SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: SKINVIVE™ by JUVÉDERM®

Device Procode: LMH

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

Date of Panel Recommendation: None.

Premarket Approval Application (PMA) Number: P110033/S059

Date of FDA Notice of Approval: May 11, 2023

The original PMA for JUVÉDERM® VOLUMA® (P110033) was approved on October 22, 2013 and is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the midface in adults over the age of 21. The SSED to support this indication is available on the CDRH website and is incorporated by reference here. SKINVIVE™ by JUVÉDERM® is being submitted as a panel-track supplement (P110033/S059) to the JUVÉDERM® VOLUMA® XC PMA (P110033) to request changes in design or performance of the device, and a new indication for the device. The current supplement was submitted for SKINVIVE™ by JUVÉDERM® for intradermal injection to improve skin smoothness of the cheeks in adults over the age of 21.

II. INDICATIONS FOR USE

SKINVIVE™ by JUVÉDERM® injectable gel is indicated for intradermal injection to improve skin smoothness of the cheeks in adults over the age of 21.

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SKINVIVE™ by JUVÉDERM® labeling.

V. DEVICE DESCRIPTION

SKINVIVE™ by JUVÉDERM® injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. The gel consists of hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, crosslinked with 1,4-Butanediol diglycidyl ether (BDDE), which contains 0.3% w/w lidocaine in a physiologic buffer. Each retail box of SKINVIVE™ by JUVÉDERM® contains two sterilized syringes prefilled with 1.0 ml of hyaluronic acid gel implant. Each syringe is sealed in a thermoformed tray with two 32 G 1/2" needles. Syringes are fitted with a luer lock adaptor, a plunger rod, a rubber stopper tip cap, and a finger grip. Syringes are labeled with the name of the product, batch number, and expiration date.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the improvement skin smoothness. Alternative therapies for improving skin smoothness include lasers, intense pulsed light, radiofrequency, microneedling, chemical peels, topicals (e.g., creams), and nutritional supplements. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with their physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

SKINVIVE™ by JUVÉDERM® is marketed as JUVÉDERM® VOLITE™ outside of the United States. JUVÉDERM® VOLITE™ without lidocaine received CE Mark as JUVÉDERM® VOLITE™ B in April 2015, and JUVÉDERM® VOLITE with lidocaine, also known as JUVÉDERM® VOLITE™ XC received CE Mark as JUVÉDERM® VOLITE™ in April 2016. JUVÉDERM® VOLITE™ is available in the European Union for

the treatment of superficial cutaneous depressions such as fine lines and for additional improvement of skin quality attributes such as hydration and elasticity. In addition to being marketed throughout the European Union, JUVEDERM® VOLITE™ is currently marketed in over 90 countries. JUVEDERM® VOLITE™ has not been removed from the marketplace for any reasons related to safety or effectiveness.

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 redness, lumps/bumps, swelling, bruising, pain, tenderness, firmness, discoloration, itching, temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

Treatment-related adverse events (TEAEs) were reported in the US clinical study by the Treating Investigator at follow-up visits. Among the 199 participants treated with SKINVIVE™ by JUVÉDERM® (treatment and treated control group participants), 6 participants (3.0%) had 21 treatment-related TEAEs. These TEAEs included pruritus (1.5%, 3/199), erythema (1.0%, 2/199), bruising (1.0%, 2/199), discoloration (0.5%, 1/199), needle abrasion (0.5%, 1/199), pain (0.5%, 1/199), and papule (0.5%, 1/199) at the injection site.

Postmarket Surveillance

The following adverse events (AEs) were received from postmarket surveillance on the use of SKINVIVE™ by JUVÉDERM® outside the United States; this includes reports received globally from all sources including scientific journals and voluntary reports. The AEs received from postmarket surveillance, with a frequency of 5 events or more, are listed in order of prevalence: inflammatory reaction, inflammatory nodule, unsatisfactory result, loss/lack of correction, allergic reaction, anxiety, varied injuries, vascular occlusion, infection, dry skin, neurological symptoms such as increase/decrease in sensation, and abscess.

In many cases, AEs resolved without any treatment. Reported treatments for these events included (in alphabetical order): antibiotics, anticholinergics, anticoagulants, antihistamines, anti-inflammatories, antimetabolites, antivirals, arnica, blood thinners, hyaluronidase, ice, laser therapy, massage, radiofrequency therapy, steroids, ultrasound therapy, and warm compress.

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Physical and Chemical Characterization

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

Table 1: Summary of Key Bench Testing on SKINVIVE™ by JUVÉDERM®

Test	Purpose	Results
NaHA Concentration	Ensures HA concentration meets specification	Passed
Lidocaine HCl Concentration	Ensure lidocaine concentration meets specification	Passed
Characterization of pH	Ensures pH meets specification	Passed
Osmolarity	Ensures osmolarity meets specification	Passed
Extrusion Force	Ensures extrusion force meets specification	Passed
Rheology	Ensures that rheology meets specification	Passed
Residual Crosslinker	Ensure residual crosslinker meets specification	Passed
Bacterial Endotoxin	Ensures endotoxin meets specification	Passed
Sterility	Ensures sterilization meets specification	Passed

Filled syringes are sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle is validated according to the ISO 17665-1 sterilization standard. The validated sterilization cycle provides a minimum Sterility Assurance Level (SAL) of 10^{-6}.

Stability data have been collected through 24 months under ICH Q1A(R) storage conditions. At each timepoint, product was evaluated for conformance with microbiological, and physical and chemical properties including lidocaine hydrochloride potency and lidocaine-related degradants. Conformance with all specifications was confirmed.

Biocompatibility Testing

SKINVIVE™ by JUVÉDERM® was evaluated with *in vitro* and *in vivo* biocompatibility studies appropriate for devices in contact with tissue for greater than 30 days. The results of the tests are summarized in Table 2 below. The biocompatibility studies were performed in accordance with the Federal Good Laboratory Practices Regulations (21 CFR Part 58), ISO 10993, and the FDA guidance document Use of International Standard ISO 10993-1 "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process."

Table 2: Summary of Biocompatibility Testing on SKINVIVE™ by JUVÉDERM®

Test	Method	Standard	Results
Cytotoxicity	Direct contact	ISO 10993-5	Non-cytotoxic
Sensitization	Guinea pig maximization test	ISO 10993-10	Non-sensitizing
Intracutaneous Reactivity	72-hour exposure in rabbits	ISO 10993-10	Non-irritant
Acute Systemic Toxicity	Intraperitoneal injection in mice	ISO 10993-11	Non-toxic
Subchronic Toxicity	Intradermal injection in rats	ISO 10993-11	Non-toxic
Genotoxicity	Bacterial reverse mutation Micronucleus Chromosomal Aberration	ISO 10993-3	Non-genotoxic Non-mutagenic
Tissue Implantation (4 and 12 Weeks)	In rats	ISO 10993-6	Non-irritant
Pyrogenicity	Rabbit pyrogen study	USP <151>	Non-pyrogenic

Carcinogenicity Risks: The excess cancer risks for SKINVIVE™ by JUVÉDERM® range from 6.1 x 10^{-5} to 1.6 x 10^{-8} from lifetime exposure to residual BDDE based on a linear extrapolation method and a dose-response model. The excess cancer risks for SKINVIVE™ by JUVÉDERM® are in the same range of acceptable cancer risks as other previously approved dermal filler products.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of microdroplet intradermal injections with the treatment of SKINVIVE™ by JUVÉDERM® for improvement of skin smoothness of the cheeks in the US under IDE G180063. 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

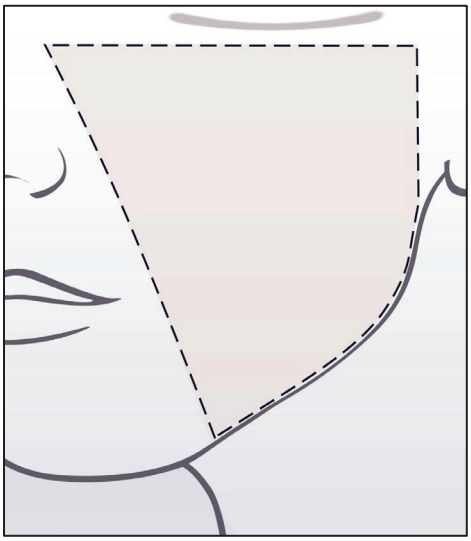
Participants were treated between November 9, 2018 and March 12, 2020. The database for this Panel Track Supplement reflected data collected through September 17, 2020 and included 209 randomized patients (SKINVIVE™ by JUVÉDERM® or no-treatment control) out of 255 enrolled patients. There were 14 investigational sites.

