SKINVIVE™ by JUVÉDERM®

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

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION

SKINVIVE™ by JUVÉDERM® injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of hyaluronic acid (HA) produced by *Streptococcus* species of bacteria crosslinked with 1,4-butanediol diglycidyl (BDDE) formulated to a concentration of 12 mg/mL with 0.3% w/w lidocaine in a physiologic buffer.

2. INTENDED USE/INDICATIONS

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

3. 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.

4. WARNINGS

The product must not be injected into blood vessels. Introduction of SKINVIVE™ by JUVÉDERM® injectable gel into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting the product, for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events (AEs) associated with the intravascular injection of injectable gels in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care professional specialist should an intravascular injection occur (see HEALTH CARE PROFESSIONAL INSTRUCTIONS #12).

Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has

been controlled.

Injection site responses consist mainly of short-term inflammatory symptoms and generally resolve within 1 week. Refer to the ADVERSE EVENTS section for details.

5. PRECAUTIONS

- SKINVIVE™ by Juvéderm® injectable gel is packaged for single-patient use. Do not resterilize. Do not use if package is open or damaged.
- In order to minimize the risk of potential complications, this product should only be used by health care professionals who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care professionals are encouraged to discuss all potential risks of soft tissue injections with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- Based on preclinical studies and a toxicological risk assessment, patients should be limited to 20 mL of any JUVÉDERM® injectable gel per 60 kg (130 lbs) body mass per year. The safety of injecting greater amounts has not been established.
- This product is intended for improving skin smoothness of the cheeks. The safety and effectiveness for the treatment of anatomic regions in other areas of the body have not been established in controlled clinical studies.
- Injections of more than 6.0 mL of SKINVIVE™ by JUVÉDERM® (initial and touch-up treatment combined) for improvement of skin smoothness of the cheeks has not been studied.
- As with all transcutaneous procedures, injections of the product carry a risk of infection. Standard precautions associated with injectable materials should be followed.
- SKINVIVE™ by JUVÉDERM® is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years has not been established.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, or pigmentation disorders has not been studied.
- SKINVIVE™ by JUVÉDERM® should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at injection sites.
- Patients may experience late onset AEs with use of injectable gel implants, including SKINVIVE™ by JUVÉDERM®. Refer to ADVERSE EVENTS section for details.
- After use, treatment syringes and needles are biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.
- SKINVIVE™ by JUVÉDERM® injectable gel is a clear, colorless gel without visible particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; notify Allergan Product Surveillance at 1-877-345-5372.

- SKINVIVE™ by JUVÉDERM® should only be used by health care professionals who have appropriate experience and who are knowledgeable about the anatomy and the product for use in the face.
- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with SKINVIVE™ by JUVÉDERM®, there is a possible risk of eliciting an inflammatory reaction at the implant site. An inflammatory reaction is also possible if the product is administered before the skin has healed completely after such a procedure.
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the LUER-LOK® and needle hub connection.

6. ADVERSE EVENTS

A. US Pivotal Study of SKINVIVE™ by JUVÉDERM®

In the randomized, controlled, multicenter clinical study to evaluate the safety and effectiveness of SKINVIVE™ by JUVÉDERM® for improving skin smoothness of the cheeks, 135 participants were randomized to treatment and received injections during the primary phase of the study. Touch-up treatments occurred approximately 30 days after initial injection, if needed. After the 1 month blinded "no treatment" control period, control participants were offered treatment; 64 control participants elected to receive treatment. Treatment group participants were offered repeat treatment 6 months after the last treatment. A total of 79 treatment group participants opted for the repeat treatment.

Participants used electronic diaries to record specific 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 all ISRs reported by > 5% of participants after initial treatment (from both the treatment and control groups) are summarized in Table 1. 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. No treatment-related AEs were reported after repeat treatment.

Table 1. 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 as "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, 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 2). 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 2: Participant-Level Summary of Treatment-Related TEAEs with SKINVIVE™ by JUVÉDERM®

TEAEs		Severity			Outcome
	Participants % (n/N[a])	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 AE after database lock

Table 3: Event-Level Summary of Treatment-Related AEs 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%	0.00%	0.0%	0.0%	4.8% (1/21)	0.0%

Safety Subgroup Analyses

Subgroup analyses for AEs were performed based on sex, Fitzpatrick skin type, age, and injection volumes. As shown in Tables 4 through 7 below, less than 5% of participants treated with SKINVIVE™ by JUVEDERM® experienced a treatment-related TEAE in all subgroups.

