RADIESSE®

INJECTABLE IMPLANT

INSTRUCTIONS FOR USE

℞ ONLY

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1 DEVICE DESCRIPTION

RADIESSE® injectable implant is a sterile, non-pyrogenic, semi-solid, cohesive implant, whose principal component is synthetic calcium hydroxylapatite suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. RADIESSE® injectable implant (1.5 mL) has a CaHA particle size range of 25–45 microns. When used in the face per the indications noted below, it should be injected with a 25-gauge Outer Diameter (O.D.) to 27-gauge Inner Diameter (I.D.) needle. When used for the correction of wrinkles in the décolleté, RADIESSE® should be diluted in a 1:2 ratio with 0.9% sterile saline solution and injected with a 22-gauge flexible cannula.

2 INTENDED USE / INDICATIONS

RADIESSE® injectable implant is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds and it is also intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus. See the associated directions for use beginning on page 42.

RADIESSE® injectable implant diluted 1:2 with 0.9% sterile saline solution is indicated for subdermal implantation for the correction of décolleté wrinkles in patients 22 years of age and older. See the associated directions for use beginning on page 45.

RADIESSE® injectable implant is also indicated for hand augmentation to correct volume loss in the dorsum of the hands. For information concerning the use of the device in the hands, please see the separate dedicated Instructions for Use (IFU) specific to this indication.

3 CONTRAINDICATIONS

- Contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Not to be used in patients with known hypersensitivity to any of the components.
- RADIESSE® injectable implant is contraindicated for patients with bleeding disorders.

4 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. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Use of RADIESSE® injectable implant 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.
- Injection procedure reactions have been observed consisting mainly of short-term (i.e., < 7 days) bruising, redness and swelling. Refer to adverse events sections for details.
- Do not overcorrect (overfill) a contour deficiency because the depression should gradually improve within several weeks as the treatment effect of RADIESSE® injectable implant 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® injectable implant injected into the lips.
- The calcium hydroxylapatite (CaHA) particles of RADIESSE® injectable implant are radiopaque and are clearly visible on CT Scans and may be visible in standard, plain radiography. Patients need to be informed of the radiopaque 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 who received treatments with

RADIESSE® for HIV-associated facial lipoatrophy and nasolabial folds, there was no indication of RADIESSE® potentially masking abnormal tissues or being interpreted as tumors in CT Scans. In a separate study assessing mammography, breast ultrasounds, and breast imaging reports for 75 patients injected with diluted RADIESSE® in the décolleté, there was no evidence of diluted RADIESSE® visualized in the breast in any of the images or reports. There were no instances of interference of diluted RADIESSE® with mammograms or breast ultrasound images when injected in the décolleté. However, imaging studies focused on the sternum or defined injection area itself have not been performed. As such, it is unknown if RADIESSE® injected into décolleté is visible on diagnostic imaging of the décolleté such as ultrasound, MRI, CT scans or standard plain radiography. Outside of the breast imaging (mammography, breast ultrasound) data covered by the study discussed above, it is presently unknown if RADIESSE® injected into the décolleté interferes with imaging studies for cancer surveillance in the décolleté area. Patients need to be informed of the potential imaging interference of RADIESSE® injectable implant, so that they can inform their health care professionals as well as radiologists.

- Some injectable implants have been associated with hardening of the tissues at an injection site, migration of particles from an injection sites to other parts of the body and/or allergic or autoimmune reactions.
- Injection of diluted RADIESSE® in the décolleté should only be made subdermally and only within the defined treatment area as shown in **Figure 16**. Injections should not be made in an area overlying or including breast tissue.

5 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.
- For the use of RADIESSE® for the correction of wrinkles in the décolleté, completion of an indication-specific training program is required for all users. This program details the anatomy and vasculature of the décolleté, safe injection techniques, and identification and management of potential adverse events, including intravascular complications. Per FDA requirements, distribution of the product is limited to health care practitioners that have taken and successfully completed this indication-specific training program.
- In order to minimize the risks of potential complications, Healthcare practitioners should fully familiarize themselves with the product, the product educational materials and the entire package insert.
- Safety of RADIESSE® injectable implant in the décolleté for use during pregnancy, in breastfeeding females, or in patients under 22 years has not been established.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that the patients are aware of signs and symptoms of potential complications.
- As with all transcutaneous procedures, RADIESSE® injectable implant 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® injectable implant, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RADIESSE® injectable implant is administered before the skin has healed completely after such a procedure.
- Safety of RADIESSE® injectable implant beyond 3 years in the face and 84 weeks in the décolleté has not been investigated in clinical trials.
- The safety of RADIESSE® injectable implant in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied.

- The safety of RADIESSE® injectable implant 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® injectable implant into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- No studies of interactions of RADIESSE® injectable implant with drugs or other substances or implants have been conducted.
- Safety of RADIESSE® injectable implant in the décolleté of patients who have had cancer or previous radiation treatment near or on the area to be treated has not been established.
- Safety of RADIESSE® injectable implant in the décolleté of patients who have had breast cancer, a history of breast cancer, or a familial history of breast cancer has not been established.
- Safety of RADIESSE® injectable implant in patients who have systemic or localized autoimmune or granulomatous disease has not been established.
- Do not use where there is active disease such as tumors in or near the intended treatment site.
- 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 bruising, 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® injectable implant 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. 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, cannulas, and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.
- No injections of RADIESSE® Injectable Implant diluted 1:2 with 0.9% sterile saline should be made in the area overlying or including breast tissue. Special caution should be exercised when treating areas in close proximity to breast implants.
- Injection of more than 18 mL diluted 1:2 RADIESSE® Injectable Implant (6 mL of RADIESSE® and 12 mL of saline solution) cumulatively over a series of 4 injections has not been studied in clinical trials.

6 ADVERSE EVENT AND CLINICAL TRIAL INFORMATION

6.1 NASOLABIAL FOLDS

6.1.1 ADVERSE EVENTS

I. NASOLABIAL FOLDS PRE-MARKET CLINICAL TRIAL

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 **Table 1** and **Table 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 **Table 3** and **Table 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)
Pruritis	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)
Pruritis	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)
Pruritis	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)
Pruritis	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 MIXING RADIESSE® INJECTABLE IMPLANT WITH 2% LIDOCAINE HCl PRE-MARKET CLINICAL TRIAL

In a prospective, randomized split-face single-blind clinical study, 50 patients were injected with syringes of 1.3 mL of RADIESSE® injectable implant mixed with 0.2 mL of 2% lidocaine HCl (lidocaine) in one nasolabial fold (Treatment) and RADIESSE® injectable implant without the 2% lidocaine (Control) in the contralateral nasolabial fold at two investigational sites in the United States. The purpose of this study was to assess the effectiveness of RADIESSE® injectable implant mixed with 2% lidocaine for the reduction of pain during injection and the incidence of adverse events through the 1 month follow-up period.

