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 ether (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.

SKINVIVE by JUVÉDERM® injectable gel is indicated for intradermal and/or subdermal injection to reduce neck lines for improvement of neck appearance 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injecting the product, for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary.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 #17).

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.
- SKINVIVE by JUVÉDERM® is intended for improving skin smoothness of the cheeks and reducing neck lines. 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 SKINVIVE by JUVÉDERM® of more than 6.0 mL (initial and touch-up treatment combined) for improvement of skin smoothness of the cheeks and 5.0 mL (initial and touch-up treatment combined) for reduction of neck lines have 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.
- The safety and effectiveness of SKINVIVE by JUVÉDERM® for improvement of neck lines have been evaluated with needle alone or with the TSK STERiGLIDE™ 25 G 1½″ cannula in conjunction with a needle.
- 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 and neck.
- 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/cannula attachment instructions could result in needle/cannula disengagement and/or product leakage at the LUER-LOK® and needle/cannula hub connection.

6. ADVERSE EVENTS

A. US Pivotal Study of SKINVIVE by JUVÉDERM® to Improve Skin Smoothness of the Cheeks

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 in 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.

Table 1. Injection Site Responses by Severity and Duration After Initial Treatment with SKINVIVE by JUVÉDERM® Occurring in > 5% of Treated Participants (Cheek Study)

Injection Site Response	Total % (n/N[c])	Severity[a]			Duration[b]				
		Mild % (n/N[c])	Moderate % (n/N[c])	Severe % (n/N[c])	1-3 Days % (n/N[c])	4-7 Days % (n/N[c])	8-14 Days % (n/N[c])	15-30 Days % (n/N[c])	> 30 Days % (n/N[c])
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] Maximum severity reported in the diary
[b] Duration is calculated based on the difference between the first and last date of occurrence
[c] N denotes the number of participants who recorded responses in the diaries after initial treatment

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 was 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 was considered a treatment-related TEAE if the event was 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. There was 1 participant with 2 treatment-related TEAEs that began more than 30 days after treatment: 2 mild noninflammatory injection site papules with onset 117 days after touch-up treatment that were ongoing at study end.

Table 2. Participant-Level Summary of Treatment-Related TEAEs with SKINVIVE by JUVÉDERM® (Cheek Study)

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® (Cheek Study)

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 (Cheek Study)

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 Skin Type for Initial and Touch-Up Treatments Combined (Cheek Study)

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 (Cheek Study)

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 (Cheek Study)

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 in 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 was conducted using 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. US Pivotal Study of SKINVIVE by JUVÉDERM® to Improve Neck Appearance

In the randomized, controlled, multicenter clinical study to evaluate the safety and effectiveness of SKINVIVE by JUVÉDERM® for reducing neck lines to improve neck appearance, 105 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 6-month blinded “no-treatment” control period, control participants were offered treatment; 43 control participants elected to receive treatment. Treatment group participants were offered repeat treatment 6 months after the last treatment. A total of 46 treatment group participants opted for the repeat treatment.

Participants used electronic diaries to record specific ISRs experienced during the 30 days after the initial, touch-up, and repeat treatments using the same severity categories as in the pivotal cheek study.

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 8. Most ISRs were mild, and their duration was short lasting (2 weeks or less). The incidence, severity, and duration of ISRs reported after touch-up and 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® Occurring in > 5% of Treated Participants (Neck Study)

