RADIESSE®+

Lidocaine

INJECTABLE IMPLANT

INSTRUCTIONS FOR USE

℞ ONLY

DEVICE DESCRIPTION

RADIESSE® (+) Lidocaine injectable implant (hereinafter referred to as RADIESSE® (+)) is an opaque, sterile, non-pyrogenic, semi-solid, cohesive implant, whose principal component is synthetic calcium hydroxylapatite suspended in a gel carrier of glycerin, sodium carboxymethylcellulose, 0.3% lidocaine hydrochloride and sterile water for injection. RADIESSE® (+) 1.5cc has a calcium hydroxylapatite particle size range of 25–45 microns and a 25 gauge Outer Diameter (O.D.) to 27 gauge Inner Diameter (I.D.) needle.

INTENDED USE / INDICATIONS

RADIESSE® (+) Lidocaine injectable implant is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

RADIESSE® (+) Lidocaine injectable implant is indicated for deep injection (subdermal and/or supraperiosteal) for soft tissue augmentation to improve moderate to severe loss of jawline contour in adults over the age of 21.

CONTRAINDICATIONS

- RADIESSE® (+) is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- RADIESSE® (+) is not to be used in patients with known hypersensitivity to any of the components.
- RADIESSE® (+) is not intended to be used in patients with known hypersensitivity to lidocaine or anesthetics of the amide type.
- RADIESSE® (+) is contraindicated for patients with bleeding disorders.

WARNINGS

- Introduction of RADIESSE® (+) into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject RADIESSE® (+) slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. The treating physician should be knowledgeable regarding any pretreatment evaluation and appropriate interventions in the event of intravascular disseminated injection. Prompt intervention by an appropriate medical specialist should be given should these signs or symptoms of intravascular injection occur (See Directions for Use: General #A12).

- Use of RADIESSE® (+) in any person with active skin inflammation or infection in or near the treatment area should be deferred until the inflammatory or infectious process has been controlled.
- Do not overcorrect (overfill) a contour deficiency because the depression should gradually improve within several weeks as the treatment effect of RADIESSE® (+) occurs.
- The safety and effectiveness for use in the lips has not been established. There have been published reports of nodules associated with the use of RADIESSE® injected into the lips.
- Injection procedure reactions have been observed consisting mainly of short-term (i.e., <7 days) bruising, redness and swelling. Refer to the Adverse Events sections for details.

PRECAUTIONS

- In order to minimize the risks of potential complications, RADIESSE® (+) should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- In order to minimize the risks of potential complications, Health care practitioners should fully familiarize themselves with the product, the product educational materials and the entire package insert.
- The safety and effectiveness of cannula used with RADIESSE® (+) for deep injection (subdermal and/or supraperiosteal) for soft tissue augmentation to improve the contour of the jawline has only been clinically evaluated in the following blunt-tip cannula (*Sterimedix Silkann*) that was 27g and 40mm in length and a 25g Pre-Hole Needle.
- The calcium hydroxylapatite (CaHA) particles of RADIESSE® (+) are radiopaque and are clearly visible on CT Scans and may be visible in standard, plain radiography. Patients need to be informed of the radio-opaque nature of RADIESSE® (+) injectable implant, so that they can inform their primary care health professionals as well as radiologists. In a radiographic study of 58 patients, there was no indication of RADIESSE® injectable implant potentially masking abnormal tissues or being interpreted as tumors in CT Scans.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injections with their patients prior to treatment and ensure that the patients are aware of signs and symptoms of potential complications.
- Injection in the jawline may temporarily alter jaw function.
- As with all percutaneous procedures, RADIESSE® (+) injection carries a risk of infection. Infection may necessitate attempted surgical removal of RADIESSE® (+). Standard precautions associated with injectable materials should be followed.
- Patients who are using medications that can prolong bleeding, such as aspirin or warfarin, may, as with any injection, experience increased bruising or bleeding at the injection site.
- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with RADIESSE® (+) , there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RADIESSE® (+) is administered before the skin has healed completely after such a procedure.
- The long-term safety of RADIESSE® (+) has not been investigated in clinical trials.
- Safety of RADIESSE® (+) for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- The safety of RADIESSE® (+) in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied.

- The safety of RADIESSE® (+) with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- Injection of RADIESSE® (+) into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- No studies of interactions of RADIESSE® (+) with drugs or other substances or implants have been conducted.
- Safety and effectiveness in the periorbital area has not been established.
- The patient should be informed that he or she should minimize exposure of the treated area to extensive sun or heat exposure for approximately 24 hours after treatment or until any initial swelling and redness has resolved.
- Universal precautions must be observed when there is a potential for contact with patient body fluids. The injection session must be conducted with aseptic technique.
- RADIESSE® (+) is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged. Do not use if the syringe end cap or syringe plunger is not in place.
- To help avoid needle breakage, do not attempt to straighten a bent needle or cannula. Discard it and complete the procedure with a replacement needle.
- Do not reshield used needles. Recapping by hand is a hazardous practice and should be avoided.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.
- Care should be taken to determine the risk versus the benefit for patients with congenital methemoglobinemia, with glucose-6-phosphate dehydrogenase deficiencies, and with patients who are receiving concomitant treatment with methemoglobin-inducing agent

NASOLABIAL FOLDS

A. ADVERSE EVENTS

I. NASOLABIAL FOLDS PRE-MARKET CLINICAL TRIAL – RADIESSE® (WITHOUT LIDOCAINE)

Tables 1-4 contain the adverse events for 117 patients in a randomized, controlled study at 4 US investigational sites. Patients in the study received RADIESSE® injectable implant in one side of the face and a collagen dermal implant as the Control in the other side of the face. Adverse events reported in patient diaries during the 14 days after treatment are listed in Tables 1 and 2. Physician reported adverse events are those reported by Investigators and patients any time outside the 2 week diaries. Those adverse events are presented in Tables 3 and 4.

Table 1 PATIENT DIARY ADVERSE EVENTS

Reported Through Patient Diaries Number of Patients with at Least One Adverse Event

By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)
Ecchymosis	74 (63.2)	50 (42.7)
Edema	81 (69.2)	62 (53.0)
Erythema	78 (66.7)	84 (71.8)
Granuloma	0 (0.0)	0 (0.0)
Nodule	1 (0.9)	1 (0.9)
Pain	33 (28.2)	26 (22.2)
Pruritus	21 (18.0)	24 (20.5)
Other*	35 (29.9)	26 (22.2)

* "Other" adverse events for both RADIESSE® injectable implant and Control include soreness, numbness, contour irregularity, tenderness, and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

There were 12 systemic adverse events reported for 9 patients. None of these systemic adverse events were related to either RADIESSE® injectable implant or Control and included emergency gallbladder surgery, breast pain, infected and exposed breast implant, gastroenteritis, uterine fibroids, headache, burning and numbness in tongue and lips, tongue ulceration and fatigue.

Table 2 PATIENT DIARY ADVERSE EVENTS

By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)	RADIESSE® Number of Days				CONTROL Number of Days			
			1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)	1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	91 (60.3)	60 (39.7)	16 (10.6)	37 (24.5)	33 (21.9)	5 (3.3)	15 (9.9)	29 (19.2)	12 (7.9)	4 (2.6)
Edema	104 (54.5)	87 (45.5)	34 (17.8)	43 (22.5)	17 (8.9)	10 (5.2)	34 (17.8)	39 (20.4)	10 (5.2)	4 (2.1)
Erythema	105 (45.1)	128 (54.9)	39 (16.7)	26 (11.2)	19 (8.2)	21 (9.0)	45 (19.3)	35 (15.0)	16 (6.9)	32 (13.7)
Granuloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
Pain	40 (54.8)	33 (45.2)	22 (30.1)	13 (17.8)	4 (5.5)	1 (1.4)	20 (27.4)	10 (13.7)	2 (2.7)	1 (1.4)
Pruritus	24 (47.1)	27 (52.9)	15 (29.4)	5 (9.8)	3 (5.9)	1 (2.0)	11 (21.6)	10 (19.6)	3 (5.9)	3 (5.9)
Other*	52 (56.5)	40 (43.5)	15 (16.3)	7 (18.5)	8 (8.7)	12 (13.0)	8 (8.7)	10 (10.9)	11 (12.0)	11 (12.0)

* "Other" adverse events for both RADIESSE® injectable implant and Control include soreness, numbness, contour irregularity, tenderness, and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