The adverse events reported during this study were generally expected, mild in nature and short in duration and are detailed in the tables below. Adverse events were reported through patient diaries and by the principal investigators, with the majority of adverse events reported through the patient diaries. Adverse events are presented by time point and in total for the Treatment and Control groups. The majority of adverse events were reported in the ≤14 day time period. There was no statistical difference with respect to occurrence of patient diary reported adverse events between the 2 groups (see **Table 5**). There were 2 adverse events reported by the investigators (depression for one patient and redness for one patient in the Control nasolabial fold).

Table 5: ADVERSE EVENTS REPORTED IN PATIENT DIARIES

N = 50

ADVERSE EVENT TYPE	NUMBER OF ADVERSE EVENTS REPORTED						
	≤ 14 DAYS		> 14 DAYS		TOTAL		
	TREATMENT	CONTROL	TREATMENT	CONTROL	TREATMENT	CONTROL	p-value
Bruising	26	25	0	0	26	25	1.0000
Itching	11	12	2	4	13	16	0.1573
Pain	22	25	0	0	22	25	0.5271
Redness	29	32	0	0	29	32	0.4795
Swelling	47	44	0	0	47	44	0.4795
Other*	5	4	1	2	6	6	N/A

* "Other" adverse events for both Treatment & Control include bleeding, small bump, numbness, needle marks, nostril sensitivity & skin tightness.

III. NASOLABIAL FOLDS LONG-TERM SAFETY POST-APPROVAL STUDY

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.

IV. NASOLABIAL FOLDS FITZPATRICK SKIN TYPE IV-VI POST-APPROVAL STUDY

Adverse events reported in the short-term Fitzpatrick Skin Type IV-VI post-approval study are presented in **Table 6**.

Table 6: 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)

6.1.2 CLINICAL STUDIES

I. NASOLABIAL FOLD PRE-MARKET CLINICAL TRIAL

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 7** which shows that the study enrolled a population of predominantly female, Caucasian non-smokers.

Table 7: 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 8** below. The total mean volume for RADIESSE® injectable implant was 1.2 mL and 2.4 mL for the Control.

Table 8: 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 9 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 9: COMPARISON OF MEAN LRS SCORES* FOR RADIESSE® INJECTABLE IMPLANT AND CONTROL

Nasolabial Folds - Baseline, 3 and 6 Months

	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 MIXING RADIESSE® INJECTABLE IMPLANT WITH 2% LIDOCAINE HCl PRE-MARKET CLINICAL TRIAL

CAUTION: The clinical study that evaluated the mixing of 2% lidocaine and RADIESSE® injectable implant was conducted ONLY on nasolabial folds. The safety and effectiveness for the mixing of 2% lidocaine and RADIESSE® injectable implant for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus has not been studied.

In a prospective, randomized split-face single-blind clinical study, 50 patients were injected with syringes of 1.3 mL of RADIESSE® injectable implant mixed with 0.2 mL of 2% lidocaine HCl (lidocaine) in one nasolabial fold (Treatment) and RADIESSE® injectable implant without the 2% lidocaine (Control) in the contralateral nasolabial fold at two investigational sites in the United States. The purpose of this study was to assess the effectiveness of RADIESSE® injectable implant mixed with 2% lidocaine for the reduction of pain during injection and the incidence of adverse events through the 1 month follow-up period.

Study Endpoints

The two primary effectiveness endpoints of the study were to evaluate if a statistically significant reduction in pain existed in the Treatment nasolabial fold when compared to the Control nasolabial fold immediately after treatment using a validated visual analog scale (VAS) and to assess whether the observed differences in pain in the Treatment nasolabial fold when compared to the Control nasolabial fold were clinically meaningful immediately after treatment.

The secondary effectiveness endpoints assessed pain in the Treatment nasolabial fold when compared to the Control nasolabial fold at various times out to 1 month post treatment, aesthetic effectiveness out to one month after treatment and subject preference by analyzing the percent of patients favoring one treatment over the other.

Study Population

The inclusion criteria for the clinical study were that the patient was at least 18 years of age, was a candidate for nasolabial fold treatment using RADIESSE® injectable implant, understood and accepted the obligation not to receive any other facial procedures in the lower half of the face for 1 month, understood and accepted the obligation to present for all scheduled follow-up visits, was logistically able to meet all study requirements and had approximately symmetrical nasolabial folds.

The exclusion criteria for the clinical study were patients that had received any type of treatment or procedures including surgery in the nasolabial folds, had received neurotoxins in the lower half of the face in the past 6 months, had received hyaluronic acid, calcium hydroxylapatite (CaHA) or collagen injections in the lower half of the face within the past 1 ½ years, had received polylactic acid, PMMA, silicone or any other permanent filler injections in the lower half of the face, had nasolabial folds that were too severe to be corrected in one treatment session, had a history of chronic or recurrent infection or inflammation that would preclude participation in the study, had a known bleeding disorder or were receiving medication that would likely increase the risk of bleeding, was female and of child bearing potential and was pregnant or not using acceptable method of birth control, had any history of hypersensitivity to Lidocaine or anesthetics of the amide type, had a history of anaphylaxis or multiple severe allergies, or had received any investigational product within 30 days prior to study enrollment or is planning to participate in another investigation during the course of this study.

Study Results

The first primary effectiveness endpoint of the study was to assess pain using the Visual Analog Scale (VAS) in the Treatment fold compared to the Control fold. The mean VAS scores at time zero resulted in a statistically significant reduction in pain in the Treatment fold compared to the Control fold. The mean difference in VAS scores was -3.85 and a paired t-test resulted in a p-value of <0.0001 (see **Table 10**).

Table 10: VISUAL ANALOG SCALE (VAS) SCORE AT TIME ZERO

	TREATMENT	CONTROL
Mean	2.8	6.6
Median	2.5	7.0
St. Deviation	1.9	2.2
Minimum	0.0	2.0
Maximum	8.5	10.0
Mean Difference	3.85	
p-value	< 0.0001	

The second primary effectiveness endpoint of the study was to assess percentage of patients in which there was a clinically meaningful reduction in pain in the Treatment fold. Forty-five (45) of the 50 patients (90%) recorded VAS scores of at least 2.0cm lower for the Treatment fold compared to the Control fold, demonstrating a clinically meaningful reduction in pain (see **Table 11**).