ISR	Incidence % (n/N[c])	Severity[a]			Duration[b]				
		Mild % (n/N[c])	Moderate % (n/N[c])	Severe % (n/N[c])	≤ 3 Days % (n/N[c])	4-7 Days % (n/N[c])	8-14 Days % (n/N[c])	15-30 Days % (n/N[c])	> 30 Days % (n/N[c])
Any ISR	89.8% (132/147)	42.9% (63/147)	42.2% (62/147)	4.8% (7/147)	6.1% (9/147)	22.4% (33/147)	24.5% (36/147)	29.3% (43/147)	7.5% (11/147)
Redness	81.6% (120/147)	63.9% (94/147)	17.0% (25/147)	0.7% (1/147)	59.2% (87/147)	15.6% (23/147)	5.4% (8/147)	1.4% (2/147)	0%
Bruising	77.6% (114/147)	49.7% (73/147)	25.2% (37/147)	2.7% (4/147)	18.4% (27/147)	25.9% (38/147)	29.3% (43/147)	3.4% (5/147)	0.7% (1/147)
Tenderness to Touch	77.6% (114/147)	59.9% (88/147)	17.0% (25/147)	0.7% (1/147)	46.3% (68/147)	18.4% (27/147)	8.2% (12/147)	4.1% (6/147)	0.7% (1/147)
Lumps/Bumps	76.2% (112/147)	46.9% (69/147)	27.2% (40/147)	2.0% (3/147)	23.1% (34/147)	13.6% (20/147)	7.5% (11/147)	25.2% (37/147)	6.8% (10/147)
Swelling	70.7% (104/147)	56.5% (83/147)	13.6% (20/147)	0.7% (1/147)	40.1% (59/147)	18.4% (27/147)	8.8% (13/147)	2.7% (4/147)	0.7% (1/147)
Firmness	64.6% (95/147)	51.0% (75/147)	12.9% (19/147)	0.7% (1/147)	34.0% (50/147)	14.3% (21/147)	9.5% (14/147)	5.4% (8/147)	1.4% (2/147)
Pain After Injection	63.3% (93/147)	50.3% (74/147)	12.2% (18/147)	0.7% (1/147)	44.9% (66/147)	12.2% (18/147)	4.1% (6/147)	1.4% (2/147)	0.7% (1/147)
Discoloration	50.3% (74/147)	39.5% (58/147)	8.8% (13/147)	2.0% (3/147)	28.6% (42/147)	12.9% (19/147)	6.8% (10/147)	2.0% (3/147)	0%
Itching	34.7% (51/147)	29.9% (44/147)	3.4% (5/147)	1.4% (2/147)	21.8% (32/147)	8.2% (12/147)	4.1% (6/147)	0%	0.7% (1/147)

[a] Maximum severity reported in the diary

[b] Duration is calculated as total days from first to last date of occurrence

[c] N denotes the number of participants who recorded responses in the diaries after initial treatment

AEs were reported by the Treating Investigator at follow-up visits following the same definitions as in the pivotal cheek study. Among the 148 participants treated with SKINVIVE by JUVÉDERM® (treatment and treated control group participants), 5 participants (3.4%) had 5 treatment-related TEAEs (Table 9). All treatment-related TEAEs were mild and resolved without sequelae. There were 2 treatment-related AEs that began more than 30 days after treatment: 1 mild injection site mass with onset 135 days after initial treatment that resolved in 8 days with massage, and 1 mild injection site papule with onset 178 days after initial treatment that resolved in 345 days without treatment. Neither of these were inflammatory reactions. No treatment-related TEAEs were reported after repeat treatment.

Table 9. Participant-Level Summary of Treatment-Related TEAEs with SKINVIVE by JUVÉDERM® (Neck Study)

TEAEs		Severity			Outcome
	Participants % (n/N[a])	Mild % (n/N[a])	Moderate % (n/N[a])	Severe % (n/N[a])	
Overall	3.4% (5/148)	3.4% (5/148)	0%	0%	Resolved without sequelae
Injection Site Papule	2.7% (4/148)	2.7% (4/148)	0%	0%	Resolved without sequelae
Injection Site Mass	0.7% (1/148)	0.7% (1/148)	0%	0%	Resolved without sequelae

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

Safety Subgroup Analyses

Subgroup analyses for TEAEs were performed based on injection volumes and injections with and without cannula. As shown in Table 10 and Table 11 below, less than 7% of participants treated with SKINVIVE by JUVEDERM® experienced a treatment-related TEAE in all subgroups, and there were none in the group receiving injections via needle plus cannula. Overall ISR rates were also similar for injections with and without cannula.

Table 10. Treatment-Related TEAEs with SKINVIVE by JUVÉDERM® by Median Volume Injected for Initial and Touch-Up Treatments Combined for Treatment Group (Neck Study)

TEAEs	≤ Median Volume Injected (N = 61)		> Median Volume Injected (N = 44)	
	Participants % (n)	Mild % (n)	Participants % (n)	Mild % (n)
Overall	6.6% (4)	6.6% (4)	2.3% (1)	2.3% (1)
Injection Site Papule	4.9% (3)	4.9% (3)	2.3% (1)	2.3% (1)
Injection Site Mass	1.6% (1)	1.6% (1)	0%	0%