Table 4: 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 5: 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 6: 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 7: 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

To evaluate the impact of the treatment to daily life, participants responded to the validated FACE-Q Recovery Early Life Impact questionnaire. Twelve items scored in the same manner as the first secondary effectiveness measure. 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.

Snellen visual acuity, confrontational visual fields, ocular motility

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.

B. European Clinical Study

In the prospective, single-arm clinical study conducted in France to evaluate the safety and effectiveness of SKINVIVE™ by JUVÉDERM® without lidocaine for treatment of fine lines and for improvement of skin quality, 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 offered repeat treatment 9 months after the last treatment.

ISRs reported in participant diaries after initial treatment are summarized by severity and duration in Table 8. 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 8. 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 AEs were reported in 16.0% (21/131) of participants. These TEAEs included injection site mass (9.2%, 12/131), 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.

C. Postmarket Surveillance

The following 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. These AEs, 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.

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

7. CLINICAL STUDIES

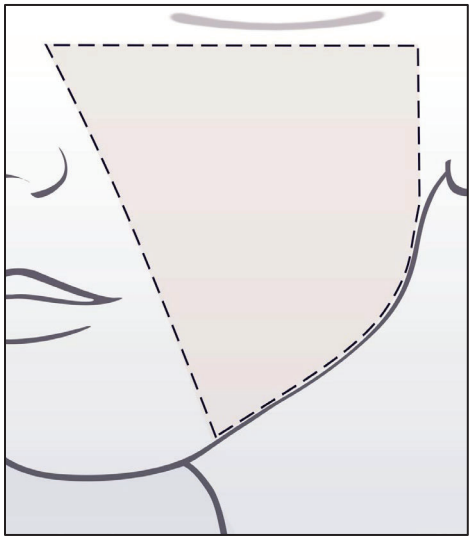
A. Pivotal Study for SKINVIVE™ by JUVÉDERM®

Pivotal Study Design

A randomized, multicenter, evaluator-blind, controlled pivotal clinical study was conducted to evaluate the safety and effectiveness of SKINVIVE™ by JUVÉDERM® for the improvement of skin smoothness of the cheeks. At the outset of the study, 135 participants were randomized and underwent treatment with SKINVIVE™ by JUVÉDERM®, while 73 participants were randomized to delayed-treatment control.

Treatment group participants underwent treatment with SKINVIVE™ by JUVÉDERM®, followed by an optional touch-up treatment 1 month after initial treatment, if deemed necessary to achieve optimal improvement, 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 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.

Figure 1: Treatment Area for Cheek Smoothness



Study Endpoints

The primary effectiveness measure for the study was the blinded Evaluating Investigator's assessment of the participant's skin smoothness on the cheeks (from the zygomatic arch to the edge of the jaw, lateral from the nasolabial fold and oral commissures to the preauricular cheek) using the validated 5-point Allergan Cheek Smoothness Scale (ACSS). 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 significantly greater than that for the control group participants.

Secondary measures included participant assessment of satisfaction with skin using the validated *Satisfaction with Skin* module of the FACE-Q questionnaire and Evaluating Investigator assessment of participant fine lines on the cheeks using the validated 5-point Allergan Fine Lines Scale (AFLS).

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

Participant Demographics

Participant demographics and pretreatment characteristics of the treatment and control groups are presented in Table 9.

Table 9. Participant Demographics and Pre-Treatment Characteristics (Safety Population)

	SKINVIVE™ by JUVÉDERM®	Control
	(N = 135) % (n/N)	(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)
Baseline Allergan Cheek Smoothness Scale (ACSS) Score		
Moderate	60.0% (81/135)	59.5% (44/74)
Severe	36.3% (49/135)	37.8% (28/74)
Other[a]	3.7% (5/135)	2.7% (2/74)

[a] A total of 6 participants assessed as mild on both cheeks and 1 participant assessed as mild on one cheek and moderate on the other cheek

Treatment Characteristics

Of the 135 treatment group participants, 98 participants (72.6%) received touch-up treatment, and 79 participants (58.5%) received repeat treatment. Injections were administered using 32G ½" and 32G 3/16" needles, with 32G ½" needles used more frequently. 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 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) ranged from 0.8 mL to 6.0 mL.