Table 11: VAS SCORE ≥ 2.0cm LOWER IN TREATMENT VS. CONTROL

N = 50

N	%
45	90.0% C.I. 78.2%-96.7%
p < 0.0001	

A secondary effectiveness endpoint of the study was to assess pain in the Treatment fold compared to the Control fold at various times out to 1 month. The Treatment fold showed a statistically significant reduction in pain at four time points within the first hour ($p < 0.0001$) when compared to the Control fold. At 2 weeks and 1 month, there was no difference between the Treatment and Control folds as all pain ratings for both groups were 0 (no pain) (see **Table 12**).

Table 12: VAS SCORE AFTER TIME ZERO

N = 50

	15 MIN		30 MIN		45 MIN		60 MIN		2 WEEK		1 MONTH	
	TX	CON-TROL	TX	CON-TROL	TX	CON-TROL	TX	CON-TROL	TX	CON-TROL	TX	CON-TROL
Mean	0.9	3.4	0.7	2.5	0.5	1.8	0.3	1.3	0.0	0.0	0.0	0.0
Median	0.5	3.0	0.5	2.3	0.0	1.0	0.0	0.5	0.0	0.0	0.0	0.0
SD	1.0	2.2	1.0	2.1	0.8	1.8	0.7	1.6	0.0	0.0	0.0	0.0
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	4.0	8.0	5.0	7.5	3.5	6.5	3.0	6.0	0.0	0.0	0.0	0.0
p-value	< 0.0001		< 0.0001		< 0.0001		< 0.0001		N/A		N/A	

Another effectiveness endpoint assessed aesthetic improvement on the Global Aesthetic Improvement Scale (GAIS) at 2 weeks and 1 month post treatment. All patients in both groups were at least “Improved” (see **Table 13**).

Table 13: GAIS DISTRIBUTION

RATING	2 WEEKS N (%)		1 MONTH N (%)	
	TREATMENT	CONTROL	TREATMENT	CONTROL
Very Much Improved	29 (58.0)	26 (52.0)	31 (62.0)	28 (56.0)
Much Improved	16 (32.0)	18 (36.0)	12 (24.0)	20 (40.0)
Improved	5 (10.0)	6 (12.0)	7 (14.0)	2 (4.0)
No Change	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TOTAL IMPROVED	50 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
p-value	1.0000		1.0000	

III. NASOLABIAL FOLDS LONG-TERM SAFETY POST-APPROVAL STUDY

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 14**.

Table 14: 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® 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® treatment during the same time period with only 11% of patients receiving RADIESSE® 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 RADIESSE® injectable implant following the correction of nasolabial folds beyond 3 years was not studied.

IV. NASOLABIAL FOLDS FITZPATRICK SKIN TYPE IV-VI POST-APPROVAL STUDY

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 4, 5, or 6, 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 4, 5 or 6 whose nasolabial folds were corrected with subdermal injections of RADIESSE® injectable implant.

Study Population

Patient demographics are provided in **Table 15**.

Table 15: 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	
4	**24 (24.0%)**
5	**35 (35.0%)**
6	**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, has Fitzpatrick Skin Type IV, V, or VI, and understands and accepts 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 has history of hyper- or hypo-pigmentation in the nasolabial folds, keloid formation, or hypertrophic scarring, has a known bleeding disorder or is receiving drug therapy that could increase the risk of bleeding, has nasolabial folds that are too severe to be corrected in one treatment session, has 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® 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. 100 patients were 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 (2) 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 (2) 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 4, 5 and 6 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.

6.2 HIV-ASSOCIATED FACIAL LIPOATROPHY

6.2.1 ADVERSE EVENTS

I. HIV-ASSOCIATED FACIAL LIPOATROPHY PRE-MARKET CLINICAL TRIAL

In a 12-month prospective, open label study of 100 patients at three U.S. sites, adverse events reported after RADIESSE® injectable implant treatments are presented below. Adverse events reported in patient diaries during the 14 days after treatment are listed in **Table 16** and **Table 17**. Physician reported adverse events (those reported by Investigators and patients any time outside the 2 week diaries) are presented in **Table 18** and **Table 19**.

Table 16: PATIENT DIARY ADVERSE EVENTS

Reported Through Patient Diaries

Maximum Severity By Adverse Event Type N = 100

ADVERSE EVENT TYPE	PATIENTS REPORTING SYMPTOMS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Ecchymosis	64	34 (53.1)	25 (39.1)	5 (7.8)
Edema	99	46 (46.5)	49 (49.5)	4 (4.0)
Erythema	55	32 (58.2)	23 (41.8)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)
Pain	37	24 (64.9)	13 (35.1)	0 (0.0)
Pruritis	21	18 (85.7)	3 (14.3)	0 (0.0)
Contour Irregularity	11	8 (72.7)	3 (27.3)	0 (0.0)
Discoloration	5	2 (40.0)	3 (60.0)	0 (0.0)
Hardness	4	2 (50.0)	2 (50.0)	0 (0.0)
Headache	3	1 (33.3)	2 (66.7)	0 (0.0)
Lump	12	8 (66.7)	4 (33.3)	0 (0.0)
*** Other - Miscellaneous**	13	9 (69.2)	4 (30.8)	0 (0.0)
Numbness	4	4 (100)	0 (0.0)	0 (0.0)
Scab	2	1 (50.0)	1 (50.0)	0 (0.0)
Soreness	3	2 (66.7)	1 (33.3)	0 (0.0)
Tenderness	3	3 (100)	0 (0.0)	0 (0.0)
Tightness	2	1 (50.0)	0 (0.0)	1 (50.0)

* 13 patients with the following event types: flushed, bloodshot eyes, fever, black eye, ear running, backed up salivary gland, spot, nerve sensitivity, dry, sinus infection, burning sensation, warm cheeks, felt stretched, rash.

