.0% (54/135) had moderate and 60.0% (81/135) had severe infraorbital hollowing based on the EI live assessment on the AIHS.

Table 3: Participant Disposition

Disposition	Number of Participants		
	Treatment	Control	Total
Enrolled	N/A	N/A	**163**
Screen Failures	N/A	N/A	**23**[a]
Randomized Participants	**105**	**35**	**140**
Lost to follow-up prior to Month 1	1	2	3
Withdrew prior to Month 1	0	1	1
Screen failure but randomized in error	1[a]	0	1
mITT Population	**103**	**32**	**135**
Participants who withdrew/lost to follow-up between Month 1 to Month 3	2	0	2
Completed Month 3 Visit (Primary Endpoint)	**101**	**32**	**133**
Treatment participants who received repeat treatment	**37**	N/A	**37**
Control Group Who Received Optional Treatment	N/A	**29**	**29**
Lost to Follow-up	3	1	4
Withdrawal by Participant	3	1	4
Other[b]	1	0	1
Completed Study	**94**	**30**	**124**
Safety Population	**105**[a,c]	**34**[c]	**139**

[a] One participant was a screen failure, but was randomized to the treatment group in error and did not receive treatment. This participant was excluded from the safety analysis.
[b] One participant moved out of state.
[c] One control group participant was treated prematurely at randomization visit. This participant is included in the treatment group for safety analyses

Among the participants who were eligible to receive repeat treatment, 60%, (55/92) participants elected not to receive repeat treatment. Study sites documented reasons participants chose not to receive repeat treatment which are listed in Table 4. Approximately half of the participants (56.4%, 31/55) opted not to receive repeat treatment either based on the TI's assessment that improvement remained or due to the participant's satisfaction with improvement.

Table 4: Reasons Not to Receive Repeat Treatment for the Participants who Completed the Study

Reasons Not to Receive Repeat Treatment	N
TI determined improvement remained at Month 12	22
Desire for prohibited procedures and/or medications	1
Procedural anxiety	1
Other	31
Scheduling issues	11
Satisfied	9
Not satisfied	8
Family issues	1
Not specified	1
Wants other filler	1
Total	**55**

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. Participant demographics and pretreatment characteristics of the JUVÉDERM® VOLBELLA® XC and control groups are presented in Table 5.

Table 5: Participant Demographics and Pretreatment Characteristics (N = 135)

Demographic	Number of Participants		
	Treatment Group	Control Group	Total
N	103	32	135
Gender			
Female	93 (90.3%)	31 (96.9%)	124 (91.9%)
Male	10 (9.7%)	1 (3.1%)	11 (8.1%)
Age			
Median	47.0	40.0	47.0
Range	23, 68	23, 59	23, 68
Race			
White	81 (78.6%)	27 (84.4%)	108 (80.0%)
Black or African American	16 (15.5%)	2 (6.3%)	18 (13.3%)
Asian	1 (1.0%)	2 (6.3%)	3 (2.2%)
American Indian/Alaska native	3 (2.9%)	1 (3.1%)	4 (3.0%)
Multiple	2 (1.9%)	0 (0%)	2 (1.5%)
Ethnicity			
Hispanic or Latino	11 (10.7%)	7 (21.9%)	18 (13.3%)
Not Hispanic or Latino	92 (89.3%)	25 (89.3%)	117 (86.7%)
Fitzpatrick Skin Type			
I/II	35 (34.0%)	11 (34.4%)	46 (34.1%)
III/IV	51 (49.5%)	18 (56.3%)	69 (59.1%)
V/VI	17 (16.5%)	3 (9.4%)	20 (14.8%)
Baseline AIHS Score			
0 (None)	0 (0%)	0 (0%)	0 (0%)
1 (Minimal)	0 (0%)	0 (0%)	0 (0%)
2 (Moderate)	40 (38.8%)	14 (43.8%)	54 (40.0%)
3 (Severe)	63 (61.2%)	18 (56.3%)	81 (60.0%)
4 (Extreme)	0 (0%)	0 (0%)	0 (0%)

The mITT population included the following:

- Treatment group participants who were randomized to the treatment group, received at least 1 study device treatment, and had a baseline and at least 1 post-treatment assessment of the primary effectiveness variable
- Control group participants who were randomized to the control group and had baseline and at least 1 follow-up assessment of the primary effectiveness variable.

The safety population included the following:

- Treatment group participants who were randomized to the treatment group and received at least 1 study device treatment
- Control group participants who were randomized to the control group

The initially treated population included participants who were randomized and received VOLBELLA® XC at the beginning of the control period (i.e., through Month 3). The repeat treatment population included participants in the initially treated population who received VOLBELLA® XC repeat treatment after 12 months. The optionally treated population included participants who were randomized to the control group and received VOLBELLA® XC treatment after the control period.

The median total volume injected for initial and touch-up treatments combined was 1.0 mL (range, 0.2-2.2 mL) for the left infraorbital hollow and 1.0 mL (range, 0.1-2.2 mL) for the right infraorbital hollow, with a median for each side of 0.7 mL for initial treatment and 0.5 mL for touch-up treatment. Injection volumes were similar for optional and repeat treatments.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety population cohort of 139 participants. The safety population included participants who were randomized to study treatment and received at least 1 study device treatment and

participants who were randomized to the control group. The key safety outcomes for this study are presented below.

Safety assessments such as Tyndall effect, visual acuity, confrontational visual fields, and ocular motility were evaluated at the screening visit and throughout the study. None of the safety assessments were remarkable or presented safety concerns after treatment with JUVÉDERM® VOLBELLA® XC.

- Of the treatment group particpants, 7 eyes in 4 participants experienced Tyndall effect at Day 30 after initial treatment and 8 eyes in 4 participants at Month 1 after last treatment. Tyndall effect was also reported in 2 eyes in 1 untreated control participants at Month 1.
- Snellen visual acuity assessments showed over 90% of treatment group participants had the same or better visual acuity at all post-treatment assessments. Only 1 or 2 eyes showed a 2-line worsening in visual acuity at any timepoint.
- Visual field assessments showed that all treatment group participants were found to have visual fields to be intact.
- Ocular motility assessmented in the treatment group participants showed that 100% of eyes had full duction and version, with no change from pre-treatment at all timepoints.