The study was a randomized, multicenter, evaluator-blind, controlled pivotal clinical study (1867-701-008) conducted to evaluate the safety and effectiveness of SKINVIVE™ by JUVÉDERM® for the improvement of skin smoothness of the cheeks. The treatment area encompasses the area from the zygomatic arch to the edge of the jaw, lateral from the nasolabial fold and oral commissures to the preauricular cheek, illustrated in Figure 1 below. At the outset of the study, 135 participants were randomized and underwent treatment with SKINVIVE™ by JUVÉDERM® in the cheeks. One participant was randomized to SKINVIVE™ by JUVÉDERM® and exited the study on the same day

without receiving treatment. A total of 73 participants were randomized to the delayed-treatment control.

The study was designed to include a maximum of 263 enrolled participants and approximately 210 randomized participants; 255 participants were enrolled, and 209 participants were randomized. The mITT population included 202 participants, and the safety population included 209 participants.

Figure 1: Treatment Area for Cheek Smoothness



Treatment group participants underwent treatment with SKINVIVE™ by JUVÉDERM® at the outset of the study, followed by an optional touch-up treatment 1 month after initial treatment, if deemed necessary to achieve optimal correction, with follow-up visits at 1, 2, 4, and 6 months after the last treatment. Repeat treatment was offered to treatment group participants at 6 months, with follow-up visits 1 and 4 months after repeat treatment. Control group participants attended a follow-up visit at 1 month during the no-treatment control period. Thereafter, control participants were offered study treatment and touch-up with post-treatment follow-up visits at 1, 2, 4, and 6 months after last treatment. Injections were administered using 32 G ½" and 32 G 3/16" needles. The most common injection technique to achieve optimal results was microdroplet intradermal injections with spacings ≤ 5 mm. Injection spacing > 5 mm to 1 cm was also used. In the treatment group, the median injection volume on both cheeks was 3.2 mL at initial treatment, 2.0 mL at touch-up treatment, and 2.7 mL at repeat treatment. The injection volume administered for the treatment group (initial and touch up combined) ranged from 0.8 to 6.0 mL

Statistical Analysis Plan

The study sample size was estimated to provide adequate power to demonstrate the effectiveness and safety of the product. The sample size calculation was based on a 2-sided Fisher's exact test at a significance level of 5% to detect a between-group difference of at least 40% in the ACSS responder rate (80% vs. 40% for treatment vs.

control, respectively). The randomization is stratified by investigator site for a 2:1 ratio for treatment vs control.

The primary effectiveness variable was the blinded evaluating investigator's assessment of cheek skin smoothness using the Allergan Cheek Smoothness Scale (ACSS) at one month following the most recent treatment (for participants in the treatment group participants) or at one month following randomization (no treatment-for participants in the control group participants). ACSS responders were defined as subjects achieving a 1-point improvement from baseline ACSS in both cheeks. Missing data in ACSS were imputed using the multiple imputation method.

The null hypothesis is that there is no difference between the SKINVIVE™ by JUVÉDERM® treatment group and the no-treatment control group in the ACSS responder rate at Month 1. The alternative hypothesis is that there is difference between the SKINVIVE™ by JUVÉDERM® treatment group and the no-treatment control group in the ACSS responder rate at Month 1. SKINVIVE™ by JUVÉDERM® was declared to be superior to the no-treatment control group if the 2-sided p-value was less than 0.05 and the responder rate was greater for SKINVIVE™ by JUVÉDERM® than for the no-treatment control group.

The secondary effectiveness endpoints at Month 1 were (1) change from baseline in the overall score of participant's self-assessed FACE-Q Satisfaction with Skin score, and (2) the blinded evaluating investigator's assessment of fine lines using the Allergan Fine Lines Scale (AFLS). Both were assessed at Month 1. Statistical significance of FACE-Q scores was determined using a 2-sided 2-sample t-test (for normally distributed data) or the Wilcoxon rank-sum test. The AFLS responder rate was analyzed based on 2-sided Fisher's exact test in the same manner as the ACSS responder rate; however, only those participants with symmetric baseline AFLS score of 2 on both cheeks or 3 on both cheeks were included in the analysis.

At least 135 of the 210 randomized participants were expected to have a baseline AFLS score of 2 on both cheeks or 3 on both cheeks. Assuming at least 65% of participants would have baseline AFLS scores of 2 on both cheeks or 3 on both cheeks, 72 participants in treatment group and 36 participants in control group would provide 94.4% power to detect a difference of at least 35% in the responder rates on AFLS between the treatment groups, based on a 2-sided Fisher's exact test at the 5% level. The treatment group was assumed to have at least an 80% responder rate at Month 1, and the control group was assumed to have at most a 45% responder rate. The assumptions of responder rates are estimated from Allergan Study V12-001.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the SKINVIVE™ by JUVÉDERM® Pivotal Study (1867-701-008) was limited to participants who met the following inclusion criteria:

   - Age 22 or over and in good general health
   - Had a score of 2 for both cheeks or 3 for both cheeks on the 5-point photonumeric Allergan Cheek Smoothness Scale (ACSS)[1] (range: 0 to 4), as judged live by the Evaluating Investigator (EI)

     OR

     Had Fitzpatrick skin phototype V or VI and had an ACSS score of 1, 2, or 3 on both cheeks (the cheeks did not need to have the same score), as judged live by the EI (Fitzpatrick V/VI safety cohort)
   - Had a FACE-Q Satisfaction with Skin Questionnaire sum score of 39 or less (sum score of 39 is equivalent to Rasch-transformed score of 69) unless enrolled as part of the Fitzpatrick V/VI safety cohort

   Participants were not permitted to enroll in the 1867-701-008 study if they met any of the following exclusion criteria:

   - Had undergone tissue augmentation with dermal fillers including HA, calcium hydroxylapatite, autologous fat, mesotherapy, or other cosmetic procedures (e.g., face-lift, laser, photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, or other ablative procedures) in the face within 12 months before screening or planned to undergo any such treatment during the study
   - Had received any crosslinked HA filler in any anatomic area within 12 months of screening
   - Had undergone treatment with botulinum toxin in the cheek area (including crow's feet) within 6 months of screening or planned to undergo such treatment during the study
   - Had ever received semipermanent fillers or permanent facial implants (e.g., poly-L-lactic acid, polymethylmethacrylate, silicone, expanded polytetrafluoroethylene) anywhere in the face or planned to be implanted with any of these products at any time during the study
   - Had a tendency to develop hypertrophic scarring
   - Had a history of allergy to lidocaine, HA products, and/or to gram-positive bacterial proteins as HA is produced by *Streptococcus*-type bacteria, or planned to undergo desensitization therapy during the term of the study

[1] Donofrio L, Carruthers A, Hardas B, Murphy DK, Carruthers J, Jones D, Sykes JM, Creutz L, Marx A, and Dill S. Development and validation of a photonumeric scale for evaluation of facial skin texture. Dermatol. Surg. 2016; 42(S1):S219-S226.

- Had current cutaneous inflammatory or infectious processes (e.g., acne, herpes), abscess, an unhealed wound, or a cancerous or precancerous lesion on the face (injection could have been delayed to allow participants with a history of recurrent oral herpes to take prophylactic antiviral/herpes medication for 2 days
- Had active autoimmune disease
- Females who were pregnant, nursing, or planning a pregnancy during the study

2. Follow-up Schedule

The follow-up period consisted of safety and effectiveness follow-up visits at 1, 2, 4, and 6 months after the last treatment (initial or touch-up). Participants were eligible for a touch-up treatment with SKINVIVE™ by JUVÉDERM® 30 days after initial treatment. An optional repeat treatment was offered to all treatment group participants after completion of the 6-month follow-up visit, with 4 months of follow-up after repeat treatment. Control participants followed a similar effectiveness evaluation schedule through 1 month. After 1 month, control participants were offered treatment and followed for an additional 6 months.

3. Clinical Endpoints

With regards to safety, participants used electronic diaries to record specific signs and symptoms of injection site responses (ISRs) experienced during the 30 days after the initial, touch-up, and repeat treatments. Adverse Events (AEs) were reported by the Treating Investigator (TI) at follow-up visits.