Table 3 PHYSICIAN REPORTED ADVERSE EVENTS

Number of Patients with at Least One Adverse Event

By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)
Ecchymosis	0 (0.0)	2 (1.7)
Edema	5 (4.3)	4 (3.4)
Erythema	6 (5.1)	9 (7.7)
Granuloma	0 (0.0)	0 (0.0)
Needle Jamming	1 (0.9)	0 (0.0)
Nodule	0 (0.0)	2 (1.7)
Pain	2 (1.7)	1 (0.9)
Pruritus	1 (0.9)	2 (1.7)
Other*	3 (2.6)	3 (2.6)

* "Other" adverse events for both RADIESSE® injectable implant and Control include soreness, numbness, contour irregularity, tenderness, and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

Table 4 PHYSICIAN REPORTED ADVERSE EVENTS

By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)	RADIESSE® Number of Days				CONTROL Number of Days			
			1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)	1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)
Edema	5 (41.7)	7 (58.3)	5 (41.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (41.7)	0 (0.0)	0 (0.0)	2 (16.7)
Erythema	9 (42.9)	12 (57.1)	4 (19.0)	2 (9.5)	2 (9.5)	1 (4.8)	2 (9.5)	3 (14.3)	4 (19.0)	3 (14.3)
Granuloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (66.7)
Pain	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Other*	4 (50.0)	4 (50.0)	1 (12.5)	0 (0.0)	2 (25.0)	1 (12.5)	1 (12.5)	1 (12.5)	0 (0.0)	2 (25.0)

* "Other" adverse events for both RADIESSE® injectable implant and Control include soreness, numbness, contour irregularity, tenderness, and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

II. NASOLABIAL FOLDS LONG-TERM SAFETY POST-APPROVAL STUDY – RADIESSE® (WITHOUT LIDOCAINE)

A post approval study was performed to 1) collect long-term safety information on use of RADIESSE® injectable implant injected into the nasolabial folds; and 2) to assess the effect of multiple injections. There were no reports of long term adverse events in this post approval study. The adverse events monitored in the post-approval study included allergic reaction, ecchymosis, edema, embolization, erosion, erythema, extrusion, granuloma, hematoma, infection, necrosis, needle jamming, nodule, and pain.

III. NASOLABIAL FOLDS FITZPATRICK SKIN TYPE IV-VI POST-APPROVAL STUDY – RADIESSE® WITHOUT LIDOCAINE

Adverse events reported in the short-term Fitzpatrick Skin Type IV-VI post-approval study are presented in Table 5.

Table 5 ADVERSE EVENTS

N = 100

ADVERSE EVENT TYPE	PATIENTS REPORTING SYMPTOMS N (%)
Hypertrophic Scarring	0 (0.0)
Keloid Formation	0 (0.0)
Hypopigmentation	0 (0.0)
Hyperpigmentation-Upper Lip	1 (1.0)
Hyperpigmentation-Other	0 (0.0)
Bumpiness	1 (1.0)
Ecchymosis	7 (7.0)
Eczema on Leg	1 (1.0)
Edema	12 (12.0)
Erythema	16 (16.0)
Eye Stye	1 (1.0)
Mild Bleeding at Injection Site	1 (1.0)
Needle Jamming	1 (1.0)
Tenderness	2 (2.0)
Urinary Tract Infection	1 (1.0)

IV. NASOLABIAL FOLDS PRE-MARKET CLINICAL TRIAL – RADIESSE® (+) (RADIESSE® WITH 0.3% LIDOCAINE)

Tables 6 and 7 contain the adverse events for 101 subjects in a randomized, controlled study at 3 Canadian investigational sites. Patients in the study received RADIESSE® (+) in one nasolabial fold (Treatment) and RADIESSE® injectable implant in the other nasolabial fold (Control). The adverse events reported during this study were generally expected, mild in nature and short in duration. The majority of adverse events were reported through the subject diaries.

Table 6 summarizes the number of adverse events reported in the subject diaries. Swelling and redness were the most frequently reported adverse events. There was no significant difference in adverse event rates between the nasolabial folds with RADIESSE® (+) and the nasolabial folds with RADIESSE® injectable implant. Needle jams occurred during the injection of the RADIESSE® (+) in three (3/101, 3%) subjects. In all cases, the needle was replaced and the RADIESSE® (+) injections were completed without further sequelae.

No vascular compromise events occurred in the RADIESSE® (+) injections.

In the RADIESSE® injectable implant injections, two (2/101, 2%) vascular compromise events occurred, requiring treatment to resolve.

Table 6 Adverse Events Reported in Subject Diaries Over the 4-Week Study Period

n = 202 Folds

Event Type *	n (%)	
	RADIESSE® (+) n = 101 Folds	RADIESSE® n = 101 Folds
Bruising	44 (43.6%)	48 (47.5%)
Itching	37 (36.6%)	34 (33.7%)
Pain	48 (47.5%)	57 (56.4%)
Redness	66 (65.3%)	71 (70.3%)
Swelling	90 (89.1%)	92 (91.1%)
Blanching	5 (5.0%)	8 (7.9%)

* "Other" adverse events reported by 19 subjects for both RADIESSE® injectable implant and Control include numbness, tenderness, lumps, bumps and discomfort.

Of the 13 blanching events described in Table 6, two were associated with previously described vascular compromise events. The remaining 11 were not determined to be vascular compromise events.

Table 7 summarizes the number of adverse events reported by the investigators. As with the patients, swelling and redness were the most frequently reported adverse events.

Table 7 Adverse Events Reported by Investigators

N = 101 Subjects

Event Type *	N (%)	
	RADIESSE® (+)	RADIESSE®
Bruising	20 (19.8%)	18 (17.8%)
Swelling	58 (57.4%)	55 (54.5%)
Erosion	0	1 (1.0%)**
Redness	51 (50.5%)	50 (49.5%)
Infection	1 (1.0%)†	0
Needle Jamming	3 (3.0%)‡	0
Nodule	0	0
Pain	0	1 (1.0%)
Vascular Compromise	0	1 (1.0%)

* "Other" adverse events for both RADIESSE® injectable implant and Control include tenderness and tingling sensation.
** Associated with vascular compromise event
†Herpes simplex infection unrelated to study device
‡Returned product evaluation regarding one subject concluded that needle jam might have resulted from needle incompletely screwed onto the RADIESSE® syringe's luer threads.

B. CLINICAL STUDIES

I. NASOLABIAL FOLD PRE-MARKET CLINICAL TRIAL – RADIESSE® (WITHOUT LIDOCAINE)

Study Design

The safety and effectiveness of RADIESSE® injectable implant for the treatment of nasolabial folds (NLFs) was evaluated in a multi-center, prospective, randomized clinical trial. Patients were randomized to receive RADIESSE® injectable implant in one fold and a commercially available collagen implant in the contralateral fold.

Patients were eligible to receive up to three injections during the initial treatment phase (week 0, week 2 and week 4). At 2 weeks after each treatment, the level of correction was determined and if correction was less than optimal, the Investigator re-treated the nasolabial fold using the same respective treatment materials as in the initial treatment. A safety follow-up was conducted 1 month after any injection and at 3 and 6 months after the last injection. Effectiveness evaluations were conducted at 3 and 6 months after the last injection. Three blinded reviewers independently evaluated the severity of the subject's nasolabial folds using a validated 6-point wrinkle severity scale.

Study Endpoints

The primary effectiveness endpoint of the study was the blinded reviewers' Lemperle Rating Scale (LRS) score of wrinkle severity at 3 months after the last touch-up (at which optimal correction was achieved). In this assessment, LRS scores were determined, (using this validated 6-point scale), via blinded, photographic assessments by 3 board certified physicians. A change in LRS of 1 was considered to be clinically significant. Secondary effectiveness endpoints included the blinded reviewers' assessment of wrinkle severity at 6 months after treatment, and the volume of material injected.

Study Population

A total of 117 subjects (31-76 years of age) were randomized and treated and 115 (98.3%) completed the 3 month primary effectiveness evaluation and 113 (96.6%) completed the 6 month follow-up visit. The baseline demographics of the study population are presented in Table 8 which shows that the study enrolled a population of predominantly female, Caucasian non-smokers.

Table 8 PATIENT DEMOGRAPHICS

N = 117

AGE (YEARS)	
Mean	54.7
Standard Deviation	8.9
Minimum	31.0
Maximum	76.0
GENDER	
Female	105 (89.7%)
Male	12 (10.3%)
RACE	
American Indian	0 (0.0%)
Asian	0 (0.0%)
Black	2 (1.7%)
Caucasian	102 (87.2%)
Hispanic	11 (9.4%)
Other	2 (1.7%)
SMOKING HISTORY	
Quit Smoking	26 (22.2%)
Never Smoked	83 (70.0%)
Smokes	8 (6.8%)

Treatment Material Delivered

Volumes injected during the initial treatment phase are detailed in Table 9. The total mean volume for RADIESSE® injectable implant was 1.2 mL and 2.4 mL for the Control.