Table 17: PATIENT DIARY ADVERSE EVENTS

Reported Through Patient Diaries

Duration By Adverse Event Type N = 100

ADVERSE EVENT TYPE	TOTAL REPORTING SYMPTOMS	NUMBER OF DAYS			
		1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	142	29 (20.4)	51 (35.9)	50 (35.2)	12 (8.5)
Edema	431	206 (47.8)	153 (35.5)	52 (12.1)	20 (4.6)
Erythema	210	114 (54.3)	69 (32.9)	22 (10.5)	5 (2.4)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	110	54 (49.1)	32 (29.1)	18 (16.4)	6 (5.5)
Pruritis	54	28 (51.9)	9 (16.7)	6 (11.1)	11 (20.4)
Contour Irregularity	30	4 (13.3)	1 (3.3)	5 (16.7)	20 (66.7)
Discoloration	6	2 (33.3)	0 (0.0)	2 (33.3)	2 (33.3)
Hardness	8	2 (25.0)	1 (12.5)	2 (25.0)	3 (37.5)
Headache	3	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)
Lump	18	6 (33.3)	2 (11.1)	4 (22.2)	6 (33.3)
*** Other - Miscellaneous**	18	9 (50.0)	4 (22.2)	2 (11.1)	3 (16.7)
Numbness	7	7 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Scab	4	1 (25.0)	2 (50.0)	1 (25.0)	0 (0.0)
Soreness	6	3 (50.0)	3 (50.0)	0 (0.0)	0 (0.0)
Tenderness	8	3 (37.5)	5 (62.5)	0 (0.0)	0 (0.0)
Tightness	4	1 (25.0)	1 (25.0)	2 (50.0)	0 (0.0)

* 18 reports of the following event types: flushed, bloodshot eyes, fever, black eye, ear running, backed up salivary gland, spot, nerve sensitivity, dry, sinus infection, burning sensation, warm cheeks, felt stretched, rash.

Table 18: PHYSICIAN REPORTED ADVERSE EVENTS

Maximum Severity By Adverse Event Type N = 100

ADVERSE EVENT TYPE	PATIENTS REPORTING SYMPTOMS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Ecchymosis	3	2 (66.7)	1 (33.3)	0 (0.0)
Edema	7	7 (100)	0 (0.0)	0 (0.0)
Erythema	3	3 (100)	0 (0.0)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	0	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)
Pain	2	1 (50.0)	0 (0.0)	1 (50.0)
Pruritis	0	0 (0.0)	0 (0.0)	0 (0.0)
Contour Irregularity	19	15 (78.9)	4 (21.1)	0 (0.0)
Discoloration	3	3 (100)	0 (0.0)	0 (0.0)
Lump	2	1 (50.0)	1 (50.0)	0 (0.0)
*** Other - Miscellaneous**	5	2 (40.0)	3 (60.0)	0 (0.0)

* 5 patients with the following event types: puffiness, hearing loss, skin tag/lesion excision, firmness.

Table 19: PHYSICIAN REPORTED ADVERSE EVENTS

Duration By Adverse Event Type N = 100

ADVERSE EVENT TYPE	TOTAL REPORTING SYMPTOMS	NUMBER OF DAYS			
		1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	5	3 (60.0)	0 (0.0)	2 (40.0)	0 (0.0)
Edema	12	9 (75.0)	1 (8.3)	1 (8.3)	1 (8.3)
Erythema	4	1 (25.0)	2 (50.0)	0 (0.0)	1 (25.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	4	2 (50.0)	0 (0.0)	2 (50.0)	0 (0.0)
Pruritis	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Contour Irregularity	44	22 (50.0)	0 (0.0)	1 (2.3)	21 (47.7)
Discoloration	6	0 (0.0)	0 (0.0)	0 (0.0)	6 (100)
Lump	3	1 (33.3)	0 (0.0)	0 (0.0)	2 (66.7)
*** Other - Miscellaneous**	10	5 (50.0)	0 (0.0)	0 (0.0)	5 (50.0)

* 10 reports of the following event types: puffiness, hearing loss, skin tag/lesion excision, firmness

II. HIV-ASSOCIATED FACIAL LIPOATROPHY LONG-TERM SAFETY STUDY

Adverse events reported at 18 months are presented below. Adverse events reported in patient diaries during the 14 days after treatment are listed in **Table 20** and **Table 21**. Physician reported adverse events (those reported by Investigators and patients any time outside the 2 week diaries) are presented in **Table 22** and **Table 23**.

Table 20: PATIENT DIARY ADVERSE EVENTS - 18 MONTHS

Reported Through Patient Diaries

Maximum Severity By Adverse Event Type N = 100

ADVERSE EVENT TYPE	PATIENTS REPORTING SYMPTOMS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Ecchymosis	22	9 (40.9)	10 (45.5)	3 (13.6)
Edema	74	47 (63.5)	23 (31.1)	4 (5.4)
Erythema	40	25 (62.5)	14 (35.0)	1 (2.5)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)
Pain	23	12 (52.2)	11 (47.8)	0 (0.0)
Pruritis	7	7 (100)	0 (0.0)	0 (0.0)
Contour Irregularity	2	1 (50.0)	1 (50.0)	0 (0.0)
Numbness	1	0 (0.0)	1 (100)	0 (0.0)

Table 21: PATIENT DIARY ADVERSE EVENTS - 18 MONTHS

Reported Through Patient Diaries

Duration By Adverse Event Type N = 100

ADVERSE EVENT TYPE	TOTAL REPORTING SYMPTOMS	NUMBER OF DAYS			
		1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	34	11 (32.4)	13 (38.2)	6 (17.6)	4 (11.8)
Edema	144	54 (37.5)	74 (51.4)	12 (8.3)	4 (2.8)
Erythema	75	51 (68.0)	20 (26.7)	4 (5.3)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	42	18 (42.9)	20 (47.6)	3 (7.1)	1 (2.4)
Pruritis	13	11 (84.6)	0 (0.0)	2 (15.4)	0 (0.0)
Contour Irregularity	2	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)
Numbness	2	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)

Table 22: PHYSICIAN REPORTED ADVERSE EVENTS - 18 MONTHS

Maximum Severity By Adverse Event Type N = 100

ADVERSE EVENT TYPE	PATIENTS REPORTING SYMPTOMS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Ecchymosis	0	0 (0.0)	0 (0.0)	0 (0.0)
Edema	1	1 (100)	0 (0.0)	0 (0.0)
Erythema	0	0 (0.0)	0 (0.0)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	0	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)
Pain	0	0 (0.0)	0 (0.0)	0 (0.0)
Pruritis	0	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (0.0)	0 (0.0)	0 (0.0)

Table 23: PHYSICIAN REPORTED ADVERSE EVENTS - 18 MONTHS

Duration By Adverse Event Type N = 100

ADVERSE EVENT TYPE	TOTAL REPORTING SYMPTOMS	NUMBER OF DAYS			
		1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	1	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritis	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse events reported at 30 months are presented below. Adverse events reported in patient diaries during the 14 days after treatment are listed in **Table 24** and **Table 25**. Physician reported adverse events (those reported by Investigators and patients any time outside the 2 week diaries) are presented in **Table 26** and **Table 27**.