Preprinted diary forms were used by participants after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch- up, and repeat treatments. A total of 132 participants underwent treatment and completed dairy forms (from both the treatment and the control groups). Participants were instructed to rate each ISR listed on the diary as “Mild (easily tolerated),” “Moderate (affecting daily activity),” “Severe (unable to do daily activity),” or “None.”

After initial treatment with JUVEDERM® VOLBELLA® XC, 56.3% (58/103) of participants reported experiencing a local ISR. Participants rated ISRs as

predominantly mild in severity with a majority resolving within 1 week. The incidence, severity, and duration of ISRs following repeat treatment were similar to that following initial treatment.

ISRs reported by participants after initial and repeat treatments are summarized by severity and duration in Table 6 and Table 7, respectively.

Table 6: ISRs by Severity and Duration After Initial Treatment for Treated Participants

Injection Site Responses	Total % (n/N[a])	Severity[b]			Duration[c]			
		Mild %(n/N)	Moderate %(n/N)	Severe %(n/N)	1-3 Days %(n/N)	4-7 Days %(n/N)	8-14 Days %(n/N)	15-30 Days %(n/N)
Tenderness to touch	47.7% (63/132)	88.9% (56/63)	9.5% (6/63)	1.6% (1/63)	57.1% (36/63)	22.2% (14/63)	15.9% (10/63)	4.8% (3/63)
Bruising	40.2% (53/132)	77.4% (41/53)	18.9% (10/53)	3.8% (2/53)	43.4% (23/53)	20.8% (11/53)	22.6% (12/53)	13.2% (7/53)
Swelling	41.7% (55/132)	80.0% (44/55)	18.2% (10/55)	1.8% (1/55)	49.1% (27/55)	20.0% (11/55)	23.6% (13/55)	7.3% (4/55)
Lumps/Bumps	38.6% (51/132)	82.4% (42/51)	17.6% (9/51)	0% (0/51)	49.0% (25/51)	15.7% (8/51)	13.7% (7/51)	21.6% (11/51)
Redness	34.8% (46/132)	87.0% (40/46)	13.0% (6/46)	0% (0/46)	67.4% (31/46)	17.4% (8/46)	6.5% (3/46)	8.7% (4/46)
Pain after Injection	33.3% (44/132)	81.8% (36/44)	18.2% (8/44)	0% (0/44)	79.5% (35/44)	11.4% (5/44)	6.8% (3/44)	2.3% (1/44)
Firmness	33.3% (44/132)	86.4% (38/44)	13.6% (6/44)	0% (0/44)	50.0% (22/44)	25.0% (11/44)	13.6% (6/44)	11.4% (5/44)
Discoloration (not redness or bruising)	18.9% (25/132)	88.0% (22/25)	12.0% (3/25)	0% (0/25)	52.0% (13/25)	16.0% (4/25)	20.0% (5/25)	12.0% (3/25)
Itching	11.4% (15/132)	80.0% (12/15)	20.0% (3/15)	0% (0/15)	53.3% (8/15)	20.0% (3/15)	13.3% (2/15)	13.3% (2/15)
Other[d]	9.1% (12/132)	66.7% (8/12)	25.0% (3/12)	8.3% (1/12)	83.3% (10/12)	0% (0/12)	8.3% (1/12)	8.3% (1/12)

[a] N denotes the number of all treated participants (treatment and control) who recorded responses in the diaries after initial treatment.

[b] Maximum reported severity in the diary. The percentages by severity are based on the number of participants with the corresponding ISR.

[c] Maximum duration reported in the diary. The percentages by duration are based on the number of participants with the corresponding ISR.

[d] Other ISRs include swelling of eyes, puffy, purple, redness, bruising, dark under eye, numbness on right lower part of face, bruising swelling in cheek area, mild headache, tightness in cheeks, twitching under the eye, tearing, persistent ache at injection site, eyelid heaviness, light headed, nauseous, very hot, almost fainted, pain like a sinus infection on left, headache, sore, huge purple black eye, and tired eyes

Table 7: ISRs by Severity and Duration After Repeat Treatment with JUVÉDERM® VOLBELLA® XC Occurring in > 5% of Treated Participants

Injection Site Response	Total % (n/N[a])	Severity[b]			Duration[c]			
		Mild %(n/N)	Moderate %(n/N)	Severe %(n/N)	1-3 Days %(n/N)	4-7 Days %(n/N)	8-14 Days %(n/N)	15-30 Days %(n/N)
Tenderness to Touch	34.3% (12/35)	83.3% (10/12)	8.3% (1/12)	8.3% (1/12)	41.7% (5/12)	25.0% (3/12)	8.3% (1/12)	25.0% (3/12)
Firmness	28.6% (10/35)	90.0% (9/10)	0% (0/10)	10% (1/10)	60.0% (6/10)	10.0% (1/10)	10.0% (1/10)	20.0% (2/10)
Pain after Injection	28.6% (10/35)	90.0% (9/10)	10% (1/10)	0% (0/10)	60.0% (6/10)	20.0% (2/10)	10.0% (1/10)	10.0% (1/10)
Swelling	28.6% (10/35)	70.0% (7/10)	20.0% (2/10)	10.0% (1/10)	40.0% (4/10)	20.0% (2/10)	20.0% (2/10)	20.0% (2/10)
Lumps/Bumps	25.7% (9/35)	77.8% (7/9)	11.1% (1/9)	11.1% (1/9)	44.4% (4/9)	11.1% (1/9)	22.2% (2/9)	22.2% (2/9)
Redness	25.7% (9/35)	77.8% (7/9)	11.1% (1/9)	11.1% (1/9)	55.6% (5/9)	44.4% (4/9)	0% (0/9)	0% (0/9)
Bruising	20.0% (7/35)	85.7% (6/7)	14.3% (1/7)	0% (0/7)	28.6% (2/7)	28.6% (2/7)	42.9% (3/7)	0% (0/7)
Discoloration	8.6% (3/35)	100% (3/3)	0% (0/3)	0% (0/3)	66.7% (2/3)	0% (0/3)	33.3% (1/3)	0% (0/3)
Itching	5.7% (2/35)	50.0% (1/2)	50.0% (1/2)	0% (0/2)	100% (2/2)	0% (0/2)	0% (0/2)	0% (0/2)

[a] N denotes the number of participants who recorded responses in the diaries after repeat treatment.
[b] Maximum severity reported in the diary. The percentages by severity are based on the number of participants with the corresponding ISR.
[c] Maximum duration reported in the diary. The percentages by duration are based on the number of participants with the corresponding ISR.