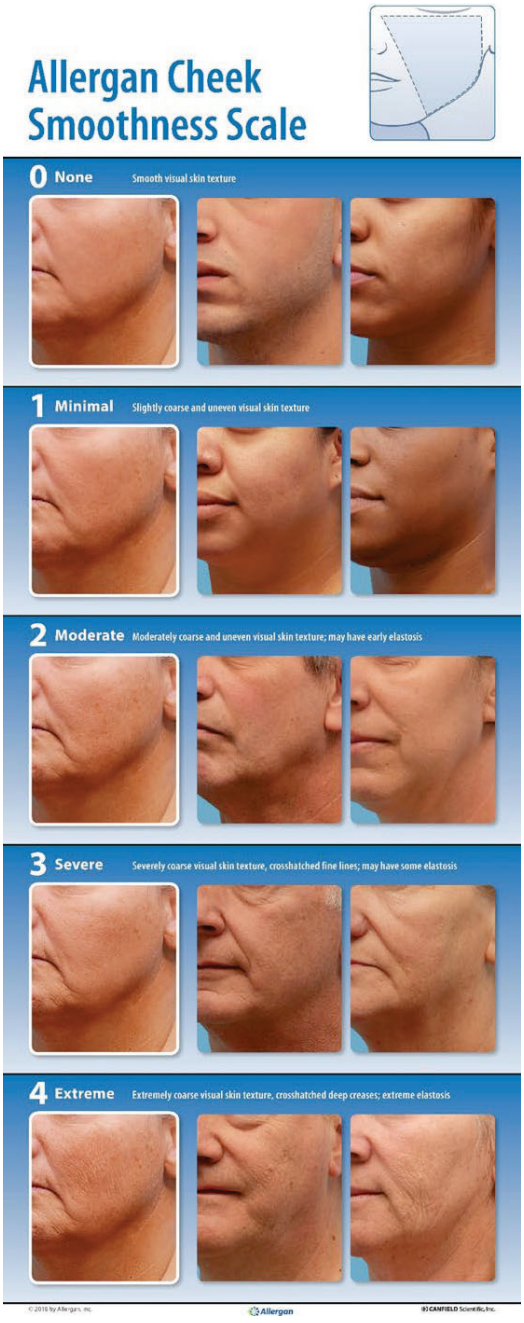
With regards to effectiveness, the primary effectiveness measure for the study was the blinded Evaluating Investigator's (EI's) assessment of the participant's skin smoothness on the cheeks using the validated 5-point ACSS (Table 3 and Figure 2).

With regard to success/failure criteria, a responder was defined as a participant with ≥ 1-point improvement in skin smoothness on both cheeks compared with the pretreatment score on the ACSS. Effectiveness of SKINVIVE™ by JUVÉDERM® was demonstrated if the responder rate at 1 month (after initial treatment or optional touch-up) for treatment group participants was statistically significantly greater than that for the control group participants. The missing data in the primary effectiveness analysis were imputed by the multiple imputation method.

Table 3: Allergan Cheek Smoothness Scale

Score	Grade	Description
0	None	Smooth visual skin texture
1	Minimal	Slightly coarse and uneven visual skin texture
2	Moderate	Moderately coarse and uneven visual skin texture; may have early elastosis
3	Severe	Severely coarse visual skin texture, crosshatched fine lines; may have some elastosis
4	Extreme	Extremely coarse visual skin texture, crosshatched deep creases; extreme elastosis

Figure 2: Allergan Cheek Smoothness Scale



Secondary measures included participant assessment of satisfaction with skin using the validated *Satisfaction with Skin*[2] module of the FACE-Q questionnaire and EI assessment of participant fine lines on the cheeks using the validated 5-point photonumeric Allergan Fine Lines Scale (AFLS)[3] shown in Table 4 and Figure 3.

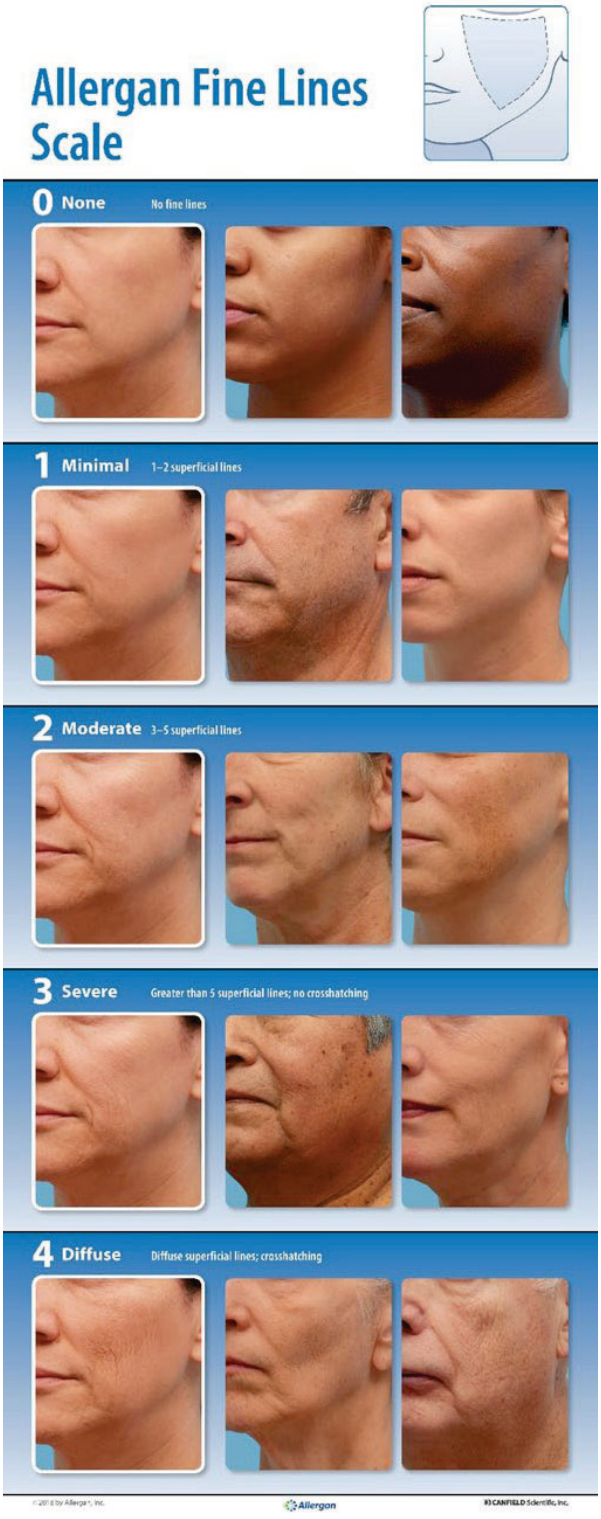
Table 4: Allergan Fine Lines Scale

Score	Grade	Description
0	None	No fine lines
1	Minimal	1-2 superficial lines
2	Moderate	3-5 superficial lines
3	Severe	Greater than 5 superficial lines; no crosshatching
4	Diffuse	Diffuse superficial lines; crosshatching

[2] Klassen AF, Cano SJ, Schwitzer JA, Baker SB, Carruthers A, Carruthers J, Chapas A, Pusic AL. Development and Psychometric Validation of the FACE-Q Skin, Lips, and Facial Rhytides Appearance Scales and Adverse Effects Checklists for Cosmetic Procedures. JAMA Dermatol 2016; 152(4): 443-451.

[3] Carruthers J, Donofrio L, Hardas B, Murphy DK, Jones D, Carruthers A, Sykes JM, Creutz L, Marx A, and Dill S. Development and validation of a photonumeric scale for evaluation of facial fine lines. *Dermatol. Surg.* 2016; 42(S1):S227-S234.

Figure 3: Allergan Fine Lines Scale



Other effectiveness measures included participant assessments of facial lines using the validated *Appraisal of Lines*[4] module of the FACE-Q questionnaire. Changes in skin hydration in the treatment area were measured using the MoistureMeterD® instrument.

The MoistureMeterD® is a clinically validated instrument to assess lymphedema and is cleared under K143310. This instrument provides a non-invasive measurement of extracellular fluids through changes in tissue dielectric constant[5].

B. Accountability of PMA Cohort

At the time of database lock, of 255 patients enrolled in the PMA study, 209 (82.0%) patients are available for analysis at the completion of the study, the 07/2020 final follow-up visit. The participant disposition is shown in Table 5.

[4] Klassen AF, Cano SJ, Scott AM, Pusic AL. Measuring Outcomes That Matter to Face-Lift Patients: Development and Validation of FACE-Q Appearance Appraisal Scales and Adverse Effects Checklist for the Lower Face and Neck. Plast Reconstr Surg. 2014; 133(1):21-30

[5] Nuutinen J, Ikäheimo R, and Lahtinen T. Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat. Physiol Meas. 2004; 25: 447-454.