Table 9 TOTAL VOLUME OF MATERIAL INJECTED (mL)

N = 117

	RADIESSE®	CONTROL
Mean	1.2	2.4
Median	1.1	2.2
Standard Deviation	0.5	0.9
Minimum	0.3	0.8
Maximum	2.7	4.7

Effectiveness Results:

Table 10 contains the mean LRS at baseline, 3 months and 6 months for the RADIESSE® injectable implant treated nasolabial folds and the Control treated nasolabial folds with the difference between the means. Baseline scores for the RADIESSE® injectable implant and Control groups were not statistically different.

Table 10 COMPARISON OF MEAN LRS SCORES* FOR RADIESSE® INJECTABLE IMPLANT AND CONTROL

	RADIESSE®	CONTROL	DIFFERENCE
Baseline	3.4	3.4	0.0
3 Months	1.9	3.5	1.6
6 Months	2.1	3.4	1.3

* Grading Scale: 0 = No wrinkles, 1 = Just perceptible wrinkle, 2 = Shallow wrinkle, 3 = Moderately deep wrinkle, 4 = Deep wrinkle, well-defined edges, 5 = Very deep wrinkle, redundant fold

Primary Effectiveness Endpoint

The primary effectiveness endpoint was to use mean LRS scores to evaluate whether RADIESSE® injectable implant was non-inferior to Control for the correction of nasolabial folds 3 months after final treatment. At 3 months, 84.6% of the RADIESSE® injectable implant treated nasolabial folds were scored at least 1-point higher than the Control, 12.8% were scored equally, and 2.6% were scored at least 1-point lower than the Control. RADIESSE® injectable implant met the statistical criteria for non-inferiority to Control at 3 months ($p<0.0001$), however, the Control scored no effectiveness at 3 months.

Secondary Effectiveness Endpoint

The pre-specified secondary superiority analyses at 6 months required a mean 1-point LRS difference between the improvements for the RADIESSE® injectable implant treated nasolabial fold versus improvement on the Control treated nasolabial fold and that in at least 50% of patients, the RADIESSE® injectable implant treated nasolabial fold be superior to the Control treated nasolabial fold. At 6 months after optimal correction was achieved, 78.6% of the RADIESSE® injectable implant treated nasolabial folds were scored at least 1-point higher than the Control-treated folds, 16.2% were scored equally, and 5.1% were scored at least 1-point lower than the Control. The mean LRS for the RADIESSE® injectable implant treated nasolabial folds demonstrated superiority when compared to the mean LRS for the Control-treated nasolabial folds at 6 months ($p< 0.0001$).

II. NASOLABIAL FOLDS LONG-TERM SAFETY POST-APPROVAL STUDY – RADIESSE® (WITHOUT LIDOCAINE)

Study Objective

A post approval study was performed to 1) collect long-term safety information on use of RADIESSE® injectable implant injected into the nasolabial folds; and 2) to assess the effect of multiple injections.

Study Design

RADIESSE® injectable implant was assessed in a prospective, open-label, multi-center study of patients whose nasolabial folds were corrected with RADIESSE® injectable implant. 102 subjects (drawn from the 117 patients who participated in the premarket clinical trial) agreed to participate in the post approval study. Patients were requested to return for visits a minimum of 2 years and then a minimum of 3 years after their initial injection. At the beginning of the post marketing study, 8 patients were already 3 years from initial injection and, therefore, required only one visit. One hundred and two (102) patients were assessed a minimum of 2 years after initial injection and 99 were assessed a minimum of 3 years after initial injection. Three (3) patients were lost to follow up.

Study Population

The patient cohort in this post approval study was the continued follow-up of the pre-market cohort. Patient demographics are provided in Table 11.

Table 11 PATIENT DEMOGRAPHICS

N =102

AGE (YEARS)	
Mean	55.1
Standard Deviation	8.8
Minimum	31.0
Maximum	76.0
GENDER	
Female	94 (92.2%)
Male	8 (7.8%)
RACE	
American Indian	1 (1.0%)
Asian	0 (0.0%)
Black	1 (1.0%)
Caucasian	87 (85.3%)
Hispanic	11 (10.8%)
Other	2(2.0%)
SMOKING HISTORY	
Quit Smoking	23 (22.6%)
Never Smoked	73 (71.6%)
Smokes	6 (5.9%)

The inclusion criterion for the study was participation in the pre-market clinical trial (Section I of the Nasolabial Folds CLINICAL STUDIES section) and signing a written informed consent for participation in the post-approval study. There were no additional exclusion criteria.

Study Endpoints

To collect long-term safety information of RADIESSE® injectable implant injected into the nasolabial folds at a minimum of 2 and 3 years after initial injection and to assess the effect of multiple injections.

Study Results

102 study patients and 204 folds received a mean of 3.7 and 1.8 RADIESSE® injectable implant injections, respectively, from the time period covering initial pre-market study injection through the last post approval study visit. 100% of patients and 98% of folds received RADIESSE® injectable implant treatment during the same time period with only 11% of patients receiving RADIESSE® injectable implant injections during the post approval study period alone. During the post approval study, 15% of patients received Botulinum toxin injections and 9% of patients received facial dermal fillers other than RADIESSE® injectable implant in the nasolabial folds.

With respect to the long term safety of RADIESSE® injectable implant, there were no reports of long term adverse events in this post approval study. The adverse events monitored in the post-approval study included allergic reaction, ecchymosis, edema, embolization, erosion, erythema, extrusion, granuloma, hematoma, infection, necrosis, needle jamming, nodule, and pain. These results demonstrate the long term safety and effectiveness of RADIESSE® injectable implant up to 3 years after the date of first injection.

Study Limitations

RADIESSE® injectable implant was studied in a limited number of predominately female patients. Safety of the RADIESSE® injectable implant following the correction of nasolabial folds beyond 3 years was not studied.

III. NASOLABIAL FOLDS FITZPATRICK SKIN TYPE IV-VI POST-APPROVAL STUDY – RADIESSE® (WITHOUT LIDOCAINE)

Study Objective

A post-approval study was performed to assess the safety of RADIESSE® injectable implant following correction of the nasolabial folds in patients with Fitzpatrick Skin Types IV, V, or VI, specifically to assess the likelihood of hypertrophic scarring, keloid formation and hyper- or hypopigmentation.

Study Design

The safety of RADIESSE® injectable implant was assessed in a prospective, open-label, multi-center study in 100 patients with Fitzpatrick Skin Types IV, V or VI whose nasolabial folds were corrected with subdermal injections of RADIESSE® injectable implant.

Study Population

Patient demographics are provided in Table 12.

Table 12 PATIENT DEMOGRAPHICS

N = 100

AGE (YEARS)	
Mean	52
Standard Deviation	11.1
Minimum	25
Maximum	78
GENDER	
Male	6 (6.0%)
Female	94 (94.0%)
RACE	
Caucasian	0 (0.0%)
Black	85 (85.0%)
Hispanic	12 (12.0%)
Asian	2 (2.0%)
Other	1 (1.0%)
FITZPATRICK SKIN TYPE	
IV	24 (24.0%)
V	35 (35.0%)
VI	41(41.0%)
INJECTION VOLUME (mL)	
Mean	1.24
Standard Deviation	0.397
Minimum	0.6
Maximum	2.8

The inclusion criteria for the post-approval study were that the patient was at least 18 years of age, was Fitzpatrick Skin Type IV, V, or VI, and understood and accepted the obligation not to receive any other procedures or treatments in the nasolabial fold for 6 months.

The exclusion criteria for the post-approval study were that the patient had a history of hyper- or hypo-pigmentation in the nasolabial folds, keloid formation, or hypertrophic scarring, had a known bleeding disorder or was receiving drug therapy that could increase the risk of bleeding, had nasolabial folds that are too severe to be corrected in one treatment session, had received any dermal filler or other injections, grafting or surgery in either nasolabial fold, is pregnant, lactating, or not using acceptable contraception.

Study Endpoints

The likelihood of hypertrophic scarring, keloid formation and hyper- or hypopigmentation was evaluated through 6 months from treatment with RADIESSE® injectable implant in the nasolabial folds.