Adverse effects that occurred in the PMA clinical study:

Adverse events (AEs) were reported by Treating Investigators at all follow-up visits, where applicable. Among the 105 treated participants, 10/105 (9.5%) experienced treatment-related AEs following initial and touch-up treatment. The most common treatment-related AEs included injection site bruising (3.8%) and injection site swelling (3.8%).

Table 8: Treatment-Related Adverse Events After Initial/Touch-up Treatment

Adverse Event	Participants % (n/N)
Injection Site Bruising	3.8% (4/105)
Injection Site Swelling	3.8% (4/105)
Dizziness	1.9% (2/105)
Injection Site Pain	1.0% (1/105)
Syncope	1.0% (1/105)

In the clinical study, 3 participants had mild swelling that occurred > 30 days after treatment. The swelling was treated with antibiotics for 1 participant; the other participants did not require treatment. These events resolved within 45 days without sequelae.

There were no treatment-related AEs after repeat treatment, no participants with treatment-related serious adverse events, no unanticipated adverse device effects, and no deaths in this study.

2. Effectiveness Results

Effectiveness analyses was based on 103 evaluable participants at the primary endpoint, Month 3.

Primary Effectiveness Results:

JUVEDÉRM® VOLBELLA® XC provided a clinically and statistically significant improvement in the volume deficit in the infraorbital hollows compared to the no-treatment control group. The primary effectiveness endpoint was met in that the treatment group responder rate was 83.1% which was statistically greater ($p < 0.0001$) than the no-treatment control group. JUVEDÉRM® VOLBELLA® XC was found to be effective in all Fitzpatrick skin photo types, for males and females, and across the studied age range.

Table 9: Effectiveness Summary Responder Rate at 3 Months Based on Evaluating Investigator's Live Assessment

	Responder Rate at Month 3	P – Value
Treatment Group	83.1%, 95% CI 75.8-90.4	N/A
Control Group	15.6%, 95% CI 3.0-28.2	N/A
Difference in Responder Rates (Treatment rate – Control rate)	67.5%, 95% CI 52.9-82.0	<0.0001

The responder rate at the 12-month follow up visit was 73.4% (69/94) based on AIHS responder rates using observed data based on the blinded EI's live assessment.

Secondary Effectiveness Results:

The FACE-Q Appraisal of Lower Eyelids overall mean score was 54.4 at baseline and improved to 72.6 at Month 3 with the improvement being statistically significant ($p < 0.0001$).

The EI and participant GAIS responder rates at Month 3 for the treatment group were 86.1% (87/101) and 84.0% (84/100), respectively, where the responder rate was the percent of participants with a score of improved or much improved on the GAIS.

Other Effectiveness Results:

At the Month 3 primary timepoint, 78.2%, (79/101) of participants reported being satisfied or definitely satisfied with the overall result of treatment, 76.2%, (77/101) with how natural the area under the eyes looked, and 78.2%, (79/101) with how natural the area under the eyes felt. At Month 12, 75.5%, (71/94) of participants reported being satisfied or definitely satisfied with the overall result of treatment,

72.3%, (68/94) with how natural the area under the eyes looked, and 75.5%, (71/94) with how natural the area under the eyes felt.

3. Subgroup Analyses

Prespecified subgroup analyses included baseline AIHS, injection volume, primary injection instrument, and investigational site, which are shown in Table 10. Subgroup analyses were performed based on baseline AIHS, injection volume, primary injection instrument (cannula or needle), gender, Fitzpatrick skin type, age, and investigational site. Treatment group subjects showed consistent responder rates across different subgroups with the exception of primary injection instrument and investigational site. The AIHS responder rate in subjects treated using cannula was 92.9%, (52/56) and 71.1%, (32/45) in subjects treated using needle at Month 3. Across all investigational sites, AIHS responder rates were consistently above 70% except at two sites, which had 0% (0/7) and 57.1% (4/7) responder rates. However, regardless of injection instrument or investigational site, the majority of subjects were satisfied across all secondary and other effectiveness measures.

Table 10: AIHS Responder Rate at Month 3 Subgroup Analyses

Subgroup	Treatment (N=101) N (%)	Control (N=32) N (%)
Baseline AIHS		
Moderate	87.2% (34/39)	14.3% (2/14)
Severe	80.6% (50/62)	16.7% (3/18)
Injection Volume		
≤ Median 1.0 mL	90.2% (46/51)	N/A
> Median 1.0 mL	76.0% (38/50)	N/A
Primary Injection Instrument		
Cannula	92.9% (52/56)	N/A

Subgroup	Treatment (N=101) N (%)	Control (N=32) N (%)
Needle	71.1% (32/45)	N/A
Gender		
Females	83.5% (76/91)	16.1% (5/31)
Males	80.0% (8/10)	0.0% (0/1)
Fitzpatrick Skin Types		
Fitzpatrick I/II	85.3% (29/34)	0.0% (0/11)
Fitzpatrick III/IV	80.0% (40/50)	27.8% (5/18)
Fitzpatrick V/VI	88.2% (15/17)	0.0% (0/3)
Race		
Non-white	90.9% (20/22)	0.0% (0/5)
White	81.0% (64/79)	18.5% (5/27)

A comparison of participant demographics and baseline characteristics between the cannula and needle subgroups was performed, and the distribution of the demographic and baseline covariates was similar for both cannula and needle subgroups.The AIHS responder rate for cannula is higher than for needle at Month 3 (93.0% [53/57] vs. 71.1% [32/45]), which could be attributed to the lack of responders at one investigational site with a 0% (0/7) AIHS responder rate. All participants at this site were treated with needle.

Secondary and other effectiveness endpoints comparing the cannula and needle subgroups are provided in Table 11 and Table 12 below. At Month 3, both subgroups showed similar responder rates for all secondary endpoints and other

effectiveness endpoints.