Table 5: Participant Disposition

Disposition	Number of Participants		
	Treatment	Control	Total
Enrolled	**N/A**	**N/A**	**255**
Screen Failures	**N/A**	**N/A**	**46**
Randomized Participants	**136**	**73**	**209**
Withdrawal by Participant	2	1	3
Lost to Follow-up	2	3	5
Discontinued Due to Protocol Deviation[a]	1	0	1
Completed Control Period (Month 1 Primary Endpoint)	**131**	**69**	**200**
Control Group – Did Not Receive Optional Treatment (Completed Study)	**N/A**	**5**	**5**
Control Group – Received Optional Treatment	**N/A**	**64**	**64**
Withdrawal by Participant	5	1	6
Lost to Follow-up	2	6	8
Other Reason for Discontinuation[b]	0	1	1
Completed Follow-up Period Through 6 Months After Treatment	**124**	**56[c]**	**180**
Treatment Group – Did Not Receive Optional Repeat Treatment (Completed Study)	**45**	**N/A**	**45**
Treatment Group – Received Optional Repeat Treatment	**79**	**N/A**	**79**
Discontinued Due to Adverse Event[d]	1	N/A	1
Withdrawal by Participant	1	N/A	1
Lost to Follow-up	6	N/A	6
Other Reason for Discontinuation[b]	3	N/A	3
Treatment Group – Completed Follow-up Period Through 4 Months After Repeat Treatment (Completed Study)	**68**	**N/A**	**68**
Completed Study (Total Participants)	**113**	**56**	**169**

[a] Participant 701005006 was randomized and not treated in the study due to the site erroneously determining that ACSS inclusion criteria were not met
[b] Discontinuation due to COVID-19
[c] Participants in control group were not offered repeat treatment at 6 months
[d] Participant 701004013 had a non-treatment-related serious adverse event of brain neoplasm

Analysis Populations

The analysis populations in the study were as follows:

- The modified intent-to-treat (mITT) Population included all randomized participants who had a baseline assessment on the ACSS for both cheeks and were not in the Fitzpatrick V/VI safety cohort
- The Observed Primary Endpoint Population included all participants who had an ACSS assessment for both cheeks at the 1-month primary endpoint

- The Safety Population included treatment group participants who were randomized and received study intervention as well as all randomized control group participants (including control group participants who did not opt for optional treatment SKINVIVE™ by JUVÉDERM®)
- The SKINVIVE™ by JUVÉDERM® Treated Population included all participants who received treatment with SKINVIVE™ by JUVÉDERM®
- The SKINVIVE™ by JUVÉDERM® Repeat Treatment Population included participants who received repeat treatment with SKINVIVE™ by JUVÉDERM®
- The Fitzpatrick Safety Cohort included participants with Fitzpatrick skin phototype V or VI and met any of the following conditions:
    - Baseline ACSS score of 1 in either cheek
    - Asymmetric baseline ACSS score of 2 or 3
    - FACE-Q overall converted score greater than 69

The analysis populations are summarized in Table 6.

Table 6: Summary of Analysis Populations

Population	Treatment	Control	Total
Modified Intent-to-Treat (mITT) Population	131	71	202
Observed Primary Endpoint Population	122	50	172
Safety Population	135	74	209
SKINVIVE™ Treated Population	135	64	199
SKINVIVE™ Repeat Treatment Population	79	N/A	79
Fitzpatrick Safety Cohort	5	2	7

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 treatment and control groups are presented in Table 7.

Table 7: Participant Demographics and Pre-Treatment Characteristics (Safety Population)

	SKINVIVE™ by JUVÉDERM (N = 135) % (n/N)	Control (N = 74) % (n/N)
Sex		
Female	81.5% (110/135)	91.9% (68/74)
Male	18.5% (25/135)	8.1% (6/74)
Age		
Median	58	56
Range	32-83	31-79
Race		
White	84.4% (114/135)	85.1% (63/74)
Black or African American	12.6% (17/135)	13.5% (10/74)
Asian	0.7% (1/135)	0%
Native Hawaiian or Other Pacific Islander	0.7% (1/135)	0%
Multiple	1.5% (2/135)	1.4% (1/74)
Ethnicity		
Hispanic or Latino	27.4% (37/135)	28.4% (21/74)
Not Hispanic or Latino	72.6% (98/135)	71.6% (53/74)
Fitzpatrick Skin Type		
I/II	30.4% (41/135)	31.1% (23/74)
III/IV	57.0% (77/135)	54.1% (40/74)
V/VI	12.6% (17/135)	14.9% (11/74)

Injections were administered using 32 G ½" or 32 G 3/16" needles, with 32 G ½" needles used more frequently. The most common injection technique to achieve optimal results was intradermal microdroplet injections using small volumes of product per injection with spacings ≤ 5 mm or > 5 mm to 1 cm. In the treatment group, the total median injection volume across all injection sites was 3.2 mL at initial treatment, 2.0 mL at touch-up treatment, and 2.7 mL at repeat treatment. The amount used ranged from 0.8 mL to 6.0 mL for initial and touch-up treatment combined.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the treated population comprising of 74 participants in the control and 135 participants in the treatment group. The key safety outcomes for this study are presented below in Table 8 to Table 10. Participants used electronic diaries to record specific signs and symptoms of injection site responses (ISRs) experienced during the 30 days after the initial, touch-up, and repeat treatments. ISRs are reactions associated with the injection

procedure. Examples of ISRs are redness, pain after injection, tenderness to touch, firmness, swelling, lumps/bumps, bruising, itching and discoloration. Participants were instructed to rate each ISR listed on the diary as None, Mild, Moderate, or Severe.

- None or not applicable.
- Mild ISRs were defined as symptoms causing little, if any, discomfort leading to little, if any, effect on daily activities.
- Moderate ISRs were defined as symptoms causing some discomfort leading to some effect on daily activities.
- Severe ISRs were defined as symptoms causing great discomfort leading to compromised performance of daily activities.

The severity and duration of ISRs reported by > 5% of participants after initial treatment (from both the treatment and control groups) are summarized in Table 8. Most ISRs were mild, and their duration was short lasting (7 days or less). The incidence, severity, and duration of ISRs reported after the touch-up and repeat treatments were lower than those reported after initial treatment. Three participants (1.5%, 3/199) had mild (2/3) and moderate (1/3) lumps/bumps that resolved 12 to 15 months after treatment.

Table 8: Injection Site Responses by Severity and Duration After Initial Treatment with SKINVIVE™ by JUVÉDERM Occurring in > 5% of Treated Participants

Injection Site Response	Total % (n/N[a])	Severity[b]			Duration[c]				
		Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])	1-3 Days % (n/N[a])	4-7 Days % (n/N[a])	8-14 Days % (n/N[a])	15-30 Days % (n/N[a])	> 30 Days % (n/N[a])
Any ISR	79.4% (158/199)	54.3% (108/199)	18.6% (37/199)	6.5% (13/199)	34.2% (68/199)	10.6% (21/199)	12.6% (25/199)	22.1% (44/199)	9.5% (19/199)
Redness	68.8% (137/199)	57.3% (114/199)	9.5% (19/199)	2.0% (4/199)	47.2% (94/199)	9.0% (18/199)	6.5% (13/199)	6.0% (12/199)	2.0% (4/199)
Lumps/Bumps	63.3% (126/199)	47.2% (94/199)	12.1% (24/199)	4.0% (8/199)	32.2% (64/199)	10.6% (21/199)	6.5% (13/199)	14.1% (28/199)	8.0% (16/199)
Swelling	61.3% (122/199)	49.7% (99/199)	9.5% (19/199)	2.0% (4/199)	40.7% (81/199)	7.5% (15/199)	9.0% (18/199)	4.0% (8/199)	1.5% (3/199)
Bruising	57.8% (115/199)	44.7% (89/199)	10.6% (21/199)	2.5% (5/199)	24.1% (48/199)	14.1% (28/199)	11.1% (22/199)	8.5% (17/199)	1.0% (2/199)
Pain	52.8% (105/199)	47.2% (94/199)	5.0% (10/199)	0.5% (1/199)	41.2% (82/199)	7.0% (14/199)	2.0% (4/199)	2.5% (5/199)	1.0% (2/199)
Tenderness	52.8% (105/199)	46.7% (93/199)	5.5% (11/199)	0.5% (1/199)	33.7% (67/199)	10.6% (21/199)	5.0% (10/199)	3.5% (7/199)	1.0% (2/199)
Firmness	47.2% (94/199)	40.7% (81/199)	5.5% (11/199)	1.0% (2/199)	32.7% (65/199)	5.5% (11/199)	5.5% (11/199)	3.5% (7/199)	2.0% (4/199)
Discoloration	34.2% (68/199)	27.1% (54/199)	6.5% (13/199)	0.5% (1/199)	19.6% (39/199)	3.5% (7/199)	4.5% (9/199)	6.5% (13/199)	2.5% (5/199)
Itching	25.1% (50/199)	22.6% (45/199)	1.5% (3/199)	1.0% (2/199)	15.1% (30/199)	6.0% (12/199)	2.0% (4/199)	2.0% (4/199)	1.5% (3/199)

[a] N denotes the number of participants who recorded responses in the diaries after initial treatment
[b] Maximum severity reported in the diary
[c] Duration is calculated based on the difference between the first and last date of occurrence

Adverse Events (AEs) were 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." An AE will be considered a treatment emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) after first administration of SKINVIVE™ by JUVÉDERM® for the treatment group and after the date of randomization for the control group. A TEAE is considered a treatment-related TEAE if the event is deemed related to the procedure or the study device by the Treating Investigator.

AEs were reported by the Treating Investigator at follow-up visits. Among the 199 participants treated with SKINVIVE™ by JUVÉDERM® (treatment and treated control group participants), 6 participants (3.0%) had 21 treatment-related TEAEs (Table 9). Most of the treatment-related TEAEs were mild 76.2% (16/21) and resolved within 30 days 76.2% (16/21) without sequelae. No treatment-related TEAEs were reported after repeat treatment.