Table 24: PATIENT DIARY ADVERSE EVENTS - 30 MONTHS

Reported Through Patient Diaries
Maximum Severity By Adverse Event Type N = 100

ADVERSE EVENT TYPE	PATIENTS REPORTING SYMPTOMS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Ecchymosis	19	12 (63.2)	7 (36.8)	0 (0.0)
Edema	70	43 (61.4)	22 (31.4)	5 (7.1)
Erythema	24	18 (75.0)	5 (20.8)	1 (4.2)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)
Pain	19	11 (57.9)	8 (42.1)	0 (0.0)
Pruritis	3	3 (100)	0 (0.0)	0 (0.0)
Headache	1	1 (100)	0 (0.0)	0 (0.0)
Lump	1	1 (100)	0 (0.0)	0 (0.0)
*** Other - Miscellaneous**	4	3 (75.0)	1 (25.0)	0 (0.0)
Numbness	1	0 (0.0)	1 (100)	0 (0.0)
Soreness	1	1 (100)	0 (0.0)	0 (0.0)
Tightness	1	1 (100)	0 (0.0)	0 (0.0)

* 4 patients with the following event types: black eye, nausea, abrasion, pimple.

Table 25: PATIENT DIARY ADVERSE EVENTS - 30 MONTHS

Reported Through Patient Diaries

Duration By Adverse Event Type N = 100

ADVERSE EVENT TYPE	TOTAL REPORTING SYMPTOMS	NUMBER OF DAYS			
		1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	34	8 (23.5)	12 (35.3)	10 (29.4)	4 (11.8)
Edema	147	57 (38.8)	68 (46.3)	16 (10.9)	6 (4.1)
Erythema	49	26 (53.1)	18 (36.7)	3 (6.1)	2 (4.1)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	34	21 (61.8)	12 (35.3)	1 (2.9)	0 (0.0)
Pruritis	5	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)
Headache	2	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)
Lump	1	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)
*** Other - Miscellaneous**	5	0 (0.0)	3 (60.0)	1 (20.0)	1 (20.0)
Numbness	2	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)
Soreness	2	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)
Tightness	2	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)

* 5 reports of the following event types: black eye, nausea, abrasion, pimple.

Table 26: PHYSICIAN REPORTED ADVERSE EVENTS - 30 MONTHS

Maximum Severity By Adverse Event Type N = 100

ADVERSE EVENT TYPE	PATIENTS REPORTING SYMPTOMS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Ecchymosis	1	0 (0.0)	1 (100)	0 (0.0)
Edema	6	5 (83.3)	1 (16.7)	0 (0.0)
Erythema	0	0 (0.0)	0 (0.0)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	0	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)
Pain	0	0 (0.0)	0 (0.0)	0 (0.0)
Pruritis	0	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (0.0)	0 (0.0)	0 (0.0)

Table 27: PHYSICIAN REPORTED ADVERSE EVENTS - 30 MONTHS

Duration By Adverse Event Type N = 100

ADVERSE EVENT TYPE	TOTAL REPORTING SYMPTOMS	NUMBER OF DAYS			
		1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	2	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	12	7 (58.3)	4 (33.3)	1 (8.3)	0 (0.0)
Erythema	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritis	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

6.2.2 CLINICAL STUDIES

I. HIV-ASSOCIATED FACIAL LIPOATROPHY PRE-MARKET CLINICAL TRIAL

Study design

The safety and effectiveness of RADIESSE® injectable implant for the treatment of facial lipoatrophy was evaluated in a prospective, open-label, multi-center study of 100 patients with facial lipoatrophy with human immunodeficiency virus. Patients received an initial treatment (initial injection and an additional injection at 1 month as needed). Six months later, all patients were assessed for the need for a touch up injection. Effectiveness was assessed at 3, 6 and 12 months from initial treatment by means of a Global Aesthetic Improvement Scale (GAIS) rating, cheek skin thickness measurements, and patient satisfaction assessment. Safety was assessed by the recording of adverse events through 12 months.

Study Endpoints

The primary endpoint of the study was to evaluate the correction of lipoatrophy 3 months after treatment by comparing changes from baseline on the GAIS. The GAIS is a 5-category scale (Very much improved, much improved, improved, no change and worse). The secondary endpoints of the study were to evaluate the correction of facial lipoatrophy 6 months after treatment by comparing changes from baseline on the GAIS, and 3 and 6 months after treatment by comparing changes from baseline in cheek skin thickness measurements.

Study Population

The inclusion criteria for the clinical study were that the patient was to be HIV positive, had a CD4 count ≥ 250 /mm3 and viral load ≤ 5000 copies/mL, had been receiving HAART therapy for a minimum of 3 years, had HIV-associated facial lipoatrophy that was a grade 2, 3, or 4 on the Facial Lipoatrophy Severity Scale, was at least 18 years of age, signed a written informed consent, understood and accepted the obligation not to receive any other facial procedures or treatment affecting facial lipoatrophy through 12 month follow-up and understood and accepted the obligation and was logistically able to present for all scheduled follow-up visits.

The exclusion criteria for the clinical study were patients that had a known bleeding disorder (e.g., thrombocytopenia, thrombasthenia, or von Willebrand's disease), had received or was anticipated to receive antiplatelets, anticoagulants, thrombolytics, vitamin E, anti-inflammatories, interferon, or prednisone from 1 week pre- to 1 month post-injection, was receiving systemic or topical corticosteroids or anabolic steroids, had another medical condition that would preclude study participation or suggested an AIDS diagnosis (e.g., Kaposi sarcoma, recurrent infection, recurrent pneumonia), had received silicone injections, facial tissue augmentation other than collagen, grafting, or any other surgery in the cheek area, had received collagen in the cheek area within the past 6 months, had received over-the-counter wrinkle products (e.g., alpha-hydroxy acids) or prescription treatments (e.g., Renova, Retin-A, microdermabrasion, chemical peels) within 4 weeks prior to study or intended to receive these products and/or treatments during the study, had facial hair that would preclude ability to assess facial lipoatrophy, had a history of keloid formation, was pregnant or lactating or not using a reliable form of birth control, if female of child bearing potential and was enrolled in an interfering study.

Study Results

Demographics / Injection Information:

The study enrolled a population of predominantly multi-ethnic, non-smoking males (94% male) with a mean age of 48 years. Forty-four (44) percent of patients were Black, Hispanic or Asian. Fifty-six (56) percent were Caucasian. Fifty-one (51) percent of patients had a Fitzpatrick Skin score of IV, V or VI. All treatments were performed with a 25 gauge, 1½ inch needle. Mean initial treatment volumes were 4.8 mL for the initial treatment and 1.8 mL at 1 month if necessary (85% of patients were treated at 1 month). At 6 months, the mean touch up volume was 2.4 mL (89% of patients). Four (4) percent of patients received only one treatment, 18% of patients received a total of two treatments and 78% of patients received a total of three treatments. No patient received more than three treatments.