Table 11. Treatment-Related TEAEs with SKINVIVE by JUVÉDERM® by Injection with and without Cannula for Initial and Touch-Up Treatments Combined (Neck Study)

TEAEs	Needle Only (N = 78)		Needle + Cannula (N = 70)	
	Participants % (n)	Mild % (n)	Participants % (n)	Mild % (n)
Overall	6.4% (5)	6.4% (5)	0%	0%
Injection Site Papule	5.1% (4)	5.1% (4)	0%	0%
Injection Site Mass	1.3% (1)	1.3% (1)	0%	0%

Other Safety Assessments

Procedural pain

Participant assessment of procedural pain after study injection was conducted using an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable). Participants assessed procedural pain during injection as minimal, with mean treatment group scores of 1.9 for initial treatment, 2.3 for touch-up treatment, and 2.0 for repeat treatment.

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 95% of participant eyes had the same or better visual acuity at all post-treatment assessments. Only 1 eye showed a ≥ 2-line worsening in visual

acuity at any assessment, and no participant eyes showed a ≥ 3-line worsening in visual acuity related to treatment at any assessment.

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.

C. 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 12. Most ISRs were mild or moderate (87.7%, 114/130) 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 12. 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

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 was considered a 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 these events resolved without sequelae. No treatment-related TEAEs were reported after repeat treatment.

D. Postmarket Surveillance

SKINVIVE by JUVÉDERM® has been marketed outside the US since 2016 and in the US since 2023. The following AEs were received globally from postmarket surveillance for SKINVIVE by JUVÉDERM® 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: subcutaneous nodule, edema, inflammatory nodule, erythema, pain, bruising, vascular occlusion, local reaction, rash, unsatisfactory result, skin discoloration, inflammation, skin inflammation, allergic reaction, itching, anxiety, dry skin, loss or lack of correction, abscess, blister, infection, device migration, hematoma, necrosis, scarring, neurological symptoms such as increase/decrease in sensation, headache, vision changes, numbness, and lymphadenopathy. No vascular occlusion event was reported for treatment on the neck area.

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, hyperbaric oxygen treatment, ice, laser therapy, massage, radiofrequency therapy, steroids, ultrasound therapy, and warm compress.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Adverse reactions should be reported to Allergan Product Surveillance Department at 1-877-345-5372.

7. CLINICAL STUDIES

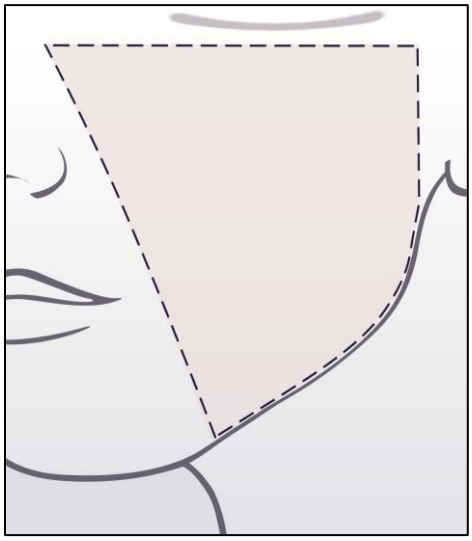
A. Pivotal Study for SKINVIVE by JUVÉDERM® to Improve Skin Smoothness of the Cheeks

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, Figure 1) using the validated 5-grade Allergan Cheek Smoothness Scale (ACSS). A responder was defined as a participant with ≥ 1-grade 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-grade 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 MoistureMeter® D instrument.

Participant Demographics

Participant demographics and pretreatment characteristics of the treatment and control groups are presented in Table 13.

Table 13. Participant Demographics and Pre-Treatment Characteristics (Cheek Study 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)
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 32 G ½" and 32 G 3/16" needles, with 32 G 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 14 and Table 15). Subgroup analyses were performed based on sex, Fitzpatrick skin type, and age. Treatment group participants showed consistent responder rates across different subgroups (Table 16 through Table 18).