Table 9: Participant-Level Summary of Treatment-Related TEAEs with SKINVIVE™ by JUVÉDERM®

TEAEs	Participants % (n/N[a])	Severity			Outcome
		Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])	
Overall	3.0% (6/199)	1.5% (3/199)	1.0% (2/199)	0.5% (1/199)	Recovered
Injection Site Pruritus	1.5% (3/199)	1.0% (2/199)	0.5% (1/199)	0.0%	Recovered
Injection Site Erythema	1.0% (2/199)	1.0% (2/199)	0.0%	0.0%	Recovered
Injection Site Bruising	1.0% (2/199)	0.5% (1/199)	0.0%	0.5% (1/199)	Recovered
Injection Site Discoloration	0.5% (1/199)	0.5% (1/199)	0.0%	0.0%	Recovered
Injection Site Injury (Needle Abrasion)	0.5% (1/199)	0.5% (1/199)	0.0%	0.0%	Recovered
Injection Site Pain	0.5% (1/199)	0.0%	0.5% (1/199)	0.0%	Recovered
Injection Site Papule	0.5% (1/199)	0.5% (1/199)	0.0%	0.0%	Recovered[b]

[a] N denotes the number of participants who received initial treatment with SKINVIVE™ by JUVÉDERM®

[b] Participant reported recovery from the TEAE after database lock

Table 10: Event-Level Summary of Treatment-Related TEAEs with SKINVIVE™ by JUVÉDERM®

TEAEs	Events % (n/N)	Time to Onset (Days after last treatment)					Duration (Days)	
		1-3 Days % (n/N)	4-7 Days % (n/N)	8-14 Days % (n/N)	15-30 Days % (n/N)	> 30 Days % (n/N)	≤ 30 days % (n/N)	> 30 Days % (n/N)
Overall	100.0% (21)	57.1% (12/21)	23.8% (5/21)	0.0%	9.5% (2/21)	9.5% (2/21)	76.2% (16/21)	23.4% (5/21)
Injection Site Bruising	23.8% (5/21)	19.0% (4/21)	4.8% (1/21)	0.0%	0.0%	0.0%	19.0% (4/21)	4.8% (1/21)
Injection Site Pruritus	23.8% (5/21)	14.3% (3/21)	9.5% (2/21)	0.0%	0.0%	0.0%	19.0% (4/21)	4.8% (1/21)
Injection Site Papule	19.0% (4/21)	9.5% (2/21)	0.0%	0.0%	0.0%	9.5% (2/21)	9.5% (2/21)	9.5% (2/21)
Injection Site Erythema	14.3% (3/21)	4.8% (1/21)	9.5% (2/21)	0.0%	0.0%	0.0%	9.5% (2/21)	4.8% (1/21)
Injection Site Discoloration	9.5% (2/21)	0.0%	0.0%	0.0%	9.5% (2/21)	0.0%	9.5% (2/21)	0.0%
Injection Site Injury (Needle Abrasion)	4.8% (1/21)	4.8% (1/21)	0.0%	0.0%	0.0%	0.0%	4.8% (1/21)	0.0%
Injection Site Pain	4.8% (1/21)	4.8% (1/21)	0.0%	0.0%	0.0%	0.0%	4.8% (1/21)	0.0%

Subgroup Analyses

Subgroup analyses for treatment-related TEAEs were performed based on sex, Fitzpatrick skin type, age, and injection volume. As shown in Table 11 through Table 14 below, less than 5% of participants treated with SKINVIVE™ by JUVEDERM® experienced a treatment-related TEAE in all subgroups.

Table 11: Treatment-Related TEAEs with SKINVIVE™ by JUVÉDERM® by Sex for Initial and Touch-Up Treatments Combined

TEAEs	Male (N = 29)				Female (N = 170)			
	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Overall	3.4% (1)	3.4% (1)	0.0%	0.0%	2.9% (5)	1.2% (2)	1.2% (2)	0.6% (1)
Injection Site Pruritus	0.0%	0.0%	0.0%	0.0%	1.8% (3)	1.2% (2)	0.6% (1)	0.0%
Injection Site Erythema	0.0%	0.0%	0.0%	0.0%	1.2% (2)	1.2% (2)	0.0%	0.0%
Injection Site Bruising	0.0%	0.0%	0.0%	0.0%	1.2% (2)	0.6% (1)	0.0%	0.6% (1)
Injection Site Discoloration	0.0%	0.0%	0.0%	0.0%	0.6% (1)	0.6% (1)	0.0%	0.0%
Injection Site Injury (Needle Abrasion)	3.4% (1)	3.4% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Pain	0.0%	0.0%	0.0%	0.0%	0.6% (1)	0.0%	0.6% (1)	0.0%
Injection Site Papule	0.0%	0.0%	0.0%	0.0%	0.6% (1)	0.6% (1)	0.0%	0.0%

Table 12: Treatment-Related TEAEs with SKINVIVE™ by JUVÉDERM® by Fitzpatrick for Initial and Touch-Up Treatments Combined

TEAEs	Fitzpatrick I/II (N = 62)				Fitzpatrick III/IV (N = 110)				Fitzpatrick V[a]/VI[a] (N = 27)			
	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Overall	4.8% (3)	1.6% (1)	1.6% (1)	1.6% (1)	2.7% (3)	1.8% (2)	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Pruritus	3.2% (2)	1.6% (1)	1.6% (1)	0.0%	0.9% (1)	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Erythema	1.6% (1)	1.6% (1)	0.0%	0.0%	0.9% (1)	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Bruising	1.6% (1)	0.0%	0.0%	1.6% (1)	0.9% (1)	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Discoloration	1.6% (1)	1.6% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Injury (Needle Abrasion)	0.0%	0.0%	0.0%	0.0%	0.9% (1)	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Pain	0.0%	0.0%	0.0%	0.0%	0.9% (1)	0.0%	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Papule	1.6% (1)	1.6% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

[a] Including participants with baseline ACSS Score of 1

Table 13: Treatment-Related TEAEs with SKINVIVE™ by JUVÉDERM® by Age for Initial and Touch-Up Treatments Combined

TEAEs	< 50 years (N = 40)				50 – 60 years (N = 90)				> 60 years (N = 69)			
	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Overall	2.5% (1)	0.0%	2.5% (1)	0.0%	3.3% (3)	3.3% (3)	0.0%	0.0%	2.9% (2)	0.0%	1.4% (1)	1.4% (1)
Injection Site Pruritus	0.0%	0.0%	0.0%	0.0%	2.2% (2)	2.2% (2)	0.0%	0.0%	1.4% (1)	0.0%	1.4% (1)	0.0%
Injection Site Erythema	0.0%	0.0%	0.0%	0.0%	2.2% (2)	2.2% (2)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Bruising	2.5% (1)	2.5% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4% (1)	0.0%	0.0%	1.4% (1)
Injection Site Discoloration	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4% (1)	1.4% (1)	0.0%	0.0%
Injection Site Injury (Needle Abrasion)	0.0%	0.0%	0.0%	0.0%	1.1% (1)	1.1% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Pain	2.5% (1)	0.0%	2.5% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Papule	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4% (1)	1.4% (1)	0.0%	0.0%

Table 14: Treatment-Related TEAEs with SKINVIVE™ by JUVÉDERM® by Median Volume Injected for Initial and Touch-Up Treatments Combined

TEAEs	≤ Median Volume Injected (N = 107)				> Median Volume Injected (N = 92)			
	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Participants % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Overall	4.7% (5)	2.8% (3)	0.9% (1)	0.9% (1)	1.1% (1)	0.0%	1.1% (1)	0.0%
Injection Site Pruritus	1.9% (2)	1.9% (2)	0.0%	0.0%	1.1% (1)	0.0%	1.1% (1)	0.0%
Injection Site Erythema	1.9% (2)	1.9% (2)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Bruising	1.9% (2)	0.9% (1)	0.0%	0.9% (1)	0.0%	0.0%	0.0%	0.0%
Injection Site Discoloration	0.9% (1)	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Injury (Needle Abrasion)	0.9% (1)	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Pain	0.9% (1)	0.0%	0.9% (1)	0.0%	0.0%	0.0%	0.0%	0.0%
Injection Site Papule	0.0%	0.0%	0.0%	0.0%	1.1% (1)	1.1% (1)	0.0%	0.0%

Other Safety Assessments

FACE-Q Recovery Early Life Impact questionnaire

The overall mean score of the FACE-Q Recovery Early Life Impact questionnaire was 90.5 for the treatment group and 89.8 for the treated control group at 3 days after initial treatment indicating that SKINVIVE™ by JUVÉDERM® treatment was not disruptive to normal daily activities.

Procedural pain

Participant assessment of procedural pain after study injection on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable). Participants assessed procedural pain during injection as minimal.

Vision Assessments

Snellen visual acuity assessments in the SKINVIVE™-Treated Population and SKINVIVE™-Repeat Treatment Population showed that over 85% of participant eyes had the same or better visual acuity at all post-treatment assessments. Only 3 eyes (3 participants) in the SKINVIVE™-Treated Population and 3 eyes (2 participants) in the SKINVIVE™- Repeat Treatment Population showed a ≥ 3-line worsening in visual acuity at any assessment, with more eyes showing a ≥ 3-line improvement. None of these vision changes were related to intravascular injection, and all were deemed not clinically significant by the TI, with the most common

reason being that participants were not wearing their prescription lenses during the assessment that showed the worse visual acuity.