Effectiveness Results:

A live GAIS rating was determined at 3, 6 and 12 months (see **Table 28**).

Table 28: GAIS RATINGS

% OF PATIENTS	3 MONTH N = 100	6 MONTH N = 98	12 MONTHS N = 98
Very Much Improved	26%	7%	31%
Much Improved	72%	86%	53%
Improved	2%	7%	16%
No Change	0%	0%	0%
Worse	0%	0%	0%
TOTAL	100%	100%	100%

Cheek thickness measurements of patients left and right cheeks were performed at baseline, 3, 6 and 12 months (see **Table 29**).

Table 29: CHEEK THICKNESS MEASUREMENTS

	BASELINE	3 MONTH			6 MONTH			12 MONTH		
	Mean (N=100)	Mean (N=100)	Δ From Baseline	P-Value	Mean (N=97)	Δ From Baseline	P-Value	Mean (N=98)	Δ From Baseline	P-Value
Left Cheek	4.7 mm	7.3 mm	2.6 mm	<0.0001	7.1 mm	2.4 mm	<0.0001	6.9 mm	2.2 mm	<0.0001
Right Cheek	4.9 mm	8.0 mm	2.1 mm	<0.0001	7.5 mm	2.7 mm	<0.0001	7.3 mm	2.5 mm	<0.0001

Patients provided responses to a 5-question patient satisfaction questionnaire at 3, 6 and 12 months (see **Table 30**).

Table 30: PATIENT SATISFACTION ASSESSMENT

	3 MONTH N=100	6 MONTH N=98	12 MONTH N = 98
	YES	**YES**	**YES**
Would you recommend RADIESSE® treatment?	**99%**	**99%**	**99%**
Has the RADIESSE® treatment been beneficial to you?	**100%**	**100%**	**100%**
Do you feel more attractive since receiving RADIESSE® treatment?	**98%**	**98%**	**99%**
Is your emotional wellbeing better since receiving RADIESSE®?	**91%**	**96%**	**97%**
Do you have more confidence in your appearance since receiving RADIESSE®?	**98%**	**98%**	**99%**

II. DATA FOR HIV-ASSOCIATED FACIAL LIPOATROPHY LONG-TERM SAFETY STUDY

Study Objective

A post-approval study was performed to evaluate adverse events after repeat injections of RADIESSE® injectable implant for the treatment of facial lipoatrophy in patients with human immunodeficiency virus.

Study Design

The safety and effectiveness of RADIESSE® injectable implant for the treatment of facial lipoatrophy was evaluated in a premarket prospective, open-label, multi-center study of 100 patients with facial lipoatrophy with human immunodeficiency virus. As a condition of approval, a post-approval study was undertaken to provide long term data on the patients enrolled in the premarket study to evaluate any adverse events after repeat injections. Effectiveness was assessed as part of the post-approval study at 18 and 30 months from initial treatment by means of a Global Aesthetic Improvement Scale (GAIS) rating, cheek skin thickness measurements, and patient satisfaction assessment. Safety was assessed by the recording of adverse events through 30 months. Touch-up injections were performed as needed at 18 and 30 months. Therefore, the 18-month and 30-month effectiveness results are one year from last touch-up injection.

Study Endpoints

The primary endpoint of the post-approval study was to evaluate the correction of lipoatrophy 18 and 30 months after treatment by comparing changes from baseline on the GAIS. The GAIS is a 5-category scale (Very much improved, much improved, improved, no change and worse). The secondary endpoint of the post-approval study was to evaluate the correction of facial lipoatrophy 18 and 30 months after treatment by comparing changes from baseline in cheek skin thickness measurements.

Study Population

The patient cohort in this post approval study was the continued follow-up of the pre-market cohort. The inclusion criterion for the post-approval study was participation in the pre-market clinical study (Section I in HIV-Associated Facial Lipoatrophy CLINICAL STUDIES section) through 12 months, signed a written informed consent, understood and accepted the obligation not to receive any other facial procedures or treatment affecting facial lipoatrophy through 30 month follow-up and understood and accepted the obligation and was logistically able to present for 18 and 30 month follow-up visits.

The exclusion criteria for the clinical study were patients that had a known bleeding disorder (e.g., thrombocytopenia, thrombasthenia, or von Willebrand's disease), had received or was anticipated to receive antiplatelets, anticoagulants, thrombolytics, vitamin E, anti-inflammatories, interferon, or prednisone from 1 week pre- to 1 month post-injection, was receiving systemic or topical corticosteroids or anabolic steroids at any time through 30 month visit, had another medical condition that would preclude continued study participation or suggested an AIDS diagnosis (e.g., Kaposi sarcoma, recurrent infection, recurrent pneumonia), intended to receive over-the-counter wrinkle products (e.g., alpha-hydroxy acids) or prescription treatments (e.g., Renova, Retin-A, microdermabrasion, chemical peels) any time through 30 month visit, had a history of keloid formation, was pregnant or lactating or not using a reliable form of birth control, if female of child bearing potential.

Follow-up Assessments

Patients enrolled in the post-approval study returned for two (2) follow-up assessments after completion of the pre-market study. The first post-approval assessment was 540 ± 45 days from initial treatment if not treated at 1 month and 570 ± 45 days from initial treatment if treated at 1 month (18/19 month visit). The second post-approval assessment was 900 ± 45 days from initial treatment if not treated at 1 month and 930 ± 45 days from initial treatment if treated at 1 month (30/31 month visit). The assessment consisted of a live GAIS rating, facial photographs, skin thickness measurements, patient satisfaction assessment, recording of CD4 counts antiviral loads, recording of relevant medications, and an assessment for adverse events.

Study Results

The study enrolled a population of predominantly multi-ethnic, non-smoking males (94% male) with a mean age of 48 years (age range of 34 – 69). Forty-four (44) percent of patients were Black, Hispanic or Asian. Fifty-six (56) percent were Caucasian. Fifty-one (51) percent of patients had a Fitzpatrick Skin score of IV, V or VI. All treatments were performed with a 25 gauge, 1½ inch needle. At 18 months, 92% of patients received a mean touch-up volume of 4.4 mL. At 30 months, 90% of patients received a mean touch-up volume of 2.8 mL. Over the course of both the premarket and post-approval studies, two (2) percent of patients received only one treatment, 3% - two treatments, 5% - 3 treatments, 12% - 4 treatments, and 78% - 5 treatments. No patient received more than five treatments.

A live GAIS rating was determined at 18 and 30 months (see **Table 31**). The last pre-market study touch up injection was allowed at 6 months. Post-market study touch-up injections were allowed at 18 and 30 months. Therefore, the 18-month and 30-month response rates of 91.0% and 90.1%, respectively, are one year from last touch-up injection.