Table 14. Effectiveness of SKINVIVE by JUVÉDERM® in the Control Period (Cheek Study 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)

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

Table 15. Treatment Group ACSS Responder Rates Based on Observed Data (Cheek Study 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. Participants with at Least 1-Point ACSS Improvement from Baseline at 1 Month (after Initial/Touch-up Treatment) by Sex (Cheek Study mITT Population)

Timepoint After Initial/Touch-up Treatment	Treatment Group Responder Rate for Males % (n/N[a])	Treatment Group Responder Rate for Females % (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 17. Participants with at Least 1-Point ACSS Improvement from Baseline at Month 1 (after Initial/Touch-up Treatment) by Fitzpatrick Skin Type (Cheek Study mITT Population)

Fitzpatrick Skin Type	ACSS 1-Point Improvement	
	SKINVIVE by JUVÉDERM® % (n/N[a])	Control % (n/N[a])
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[b]	44.4% (4/9)	0% (0/5)
VI[b]	66.7% (4/6)	33.3% (1/3)

[a] Number of participants with data at baseline and the specified timepoint
[b]Including participants with baseline ACSS Score of 1

Table 18. Participants with at Least 1-Point ACSS Improvement from Baseline at 1 Month (after Initial/Touch-up Treatment) by Age (Cheek Study mITT Population)

Age Group	SKINVIVE by JUVÉDERM® % (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:

- Compared to 11.1% (15/135) at baseline, 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 23.7% (32/135) 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 15.6% (21/135) 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 37.8% (51/135) 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 29.6% (40/135) 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

Most treatment group subjects with baseline scores of moderate or severe on the AFLS showed improvement in fine lines and crepiness 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 19.

Table 19. Treatment Group AFLS Responder Rates (Cheek Study SKINVIVE Treated Population, SKINVIVE Repeat Treatment Population)

Visit After Initial/Touch-up Treatment	Treatment Group Responder Rate % (n/N[a])
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)

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

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 MoistureMeter® D 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. Pivotal Study for SKINVIVE by JUVÉDERM® to Improve Neck Appearance

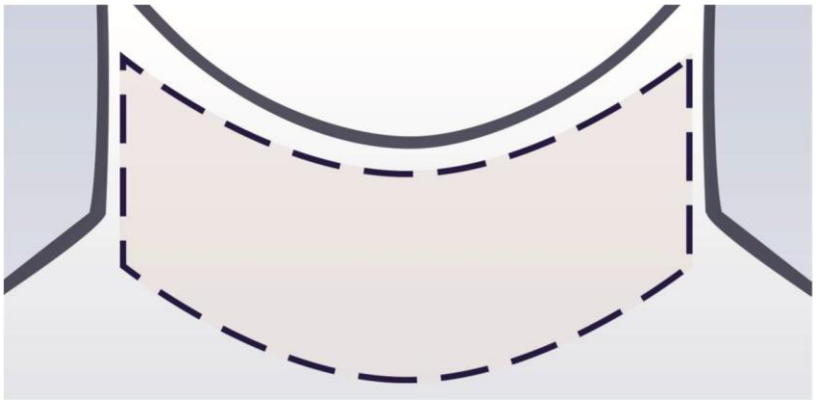
Pivotal Study Design

A multicenter, evaluator-blind, randomized, controlled pivotal clinical study was conducted to evaluate the safety and effectiveness of SKINVIVE by JUVÉDERM® for the reduction of neck lines to improve neck appearance. At the outset of the study, 105 participants were randomized and underwent treatment with SKINVIVE by JUVÉDERM®, while 54 participants were randomized to delayed-treatment control.

Treatment group participants were given initial study treatment and an optional touch-up treatment at Month 1 after initial treatment, if deemed necessary to achieve optimal improvement, with follow-up visits at day 3 (telephone call) and day 14 after each treatment and at Months 1, 2, 4, and 6 after the last treatment. Repeat treatment was offered to treatment group participants at Months 6, with follow-up visits at Day 3 (telephone call) and Day 14 and at Months 1, 2, and 4 after repeat treatment. The Treating Investigator determined the appropriate

volume of SKINVIVE by JUVÉDERM® to be injected intradermally and/or subdermally into the neck area of all participants, as depicted in Figure 2, using the supplied 32 G ½" needle. The Treating Investigator was given an option of using a 25 G 1½" cannula in addition to the needle for additional subdermal injections, if deemed necessary for optimal treatment.