Table 11: GAIS Responder Rates at Month 3 for Cannula vs Needle Subgroups

Statistics	EI		Participant	
	Cannula (N=57)	Needle (N=44)	Cannula (N=56)	Needle (n=44)
Responder, % (n)	89.5% (51)	81.8% (36)	83.9% (47)	84.1% (37)

Table 12: Cannula vs Needle Comparing Other Effectiveness Measures at Month 3

Other Effectiveness Measure	Cannula	Needle
FACE-Q Appraisal of Lower Eyelids: Mean Change from Baseline	16.4 N=56	19.7 N=45
Satisfied or Definitely Satisfied with Treatment – Overall Result, % (n/N)	78.6% (44/56)	77.8% (35/45)
Assessment of Dark Circles – Moderately or Very Bothered, % (n/N)	17.5% (10/57)	24.4% (11/45)

Additionally, 3D imaging of the infraorbital area volume change and mean injection volumes are presented in Table 13 and show similar results when comparing both injection tools. The volume change for each side was similar to the mean injection volume at initial treatment.

Table 13: 3D Volume Change at Month 3 for Cannula vs Needle Subgroups

Other Effectiveness Measure	Cannula (N=59)		Needle (N=46)	
	Left Side N = 56	Right Side N = 56	Left Side N = 44	Right Side N = 44
Mean 3D Volume Change (mL)	0.82	0.80	0.90	0.96
Mean Injection Volume (mL)	0.72	0.71	0.79	0.77

No significant differences were observed in the demographics and baseline characteristics of participants in the cannula and needle subgroups. Although the responder rate with treatment using cannula is higher when compared to needle, the results could be attributed to the responder rate data from 1 investigational site. All secondary and other endpoints demonstrated similar effectiveness results

between both injection tools.

A subgroup analysis for participants treated using cannula versus needle subgroups demonstrated a higher incidence of ISRs in participants treated with cannula. Although the cannula subgroup experienced a higher incidence rate of overall ISRs compared to the needle subgroup, the confidence intervals of the individual ISR incidence rates for the two subgroups overlap. Additionally, ISR severity, ISR duration, and treatment-related AEs were similar between the cannula and needle subgroups.

Table 14: Frequency of ISRs for Cannula and Needle Subgroups after Initial Treatment

ISR	Cannula		Needle	
	ISR% (n/N[a])	95% CI	ISR% (n/N[a])	95% CI
Any ISR	62.1% (36/58)	48.4%-74.5%	48.9% (22/45)	33.7%-64.2%
Tenderness to touch	56.9% (33/58)	43.2%-69.8%	40.0% (18/45)	25.7%-55.7%
Swelling	51.7% (30/58)	38.2%-65.0%	28.9% (13/45)	16.4%-44.3%
Firmness	43.1% (25/58)	30.2%-56.8%	24.4% (11/45)	12.9%-39.5%
Lumps/Bumps	43.1% (25/58)	30.2%-56.8%	33.3% (15/45)	20.0%-49.0%
Bruising	43.1% (25/58)	30.2%-56.8%	42.2% (19/45)	27.7%-57.8%
Redness	41.4% (24/58)	28.6%-55.1%	28.9% (13/45)	16.4%-44.3%
Pain after injection	37.9% (22/58)	25.5%-51.6%	31.1% (14/45)	18.2%-46.6%
Discoloration (not redness or bruising)	25.9% (15/58)	15.3%-39.0%	13.3% (6/45)	5.1%-26.8%
Itching	13.8% (8/58)	6.1%-25.4%	11.1% (5/45)	3.7%-24.1%
Other[b]	12.1% (7/58)	5.0%-23.3%	8.9% (4/45)	2.5%-21.2%

[a]N denotes the number of participants with a diary record

[b]Other ISRs include swelling of eyes, puffy, purple, redness, bruising, dark under eye, numbness on right lower part of face, bruising swelling in cheek area, mild headache, tightness in cheeks, twitching under the eye, tearing, persistent ache at injection site, eyelid heaviness, light headed, nauseous, very hot, almost fainted, pain like a sinus infection on left, headache, sore, huge purple black eye, and tired eyes

Table 15: Severity of ISRs for Cannula and Needle Subgroups after Initial Treatment

Injection Site Response	Cannula (N=58)				Needle (N=45)			
	N	Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])	N	Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])
Tenderness to touch	33	81.8% (27/33)	15.2% (5/33)	3.0% (1/33)	18	94.4% (17/18)	5.6% (1/18)	0% (0/18)

Injection Site Response	Cannula (N=58)				Needle (N=45)			
	N	Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])	N	Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])
Swelling	30	73.3% (22/30)	23.3% (7/30)	3.3% (1/30)	13	84.6% (11/13)	15.4% (2/13)	0% (0/13)
Firmness	25	80.0% (20/25)	20.0% (5/25)	0% (0/25)	11	90.9% (10/11)	9.1% (1/11)	0% (0/11)
Lumps/Bumps	25	72.0% (18/25)	28.0% (7/25)	0% (0/25)	15	93.3% (14/15)	6.7% (1/15)	0% (0/15)
Bruising	25	72.0% (18/25)	20.0% (5/25)	8.0% (2/25)	19	78.9% (15/19)	21.1% (4/19)	0% (0/19)
Redness	24	83.3% (20/24)	16.7% (4/24)	0% (0/24)	13	92.3% (12/13)	7.7% (1/13)	0% (0/13)
Pain after injection	22	77.3% (17/22)	22.7% (5/22)	0% (0/22)	14	85.7% (12/14)	14.3% (2/14)	0% (0/14)
Discoloration (not redness or bruising)	15	80.0% (12/15)	20.0% (3/15)	0% (0/15)	6	100.0% (6/6)	0% (0/6)	0% (0/6)
Itching	8	75.0% (6/8)	25.0% (2/8)	0% (0/8)	5	100.0% (5/5)	0% (0/5)	0% (0/5)
Other[b]	7	71.4% (5/7)	28.6% (2/7)	0% (0/7)	4	50.0% (2/4)	25.0% (1/4)	25.0% (1/4)

[a]N denotes the number of participants who recorded responses with the specific ISR
[b]Other ISRs include swelling of eyes, puffy, purple, redness, bruising, dark under eye, numbness on right lower part of face, bruising swelling in cheek area, mild headache, tightness in cheeks, twitching under the eye, tearing, persistent ache at injection site, eyelid heaviness, light headed, nauseous, very hot, almost fainted, pain like a sinus infection on left, headache, sore, huge purple black eye, and tired eyes

Table 16: Duration of ISRs for Cannula and Needle Subgroups After Initial Treatment