Table 31: GAIS RATINGS

RATING	18 MONTHS N = 94	30 MONTHS N = 91
Very Much Improved	9.6%	3.3%
Much Improved	43.6%	28.6%
Improved	38.3%	58.2%
No Change	8.5%	8.8%
Worse	0.0%	1.1%
TOTAL IMPROVED	91.0%	90.1%

Cheek thickness measurements of patients left and right cheeks were performed at 18 and 30 months and are one year from last touch up injection (see **Table 32**).

Table 32: CHEEK THICKNESS MEASUREMENTS

	MEAN						
	BASELINE N=100	**18 MONTHS** N = 93			**30 MONTHS** N = 91		
	mm	mm	Δ From Baseline	p-value	mm	Δ From Baseline	p-value
Left Side	4.7	6.2	1.45	<0.0001	6.8	2.1	<0.0001
Right Side	4.9	6.5	1.71	<0.0001	7.2	2.3	<0.0001

Patients provided responses to a 5-question patient satisfaction questionnaire at 18 and 30 months, one year from last touch up injection (see **Table 33**).

Table 33: PATIENT SATISFACTION ASSESSMENT

QUESTIONS	% ANSWERING "YES"	
	18 MONTHS N=94	**30 MONTHS** N=91
Would you recommend RADIESSE® treatment?	98.9%	100%
Has the RADIESSE® treatment been beneficial to you?	98.9%	100%
Do you feel more attractive since receiving RADIESSE® treatment?	97.9%	100%
Is your emotional wellbeing better since receiving RADIESSE®?	94.7%	95.6%
Do you have more confidence in your appearance since receiving RADIESSE®?	98.9%	100%

Study Limitations

RADIESSE® injectable implant was studied in a limited number of predominately male HIV positive patients. The safety of RADIESSE® injectable implant following treatment of HIV associated Lipoatrophy beyond 30 months was not studied.

6.3 DÉCOLLETÉ

6.3.1 ADVERSE EVENTS

A randomized, controlled, evaluator-blind, multicenter, clinical trial was carried out to evaluate the safety and effectiveness of RADIESSE® diluted 1:2 with sterile saline (1.5 mL RADIESSE®:3.0 mL sterile saline) for the correction of wrinkles in the décolleté. A total of 152 subjects were enrolled and randomized to treatment (n=116) or control (delayed treatment) (n=36). Subjects in the treatment group were scheduled to receive treatments Day 1, Week 6, and Week 12 with optional retreatment at Week 36, while those in the control/delayed treatment group were to receive treatment at Week 24, Week 30, and Week 36 with no option for an additional retreatment. Subjects in both groups were followed for 84 weeks.

All adverse events (AEs) reported by subjects, treating investigators, or other study staff after the time of informed consent through the end of study were recorded, regardless of causality. Treatment-emergent adverse events (TEAEs) were defined as AEs with onset or worsening at or after first administration of study treatment. TEAEs were determined by the treating investigator to be either treatment-related (related either to the injection procedure or diluted RADIESSE®) or non-treatment related. Common Treatment Responses (CTRs) were defined as common clinical presentations and/or side effects that a study subject could experience following treatment. Subjects self-reported CTRs via completion of a 28-day eDiary beginning on the day of each treatment. The treating investigator reviewed the eDiary and determined if any entries were beyond what would be typically expected following injection. A CTR which was more severe than what would generally be expected and/or did not resolve would be evaluated by the investigator as a possible AE. A CTR which had not resolved and was still ongoing upon eDiary completion was recorded as an AE by the investigator.

Among the 137 subjects treated in the study (treatment group and control/delayed treatment group subjects) 16 subjects (11.7%) reported a total of 31 treatment-related TEAEs in this study (see **Table 34** and **Table 35** below). All treatment related TEAEs were observed in the treatment group, with none recorded for the control/delayed treatment group. Most treatment-related TEAEs were mild and lasted < 52 days (duration: “> 1 day but ≤ 28 days” = 11 events; “> 28 days but ≤ 52 days” = 11 events; “> 52 days” = 9 events). None of the subjects had treatment-related TEAEs that were severe and all events resolved without sequelae. 12.4% (11/89) of subjects that received all 3 mandatory treatments and 27.8% (5/18) of subjects who did not receive all 3 mandatory treatments reported experiencing TEAEs related to investigational product and/or injection procedure. In this group, 16.7% (3/18) of subjects had TEAEs that lasted more than 28 days and 11.1% (2/18) had adverse events of moderate severity. These differences in safety reporting may be linked to the smaller relative size of the subgroup of subjects who did not receive all 3 mandatory treatments.

Table 34: TREATMENT-RELATED TEAEs

Number of Subjects and Maximum Severity, N=137

MedDRA Preferred Term	SUBECTS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Injection site bruising	7	7 (5.1)	0 (0.0)	0 (0.0)
Injection site discoloration	4	4 (2.9)	0 (0.0)	0 (0.0)
Injection site mass	3	2 (1.5)	1 (0.7)	0 (0.0)
Injection site pain	3	2 (1.5)	1 (0.7)	0 (0.0)
Injection site erythema	2	1 (0.7)	1 (0.7)	0 (0.0)
Injection site pruritus	2	2 (1.5)	0 (0.0)	0 (0.0)

MedDRA Preferred Term	SUBECTS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Injection site swelling	2	1 (0.7)	1 (0.7)	0 (0.0)
Capillary fragility	1	1 (0.7)	0 (0.0)	0 (0.0)
Injection site discomfort	1	1 (0.7)	0 (0.0)	0 (0.0)
Injection site injury	1	0 (0.0)	1 (0.7)	0 (0.0)
Pruritus	1	1 (0.7)	0 (0.0)	0 (0.0)

Table 35: TREATMENT-RELATED TEAEs

Number of Subjects and Maximum Duration, N=137

MedDRA Preferred Term	SUBECTS REPORTING SYMPTOMS	NUMBER OF DAYS				
		1-3 N (%)	4-7 N (%)	8-14 N (%)	15-28 N (%)	> 28 N (%)
Injection site bruising	7	0 (0.0)	0 (0.0)	3 (2.2)	2 (1.5)	2 (1.5)
Injection site discoloration	4	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	3 (2.2)
Injection site mass	3	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.5)
Injection site pain	3	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.5)
Injection site erythema	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)
Injection site pruritus	2	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)
Injection site swelling	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)
Capillary fragility	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Injection site discomfort	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Injection site injury	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Pruritus	1	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)

CTRs observed in the study after the initial treatment are outlined by severity and duration in **Table 36** and **Table 37** below. As noted, among the 135 subjects that completed eDiaries, 108/135 (80.0%) subjects reported experiencing at least one CTR after initial treatment (i.e., Day 1 for the treatment group or Week 24 for the delayed-treatment group). Overall, the majority of subjects reported CTRs that were mild to moderate and had a maximum duration of ≤ 14 days after initial treatment. CTRs reported in the study were in line with expectations for dermal filler injection procedures and the expected safety profile of RADIESSE® from a subject-reporting perspective. The overall incidence, severity, and duration of CTRs were comparable in all four diaries distributed (initial treatment, 6 weeks post initial injection (PII), 12 weeks PII, and optional retreatment), although incidences and severity tended to be lower after 6 weeks PII treatment, 12 weeks PII treatment, and retreatment when compared to those reported after initial treatment.