Length of Follow-up and Assessments

Patients were followed for 6 months from RADIESSE® injectable implant treatment (injection visit). Ninety days (90) ± 30 days from the injection visit, patients returned for a safety assessment of their nasolabial folds (3 month visit). One hundred eighty days (180) ± 30 days from the initial injection, patients returned for a safety assessment of their nasolabial folds (6 month visit).

Subject Accountability

One hundred (100) patients were enrolled in the post-approval study and assessed at the 3 month visit (100% follow-up rate). Ninety-eight (98) patients were assessed at the 6 month visit (98% follow-up rate). Two patients were lost to follow-up.

Study Results

At 3 months, 100% of patients were assessed and there were no reports of hypertrophic scarring, keloid formation, hyperpigmentation or hypopigmentation at the injection site. At 6 months 98% of patients were assessed. Two patients were lost to follow-up. Of the 98 patients assessed, no occurrence of hypertrophic scarring, keloid formation, hyperpigmentation or hypopigmentation at the injection site was reported. One patient reported erythema in the upper left nasolabial fold that was treated with hydrocortisone and lasted for 111 days. Another patient experienced mild hyperpigmentation in the upper lip that lasted 159 days. No treatment was required.

The use of RADIESSE® injectable implant did not cause hypertrophic scarring, keloid formation, hyperpigmentation or hypopigmentation at the injection site in persons with Fitzpatrick Skin Types of IV, V, and VI in this study throughout the follow-up period of 6 months.

Study Limitations

RADIESSE® injectable implant was studied in a limited number of predominately female patients. Likelihood of keloid formation, hypertrophic scarring, and hypo- or hyperpigmentation after use of RADIESSE® injectable implant for the correction of nasolabial folds in patients with Fitzpatrick Skin Type 4, 5 and 6 beyond 6 months was not studied.

IV. NASOLABIAL FOLD PRE-MARKET CLINICAL TRIAL – RADIESSE® (+) (RADIESSE® WITH 0.3% LIDOCAINE)

Study Design

The safety and effectiveness of RADIESSE® (+) for the treatment of nasolabial folds (NLFs) was evaluated in a multi-center, prospective, randomized clinical trial. The primary objective of the study was to assess pain control when RADIESSE® containing lidocaine was used to treat nasolabial folds.

Subjects were randomized to receive RADIESSE® (+) in one fold and the commercially available RADIESSE® injectable implant (Control), in the contralateral fold.

Effectiveness evaluations were conducted at 15, 30, 45, and 60 minutes after injection; and at 1, 2, and 4 weeks after injection. At weeks 1, 2, and 4, subjects returned for a pain assessment using the 10 cm visual analog scale (VAS) and a safety assessment by the blinded assessing physician. Aesthetic outcomes were assessed by the blinded assessing investigator using the validated Merz Nasolabial Fold Scale and the Global Aesthetic Improvement Scale (GAIS).

Study Endpoints

The primary effectiveness endpoint of the study was to assess whether there was a statistically significant reduction in pain in the nasolabial fold injected with RADIESSE® (+) compared to the nasolabial fold injected with RADIESSE® injectable implant immediately after treatment using the visual analog pain scale (VAS).

There were five secondary effectiveness endpoints that (1) evaluated whether the difference of nasolabial fold pain when injected with RADIESSE® (+) versus RADIESSE® injectable implant (without lidocaine) was clinically meaningful immediately after treatment (defined as a minimum of 2.0 cm reduction on the VAS); (2) assessed pain in the nasolabial fold treated with RADIESSE® (+) compared to the assessed pain in the nasolabial fold treated with RADIESSE® at 15, 30, 45, and 60 minutes, and at 1, 2, and 4 weeks after treatment using the VAS; (3) assessed aesthetic effectiveness by a blinded assessing investigator at 1, 2, and 4 weeks after nasolabial fold treatment using the validated Merz Nasolabial Fold Scale and the Global Aesthetic Improvement Scale (GAIS); (4) assessed subject preference with respect to pain 60 minutes after treatment; and (5) assessed subject preference with respect to aesthetic outcome 1, 2, and 4 weeks after nasolabial fold correction.

Study Population

Table 13 presents subject demographics which show that most subjects were female and Caucasian. Eighteen percent of subjects enrolled were fairly evenly distributed across Fitzpatrick Skin Types (FST) IV, V, and VI.

Table 13 Subject Demographics
N = 102 Subjects

AGE (years)	
Mean (SD, Range)	48.85 (9.43, 30 - 77)
GENDER – N (%)	
Female	87 (85.3%)
Male	15 (14.7%)
RACE – N (%)	
Caucasian	88 (86.3%)
African American	8 (7.8%)
Hispanic	2 (2.0%)
Asian	1 (1.0%)
Other	3 (2.9%)
FITZPATRICK SKIN TYPE – N (%)	
I	6 (5.9%)
II	19 (18.6%)
III	59 (57.8%)
IV	8 (7.8%)
V	5 (4.9%)
VI	5 (4.9%)

Treatment Material Delivered

The volume of filler injected in each fold is detailed in Table 14 showing that the volume injected between the two products was nearly identical.

Table 14 Injection Volumes (cc)
n = 202 Folds

	n (%)	
	RADIESSE® (+) n = 101 Folds	**RADIESSE®** n = 101 Folds
Mean (cc) (SD, Range)	0.84 (0.32, 0.2 -1.5)	0.83 (0.34, 0.25 -1.8)

Effectiveness Results:

Primary Effectiveness Endpoint

The difference of the visual analog pain scale (VAS) scores between the two groups showed a statistically significant reduction in pain with RADIESSE® (+) compared to RADIESSE® (p-value <0.0001).

Secondary Effectiveness Endpoints

The first of five secondary effectiveness endpoints was to assess whether the difference in pain in the nasolabial fold treated with RADIESSE® (+) versus the nasolabial fold treated with RADIESSE® was clinically meaningful immediately after treatment (defined as a minimum of 2.0 cm reduction on the VAS). This analysis showed that in 91 of 101 subjects VAS scores were ≥ 2.0 cm lower for RADIESSE® (+) compared to RADIESSE® in a given subject, demonstrating a clinically meaningful reduction in pain that was statistically significant (p-value < 0.0001).

The second secondary effectiveness endpoint was to assess pain in the nasolabial fold injected with RADIESSE® (+) compared to the nasolabial fold injected with RADIESSE® at 15, 30, 45, and 60 minutes and 1, 2, and 4 weeks after treatment using the VAS. This analysis showed that for all of these time-points there was a statistically significant difference in pain with RADIESSE® (+) compared to RADIESSE®.

The third secondary effectiveness endpoint was to assess aesthetic improvement on the GAIS and the Merz Nasolabial Fold Scale at 1, 2, and 4 weeks post treatment by the blinded assessing investigators. The vast majority of subjects were improved on the GAIS and there were no statistical differences between the two groups with respect to GAIS improvement. There were no significant differences between RADIESSE® (+) and RADIESSE® on the Merz Nasolabial Fold Scale. The RADIESSE® (+) and the RADIESSE® ratings on the Merz Nasolabial Fold Scale were improved from baseline condition. These results were the same across all time-points.

The fourth secondary effectiveness endpoint was to assess subject pain preference at time zero. These data showed that 98 subjects (97%) indicated that one treatment was less painful than the other and 87 subjects (88%) determined the difference in pain level was significant enough to affect their preference for one dermal filler versus the other. Of the 87 subjects who indicated that the difference in pain levels would affect treatment preference, 86/87 had lower VAS scores with RADIESSE® (+).

The fifth secondary effectiveness endpoint was for study subjects to assess preference with respect to aesthetic outcome 1, 2, and 4 weeks after nasolabial fold correction. Less than half of subjects stated that one nasolabial fold looked better at any of these post-treatment time-points. Of those, only half stated that the aesthetic preference was significant enough to choose one treatment over the other.

JAWLINE

A. ADVERSE EVENTS

In a randomized, controlled clinical trial to evaluate the safety and effectiveness of RADIESSE® (+) to improve the contour of the jawline, a total of 180 subjects were enrolled. All subjects were randomized to treatment (n=123) or control (delayed treatment) (n=57). All subjects were also randomized to be treated with either needle or cannula (1:1 allocation ratio). Touch-up treatments were permitted 4 weeks after initial injection, if needed to achieve optimal correction. After the primary endpoint assessment the control group was eligible to receive treatment and 53 control subjects received treatment. All subjects were followed for 48 weeks post initial treatment, at which time only the treatment group was eligible for retreatment.