Confrontational visual fields and ocular motility assessments showed that 100% of eyes were full to confrontation and had full duction and version, with no changes from pre-treatment at all assessments.

2. Effectiveness Results

SKINVIVE™ by JUVÉDERM® provided a clinically and statistically significant improvement in skin smoothness on the cheeks compared to the no-treatment control group at 1 month after last treatment (initial or optional touch-up). The primary endpoint was met. At 1 month (after initial treatment or optional touch-up) for the mITT Population with missing data imputed, the ACSS responder rate based on a multiple imputation method in the treatment group (57.9%, 75.9/131, 49.3% to 66.6% confidence interval) was statistically superior ($p < 0.001$) to the responder rate for the untreated control group (4.5%, 3.2/71, - 0.5% to 9.4% confidence interval). The majority of treatment group participants in the SKINVIVE™- Treated Population maintained a clinically significant improvement in skin smoothness (≥ 1-point improvement on the ACSS) through 6 months after initial/touch-up treatment and 4 months after repeat treatment (Table 15).

Table 15: Treatment Group ACSS Responder Rates Based on Observed Data (SKINVIVE™ Treated Population, SKINVIVE™ Repeat Treatment Population)

Timepoint After Initial/Touch-up Treatment	Treatment Group Responder Rate % (n/N[a])
1 Month	58.4% (73/125)
2 Months	61.7% (79/128)
4 Months	59.1% (75/127)
6 Months	55.6% (69/124)
1 Month after Repeat Treatment	68.5% (50/73)
4 Months after Repeat Treatment	65.7% (44/67)

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

Table 16: ACSS Participants with at Least 1-Point Improvement from Baseline at 1 Month (after Initial Treatment or Optional Touch up) in the Control Period by Sex (mITT Population, SKINVIVE™ Treated Population)

Timepoint After Initial/Touch-up Treatment	Treatment Group Responder Rate by Male % (n/N[a])	Treatment Group Responder Rate by Female % (n/N[a])
1 Month	52.4% (11/21)	60.4% (61/101)

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

Participant satisfaction with skin improved significantly after treatment as measured by the FACE-Q *Satisfaction with Skin* questionnaire. In the mITT Population, the mean change from baseline at 1 month (after initial treatment or optional touch-up) in *Satisfaction with Skin* score was 32.0 for the treatment group (mean overall scores

of 34.3 at baseline and 66.5 at 1 month) compared to 1.4 for the untreated control group (mean overall scores of 32.5 at baseline and 35.0 at 1 month). The treatment versus untreated control difference of 28.0 at 1 month (after initial treatment or optional touch-up) was significant ($p < 0.001$).

The treatment group satisfaction results from the individual questions of the FACE-Q *Satisfaction with Skin* questionnaire, which contribute to the overall score, for the SKINVIVE™ Treated Population showed participant satisfaction (Table 17). Treatment group participants in the SKINVIVE™ Treated Population continued to show satisfaction through 6 months (mean overall score of 60.2) 25.4.

Table 17: Treatment Group Results for Individual Questions Selected from FACE-Q *Satisfaction with Skin* Module (SKINVIVE™ Treated Population)

Question	% (n/N) of Participants Somewhat or Very Satisfied			% (n/N) of Participants Somewhat or Very Dissatisfied		
	Baseline	Month 1	Month 6	Baseline	Month 1	Month 6
How facial skin looks at end of day?	23.0% (31/135)	82.4% (103/125)	75.8% (94/124)	77.0% (104/135)	17.6% (22/125)	24.2% (30/124)
How healthy your facial skin looks?	37.8% (51/135)	84.0% (105/125)	83.1% (103/124)	62.2% (84/135)	16.0% (20/125)	16.9% (21/124)
How attractive your facial skin makes you look?	20.7% (28/135)	76.0% (95/125)	72.6% (90/124)	79.3% (107/135)	24.0% (30/125)	27.4% (34/124)
How smooth your facial skin looks?	20.0% (27/135)	79.2% (99/125)	68.5% (85/124)	80.0% (108/135)	20.8% (26/125)	31.5% (39/124)
How clear your facial skin looks?	37.0% (50/135)	76.0% (95/125)	71.0% (88/124)	63.0% (85/135)	24.0% (30/125)	29.0% (36/124)
How refreshed your facial skin makes you look?	15.6% (21/135)	79.2% (99/125)	69.4% (86/124)	84.4% (114/135)	20.8% (26/125)	30.6% (38/124)
How hydrated your facial skin looks?	23.7% (32/135)	78.4% (98/125)	71.8% (89/124)	76.3% (103/135)	21.6% (27/125)	28.2% (35/124)
How facial skin looks when first wake up?	16.3% (22/135)	73.6% (92/125)	63.7% (79/124)	83.7% (113/135)	26.4% (33/125)	36.3% (45/124)
How radiant your facial skin looks?	11.1% (15/135)	74.4% (93/125)	62.9% (78/124)	88.9% (120/135)	25.6% (32/125)	37.1% (46/124)
How the tone of your facial skin looks?	23.0% (31/135)	74.4% (93/155)	68.5% (85/124)	77.0% (104/135)	25.6% (32/125)	31.5% (39/124)
How your pores look?	29.6% (40/135)	80.8% (101/125)	68.5% (85/124)	70.4% (95/135)	19.2% (24/125)	31.5% (39/124)
How even-colored facial skin looks?	18.5% (25/135)	68.0% (85/125)	62.9% (78/124)	81.5% (110/135)	32.0% (40/125)	37.1% (46/124)

The Allergan Fine Lines Scale (AFLS) responder rates were determined for participants who had symmetric baseline scores of 2 or 3 on the AFLS. In the mITT population, the AFLS responder rate at 1 month (after initial treatment or optional touch-up) for the treatment group (58.3%, 49/84) was statistically superior to the untreated control group (5.4%, 2/37). As shown in Table 18, 63.2% of treatment group participants in the SKINVIVE™ Treated Population continued to show a clinically significant improvement in fine lines (≥ 1-point improvement on the AFLS) through 6 months after initial/touch-up treatment and 4 months after repeat treatment (68.8%).

Table 18: Treatment Group AFLS Responder Rates (SKINVIVE™ Treated Population, SKINVIVE™ Repeat Treatment Population)

Visit After Initial/Touch-up Treatment	Responder Rate
1 Month	57.5% (50/87)
2 Months	65.9% (58/88)
4 Months	62.9% (56/89)
6 Months	63.2% (55/87)
1 Month after Repeat Treatment	75.9% (44/58)
4 Months after Repeat Treatment	68.8% (33/48)

The mean score on the *Appraisal of Lines* module of the FACE-Q questionnaire for the treatment group improved from 31.5 at baseline to 54.0 at 1 month (after initial treatment or optional touch-up) and 50.4 at 6 months.

Treatment group participants showed an improvement in skin hydration of the cheeks compared to the no-treatment control group at 1 month (after initial treatment or optional touch-up) based on the *post-hoc* analyses of MoistureMeterD® measurements. Treatment group participants showed a mean increase from baseline to Month 1 of 2.35 versus 0.11 for the untreated control group indicating statistically significant improvement in skin hydration after treatment.

2.1 Independent Photographic Assessment

An Independent Photographic Assessment (IPA) was conducted to evaluate the treatment of SKINVIVE™ by JUVÉDERM® in participants' cheeks. A total of 326 participant cheek photos from 163 participants who had an ACSS score at baseline and Month 1 were evaluated. Three independent, blinded raters who did not participate in the SKINVIVE™ by JUVÉDERM® pivotal study were selected to assess images of the participants' cheeks.

Clinical changes in skin smoothness and skin texture following treatment are not well-captured in photographs. A live assessment is considered more appropriate to assess changes in skin smoothness. Nevertheless, the effectiveness results from the IPA are consistent with the live assessment results in the SKINVIVE™ clinical study. The

IPA analysis by participant in provided in Table 19 below. When IPA raters assessed the photos by participant, the difference in the SKINVIVE™-treated group was statistically significantly better than the control group.

Table 19: Overall Clinical Improvement at Month 1 Control Period (mITT Population with IPA Results Available for Both Cheeks)

	SKINVIVE™	Control
Month 1 Photo Better than Baseline on Both Cheeks	38.8% (47/121)	9.5% (4/42)
95% CI	30.1% - 48.1%	2.7% - 22.6%

2.2 Fitzpatrick Safety Cohort

The ACSS responder rates by Fitzpatrick Skin Phototypes are provided in Table 20 below. The Fitzpatrick Skin Phototypes V and VI include 7 subjects of the Fitzpatrick safety V/VI cohort who had ACSS baseline scores of 1).