Figure 2. Neck Treatment Area



Study Endpoints

The primary effectiveness measure for the study was based on the Evaluating Investigator's live assessment at Month 1 after initial treatment/touch-up of horizontal neck lines using the validated 5-grade photonumeric Allergan Transverse Neck Lines Scale (ATNLS) described in Table 20. A responder was defined as a participant with ≥ 1-point improvement in ATNLS score from baseline. Effectiveness of SKINVIVE by JUVÉDERM® was demonstrated if the responder rate for the treatment group was statistically superior to that of the no-treatment control group at Month 1 and the lower bound of the 95% CI was greater than 50%.

Table 20. Allergan Transverse Neck Lines Scale

Score	Grade	Description
0	None	No transverse neck lines
1	Minimal	Superficial transverse neck lines
2	Moderate	Moderate, effaceable transverse neck lines
3	Severe	Deep, non-effaceable transverse neck lines
4	Extreme	Non-effaceable transverse neck furrows with redundant skin

Secondary effectiveness measures included participant assessments of neck appearance using the validated *Appraisal of the Neck* module of the FACE-Q questionnaire and independent, noncollaborative assessments by both the Evaluating Investigator and the participant of global aesthetic improvement on the neck area using the 5-point Global Aesthetic Improvement Scale (GAIS).

Other effectiveness measures included participant assessments of overall treatment outcomes on the neck area (feel, appearance, psychosocial, and satisfaction) using the Allergan Neck Satisfaction Scale and Allergan Neck Treatment Outcomes Scale questionnaires. Changes in

skin hydration in the treatment area were also measured using the MoistureMeter® D instrument.

Reduction in neck lines is defined as a ≥ 1-grade improvement in ATNLS score from baseline, and improvement of neck appearance is defined as GAIS score of *improved* or *much improved*. Improvement in skin smoothness is defined as participant satisfaction with smoothness score of *satisfied* or *very satisfied* on the Allergan Neck Satisfaction Scale.

Participant Demographics

The demographics of the study population are typical for a study performed in the US. Subject demographics and pre-treatment characteristics are presented in Table 21.

Table 21. Subject Demographics and Pre-Treatment Characteristics (Neck Study ITT Population)

	SKINVIVE by JUVÉDERM® (N = 105) % (n/N)	Control (N = 54) % (n/N)
Sex		
Female	96.2% (101/105)	98.1% (53/54)
Male	3.8% (4/105)	1.9% (1/54)
Age		
Median	52	48
Range	26 - 71	26 - 65
Race		
White	79.0% (83/105)	75.9% (41/54)
Black or African American	4.8% (5/105)	11.1% (6/54)
Asian	7.6% (8/105)	5.6% (3/54)
American Indian or Alaskan Native	3.8% (4/105)	5.6% (3/54)
Native Hawaiian or Other Pacific Islander	1.9% (2/105)	0% (0/54)
Multiple	2.9% (3/105)	1.9% (1/54)
Ethnicity		
Hispanic or Latino	35.2% (37/105)	33.3% (18/54)
Not Hispanic or Latino	64.8% (68/105)	66.7% (36/54)
Fitzpatrick Skin Type*		
I/II	24.8% (26/105)	29.6% (16/54)
III/IV	63.8% (67/105)	59.3% (32/54)
V/VI	11.4% (12/105)	11.1% (6/54)
Baseline ATNLS Scale Score		
Moderate	33.3% (35/105)	40.7% (22/54)
Severe	66.7% (70/105)	59.3% (32/54)

*Fitzpatrick skin type classification based on Investigator live assessment of subjects; post-hoc photo assessments for treatment group: I/II 24.8% (26/105), III/IV 71.4% (75/105), and V/VI 3.8% (4/105); for control group: I/II 29.6% (16/54), III/IV 62.9% (34/54), and V/VI 7.4% (4/54)

Treatment Characteristics

Of the 105 treatment group participants, 72 (68.6%) received touch-up treatment and 46 (43.8%) received repeat treatment. All participants received injections using a 32 G ½" needle,

and nearly half (48.6%) also received injections with a 25 G 1½" cannula. The most common injection technique to achieve optimal results was microdroplet subdermal or intradermal injections. In the treatment group, the median injection volume was 2 mL at initial treatment, 1.45 mL at touch-up treatment, and 1.6 mL at repeat treatment. The injection volume administered for the treatment group (initial and touch-up) ranged from 0.55 mL to 5.0 mL. Treating Investigators rated ease of injection and product moldability on 11-point scales (0 = difficult and 10 = easy or 0 = stiff and 10 = moldable, respectively). In the treatment group, the median score at initial treatment was 10 for injection ease and 9 for moldability, indicating the product was easy to inject and mold.