Effectiveness Results

Follow-up After Initial Treatment

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 initial treatment or optional touch-up). The primary effectiveness endpoint was met in that the treatment group ACSS responder rate was significantly greater ($p < 0.001$) than the control group responder rate. Most treatment group participants maintained a clinically significant improvement in skin smoothness on the cheeks (≥ 1-point improvement on the ACSS) through the 6-month follow-up period (Table 10 and 11). Subgroup analyses were performed based on sex, Fitzpatrick skin type, and age. Treatment group participants showed consistent responder rates across different subgroups (Table 12 through 14).

Table 10. Effectiveness of SKINVIVE™ by JUVÉDERM® in the Control Period mITT Population

Timepoint After Initial/Touch-up Treatment		Treatment Group Responder Rate % (n/N[a])	Control Group Responder Rate % (n/N[a])
1 Month	57.9% (75.9/131)	4.5% (3.2/71)	

Table 11: 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 12: 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

Table 13: Primary Effectiveness at Month 1 (after Initial Treatment or Optional Touch-up) for All Randomized Participants by Fitzpatrick Skin Phototype

Fitzpatrick Skin Phototype	ACSS 1-Point Improvement	
	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

Table 14: 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

The mean score on the *Satisfaction with Skin* module of the FACE-Q questionnaire for the treatment group improved from 34.9 at baseline to 66.8 at 1 month (after initial treatment or optional touch-up) and 60.2 at 6 months. These mean scores indicate that participants treated with SKINVIVE™ by JUVÉDERM® reported higher satisfaction with aspects of their skin. Within the *Satisfaction with Skin* module of the FACE-Q questionnaire, participants reported the following:

- 74.4% (93/125) of participants at 1 month (after initial treatment or optional touch-up) and 62.9% (78/124) of participants at 6 months were satisfied with how radiant their facial skin looked compared to 11.1% (15/135) at baseline
- 78.4% (98/125) of participants at 1 month (after initial treatment or optional touch-up) and 71.8% (89/124) of participants at 6 months were satisfied with how hydrated their facial skin looked compared to 23.7% (32/135) at baseline
- 79.2% (99/125) of participants at 1 month (after initial treatment or optional touch-up) and 69.4% (86/124) of participants at 6 months were satisfied with how refreshed their facial skin made them look compared to 15.6% (21/135) at baseline
- 84.0% (105/125) of participants at 1 month (after initial treatment or optional touch-up) and 83.1% (103/124) of participants at 6 months were satisfied with how healthy their facial skin looked compared to 37.8% (51/135) at baseline
- 80.8% (101/125) of participants at 1 month (after initial treatment or optional touch-up) and 68.5% (85/124) of participants at 6 months were satisfied with how their pores looked compared to 29.6% (40/135) at baseline

Most treatment group subjects with baseline scores of moderate or severe on the AFLS showed improvement in fine lines on the cheeks at 1 month after initial treatment or optional touch-up, (57.5%, 50/87) which continued through 6 months (63.2%, 55/87) as shown in Table 15.

Table 15: 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. These mean scores indicate that participants treated with SKINVIVE™ by JUVÉDERM® reported improvement in the appearance of lines on their face.

Treatment group participants showed a significant improvement in skin hydration of the cheeks compared to the no-treatment control at 1 month (after initial treatment or optional touch-up) based on the MoistureMeterD® measurements.

Follow-up After Repeat Treatment
Repeat treatment with SKINVIVE™ by JUVÉDERM® was administered to 79 participants. The effectiveness profile after repeat treatment was similar to that after initial treatment. The ACSS responder rate after repeat treatment was 68.5% (50/73) at 1 month and 65.7% (44/67) at 4 months.

B. European Clinical Study
A prospective, single-arm clinical study was conducted in France to evaluate the safety and effectiveness of SKINVIVE™ (without lidocaine) by JUVÉDERM® for treatment of superficial cutaneous depressions such as fine lines and for improvement of skin quality. A total of 131 participants were treated with SKINVIVE™ by JUVÉDERM® 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.