Adverse events (AEs) were reported by Treating Investigators and collected at all follow-up visits. Of the 175 treated subjects, 42.9% (75/175)), reported an AE. A treatment-emergent AE (TEAE) was defined as an AE with onset date on or after date of initial treatment. Overall, 26.3% (46/175) subjects had at least one TEAE that was deemed to be related to either injection procedure or RADIESSE® (+) by the investigator: 19.4% (34/175) subjects had TEAEs related to RADIESSE® (+) and 24.0% (42/175) subjects had TEAEs related to the injection procedure. As outlined in Table 15, the most common TEAEs consisted mostly of administration site conditions including injection site mass, injection site bruising, and injection site pain.

Table 15 Subjects with TEAEs with Incidence of >5%

	Total (N=175)	
MedDRA Preferred Term	**n**	**(%)**
Subjects with at least one TEAE	74	(42.3)
Injection site mass	19	(10.9)
Injection site bruising	12	(6.9)
Injection site pain	12	(6.9)

The majority of treatment-related TEAEs were mild, lasted less than 15 days and resolved without sequelae (Table 16). Importantly, only 1 subject had treatment-related TEAEs that were severe: injection site bruising (1 event, lasting 16 days) and injection site swelling/oedema (1 event, lasting 16 days).

Table 16 Treatment-related TEAEs by Worst Severity and Duration

	Total (N=175)		
Patients with at least one treatment-related TEAE	**n**	**(%)**	**m**
Severity			
Mild	44	(25.1)	88
Moderate	1	(0.6)	1
Severe	1	(0.6)	2
Duration			
≤ 14 days	21	(12.0)	59
15-28 days	6	(3.4)	12
> 28 days	19	(10.9)	20

N: number of patients exposed; n: number of patients with at least one treatment-related TEAE; (%): percentage of patients with at least one treatment-related TEAE; m: number of treatment-related TEAEs (events).

For number of TEAEs, each TEAE was counted at the duration category of this event and at the severity of this event. A subject with more than one TEAE was counted once at the subject's worst severity and subject's maximum duration category, respectively.

The highest incidence of treatment-related TEAEs was reported after initial treatment (initial treatment in 20.6% (36/175) subjects; touch-up in 9.8%(13/132) subjects; and retreatment in 6.6% (5/76) subjects). During the retreatment period, only 6.6% (5/76) subjects had a total of 5 mild treatment related TEAEs including: injection site mass (1 event), injection site bruising (2 events), device dislocation (1 event), and product distribution issue (1 event). No treatment-related serious adverse events (SAEs) and no unexpected or atypical events with use of RADIESSE® (+) were reported.

In general, treatment-related TEAEs observed in the cannula and needle subgroups were comparable in incidence, severity, and duration. Overall, no safety issues were observed when stratifying TEAEs by injection type (cannula versus needle), Fitzpatrick skin type categories (I-III versus IV-VI) and sex (females versus males).

For most subjects with treatment-related TEAEs (28 of 46 subjects with treatment-related TEAEs) these events began within seven (7) days of initial treatment. Hence, 16% (28/175) of all treated subjects experienced a total of 56 treatment related TEAEs with onset within seven (7) days of initial treatment. Over the course of this study, six (6) subjects reported a total of seven (7) injection procedure related, or treatment related, events presenting > 28 days after last injection (onset ranging from 30 to 129 days). Five (5) subjects reported 1 event (including injection site mass, injection site nodule, device dislocation and product distribution issue), and 1 subject reported two (2) events (injection site extravasation and injection site inflammation). All events were considered mild in intensity. All events resolved by study end except for one (1) nonserious event of injection site nodule that remained unknown at the study end due to the subject being lost to follow up after day 100 and one (1) mild device dislocation from retreatment which resolved after the study end. None of these AEs were serious or required treatment.

Electronic diaries were used by subjects to record specific signs and symptoms Common Treatment Responses -CTRs) experienced during each of the first 28 days after initial, touch-up, and repeat treatments. Subjects were instructed to report the severity of each of the specified CTRs as mild, moderate, severe or none. After initial treatment, 94.9% (166/175) reported at least 1 CTR after initial treatment, 77.8% (98/126) reported at least 1 CTR after touch-up treatment, and 83.8% (62/74) subject reported at least 1 CTR after repeat treatment. After initial treatment (i.e., initial treatment at Day 1 or delayed treatment at Week 12), the majority of subjects self-reported CTRs that were mild (46.3%; 81/175) to moderate (46.3%; 81/175) and had a longest duration of 14 days or less (1-3 days: 12.6%, 22/175; 4-7 days: 38.9%, 68/175; and 8-14 days: 26.3%, 46/175). One patient experienced a mild CTR of discomfort/pain with palpation in both the left and right jawline lasting 29 days after initial treatment that did not require clinical intervention and resolved without sequelae.

The overall incidence, severity, and duration of CTRs were comparable in all three subject diaries (initial treatment, touch up and retreatment). Furthermore, no unexpected clinically relevant trends on CTRs incidences were identified between the needle and cannula subgroups, nor among differing Fitzpatrick Skin Types. CTRs reported by > 5% of subjects after initial treatment are summarized by severity in Table 17 and by duration in Table 18.

Some differences were noted on worst CTR intensity self-reported as moderate:

• more subjects in the needle subgroup self-reported rash (needle: 6/88, 6.8% and cannula: 2/87, 2.3%), or bruising (needle: 25/88, 28.4% and cannula: 18/87, 20.7%); while

• more subjects in the cannula subgroup self-reported swelling (needle: 20/88, 22.7% and cannula: 28/87, 32.2%), firmness (needle: 11/88, 12.5% and cannula: 19/87, 21.8%), lumps/bumps (needle: 15/88, 17.0% and cannula: 33/87, 37.9%), movement or shifting of product (needle: 1/88, 1.1% and cannula: 5/87, 5.7%) or discomfort/pain with palpation (needle: 21/88, 23.9% and cannula: 26/87, 29.9%).

Some differences between needle and cannula were noted on subjects that self-reported CTRs to last 15 days or more:

• more subjects in the needle subgroup self-reported swelling (needle: 5/88, 5.7% and cannula: 2/87, 2.3%) and bruising (needle: 7/88, 8.0% and cannula: 1/87, 1.1%); while

• more subjects in the cannula subgroup self-reported firmness (needle: 3/88, 3.4% and cannula: 8/87, 9.2%), lumps/bumps (needle: 6/88, 6.8% and cannula: 10/87, 11.5%), and discomfort with palpation (needle: 2/88, 2.3% and cannula: 6/87, 6.9%).

Table 17 CTRs by worst severity occurring in > 5% of subjects after initial treatment

Treatment site response	Severity M=175			
	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Any CTR	9 (5.1%)	81 (46.3%)	81 (46.3%)	4 (2.3%)
Rash	132 (75.4%)	35 (20.0%)	8 (4.6%)	0 (0.0%)
Swelling	25 (14.3%)	100 (57.1%)	48 (27.4%)	2 (1.1%)
Firmness	41 (23.4%)	103 (58.9%)	30 (17.1%)	1 (0.6%)
Lumps/Bumps	46 (26.3%)	78 (44.6%)	48 (27.4%)	3 (1.7%)
Bruising	60 (34.3%)	70 (40.0%)	43 (24.6%)	2 (1.1%)
Redness	106 (60.6%)	57 (32.6%)	12 (6.9%)	0 (0.0%)
Discoloration (not redness or bruising)	153 (87.4%)	18 (10.3%)	4 (2.3%)	0 (0.0%)
Itching	144 (82.3%)	25 (14.3%)	6 (3.4%)	0 (0.0%)
Stinging/burning	157 (89.7%)	15 (8.6%)	3 (1.7%)	0 (0.0%)
Movement or shifting of product	134 (76.6%)	35 (20.0%)	6 (3.4%)	0 (0.0%)
Difficulty drinking	166 (94.9%)	8 (4.6%)	1 (0.6%)	0 (0.0%)
Difficulty chewing	135 (77.1%)	33 (18.9%)	7 (4.0%)	0 (0.0%)
Difficulty speaking	163 (93.1%)	11 (6.3%)	1 (0.6%)	0 (0.0%)
Discomfort/Pain with palpation	46 (26.3%)	81 (46.3%)	47 (26.9%)	1 (0.6%)
Discomfort/Pain without palpation	88 (50.3%)	73 (41.7%)	14 (8.0%)	0 (0.0%)

CTR = Common treatment site response.