Primary Effectiveness Results

SKINVIVE by JUVÉDERM® provided a clinically and statistically significant improvement in horizontal neck lines at Month 1 (after initial treatment or optional touch-up) with an ATNLS treatment group responder rate of 74.8% compared to the ATNLS no-treatment control group responder rate of 16.1% based on a single blinded-evaluator's live assessment. Success criteria for the primary effectiveness endpoint were met as the treatment group ATNLS responder rate was statistically superior ($p < 0.001$) to that of the no-treatment control group, with the lower bound of the 95% CI exceeding 50%. Two-thirds of treatment group participants 66.0% (64/97) showed continued improvement in neck lines (≥1-grade ATNLS improvement based on blinded Evaluating Investigator's assessment) at 6 months after initial/touch-up treatment. (Table 22 and Table 23). Subgroup analyses were performed based on sex, Fitzpatrick skin type, and age. Treatment group participants showed consistent responder rates across different subgroups (Table 24 through Table 26).

Table 22. Primary Effectiveness of SKINVIVE by JUVÉDERM® in the Control Period (Neck Study ITT Population)

Timepoint After Initial/ Touch-up Treatment	ATNLS Responder Rate[a]		
	SKINVIVE by JUVÉDERM® % (n/N[b])	Control % (n/N[b])	Difference in Responder Rates[c]
1 Month	74.8% (78.5/105)	16.1% (8.7/54)	58.7%
P-value	N/A	N/A	< 0.0001

[a] Average number of responders across multiple imputed datasets
[b] Number of participants randomized
[c] SKINVIVE by JUVÉDERM® treatment rate minus no-treatment control rate

Table 23. ATNLS Responder Rates Based on Observed Data (Neck Study SKINVIVE ITT Population, SKINVIVE Repeat Treatment Population)

Timepoint After Treatment	ATNLS Responder Rate	
	SKINVIVE by JUVÉDERM® % (n/N[a])	Control % (n/N[a])
1 Month	76.8% (73/95)	14.6% (7/48)
2 Months	78.0% (78/100)	12.2% (5/41)
4 Months	75.0% (69/92)	9.5% (4/42)
6 Months	66.0% (64/97)	9.1% (4/44)
1 Month after Repeat Treatment	88.1% (37/42)	N/A
2 Months after Repeat Treatment	88.6% (39/44)	N/A
4 Months after Repeat Treatment	84.4% (38/45)	N/A

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

Table 24. Participants with at Least 1-Point ATNLS Improvement from Baseline at Month 1 (after Initial/Touch-up Treatment) by Sex (Neck Study ITT Population)

Sex	ATNLS 1-Point Improvement	
	SKINVIVE by JUVÉDERM® % (n/N[a])	Control % (n/N[a])
Female	76.1% (70/92)	14.9% (7/47)
Male	100% (3/3)	0% (0/1)

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

Table 25. Participants with at Least 1-Point ATNLS Improvement from Baseline at Month 1 (after Initial/Touch-up Treatment) by Fitzpatrick Skin Type (Neck Study ITT Population)

Fitzpatrick Skin Type	ATNLS 1-Point Improvement	
	SKINVIVE by JUVÉDERM® % (n/N[a])	Control % (n/N[a])
I/II	76.0% (19/25)	28.6% (4/14)
III/IV	75.4% (46/61)	10.3% (3/29)
V/VI	88.9% (8/9)	0% (0/5)

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

Table 26. Participants with at Least 1-Point ATNLS Improvement from Baseline at Month 1 (after Initial/Touch-up Treatment) by Median Age (Neck Study ITT Population)

Age Group	SKINVIVE by JUVÉDERM® % (n/N[a])	Control % (n/N[a])
≤ 51 years	79.6% (43/54)	14.8% (4/27)
> 51 years	73.2% (30/41)	14.3% (3/21)

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

Secondary Effectiveness Results

The blinded Evaluating Investigator and participant GAIS responder rates (percent of participants with a score of *improved* or *much improved*) at Month 1 were 88.3% (83/94) and 89.4% (84/94), respectively, for the treatment group, and the Evaluating Investigator responder rate was 12.5% (6/48) for the no-treatment control group based on observed data. The

Evaluating Investigator and participant GAIS responder rates remained high for the treatment group through Month 6 (80.4% and 78.4%, respectively).