Injection Site Response	Cannula (N=58)					Needle (N=45)				
	N	1-3 Days (n/N[a])	4-7 Days (n/N[a])	8-14 Days (n/N[a])	15-30 Days (n/N[a])	N	1-3 Days (n/N[a])	4-7 Days (n/N[a])	8-14 Days (n/N[a])	15-30 Days (n/N[a])
Tenderness to touch	33	57.6% (19/33)	21.2% (7/33)	15.2% (5/33)	6.1% (2/33)	18	55.6% (10/18)	22.2% (4/18)	16.7% (3/18)	5.6% (1/18)
Swelling	30	46.7% (14/30)	26.7% (8/30)	20.0% (6/30)	6.7% (2/30)	13	46.2% (6/13)	15.4% (2/13)	23.1% (3/13)	15.4% (2/13)

Injection Site Response	Cannula (N=58)					Needle (N=45)				
	N	1-3 Days (n/N[a])	4-7 Days (n/N[a])	8-14 Days (n/N[a])	15-30 Days (n/N[a])	N	1-3 Days (n/N[a])	4-7 Days (n/N[a])	8-14 Days (n/N[a])	15-30 Days (n/N[a])
Bruising	25	32.0% (8/25)	28.0% (7/25)	28.0% (7/25)	12.0% (3/25)	19	52.6% (10/19)	10.5% (2/19)	15.8% (3/19)	21.1% (4/19)
Lumps/Bumps	25	36.0% (9/25)	20.0% (5/25)	16.0% (4/25)	28.0% (7/25)	15	60.0% (9/15)	6.7% (1/15)	20.0% (3/15)	13.3% (2/15)
Firmness	25	48.0% (12/25)	20.0% (5/25)	12.0% (3/25)	20.0% (5/25)	11	54.5% (6/11)	27.3% (3/11)	18.2% (2/11)	0% (0/11)
Redness	24	62.5% (15/24)	16.7% (4/24)	4.2% (1/24)	16.7% (4/24)	13	61.5% (8/13)	23.1% (3/13)	15.4% (2/13)	0% (0/13)
Pain after injection	22	72.7% (16/22)	13.6% (3/22)	9.1% (2/22)	4.5% (1/22)	14	85.7% (12/14)	7.1% (1/14)	7.1% (1/14)	0% (0/14)
Discoloration (not redness or bruising)	15	40.0% (6/15)	20.0% (3/15)	20.0% (3/15)	20.0% (3/15)	6	83.3% (5/6)	0% (0/6)	16.7% (1/6)	0% (0/6)
Itching	8	75.0% (6/8)	0% (0/8)	0% (0/8)	25.0% (2/8)	5	20.0% (1/5)	40.0% (2/5)	40.0% (2/5)	0% (0/5)
Other[b]	7	85.7% (6/7)	0% (0/7)	0% (0/7)	14.3% (1/7)	4	75.0% (3/4)	0% (0/4)	25.0% (1/4)	0% (0/4)

[a]N denotes the number of participants who recorded responses with the specific ISR
[b]Other ISRs include swelling of eyes, puffy, purple, redness, bruising, dark under eye, numbness on right lower part of face, bruising swelling in cheek area, mild headache, tightness in cheeks, twitching under the eye, tearing, persistent ache at injection site, eyelid heaviness, light headed, nauseous, very hot, almost fainted, pain like a sinus infection on left, headache, sore, huge purple black eye, and tired eyes

Table 17: Treatment Related AEs by Injection Tool

Adverse Event	Cannula (N=59)	Needle (N=46)
Participant with at least 1 AE	10.2% (6)	8.7% (4)
Injection Site Bruising	1.7% (1)	6.5% (3)
Injection Site Swelling	3.4% (2)	2.2% (1)
Dizziness	3.4% (2)	0
Injection Site Pain	0	2.2% (1)
Syncope	0	2.2% (1)
Injection Site Oedema	1.7% (1)	0

The individual Fitzpatrick skin type subgroup analyses are provided below in Table 18. In general, the safety and effectiveness of JUVÉDERM® VOLBELLA® XC for the improvement of infraorbital hollowing was similar across all of the individual Fitzpatrick skin types. Table 18 and Table 19 show the primary and secondary effectiveness results at Month 3. A majority of participants were responders across all of the individual Fitzpatrick skin types.

Table 18: AIHS Responder Rate (Month 3) by Fitzpatrick Skin type

Fitzpatrick Skin Type	AIHS Responder Status (N=103)
Type I	66.7% (2/3)
Type II	87.1% (27/31)
Type III	74.2% (23/31)
Type IV	89.5% (17/19)
Type V	90.0% (9/10)
Type VI	85.7% (6/7)

Table 19: Secondary Effectiveness (Month 3) by Fitzpatrick Skin Type

Fitzpatrick Skin type	Investigator GAIS % (n)	Participant GAIS % (n)	Change from Baseline FACE-Q Appraisal of Lower Eye Lids
Type I (N=3)	66.7% (2)	100.0% (3)	10.3
Type II (N=31)	83.9% (26)	74.2% (23)	18.8
Type III (N=31)	87.1% (27)	90.3% (28)	21.1
Type IV (N=19)	89.5% (17)	84.2% (16)	14.1
Type V (N=9)	88.9% (8)	88.9% (8)	19.7
Type VI (N=7)	85.7% (6)	85.7% (6)	10.1

ISR severity and duration by individual Fitzpatrick skin type are provided in Table 20 and Table 21, respectively. The majority of ISRs were mild in severity and resolved within 7 days among the individual Fitzpatrick skin types. In general, ISR severity and duration are comparable across all Fitzpatrick skin types.