N = number of subjects exposed in the respective treatment group/period; M = number of subjects with at least one entry in the eDiary in the respective treatment group/period. % is calculated based on N/M.

Table 18 CTRs by maximum duration occurring in > 5% of subjects after initial treatment

Treatment site response	Duration M=175					
	None n (%)	1-3 days n (%)	4-7 days n (%)	8-14 days n (%)	15-28 days n (%)	> 28 days n (%)
Any CTR	9 (5.1%)	22 (12.6%)	68 (38.9%)	46 (26.3%)	29 (16.6%)	1 (0.6%)
Rash	132 (75.4%)	38 (21.7%)	4 (2.3%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Swelling	25 (14.3%)	61 (34.9%)	67 (38.3%)	15 (8.6%)	7 (4.0%)	0 (0.0%)
Firmness	41 (23.4%)	59 (33.7%)	48 (27.4%)	16 (9.1%)	11 (6.3%)	0 (0.0%)
Lumps/Bumps	46 (26.3%)	53 (30.3%)	39 (22.3%)	21 (12.0%)	16 (9.1%)	0 (0.0%)
Bruising	60 (34.3%)	20 (11.4%)	54 (30.9%)	33 (18.9%)	8 (4.6%)	0 (0.0%)
Redness	106 (60.6%)	56 (32.0%)	13 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration (not redness or bruising)	153 (87.4%)	18 (10.3%)	1 (0.6%)	2 (1.1%)	1 (0.6%)	0 (0.0%)
Itching	144 (82.3%)	19 (10.9%)	7 (4.0%)	4 (2.3%)	1 (0.6%)	0 (0.0%)
Stinging/burning	157 (89.7%)	16 (9.1%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Movement or shifting of product	134 (76.6%)	33 (18.9%)	4 (2.3%)	4 (2.3%)	0 (0.0%)	0 (0.0%)
Difficulty drinking	166 (94.9%)	9 (5.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difficulty chewing	135 (77.1%)	32 (18.3%)	7 (4.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Difficulty speaking	163 (93.1%)	11 (6.3%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discomfort/Pain with palpation	46 (26.3%)	56 (32.0%)	45 (25.7%)	19 (10.9%)	8 (4.6%)	1 (0.6%)
Discomfort/Pain without palpation	88 (50.3%)	59 (33.7%)	27 (15.4%)	0 (0.0%)	1 (0.6%)	0 (0.0%)

CTR = Common treatment site response.

N = number of subjects exposed in the respective treatment group/period; M = number of subjects with at least one entry in the eDiary in the respective treatment group/period. % is calculated based on N/M.

Jaw Function Safety Assessments: At all study visits, treating investigators performed jaw function assessments (evaluating symptoms such as difficulties with drinking, chewing, speaking, pain, sensitivity to hot/cold or any other symptoms) and intraoral exams (assessing abnormalities, such as product migration, nodule formation, ulceration, fluctuance, erythema, tenderness, occlusion instability, sensory deficiency, muscle paralysis, or any other abnormalities). Additionally, subjects assessed their perception of mandibular function impairment on the Mandibular Function Impairment Questionnaire at all study visits.

No safety concerns were noted on the treating investigator jaw function assessments and intraoral exams.

Two subjects had tenderness on the jaw function assessment at week 2 that resolved by week 4. Five subjects reported a score of 1 on the FIRS (Functional Impairment Rating Scale) for the patient reported mandibular function impairment questionnaire. This indicates a low level of functional impairment with no intervention needed. On intraoral examination, the investigators did not report any functional impairment. In all cases the symptoms resolved without clinical intervention over the course of the study.

Vascular occlusion assessments: Subjects were instructed to report any new or unusual symptoms related to a potential vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis) in patient diaries for 28 days after each treatment. No events related to a potential vascular occlusion were reported over the course of the study.

B. CLINICAL STUDIES

Study Design

A randomized, controlled study was conducted at 15 US investigational sites. Patients in the study were randomized to receive treatment (n=123) or control (delayed treatment) (n=57) with RADIESSE® (+) in both jawlines. All subjects were randomized to receive treatment with either a needle (n=88) or cannula (n=87). After the primary endpoint assessment, the control group was eligible to receive treatment. Subjects could receive a touch-up 4 weeks post treatment, if needed. All subjects were followed for 48 weeks post initial treatment, at which time the treatment group was eligible for retreatment.

Study Endpoints

Primary effectiveness endpoint was the comparison of the responder rate between the treatment group and the untreated control group at Week 12, according to the MJAS, as assessed by a blinded evaluator. Treatment response was defined as ≥ 1-point improvement on both jawlines compared to baseline. Secondary effectiveness endpoints assessed at Week 12 included descriptive summary of the FACE-Q™ Satisfaction with Lower Face and Jawline, and Global Aesthetic Improvement Scale (GAIS).

Study Population

A total of 180 subjects with a MJAS score of 2 (55.0%) or 3 (45.0%) were enrolled and randomized. The intent-to-treat population consisted of 123 (100.0%) subjects in the treatment group and 57 (100.0%) subjects in the control/delayed-treatment group. In total, 111 (90.2%) subjects in the treatment group and 52 (91.2%) subjects in the control/delayed-treatment group were included in the per protocol population. The safety evaluation set included all treated subjects: 122 (99.2%) subjects in the treatment group and 53 (93.0%) subjects in the control/delayed treatment group. A total of 87 subjects were treated with cannula and 88 subjects were treated with needle.

As shown in Table 19, the majority of subjects were female (81.1% female and 18.9% male). Age ranged from 26 to 65 years with a mean of 55.3 years. Majority of the subjects (80.6%) self-identified as White, 13.3% as Black/African American, 5.6% as Asian, and 0.6% as American Indian or Alaska Native. Regarding Fitzpatrick Skin type categories, 60.6% subjects had skin types I, II, or III, and 39.4% had skin types IV, V, or VI.

Table 19 Subject Demographics

	Treatment (N=123)	Control/DT (N=57)	Total (N=180)
Sex, (n (%))			
Male	21 (17.1)	13 (22.8)	34 (18.9)
Female	102 (82.9)	44 (77.2)	146 (81.1)
Age [years]			
Mean (SD)	55.5 (7.3)	55.0 (6.6)	55.3 (7.1)
Median	57.0	55.0	56.0
Min, max	26, 65	41, 65	26, 65
Ethnicity (n (%))			
Hispanic or Latino	22 (17.9)	9 (15.8)	31 (17.2)
Not Hispanic or Latino	101 (82.1)	48 (84.2)	149 (82.8)
Race (n (%))			
White	103 (83.7)	42 (73.7)	145 (80.6)
Asian	5 (4.1)	5 (8.8)	10 (5.6)
Black or African American	14 (11.4)	10 (17.5)	24 (13.3)
American Indian or Alaska Native	1 (0.8)	0 (0.0)	1 (0.6)
Fitzpatrick skin type (n (%))			
I	2 (1.6)	0 (0.0)	2 (1.1)
II	31 (25.2)	13 (22.8)	44 (24.4)
III	44 (35.8)	19 (33.3)	63 (35.0)
IV	25 (20.3)	11 (19.3)	36 (20.0)
V	10 (8.1)	5 (8.8)	15 (8.3)
VI	11 (8.9)	9 (15.8)	20 (11.1)
MJAS score by blinded evaluator Left jawline			
2=Moderate	65 (52.8)	34 (59.6)	99 (55.0)
3=Severe	58 (47.2)	23 (40.4)	81 (45.0)
MJAS score by blinded evaluator Right jawline			
2=Moderate	65 (52.8)	34 (59.6)	99 (55.0)
3=Severe	58 (47.2)	23 (40.4)	81 (45.0)

Primary Effectiveness Endpoint

RADIESSE® (+) provided a clinically and statistically significant improvement in the contour of the jawline compared to the no treatment control group. As shown in Table 20, the treatment response rate at Week 12 for the treatment group was 75.6% (93/123), exceeding the targeted margin of 50% ($p < 0.0001$), while the treatment response rate in the control/delayed-treatment group was 8.8% (5/57). The difference between the response rates was statistically significant ($p < 0.0001$) showing superiority over the no treatment control.