The Investigators evaluated skin texture on the cheeks using the validated 5-point ACSS. 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 Investigators 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 a ≥ 1-point improvement on the ACSS.

8. INSTRUCTIONS FOR USE

A. To Attach Needle to Syringe

To ensure proper attachment to the syringe, use the needle provided.

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

Figure A

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

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

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

Figure B

Figure C

Figure D

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

Figure E

B. Health Care Professional Instructions

1. SKINVIVE™ by JUVÉDERM® injectable gel is a crosslinked, soft, smooth gel formulation that can be injected using a fine gauge (e.g., 32 G) needle to improve skin smoothness of the cheeks.

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

3. The patient's treatment goals should be characterized by improvement of skin smoothness of the cheeks.

4. Supplementary anesthesia may be used for additional pain management during and after injection.

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

6. After insertion of the needle into the skin, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular.

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

8. The injection technique may vary with regard to the angle and orientation of the bevel, the depth and spacing of injections, and the quantity administered. Microdroplet injections is the most common technique used to achieve optimal results. Injecting the product too superficially may result in visible lumps and/or discoloration.

9. Inject SKINVIVE™ by JUVÉDERM® by applying even pressure on the plunger rod. It is important that the injection be stopped before the needle is pulled out of the skin to prevent material from leaking out or being placed too superficially in the skin.

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

11. The typical volume to achieve optimal improvement in skin smoothness of the cheeks is 4.0 mL. Injection volumes after repeat treatment tended to be lower, with the typical injection volume to maintain optimal effect being 2.7 mL.

12. Microdroplet injections of 0.01 mL to 0.05 mL, spaced approximately 0.5 cm to 1 cm apart are recommended. However, this will vary based on the patient's treatment goals.

13. Inject to 100% of the desired correction. Do not over-inject. The degree and duration of the effect depend on the character of the area being treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated

defects may be difficult to treat.

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

15. When injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If over-injection, visible lumps, or discoloration occurs, massage the area with your fingers or against the underlying superficial bone to obtain optimal results.

16. With patients who have localized swelling, the degree of effect is sometimes difficult to judge at the time of treatment. In this case, it is better to invite the patient back to the office for a touch-up treatment.

17. After the initial treatment, an additional treatment may be necessary to achieve the desired level of effect. If further treatment is needed, the same procedure should be repeated until a satisfactory result is obtained. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as skin texture, skin elasticity, and dermal thickness at the treatment site.

18. Patients may experience mild to moderate injection site responses after treatment, which typically resolve within 7 days. Ice using gentle pressure for a brief period following treatment to minimize swelling and reduce pain.

19. The health care professional should instruct the patient to promptly report to her/him any evidence of problems possibly associated with the use of SKINVIVE™ by JUVÉDERM®.

C. Patient Instructions

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

Avoid applying makeup for 12 hours after treatment. Within the first 24 hours, patients should avoid strenuous exercise, extensive sun or heat exposure, and alcoholic beverages. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the injection sites.
To report an adverse reaction, phone the Allergan Product Surveillance Department at 1-877-345-5372.

9. HOW SUPPLIED

SKINVIVE™ by JUVÉDERM® injectable gel is supplied in individual treatment syringes with 32 G needles for single-patient use and ready for injection (implantation). The volume in each syringe is as stated on the syringe label and on the carton. The contents of the syringe are sterile and non-pyrogenic. Do not resterilize. Do not use if package is open or damaged.

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[1] Jones DH, Fitzgerald R, Cox SE, et al. Preventing and treating adverse events of injectable fillers: evidence-based recommendations from the American Society for Dermatologic Surgery Multidisciplinary Task Force. *Dermatol Surg*. 2021;47(2):214-226.

10. SHELF LIFE AND STORAGE

SKINVIVE™ by JUVÉDERM® injectable gel should not be used after the expiration date printed on the label.

Store at room temperature (up to 25°C/77°F). DO NOT FREEZE.

SKINVIVE™ by JUVÉDERM® injectable gel has a clear appearance. In the event that a syringe contains material that is not a clear, do not use the syringe; notify Allergan Product Support immediately at 1-877-345-5372.

To place an order, contact Allergan at 1-800-377-7790.

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