Table 20: Severity of ISRs by Fitzpatrick Skin Type

ISR	Fitzpatrick Skin Type					
	Type I %(n/N)	**Type II %(n/N)**	**Type III %(n/N)**	**Type IV %(n/N)**	**Type V %(n/N)**	**Type VI %(n/N)**
Tenderness to Touch						
Mild	100% (2/2)	94.1% (16/17)	77.8% (14/18)	88.9% (8/9)	75.0% (3/4)	100% (1/1)
Moderate	0% (0/2)	5.9% (1/17)	22.2% (4/18)	0% (0/9)	25.0% (1/4)	0% (0/1)
Severe	0% (0/2)	0% (0/17)	0% (0/18)	11.1% (1/9)	0% (0/4)	0% (0/1)
Bruising						
Mild	100% (2/2)	75.0% (12/16)	68.8% (11/16)	71.4% (5/7)	100% (2/2)	100% (1/1)
Moderate	0% (0/2)	25.0% (4/16)	25.0% (4/16)	14.3% (1/7)	0% (0/2)	0% (0/1)
Severe	0% (0/2)	0% (0/16)	6.3% (1/16)	14.3% (1/7)	0% (0/2)	0% (0/1)
Redness						
Mild	100% (1/1)	78.6% (11/14)	93.8% (15/16)	80.0% (4/5)	100% (1/1)	0% (0/0)
Moderate	0% (0/1)	21.4% (3/14)	6.3% (1/16)	20.0% (1/5)	0% (0/1)	0% (0/0)
Severe	0% (0/1)	0% (0/14)	0% (0/16)	0% (0/5)	0% (0/1)	0% (0/0)
Firmness						
Mild	100% (1/1)	100% (10/10)	68.8% (11/16)	85.7% (6/7)	100.0% (1/1)	100% (1/1)
Moderate	0% (0/1)	0% (0/10)	31.3% (5/16)	14.3% (1/7)	0% (0/1)	0% (0/1)
Severe	0% (0/1)	0% (0/10)	0% (0/16)	0% (0/7)	0% (0/1)	0% (0/1)
Swelling						
Mild	100% (1/1)	81.3% (13/16)	66.7% (10/15)	71.4% (5/7)	100% (3/3)	100% (1/1)
Moderate	0% (0/1)	18.8% (3/16)	33.3% (5/15)	14.3% (1/7)	0% (0/3)	0% (0/1)
Severe	0% (0/1)	0% (0/16)	0% (0/15)	14.3% (1/7)	0% (0/3)	0% (0/1)
Lumps/Bumps						
Mild	100% (1/1)	92.9% (13/14)	61.5% (8/13)	75.0% (6/8)	100% (3/3)	100% (1/1)
Moderate	0% (0/1)	7.1% (1/14)	38.5% (5/13)	25.0% (2/8)	0% (0/3)	0% (0/1)

ISR	Fitzpatrick Skin Type					
	Type I %(n/N)	**Type II %(n/N)**	**Type III %(n/N)**	**Type IV %(n/N)**	**Type V %(n/N)**	**Type VI %(n/N)**
Severe	0% (0/1)	0% (0/14)	0% (0/13)	0% (0/8)	0% (0/3)	0% (0/1)
Pain after Injection						
Mild	0% (0/0)	91.7% (11/12)	73.3% (11/15)	85.7% (6/7)	0% (0/1)	100% (1/1)
Moderate	0% (0/0)	8.3% (1/12)	26.7% (4/15)	14.3% (1/7)	100% (1/1)	0% (0/1)
Severe	0% (0/0)	0% (0/12)	0% (0/15)	0% (0/7)	0% (0/1)	0% (0/1)
Itching						
Mild	0% (0/0)	100% (3/3)	66.7% (4/6)	100% (3/3)	0% (0/0)	100% (1/1)
Moderate	0% (0/0)	0% (0/3)	33.3% (2/6)	0% (0/3)	0% (0/0)	0% (0/1)
Severe	0% (0/0)	0% (0/3)	0% (0/6)	0% (0/3)	0% (0/0)	0% (0/1)
Discoloration (not redness or bruising)						
Mild	0% (0/0)	83.3% (5/6)	87.5% (7/8)	75.0% (3/4)	100% (2/2)	100% (1/1)
Moderate	0% (0/0)	16.7% (1/6)	12.5% (1/8)	25.0% (1/4)	0% (0/2)	0% (0/1)
Severe	0% (0/0)	0% (0/6)	0% (0/8)	0% (0/4)	0% (0/2)	0% (0/1)
Other[a]						
Mild	0% (0/0)	66.7% (2/3)	50.0% (2/4)	66.7% (2/3)	100% (1/1)	0% (0/0)
Moderate	0% (0/0)	33.3% (1/3)	25.0% (1/4)	33.3% (1/3)	0% (0/1)	0% (0/0)
Severe	0% (0/0)	0% (0/3)	25.0% (1/4)	0% (0/3)	0% (0/1)	0% (0/0)

[a]Other ISRs include swelling of eyes, puffy, purple, redness, bruising, dark under eye, numbness on right lower part of face, bruising swelling in cheek area, mild headache, tightness in cheeks, twitching under the eye, tearing, persistent ache at injection site, eyelid heaviness, light headed, nauseous, very hot, almost fainted, pain like a sinus infection on left, headache, sore, huge purple black eye, and tired eyes

Table 21: Duration of ISRs by Fitzpatrick Skin Type

ISR	Fitzpatrick Skin Type					
	Type I %(n/N)	**Type II %(n/N)**	**Type III %(n/N)**	**Type IV %(n/N)**	**Type V %(n/N)**	**Type VI %(n/N)**
Tenderness to Touch						
1-3 Days	50.0% (1/2)	58.8% (10/17)	55.6% (10/18)	55.6% (5/9)	75.0% (3/4)	0% (0/1)
4-7 Days	50.0% (1/2)	35.3% (6/17)	16.7% (3/18)	11.1% (1/9)	0% (0/4)	0% (0/1)
8-14 Days	0% (0/2)	5.9% (1/17)	22.2% (4/18)	22.2% (2/9)	25.0% (1/4)	0% (0/1)
15-30 Days	0% (0/2)	0% (0/17)	5.6% (1/18)	11.1% (1/9)	0% (0/4)	100% (1/1)
Bruising						
1-3 Days	50.0% (1/2)	37.5% (6/16)	37.5% (6/16)	57.1% (4/7)	0% (0/2)	100% (1/1)
4-7 Days	50.0% (1/2)	37.5% (6/16)	6.3% (1/16)	0% (0/7)	50.0% (1/2)	0% (0/1)
8-14 Days	0% (0/2)	18.8% (3/16)	37.5% (6/16)	14.3% (1/7)	0% (0/2)	0% (0/1)
15-30 Days	0% (0/2)	6.3% (1/16)	18.8% (3/16)	28.6% (2/7)	50.0% (1/2)	0% (0/1)
Redness						
1-3 Days	100% (1/1)	57.1% (8/14)	56.3% (9/16)	80.0% (4/5)	100% (1/1)	0% (0/0)
4-7 Days	0% (0/1)	14.3% (2/14)	31.3% (5/16)	0% (0/5)	0% (0/1)	0% (0/0)
8-14 Days	0% (0/1)	14.3% (2/14)	6.3% (1/16)	0% (0/5)	0% (0/1)	0% (0/0)
15-30 Days	0% (0/1)	14.3% (2/14)	6.3% (1/16)	20.0% (1/5)	0% (0/1)	0% (0/0)
Firmness						
1-3 Days	0% (0/1)	60.0% (6/10)	62.5% (10/16)	28.6% (2/7)	0% (0/1)	0% (0/1)
4-7 Days	100% (1/1)	20.0% (2/10)	18.8% (3/16)	14.3% (1/7)	0% (0/1)	100% (1/1)
8-14 Days	0% (0/1)	10.0% (1/10)	6.3% (1/16)	42.9% (3/7)	0% (0/1)	0% (0/1)
15-30 Days	0% (0/1)	10.0% (1/10)	12.5% (2/16)	14.3% (1/7)	100% (1/1)	0% (0/1)
Swelling						
1-3 Days	100% (1/1)	68.8% (11/16)	40.0% (6/15)	28.6% (2/7)	0% (0/3)	0% (0/1)