Table 20 Responder rates based on MJAS at Week 12

Responder Rates		Difference in responder rates	95% CI	P – Value
Treatment	Control			
75.6% (93/123)	8.8% (5/57)	66.8%	[53.7%, 75.2%]	< 0.0001

*95% CI (53.7, 75.2)

Secondary Effectiveness Endpoints

In the treatment group, the mean (standard deviation; SD) Rasch-transformed scores on the FACE-Q Satisfaction with Lower Face and Jawline increased from 21.5 (18.9) at baseline to 75.2 (22.3) at Week 12. The mean (SD) change from baseline to Week 12 was 53.9 (25.7) and the respective 95% confidence interval (CI) of [49.2, 58.7] excluded zero. Overall, the improvement in mean Rasch-transformed scores among treated subjects indicated that subjects were more satisfied with how prominent, sculpted, nice, and smooth their jaw looked and with the profile of their jawline.

All but one subject (115/116; 99.1%) in the treatment group showed improvement on the GAIS scores as determined by the treating investigator. More specifically, the treating investigator scored 31.9% (37/116) of subjects as “very much improved”, 44.0% (51/116) of subjects as “much improved”, and 23.3% of subjects as “improved”.

The majority of patient (109/116; 94.0%) in the treatment group self-reported some level of improvement on the GAIS. More specifically, subjects self-reported the following improvement scores: “very much improved” in 27.6% (32/116) of subjects, “much improved” in 32.8% (38/116) of subjects and “improved” in 33.6% (39/116) of subjects.

Other Effectiveness Results

Subject’s perceived age was evaluated using the FACE-Q patient-perceived age visual analogue scale. On average, subjects in the treatment group reported looking younger by 2.9 years at Week 12 when compared to baseline.

The proportion of subjects that retained treatment success as assessed live by blinded evaluators using the MJAS was investigated in those subjects who responded to treatment 12 weeks after initial injection. Based on observed cases, a total of 76/113 (67.3%) subjects retained treatment response 48 weeks after initial treatment and before a retreatment was offered (if applicable). The 113 subjects correspond to those subjects that had a response 12 weeks after treatment and that also had MJAS assessment data 48 weeks after treatment. These findings support the sustained effect of RADIESSE® (+) injectable implant treatment for up to 48 weeks when injected in the jawline.

Overall, treatment response rates for the RADIESSE® (+) group were comparable for needle (73.3%, 44/60) and cannula (77.8%, 49/63). Similar results were also observed when stratifying MJAS responder rates at Week 12 by Fitzpatrick skin type categories (I-III: 71.4%, 55/77 and IV-VI: 82.6%, 38/46) and gender (females: 77.5%, 79/102 and males: 66.7%, 14/21). This objective primary endpoint measure was further supported by multiple subject and investigator reported endpoints demonstrating aesthetic improvements post treatment.

Subgroup analyses

The following prespecified subgroup analyses were evaluated: injection instrument (cannula and needle; Table 21), gender (Table 22), Fitzpatrick skin type (FST; I-III and IV-VI; Table 23). Further analyses by age group (≤50 years and >50 years), race (White and Non-White), and ethnicity (Hispanic or Latino and Not Hispanic or Latino) were conducted.

Safety: No differences in safety were observed when stratifying TEAEs by the different subgroups. Overall, proportions of subjects experiencing at least one treatment related TEAEs were similar for all subgroups.

Results of the subgroup analysis by age, race or ethnicity did not raise questions about the safety in these subgroups. Subjects in both groups (treatment and control/delayed treatment) received treatment and safety data was analyzed for the whole population at study. See Tables 21, 22, and 23 below. Reporting rates for treatment related TEAEs were similar in the White subgroup (26.6%, 38/143) and in the Non-White subgroup (25.0%, 8/32). Regarding ethnicity, treatment related TEAEs rates were also similar in the Hispanic or Latino subgroup (30.0%, 9/30) and the Not Hispanic or Latino subgroup (25.5%, 37/145). As for age, reporting rates were similar if slightly higher in the >50 years age group (≤50 years: 17.9%, 7/39; >50 years: 28.7%, 39/136).

No clinically significant tolerability concerns, regarding the injection procedure, or safety concerns associated to RADIESSE® (+) injectable implant were identified for any of the subgroups analyzed.

Effectiveness: To evaluate the consistency of the primary effectiveness analysis, results across different subgroups (i.e., injection instrument, gender, FST, age, race and ethnicity) demonstrated that the results at Week 12 were consistent with the primary analysis. Overall, the primary endpoint results for those subjects who received treatment with RADIESSE® (+) were positive for all subgroups (see Tables 21, 22 and 23). MJAS responder rates for subjects in the treatment group were also positive when analyzed by age (≤50 years: 73.1%, 19/26; >50 years: 76.3%, 74/97), race (White: 76.7%, 79/103; Non-White: 70.0%, 14/20), and ethnicity (Hispanic or Latino: 81.8%, 18/22; Not Hispanic or Latino: 74.3%, 75/101). Results of the subgroup analyses did not raise questions about the effectiveness in these subgroups.

For all the above subgroups, the difference in responder rates favored the treatment with RADIESSE® (+) when compared to no treatment, with lower bounds of CIs for the difference in responder rates being greater than zero.

Consistent with the high MJAS responder rates, the FACE-Q Satisfaction with Lower Face and Jawline questionnaire and the treating investigator and subject GAIS scores assessments at Week 12 also showed overall aesthetic improvements after treatment with RADIESSE® (+) when stratifying results by injection instrument (cannula versus needle), FST categories, and gender.

Table 21 Effectiveness and Safety Results by Injection Instrument

Assessment	Group	Injection Instrument	
		Cannula	Needle
EFFECTIVENESS at Week 12			
MJAS Responder Rate, % (n/N)	Treatment	77.8% (49/63)	73.3% (44/60)
	Control	7.7% (2/26)	9.7% (3/31)
FACE-Q Satisfaction with Lower Face and Jawline, mean change from baseline (SD)	Treatment	54.3 (27.9)	53.5 (23.5)
	Control	-3.6 (11.5)	-0.4 (14.8)
Treating Investigator GAIS, any improvement, % (n/N)	Treatment	100.0% (59/59)	98.2% (56/57)
Subject GAIS, any improvement, % (n/N)	Treatment	93.2% (55/59)	94.7% (54/57)
SAFETY			
Subjects with at least one TEAE, % (n/N)	Total	47.1% (41/87)	37.5% (33/88)
TEAEs related to injection procedure or RADIESSE® (+), % (n/N)	Total	28.7% (25/87)	23.9% (21/88)
Subjects with at least one CTR after initial treatment, % (n/N)	Total	96.6% (84/87)	93.2% (82/88)

Table 22 Effectiveness and Safety Results by Gender

Assessment	Group	Gender	
		Male	Female
EFFECTIVENESS at Week 12			
MJAS Responder Rate, % (n/N)	Treatment	66.7% (14/21)	77.5% (79/102)
	Control	15.4% (2/13)	6.8% (3/44)
FACE-Q Satisfaction with Lower Face and Jawline, mean change from baseline (SD)	Treatment	55.3 (23.1)	53.6 (26.3)
	Control	-1.8 (17.3)	-2.0 (12.4)
Treating Investigator GAIS, any improvement, % (n/N)	Treatment	100.0% (19/19)	99.0% (96/97)
Subject GAIS, any improvement, % (n/N)	Treatment	100.0% (19/19)	92.8% (90/97)
SAFETY			
Subjects with at least one TEAE, % (n/N)	Total	48.4% (15/31)	41.0% (59/144)
TEAEs related to injection procedure or RADIESSE® (+), % (n/N)	Total	29.0% (9/31)	25.7% (37/144)
Subjects with at least one CTR after initial treatment, % (n/N)	Total	80.6% (25/31)	97.9% (141/144)

Table 23 Effectiveness and Safety Results by Fitzpatrick Skin Type

Assessment	Group	Fitzpatrick Skin Type Subgroup	
		I-III	IV-VI
EFFECTIVENESS at Week 12			
MJAS Responder Rate, % (n/N)	Treatment	71.4% (55/77)	82.6% (38/46)
	Control	6.3% (2/32)	12.0% (3/25)
FACE-Q Satisfaction with Lower Face and Jawline, mean change from baseline (SD)	Treatment	51.3 (26.3)	58.4 (24.2)
	Control	-2.9 (10.6)	-0.4 (16.9)
Treating Investigator GAIS, any improvement, % (n/N)	Treatment	98.6% (73/77)	100.0% (42/42)
Subject GAIS, any improvement, % (n/N)	Treatment	91.9% (68/77)	97.6% (41/46)
SAFETY			
Patients with at least one TEAE, % (n/N)	Total	43.1% (47/109)	40.9% (27/66)
TEAEs related to injection procedure or RADIESSE® (+), % (n/N)	Total	27.5% (30/109)	24.2% (16/66)
Patients with at least one CTR after initial treatment, % (n/N)	Total	95.4% (104/109)	93.9% (62/66)

OTHER SHORT TERM AND LONG TERM RADIOGRAPHIC EVALUATION – RADIESSE® (WITHOUT LIDOCAINE)

RADIESSE® (+) and RADIESSE® injectable implant contain calcium hydroxylapatite particles (25-45 microns) that are radiopaque. A radiographic study was conducted to assess the radiographic appearance of RADIESSE® injectable implant in patients with both short-term and long-term follow-up after injection for HIV-associated facial lipoatrophy and treatment of nasolabial folds. The radiographic assessment consisted of standard, plain radiography and CT scanning. X-rays and CT Scans were assessed by two blinded, licensed radiologists. The inclusion of these patients allowed assessment of patients immediately after initial injection, at least 12 months after initial injection, and patients with varying volumes implanted.