The mean score on the *Appraisal of the Neck* module of the FACE-Q questionnaire for the treatment group improved from 45.2 at baseline to 70.2 at Month 1 (after initial treatment or optional touch-up) and 63.3 at Month 6. These mean scores indicate that participants were less bothered by their neck after treatment with SKINVIVE by JUVÉDERM®. The treatment group responder rate (participants who demonstrated improvement from baseline in overall score) stayed above 78% at all timepoints (Table 27).

Table 27. Treatment Group FACE-Q *Appraisal of the Neck* Responder Rates (Neck Study SKINVIVE Treated Population, SKINVIVE Repeat Treatment Population)

Timepoint After Treatment	SKINVIVE by JUVÉDERM® % (n/N)
1 Month	89.2% (83/93)
2 Months	93.8% (91/97)
4 Months	84.8% (78/92)
6 Months	78.4% (76/97)
1 Month after Repeat Treatment	90.5% (38/42)
2 Months after Repeat Treatment	95.3% (41/43)
4 Months after Repeat Treatment	88.9% (40/45)

Within the *Appraisal of the Neck* module of the FACE-Q questionnaire, participants reported improvement from baseline in each individual question (Table 28).

Table 28. Treatment Group FACE-Q *Appraisal of the Neck* Individual Questions (Neck Study SKINVIVE Treated Population)

Percentage of Participants who were not at all or a little bothered with:	% of Participant Responses at Baseline (N = 105) (n)	% of Participant Responses at Month 1 (N = 93) (n)	% of Participant Responses at Month 6 (N = 97) (n)
Having to cover up their neck with clothing	57.1% (60)	87.1% (81)	77.3% (75)
How their neck looks compared with other people their age	34.3% (36)	87.1% (81)	71.1% (69)
How deep the horizontal lines on their neck are	21.0% (22)	79.6% (74)	71.1% (69)
How their neck looks in collared shirts	43.8% (46)	84.9% (79)	75.3% (73)
Hanging skin on their neck	49.5% (52)	87.1% (81)	75.3% (73)
How their neck looks when they grimace	39.0% (41)	81.7% (76)	72.2% (70)
How their neck looks in profile	30.5% (32)	78.5% (73)	67.0% (65)
How wrinkled their neck skin looks	34.3% (36)	80.6% (75)	62.9% (61)
How old their neck makes them look	21.0% (22)	71.0% (66)	60.8% (59)
Sagging skin on their neck	42.9% (45)	83.9% (78)	73.2% (71)

Other Effectiveness Results

Treatment group participants showed an observed objective mean increase from baseline of 4.6% in percentage of water content in the skin at the 1-month primary timepoint based on the MoistureMeter® D measurements. Participants also reported observed satisfaction rate of 73.7% with neck skin smoothness (crepiness) after treatment and above 68.4% for other attributes on the Allergan Neck Satisfaction Scale and Allergan Neck Treatment Outcomes Scale (Table 29).

Table 29. Additional Treatment Group Effectiveness Results

Assessment	1 Month
MoistureMeter® D Instrument	
Percentage of Water Content (Mean Increase from Baseline)	4.6%
Allergan Neck Satisfaction Scale	
Participant Satisfaction with Natural Look (% *Satisfied* or *Very Satisfied*)	85.3%
Participant Satisfaction with Feel (% *Satisfied* or *Very Satisfied*)	83.2%
Participant Satisfaction with Smoothness (% *Satisfied* or *Very Satisfied*)	73.7%
Participant Happiness with Neck (% *Moderately* or *Very Happy*)	68.4%
Allergan Neck Treatment Outcomes Scale	
Participant Satisfaction with Treatment (% *Mostly Satisfied* or *Very Satisfied*)	71.6%
Participant Willingness to Recommend Treatment (% *Moderately*, *Quite a Bit*, or *Extremely* likely)	87.4%

Follow-up After Repeat Treatment

Repeat treatment with SKINVIVE by JUVÉDERM® was administered to 46 participants. The ATNLS responder rate after repeat treatment was 88.1% (37/42) at Month 1 and 84.4% (38/45) at Month 4.