ISR	Fitzpatrick Skin Type					
	Type I %(n/N)	**Type II %(n/N)**	**Type III %(n/N)**	**Type IV %(n/N)**	**Type V %(n/N)**	**Type VI %(n/N)**
4-7 Days	0% (0/1)	12.5% (2/16)	33.3% (5/15)	0% (0/7)	100% (3/3)	0% (0/1)
8-14 Days	0% (0/1)	18.8% (3/16)	20.0% (3/15)	42.9% (3/7)	0% (0/3)	0% (0/1)
15-30 Days	0% (0/1)	0% (0/16)	6.7% (1/15)	28.6% (2/7)	0% (0/3)	100% (1/1)
Lumps/Bumps						
1-3 Days	0% (0/1)	64.3% (9/14)	38.5% (5/13)	37.5% (3/8)	33.3% (1/3)	0% (0/1)
4-7 Days	100% (1/1)	7.1% (1/14)	15.4% (2/13)	12.5% (1/8)	33.3% (1/3)	0% (0/1)
8-14 Days	0% (0/1)	0% (0/14)	30.8% (4/13)	37.5% (3/8)	0% (0/3)	0% (0/1)
15-30 Days	0% (0/1)	28.6% (4/14)	15.4% (2/13)	12.5% (1/8)	33.3% (1/3)	100% (1/1)
Pain after Injection						
1-3 Days	0% (0/0)	83.3% (10/12)	73.3% (11/15)	85.7% (6/7)	0% (0/1)	100% (1/1)
4-7 Days	0% (0/0)	8.3% (1/12)	13.3% (2/15)	0% (0/7)	100% (1/1)	0% (0/1)
8-14 Days	0% (0/0)	8.3% (1/12)	6.7% (1/15)	14.3% (1/7)	0% (0/1)	0% (0/1)
15-30 Days	0% (0/0)	0% (0/12)	6.7% (1/15)	0% (0/7)	0% (0/1)	0% (0/1)
Itching						
1-3 Days	0% (0/0)	66.7% (2/3)	33.3% (2/6)	66.7% (2/3)	0% (0/0)	100% (1/1)
4-7 Days	0% (0/0)	33.3% (1/3)	0% (0/6)	33.3% (1/3)	0% (0/0)	0% (0/1)
8-14 Days	0% (0/0)	0% (0/3)	33.3% (2/6)	0% (0/3)	0% (0/0)	0% (0/1)
15-30 Days	0% (0/0)	0% (0/3)	33.3% (2/6)	0% (0/3)	0% (0/0)	0% (0/1)
Discoloration (not redness or bruising)						
1-3 Days	0% (0/0)	66.7% (4/6)	37.5% (3/8)	50.0% (2/4)	50.0% (1/2)	100% (1/1)
4-7 Days	0% (0/0)	0% (0/6)	25.0% (2/8)	0% (0/4)	50.0% (1/2)	0% (0/1)
8-14 Days	0% (0/0)	16.7% (1/6)	25.0% (2/8)	25.0% (1/4)	0% (0/2)	0% (0/1)

ISR	Fitzpatrick Skin Type					
	Type I %(n/N)	Type II %(n/N)	Type III %(n/N)	Type IV %(n/N)	Type V %(n/N)	Type VI %(n/N)
15-30 Days	0% (0/0)	16.7% (1/6)	12.5% (1/8)	25.0% (1/4)	0% (0/2)	0% (0/1)
Other[a]						
1-3 Days	0% (0/0)	66.7% (2/3)	100% (4/4)	66.7% (2/3)	100% (1/1)	0% (0/0)
4-7 Days	0% (0/0)	0% (0/3)	0% (0/4)	0% (0/3)	0% (0/1)	0% (0/0)
8-14 Days	0% (0/0)	33.3% (1/3)	0% (0/4)	0% (0/3)	0% (0/1)	0% (0/0)
15-30 Days	0% (0/0)	0% (0/3)	0% (0/4)	33.3% (1/3)	0% (0/1)	0% (0/0)

[a]Other ISRs include swelling of eyes, puffy, purple, redness, bruising, dark under eye, numbness on right lower part of face, bruising swelling in cheek area, mild headache, tightness in cheeks, twitching under the eye, tearing, persistent ache at injection site, eyelid heaviness, light headed, nauseous, very hot, almost fainted, pain like a sinus infection on left, headache, sore, huge purple black eye, and tired eyes

Table 22: Treatment-Related AEs by Fitzpatrick Skin Type

AE	Fitzpatrick Skin type					
	Type I (N=3)	Type II (N=32)	Type III (N=33)	Type IV (N=19)	Type V (N=11)	Type VI (N=7)
Injection site bruising	0% (0/3)	3.1% (1/32)	9.1% (3/33)	5.3% (1/19)	0% (0/11)	0% (0/7)
Injection site swelling	0% (0/3)	0% (0/32)	0% (0/33)	1.6% (3/19)	0% (0/11)	0% (0/7)
Injection site pain	0% (0/3)	0% (0/32)	0% (0/33)	5.3% (1/19)	0% (0/11)	0% (0/7)
Injection site edema	0% (0/3)	0% (0/32)	3.0% (1/33)	0% (0/19)	0% (0/11)	0% (0/7)
Dizziness	3.3% (1/3)	0% (0/32)	3.0% (1/33)	0% (0/19)	0% (0/11)	0% (0/7)

4. Pediatric Extrapolation

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

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 34 investigators. Of the 34 investigators, 30 investigators have by way of a signed Financial Disclosure/Certification Form, verified that they have no applicable financial arrangements with Allergan 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.