A total of 58 patients in three patients groups were enrolled into the study. RADIESSE® injectable implant was determined to be visualizable in the X-ray radiographs by both evaluators, but the X-ray readings were not conclusive for the presence of the implant, when in fact it was present. This may be due to the fact that the volume of RADIESSE® injectable implant in some patients was small and the sensitivity of X-ray imaging may not be sufficient to detect small volumes of implant. RADIESSE® injectable implant was more readily visualizable by CT scan when compared to X-ray, and the CT scan results were read more consistently between two evaluators. RADIESSE® injectable implant was easily seen when imaging was done soon after an injection and was also seen when imaging was done several months after injection (minimum of 12 months). As expected, the results of the CT scan provided a superior image capability as compared to X-ray when visualizing RADIESSE® injectable implant (without lidocaine).

POST MARKETING SURVEILLANCE

The following adverse events have been identified during post-approval use of RADIESSE® injectable implant. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to RADIESSE® injectable implant. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to RADIESSE®: infection, cellulitis, impetigo, loss of effect, product displacement/migration, allergic reaction, anaphylaxis, hives, rash, pruritus, urticaria, angioedema, inflammation, necrosis, granuloma, nodules, induration, erythema, skin discoloration, pustule, skin pallor, hair loss, paresthesia, ptosis, pain, headache, swelling, asymmetry, abscess, herpetic infection including herpes simplex and herpes zoster, hematoma, blanching, blistering, dizziness, festoons, flu-like symptoms, Guillain-Barre syndrome, tachypnea, ischemic reaction, lymphoid hyperplasia, nausea, pericarditis, scarring, sensitivity to cold, vascular occlusion/obstruction, vascular compromise, ocular ischemia, diplopia, visual impairment/blindness, facial muscle paralysis, Bell's palsy.

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.

The following interventions have been reported: antibiotics, anti-inflammatories, corticosteroids, anti-histamines, analgesics, massage, warm compress, excision, drainage, and surgery. This information does not constitute and is not intended to be medical advice, a recommendation on how to treat an adverse event or an exhaustive list of possible interventions. Physicians should evaluate each case on an individual basis, and independently determine, based on their professional experience, what treatment(s) are appropriate, if any, for their patients.

INDIVIDUALIZATION OF TREATMENT

Before treatment, the patient's suitability for the treatment and the patient's need for pain relief should be assessed. The outcome of treatment with RADIESSE® (+) will vary between patients. In some instances, additional treatments may be necessary depending on the size of the defect and the needs of the patient.

DIRECTIONS FOR USE

A. GENERAL

The following is required for the percutaneous injection procedure:

- RADIESSE® (+) syringe(s)
- 25 gauge OD - 27 gauge ID needle(s) with Luer lock fittings OR
- 27g x 40mm Straight Dermal Cannula with 25g Pre-Hole Needle with Luer lock fittings [for jawline only]

1. Remove foil pouch from the carton. Open the foil pouch by tearing at the notches (marked 1 and 2) and remove the syringe from the foil pouch. *There is a small amount of moisture normally present inside the foil pouch for sterilization purposes; this is **not** an indication of a defective product.* Visually inspect the syringes of RADIESSE® (+) and the injection needle(s) or cannula(s) for any damage, debris, bent needle/cannula, etc. prior to preparing the syringes.
2. Prepare the syringes of RADIESSE® (+) and the injection needle(s) or cannula(s) before the percutaneous injection. A new injection needle should be used for each syringe.
3. Peel or twist apart the needle or cannula packaging to expose the hub. For use of needles or cannulas other than those provided with this package, follow the directions provided by the manufacturer.
4. Remove the Luer syringe cap from the distal end of the syringe prior to attaching the needle or cannula. The syringe of RADIESSE® (+) can then be twisted onto the Luer lock fitting of the needle or cannula taking care not to contaminate the needle or cannula. Discard the package. **The needle or cannula must be tightened securely to the syringe and primed with RADIESSE® (+). Do not over-tighten as this may break the needle/cannula and/or dislodge the syringe. Be careful not to bend the needle or cannula.**
5. If excess implant is on the surface of the Luer lock fittings, it will need to be wiped clean with sterile gauze. Slowly push the syringe plunger until RADIESSE® (+) extrudes from the end of the needle/cannula. If leakage is noted at the Luer fitting, it may be necessary to tighten the needle/cannula, or to remove the needle/cannula and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle/cannula.
6. Prepare patient for percutaneous injection using standard methods. The treatment injection site should be marked and prepared with a suitable antiseptic.
7. Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing.
8. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:
    - ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines
    - identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection
    - conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits

9. Locate the initial site for the implant. Scar tissue and cartilage may be difficult or impossible to treat. Avoid if possible, passing through these tissue types when advancing the injection needle.
10. The amount injected will vary depending on the site and extent of the restoration or augmentation desired. RADIESSE® (+) should be injected in a subdermal location for NLF, and in a subdermal or supraperiosteal location for correction of jawline. Note: Use a 1:1 correction factor. No overcorrection is needed.
11. Use once and discard in accordance with local safety standards.
12. 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. Follow the most current expert guidelines from American Society for Dermatologic Surgery.

B. FOR TREATMENT OF NASOLABIAL FOLDS:

1. Insert needle with bevel down at approximately a 30° angle to the skin. Needle should slide under the dermis to the point you wish to begin the injection. This should be easily palpable with the non-dominant hand.
2. Advance the needle into the subdermis to the starting location. Carefully push the plunger of the RADIESSE® (+) syringe to start the injection and slowly inject the material in linear threads while withdrawing the needle. Continue placing additional lines of material until the desired level of correction is achieved.
3. Apply slow continuous even pressure to the syringe plunger to inject the material as you withdraw the needle. The material should be completely surrounded by soft tissue without leaving globular deposits. The injected area may be massaged as needed to achieve even distribution of the implant.
4. Note: If significant resistance is encountered when pushing the plunger, the injection needle/cannula may be moved slightly to allow easier placement of the material or it may be necessary to change the injection needle. Needle jams are more likely with use of needles/cannula smaller than 27 gauge ID.

C. FOR TREATMENT OF JAWLINE:

1. When using a needle, directly insert into the desired injection region. When using a cannula, a skin puncture should be made at the desired injection point(s) using the pre-hole needle. The cannula will be inserted through the established skin puncture.
2. Advance the needle or cannula down to the desired depth. Carefully push the plunger of the RADIESSE® (+) syringe to start the injection and place the product using small aliquots. Linear-threading/tunneling, fanning, serial puncture or a combination of these techniques can be used to achieve optimal results. Continue placing additional lines of material until the desired level of correction is achieved. Care must be used to avoid intravascular injection regardless of technique used.
3. Apply slow continuous even pressure to the syringe plunger to inject the material. The material should be completely surrounded by soft tissue without leaving globular deposits. The injected area may be massaged as needed to achieve even distribution of the implant and mold to contour of the jawline.
4. Note: If significant resistance is encountered when pushing the plunger, the injection needle/cannula may be moved slightly to allow easier placement of the material or it may be necessary to change the injection needle. Be careful not to bend the needle or cannula. Needle jams are more likely with use of needles/cannula smaller than 27 gauge ID.

PATIENT COUNSELING INFORMATION

Refer to the RADIESSE® (+) Patient Information Guide.

STORAGE

RADIESSE® (+) should be stored at a controlled room temperature between 15°C and 32°C (59°F and 90°F). The expiration date, when stored in these temperatures, is two years from date of manufacture. Do not use if the expiration date has been exceeded.

DISPOSAL

Used and partially used syringes and injection needles could be biohazardous and should be handled and disposed of in accordance with facility medical practices and local, state or federal regulations.

WARRANTY

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