C. European Clinical Study

A prospective, single-arm clinical study was conducted in France to evaluate the safety and effectiveness of SKINVIVE by JUVÉDERM® (without lidocaine) 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 (96 participants). 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-grade 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).

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.

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-grade 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). This indicates an improvement in fine lines and crepiness.

Other instrument measures performed on the neck included the Fringe Project System for skin smoothness, Cutometer for elasticity, and DermaScan C for skin thickness. Results from these instruments showed improvement in skin crepiness (smoothness, elasticity, and thickness) at 1 month after initial/touch-up treatment.

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

8. INSTRUCTIONS FOR USE

A. To Attach Needle or Cannula to Syringe

To ensure proper attachment to the syringe, use the 32 G ½″ needle provided or the recommended 25 G 1½″ cannula (see Section 5).

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 or cannula

Hold the syringe body and firmly insert the hub of the needle (provided in the SKINVIVE by JUVÉDERM® package) or cannula into the LUER-LOK® end of the syringe.

STEP 3: Tighten the needle or cannula

Tighten the needle or cannula 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 or cannula cap is as shown in Figure D, it is not attached correctly. Continue to tighten until the needle or cannula is seated in the proper position.

FIGURE B

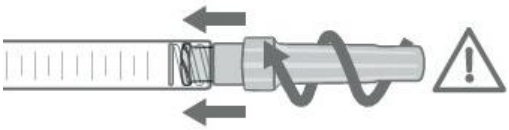


FIGURE C

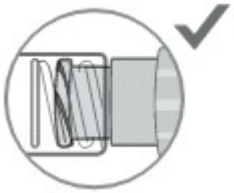
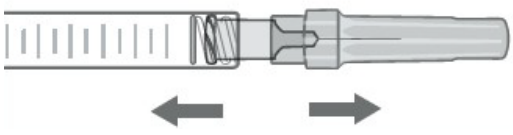


FIGURE D

STEP 4: Remove the needle or cannula cap

Hold the syringe body in one hand and the needle or cannula 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 or a cannula (25 G).
2. Educational resources are available through Allergan Aesthetics, which provides training in facial anatomy and vasculature, safe injection techniques, and identification and management of potential adverse events, including vascular complications. Health care practitioners may contact Allergan for educational and training resources.
3. Completion of device-specific use training is required and will be verified prior to purchase of SKINVIVE™ by JUVÉDERM®.
4. Prior to treatment, the patient's medical history should be obtained, and the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental touch-up injections may be required to achieve and maintain optimal effect.
5. The patient's treatment goals should be characterized by improvement of cheek skin smoothness or neck appearance.
6. Supplementary anesthesia may be used for additional pain management during and after injection.
7. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be prepped with alcohol or other antiseptic. Prior to injecting, depress the plunger rod until the product flows out of the needle/cannula.
8. After insertion of the needle/cannula into the skin, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle/cannula is not intravascular.
9. 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.
10. 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.
11. Inject SKINVIVE by JUVÉDERM® by applying even pressure on the plunger rod. It is important that the injection be stopped before the needle/cannula is pulled out of the skin to prevent material from leaking out or being placed too superficially in the skin.
12. When using a cannula, an entry point is made on the skin using the 23 G introducer needle, co-packaged with the 25 G 1 ½″ cannula.
13. If the needle/cannula is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle/cannula.
14. The typical volume to achieve optimal improvement is 4.0 mL for cheek skin smoothness and 3.0 mL for neck appearance. Injection volumes after repeat treatment tended to be lower, with the typical injection volume to maintain optimal effect being 2.7 mL for cheek and 1.6 mL for neck.

15. 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. Tunneling, fanning, or microdroplet injections can also be utilized for neck lines.
16. 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.
17. If immediate blanching occurs, the injection should be stopped, and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.[1]
18. 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.
19. 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.
20. 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.
21. Patients may experience mild to moderate injection site responses after treatment, which typically resolve within 7-14 days. Ice using gentle pressure for a brief period following treatment to minimize swelling and reduce pain.
22. 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.

[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.

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 TSK STERiGLIDE® 25 G 1 ½″ cannula is not supplied with SKINVIVE by JUVÉDERM® but is available for purchase through Allergan. The volume in each syringe is as stated on the syringe label and on the carton. The contents of the syringe are sterile and non-pyrogenic. Do not resterilize. Do not use if package is open or damaged.

10. SHELF LIFE AND STORAGE

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 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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