Four of the 34 investigators had financial arrangements with Allergan to be disclosed under 21 CFR 54.2 (b), not affecting the outcome of the 1932-701-008 clinical study.

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

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

On March 23, 2021, a general issues panel meeting was convened to discuss and make recommendations regarding the risks and benefits of dermal fillers. The panel discussed and made recommendations on the inclusion of vision assessments to actively and deliberately monitor for intravascular injection in clinical trials and clinical practice. The panel recommended that for clinical trials, the collection of this data is appropriate and important to the continuing study of these adverse events. The panel did not think that there should be different approaches in clinical trials for different anatomic areas, as there is not sufficient data to determine what areas may be at higher risk for intravascular injection. In clinical practice, there was consensus from the panel that brief vision assessments before and after treatment should be recommended regardless of indication for use. In addition, the panel recommended that injectors have a treatment plan in place, which includes establishing a relationship with a nearby ophthalmologist or retinal specialist. There was a consensus that training is one of the key tools available to prevent

intravascular injection events. Recommendations from the panel included establishing uniform training as well as annual refresher training to ensure that all injectors have up-to-date information.

Post-panel, the Agency has implemented labeling changes in the current submission in line with the panel recommendations, including recommendations for brief vision assessments before and after treatment and establishing a relationship with a nearby ophthalmologist or retinal specialist. In addition, the Agency has included requirements for the development of training as a key tool to mitigate the risk of intravascular injection events as conditions of approval.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

JUVEDÉRM® VOLBELLA® XC met the pre-specified primary endpoint, and the secondary endpoints support product effectiveness. The balance of the data indicates that JUVEDÉRM® VOLBELLA® XC is effective in treating the infraorbital hollows to improve volume deficit in the infraorbital hollows at the 3-month primary effectiveness time point.

Subgroup analyses were performed based on baseline AIHS, injection volume, primary injection instrument (cannula or needle), gender, Fitzpatrick skin type, age, and investigational site. Treatment group subjects showed consistent responder rates across different subgroups with the exception of primary injection instrument and investigational site. The AIHS responder rate in subjects treated using cannula was 92.9%, (52/56) and 71.1% (32/45) in subjects treated using needle at Month 3. Across all investigational sites, AIHS responder rates were consistently above 70% except at two sites, which had 0% (0/7) and 57.1% (4/7) responder rates. However, regardless of injection instrument or investigational site, the majority of subjects were satisfied across

all secondary and other effectiveness measures.

B. Safety Conclusions

The potential risks and adverse effects of the device are based on data collected in the clinical study conducted to support the indication expansion as described above as well as evaluation of device use in the Post-Marketing setting. The data submitted provide a reasonable assurance that the device is safe for deep (subcutaneous and/or supraperiosteal) injection for the improvement of the infraorbital hollows in adults over the age of 21. The specific conclusions are:

- Safety assessments such as Tyndall effect, visual acuity, confrontational visual fields, and ocular motility were evaluated at the screening visit and throughout the study. None of the safety assessments were remarkable or presented safety concerns after treatment with JUVÉDERM® VOLBELLA® XC.
- For initial, touch-up, and repeat treatments, most ISRs were mild to moderate in severity, resolved within 1 week, and were as expected for soft tissue filler treatments
- The most common ISRs were tenderness to touch, bruising, and swelling
- Injections with needle had a lower incidence rate of ISRs than injections with cannula
- Participants assessed procedural pain during injection as minimal
- The most common treatment-related AEs after initial/touch-up treatment were injection site bruising and injection site swelling, and all others occurred in less than 2% of participants
- Three participants experienced 3 mild swelling > 30 days after treatment. The swelling was treated with antibiotics for 1 participant; the other participants did not require treatment. All of these events resolved without sequelae.
- There were no deaths or treatment-related serious adverse events (SAEs) reported in the study.
- Treatment with JUVEDÉRM® VOLBELLA® XC did not lead to serious vision-related adverse events in the study.

C. Benefit-Risk Determination

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. In the JUVEDÉRM® VOLBELLA® XC group at Month 3, 83.3% (85/102) were responders and the effect lasted through 1 year with a majority of the participants still responders (73.4%, 69/94) at Month 12. The findings of the primary effectiveness assessment were supported by the secondary endpoints. The improvement in the FACE-Q Appraisal of the Lower Eyelids overall means score from baseline to Month 3 was statistically significant ($p < 0.0001$). The Month 3 GAIS investigator and participant assessments were 86.0% and 84.0%, respectively. Of the of the participants who were eligible to receive repeat treatment 40% (22/55) declined repeat treatment because improvement remained.

The probable risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above. Most of the participants experienced common ISRs which included tenderness, bruising, swelling, lumps/bumps, redness, pain after injection, firmness, discoloration (not redness or bruising), and itching. Participants rated ISRs as predominantly mild in severity with a majority resolving within 1 week. Three participants had mild swelling which developed more than 30 days after treatment. All adverse events resolved either spontaneously or with treatment.

The probable benefits outweigh the probable risks, as determined by the short-term adverse outcomes and rare late adverse events seen after injection, balanced against the improvement seen on the Allergan Infraorbital Hollows Scale and patient satisfaction.

1. Patient Perspective

   Patient perspectives considered during the review included:

   - FACE-Q Appraisal of Lower Eyes Questionnaire (to assess patient satisfaction) Results for FACE-Q are discussed in Section X.D.2 of this document.

- GAIS assessed by the participants at Month 1, 3, 6, 9, and 12. Results for GAIS assessments are discussed in Section X.D.2 of this document.
- Adverse events were obtained from sign and symptoms reported by patients during visits. Adverse events that were reported during the study are summarized in Section X.D.1 and Table 8 of this document.
- Participant diaries which were completed by participants for 30 days after each treatment, were used to collect information about predefined, injection related events at the treated area.

In conclusion, given the available information above, the data support the improvement of infraorbital hollowing in adults over the age of 21, the probable benefits outweigh the probable risks.

D. Overall Conclusions

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

XIII. CDRH DECISION

CDRH issued an approval order on May 28, 2021.

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.