Table 20: Primary Effectiveness at Month 1 (after Initial Treatment or Optional Touch-up) for All Randomized Participants by Fitzpatrick Skin Phototype

	ACSS 1-Point Improvement	
Fitzpatrick Skin Phototype	**SKINVIVE™**	**Control**
I	40.0% (2/5)	NA
II	57.6% (19/33)	14.3% (2/14)
III	59.2% (29/49)	6.3% (1/16)
IV	65.2% (15/23)	0% (0/13)
V[a]	44.4% (4/9)	0% (0/5)
VI[a]	66.7% (4/6)	33.3% (1/3)

[a]Including participants with baseline ACSS Score of 1

Patient-reported outcomes included FACE-Q *Satisfaction with Skin* questionnaire and FACE-Q *Appraisal of Lines* questionnaire. As summarized in Table 21 below, participants with all Fitzpatrick skin phototypes achieved mean improvement in satisfaction with their skin and lines (after initial treatment or optional touch-up).

Table 21: Patient-Reported Outcomes at Month 1 (after Initial Treatment or Optional Touch-up) of the Control Period by Fitzpatrick Skin Phototype for All Randomized Participants

Fitzpatrick Skin Phototype	Mean Change from Baseline for FACE-Q Satisfaction with Skin		Mean Change from Baseline for FACE-Q Appraisal of Lines	
	Treatment (N=136)	Control (N=73)	Treatment (N=136)	Control (N=73)
I	21.4	0	17.2	0
II	27.8	9.1	12.7	-3.7
III	30.9	-0.6	23.2	0.2
IV	34.5	2.6	20.8	1.5
V	42.4	-7.4	50.6	5.4
VI	38.2	-3.7	39.3	-9.3

2.3 Subgroup Analyses

As shown in Table 22 through Table 25 below, participants in all subgroup analyses achieved improvement based on the ACSS and substantial mean improvement in satisfaction with their skin and fine lines at Month 1 (after initial treatment or optional touch-up).

Table 22: ACSS Participants with at Least 1-Point Improvement from Baseline at 1 Month (after Initial Treatment or Optional Touch-up) in the Control Period by Age (mITT Population)

Age Group	SKINVIVE™ % (n/N[a])	Control % (n/N[a])
<50 years	82.4% (14/17)	0% (0/16)
50-60 years	62.5% (35/56)	5.6% (1/18)
> 60 years	46.9% (23/49)	12.5% (2/16)

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

Table 23: AFLS: Number (%) of Participants with at Least 1-Point Improvement from Baseline at Month 1 (after initial or optional touch-up) in the Control Period by Age (mITT Population)

Age Group	SKINVIVE™ % (n/N[a])	Control % (n/N[a])
<50 years	75.0% (9/12)	0% (0/12)
50-60 years	67.5% (27/40)	8.3% (1/12)
> 60 years	40.6% (13/32)	7.7% (1/13)

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

Table 24: Patient Reported Outcomes by Age Groups for SKINVIVE™ Group (of mITT Population)

Age Group	Mean Change from Baseline at Month 1 for FACE-Q Satisfaction with Skin		Mean Change from Baseline at Month 1 for FACE-Q Appraisal of Lines	
	Treatment N = 131	Control N =71	Treatment N = 131	Control N =71
< 50 years	27.1	-0.9	20.9	-0.7
50-60 years	35.4	2.6	22.4	2.4
> 60 years	29.8	2.4	25.2	-0.8

Table 25: ACSS: Number (%) of Participants with at Least 1-Point Improvement from Baseline in the Control Period by Median Volume Injected of Initial and Touch-Up Treatments Combined (mITT Population)

Volume Injected	SKINVIVE™ by JUVÉDERM® % (n/N[a])	95% CI
≤ Median[b]	59.7% (37/62)	47.5, 71.9
> Median[b]	58.3% (35/60)	45.9, 70.8

[a] Number of participants with data at baseline and the timepoint
[b] Median injection volume was 4.0 mL for initial and touch-up treatments combined

4. Pediatric Extrapolation

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

E. Financial Disclosure

DISCLOSABLE FINANCIAL ARRANGEMENTS: NO EFFECT ON RELIABILITY OF DATA

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 26 investigators of which none of investigators were full-time or part-time employees of the sponsor and 8 of investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 8 investigators

Significant payment of other sorts: 8 investigators
Proprietary interest in the product tested held by the investigator: None of the investigators

Significant equity interest held by investigator in sponsor of covered study: None of the investigators

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

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. European Clinical Study (V12-001)

A prospective, single-arm clinical study was conducted in France with injecting physicians from 6 countries to evaluate the safety and effectiveness of SKINVIVE™ by JUVÉDERM® without lidocaine for treatment of fine lines and for improvement of skin quality. A total of 131 participants were treated with SKINVIVE™ by JUVÉDERM® without lidocaine on both sides of the face (cheeks and forehead) and optionally the neck. Touch-up treatment, if needed to correct asymmetry, occurred approximately 30 days after the initial treatment. Participants were followed for 9 months after the last treatment. Repeat treatment was offered to participants at 9 months, with 1 month of follow-up after repeat treatment.

1. Safety Results

   ISRs reported after initial treatment are summarized by severity and duration in Table 26. Most ISRs were mild or moderate (114/130, 87.7%) in severity. The incidence, severity, and duration of ISRs reported after repeat treatment were similar to or better than those reported after initial treatment.

Table 26: Injection Site Responses by Severity and Duration After Initial Treatment with SKINVIVE™ by JUVÉDERM® without lidocaine

Injection Site Response	Total % (n/N[a])	Severity[b]			Duration[c]			
		Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])	1-3 Days % (n/N[a])	4-7 Days % (n/N[a])	8-14 Days % (n/N[a])	≥ 15 Days % (n/N[a])
Redness	96.9% (127/131)	58.8% (77/131)	32.8% (43/131)	5.3% (7/131)	64.1% (84/131)	27.5% (36/131)	5.3% (7/131)	0.0%
Swelling	92.4% (121/131)	71.0% (93/131)	19.1% (25/131)	2.3% (3/131)	61.1% (80/131)	22.1% (29/131)	6.9% (9/131)	3.1% (4/131)
Tenderness	90.1% (118/131)	73.3% (96/131)	15.3% (20/131)	1.5% (2/131)	55.7% (73/131)	29.8% (39/131)	3.8% (5/131)	0.8% (1/131)
Firmness	87.8% (115/131)	71.8% (94/131)	15.3% (20/131)	0.8% (1/131)	59.5% (78/131)	21.4% (28/131)	4.6% (6/131)	3.1% (4/131)
Bruising	87.0% (114/131)	53.4% (70/131)	27.5% (36/131)	6.1% (8/131)	22.9% (30/131)	29.0% (38/131)	33.6% (44/131)	1.5% (2/131)
Lumps/Bumps	85.5% (112/131)	55.7% (73/131)	27.5% (36/131)	2.3% (3/131)	43.5% (57/131)	26.0% (34/131)	9.9% (13/131)	6.1% (8/131)
Pain	81.7% (107/131)	65.6% (86/131)	16.0% (21/131)	0.0%	66.4% (87/131)	13.7% (18/131)	1.5% (2/131)	0.0%
Itching	30.5% (40/131)	29.0% (38/131)	1.5% (2/131)	0.0%	27.5% (36/131)	1.5% (2/131)	1.5% (2/131)	0.0%
Discoloration	29.0% (38/131)	25.2% (33/131)	3.8% (5/131)	0.0%	26.7% (35/131)	1.5% (2/131)	2.3% (3/131)	0.0%

[a] N denotes the number of participants who recorded responses in the diaries after initial treatment
[b] Maximum severity reported in the diary
[c] Maximum reported successive occurrence of an injection site response

Adverse Events (AEs) were 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." An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the first study treatment or was present before the first study treatment and increased in severity after the first study treatment. A treatment-related adverse event is defined in accordance with ISO 14155 as "an adverse event related to the use of an investigational medical device.

AEs were recorded when observed by the Investigator or reported by participants. After initial treatment (or touch-up treatment, if performed), treatment-related TEAEs were reported in 16.0% (21/131) of participants. These TEAEs for these participants included injection site mass (9.2%, 12/131 participants), hemorrhage (3.1%, 4/131), bruising (1.5%, 2/131), hematoma (1.5%, 2/131), erythema (0.8%, 1/131), nodule (0.8%, 1/131), and oral herpes (0.8%, 1/131). All treatment-related TEAEs were mild to moderate in severity. Most treatment-related TEAEs required no action to be taken and resolved without sequelae. One participant experienced two events of moderate

injection site nodule and erythema of the neck that began greater than 90 days after treatment. The participant received treatment with oral methylprednisolone. All of these events resolved without sequelae. No treatment-related TEAEs were reported after repeat treatment.

2. Effectiveness Results

The Investigator evaluated skin texture on the cheeks using the validated 5-point ACSS (named Allergan Skin Roughness Scale in this study). The ACSS responder rate (the percent of participant cheeks with ≥ 1-point improvement on the ACSS compared to baseline) was determined for the primary effectiveness analysis. At 1 month (after initial treatment or optional touch-up), most treated cheeks (96.2%, 251/261) were responders on the ACSS, with the majority continuing to show improvement through 4 months (76.3%, 196/257), and some showing improvement through 9 months (15.7%, 39/249).

Participants assessed satisfaction with skin using the validated *Satisfaction with Skin* module of the FACE-Q questionnaire. The mean score on the *Satisfaction with Skin* module of the FACE-Q questionnaire improved from 43.5 at baseline to 64.6 at 1 month (after initial treatment or optional touch-up) and 55.6 at 9 months, indicating higher participant satisfaction with their skin.

The Investigator evaluated fine lines on the cheeks using the validated 5-point AFLS. The AFLS responder rate was the percent of participant cheeks with AFLS baseline scores of moderate or severe showing ≥ 1-point improvement on the AFLS compared to baseline. At 1 month (after initial treatment or optional touch-up), most treated cheeks (89.4%, 169/189) with AFLS baseline scores of moderate or severe were responders on the AFLS, with the majority continuing to show improvement through 4 months (66.7%, 124/186), and some showing improvement through 9 months (15.6%, 28/180).

Skin hydration in the cheeks, forehead, and neck were measured using the MoistureMeterD® instrument. The measurements showed an increase in all treatment areas through 9 months, which indicates improved skin hydration.

The effectiveness profile after repeat treatment was similar to that after initial treatment. At 1 month after repeat treatment, the responder rate was similar to that at 1 month after initial treatment or optional touch-up, with 87.1% (108/124) of treated cheeks showing at least a 1-point improvement on the ACSS.

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

Device didn't go to Panel

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

because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The data submitted provide a reasonable assurance that the device is effective for improving skin smoothness of the cheeks. The specific conclusions from the pivotal study are:

- The primary endpoint (57.9%, 75.9/131) was met that the Month 1 ACSS responder rate for the treatment group was clinically relevant and statistically superior ($p < 0.001$) to that for the untreated control group (4.5%, 3.2/71).
- The secondary endpoints were met:
    - At Month 1, the overall mean score was 66.5, improved by a mean of 32.0 from baseline, on the FACE-Q *Satisfaction with Skin* questionnaire for the treatment group which was clinically relevant and statistically superior ($p < 0.001$) to that for the untreated control group
    - At Month 1, the AFLS responder rate for the treatment group (58.3%, 49/84) was clinically relevant and statistically superior to that for the untreated control group (5.4%, 2/37)
- Improvements in cheek skin smoothness lasted through 6 months (55.6%, 69/124) after SKINVIVE™ by JUVÉDERM® treatment based on EI ACSS assessment.
- Over 70% of participants were satisfied with how smooth, refreshed, hydrated, and radiant their skin looked 6 months after SKINVIVE™ by JUVÉDERM® treatment based on the FACE-Q *Satisfaction with Skin* questionnaire
- Improvements in fine lines lasted through 6 months (63.2%, 55/87) after SKINVIVE™ by JUVÉDERM® treatment based on EI AFLS assessment.
- Participant assessments of facial lines using the validated *Appraisal of Lines* module of the FACE-Q questionnaire improved from an overall mean score of 31.0 at baseline to 54.1 at Month 1 for the treatment group compared with a change in the overall mean score of 32.5 at baseline to 34.0 at Month 1 for the untreated control group.
- Participants reported that their cheek skin looked and felt natural one month after SKINVIVE™ by JUVÉDERM® treatment (median score of 9 and 10 out

of a maximum score of 10 for natural look and feel, respectively and 68.8%, 86/125 reported a score of 9 or 10 for natural look and 72.0%, 90/125 for natural feel).

- Repeat treatment 6 months later produced similar or better results with approximately half the injection volume.
- Subgroup analyses demonstrated that SKINVIVE™ by JUVÉDERM® is effective for moderate (53.3%, 40/75) and severe (68.1%, 32/47) ACSS scores and all Fitzpatrick skin types I/II (55.3%, 21/38), III/IV (61.1%, 44/72), V/VI (58.3%, 7/12).
- Changes in skin hydration in the treatment area were measured by the MoistureMeterD® instrument. Treatment group participants showed a mean increase from baseline to Month 1 of 2.35 (from a mean of 40.24 to 42.93) versus 0.11 (from a mean of 40.86 to 40.99) for the untreated control group indicating statistically significant improvement in skin hydration after treatment.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The data submitted provide a reasonable assurance that the device is safe for intradermal injection to improve skin smoothness of the cheeks in adults over the age of 21. The specific conclusions with regard to safety from the pivotal study are:

- For initial treatment, most ISRs were mild or moderate in severity (72.9%, 145/199) and resolved within 7 days.
- The ISRs reported were redness (68.8%, 137/199), lumps/bumps (63.3%, 126/199), swelling (61.3% (122/199), bruising (57.8%, 115/199), pain (52.8%, 105/199), tenderness (52.8%, 105/199), firmness (47.2%, 94/199), discoloration (34.2%, 68/199), and itching (25.1%, 50/199)
- The incidence of ISRs was lower for touch-up (51.4%, 72/140) and repeat treatments (54.4%, 43/79) than for initial treatment (79.4%, 158/199).
- Participants assessed procedural pain during injection as minimal.
- The most common treatment-related TEAEs after initial/touch-up treatment were injection site pruritus and injection site erythema, in 1.5% and 1.0% of participants, respectively.

- Most treatment-related TEAEs were mild (76.2%, 16/21) in severity and resolved within 30 days (76.2%, 16/21).
- Most treatment-related TEAEs began within 7 days after the last treatment (81.0%, 17/21)
- There were no deaths, unanticipated adverse device effects, or treatment-related serious TEAEs or AEs of special interest.
- Treatment with SKINVIVE™ by JUVÉDERM® did not compromise vision.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The results of the 1867-701-008 study demonstrate the effectiveness of SKINVIVE™ by JUVÉDERM® for improvement in skin smoothness of the cheeks. The predefined primary endpoint was met in that the ACSS responder rate at 1 month (after initial treatment or optional touch-up) for the treatment group was statistically significantly greater ($p < 0.001$) than that for the untreated control group.

The secondary and other effectiveness endpoints further demonstrate that SKINVIVE™ by JUVÉDERM® is effective for improvement in skin smoothness of the cheeks based on patient reported outcome measures, and other subjective and objective measures. The treatment versus untreated control difference in overall scores on the FACE-Q *Satisfaction with Skin* questionnaire was statistically significant at 1 month (after initial treatment or optional touch-up), and treatment group participants continued to show improved satisfaction through 6 months. The AFLS responder rate at 1 month (after initial treatment or optional touch-up) for the treatment group was statistically superior to the untreated control group. Most treatment group participants continued to show improvement in fine lines through 6 months. Treatment group participants reported improvement in the appearance of lines on their face after treatment through 6 months based on the FACE-Q *Appraisal of Lines* questionnaire. Participants rated the look and feel of their skin as natural at every visit after treatment. Furthermore, objective hydration measurements from the MoistureMeterD® instrument showed an increase in skin hydration at 1 month after treatment with SKINVIVE™ by JUVÉDERM®. Treatment group participants showed a mean increase from baseline to Month 1 of 2.35 versus 0.11 for the untreated control group indicating improvement in skin hydration after treatment.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The clinical study results

demonstrated that the safety profile of SKINVIVE™ by JUVÉDERM® injection for improvement in skin smoothness of the cheeks is consistent with other HA fillers. Most participants in the clinical study experienced common ISRs, such as redness, swelling and lumps/bumps after treatment, the majority of which were mild to moderate in severity and resolved within 7 days of treatment. There were no treatment-related serious TEAEs, treatment-related TEAEs of special interest, or unanticipated TEAEs. Most treatment-related TEAEs were mild in nature, began within 7 days of treatment, and resolved within 30 days. There was 1 participant with 2 treatment-related TEAEs (mild injection site papules) that began greater than 30 days after treatment (117 days after touch-up treatment) and were resolved after study end.

1. Patient Perspective

Patient perspectives considered during the review included:

- The mean change from baseline at 1 month in the FACE-Q *Satisfaction with Skin* score was 32.0 for the treatment group compared to 1.4 for the untreated control group. The treatment versus untreated control difference of 28.0 at 1 month.
- The FACE-Q *Appraisal of Lines* questionnaire mean overall score for treatment group increased from 31.5 at baseline to 54.0 at 1 month.

The data support a favorable benefit-risk profile of SKINVIVE™ by JUVÉDERM® for intradermal injection to improve skin smoothness of the cheeks in adults over the age of 21.

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. The data demonstrate the benefits of SKINVIVE™ by JUVÉDERM® for improvement of cheek smoothness outweigh the risks and the intended patient populations will achieve clinically significant results. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XIV. CDRH DECISION

CDRH issued an approval order on May 11, 2023.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.