A total of 8 subjects were enrolled in the study with Fitzpatrick Skin Types V-VI (FST V: 7 subjects; FST VI 1 subject) and in this category, 1 subject had TEAEs reported. This subject experienced moderate treatment related injection site injury and mild injection site discoloration. Both events resolved. Among the 7 with FST V-VI that completed eDiaries after initial treatment,

5 subjects experienced at least one CTR. Three subjects completed eDiaries after 6 weeks PII treatment, 12 weeks PII treatment, and 2 subjects completed eDiaries after retreatment, all of which experienced at least one CTR.

Merz has previously conducted a post-approval study (PAS; see Subsection IV of **Section 6.1.2** above) to assess the safety of RADIESSE® following correction of the nasolabial folds in 100 subjects with FST IV, V, or VI, specifically to evaluate the likelihood of hypertrophic scarring, keloid formation and hyper- or hypopigmentation through 6 months from treatment with RADIESSE® injectable implant in the nasolabial folds. In this post-approval study, there were no reports of hypertrophic scarring, keloid formation, hyperpigmentation or hypopigmentation at the injection site. Overall, the evaluated data do not indicate a higher risk of hypertrophic/ hyperpigmented scarring related to injections or skin trauma after RADIESSE® treatment on subjects with higher FSTs neither from the pivotal study nor the post-approval study.

Note that Merz carried out a retrospective addendum study to demonstrate the safety of treatment with diluted RADIESSE® in the décolleté and its lack of interference in mammograms and/or breast ultrasound images collected after treatment. Participants who received treatment in the décolleté while in the pivotal study (with results described above) and completed the study were contacted for participation in this retrospective study. None of the 81 participants who enrolled in this retrospective study reported any new treatment related TEAEs.

Table 36: COMMON TREATMENT RESPONSES

After Initial Treatment, Reported Through Patient Diaries

Maximum Severity by Adverse Event Type N = 135

CTR TYPE	PATIENTS REPORTING SYMPTOMS	MILD N (%)	MODERATE N (%)	SEVERE N (%)
Redness	82	67 (49.6)	15 (11.1)	0 (0.0)
Bruising	80	66 (48.9)	14 (10.4)	0 (0.0)
Pain/Discomfort (including burning/stinging)	63	52 (38.5)	11 (8.1)	0 (0.0)
Lumps/bumps	42	41 (30.4)	1 (0.7)	0 (0.0)
Swelling	42	36 (26.7)	6 (4.4)	0 (0.0)
Discoloration	39	36 (26.7)	3 (2.2)	0 (0.0)
Itching	34	30 (22.2)	3 (2.2)	1 (0.7)

Table 37: COMMON TREATMENT RESPONSES

After Initial Treatment, Reported Through Patient Diaries

Maximum Duration By Adverse Event Type N = 135

CTR TYPE	PATIENTS REPORTING SYMPTOMS	NUMBER OF DAYS			
		1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Redness	82	46 (34.1)	26 (19.3)	9 (6.7)	1 (0.7)
Bruising	80	27 (20.0)	24 (17.8)	24 (17.8)	5 (3.7)
Pain/Discomfort (including burning/stinging)	63	43 (31.9)	13 (9.6)	5 (3.7)	2 (1.5)
Lumps/bumps	42	16 (11.9)	18 (13.3)	6 (4.4)	2 (1.5)
Swelling	42	19 (14.1)	15 (11.1)	6 (4.4)	2 (1.5)
Discoloration	39	17 (12.6)	11 (8.1)	7 (5.2)	4 (3.0)
Itching	34	26 (19.3)	3 (2.2)	3 (2.2)	2 (1.5)

Safety assessments such as visual acuity, confrontational visual field test, and ocular motility exams were evaluated at screening and throughout the study. Pulse oximetry and neurological exams were evaluated at each visit where treatment was administered. Nine subjects experienced a temporary and self-resolving greater than one line change in visual acuity. All visual acuity events were changes in values assessed at different visits, were reported as TEAEs not related to the investigational product or injection procedure and were not considered clinically significant by investigators. None of these visual acuity changes were related to intravascular injection. All other confrontational visual field test, ocular motility exams, pulse oximetry, and neurological exams were normal.

6.3.2 CLINICAL STUDIES

Study Design

An 84-week prospective, multicenter, randomized, evaluator-blind, parallel-group study was conducted to evaluate the safety and effectiveness of treatment with diluted RADIESSE® for correction of moderate to severe décolleté wrinkles. A total of 152 subjects were enrolled in the study across nine investigational sites in the United States. Each treatment consisted of subdermal injection via a flexible cannula of RADIESSE® diluted 1:2 with sterile saline (1.5 mL RADIESSE®:3.0 mL sterile saline) in the décolleté region defined in **Figure 16**. Details of dilution and injection components utilized in this study are listed in **Table 43**. Subjects in the study were randomized at a 3:1 ratio to treatment with diluted RADIESSE® or to untreated control followed by delayed treatment with diluted RADIESSE®. Those in the treatment group received treatment on Day 1, Week 6, and Week 12 with optional retreatment at Week 36, while those in the control/delayed treatment group received the same treatment at Week 24, Week 30, and Week 36 with no option for an additional retreatment.

This study utilized the following appropriately validated 5-points (0-4) Merz Aesthetic Scales (MAS) for Décolleté Wrinkles: At Rest (subjects with arms at rest alongside the body) and Dynamic (subjects positioned with each hand touching the opposite elbow with breasts leaning on the arms)[1].

All subjects eligible for enrollment were healthy females between the ages of 30 and 65 at the time of screening with a MAS Décolleté Wrinkles-At Rest score of 2 or 3 (moderate or severe), as assessed live by a blinded evaluator.

Study Endpoints

The primary effectiveness endpoint was the proportion of responders at Week 24 on the Merz Aesthetic Scale (MAS) Décolleté Wrinkles - At Rest, as assessed live by a blinded evaluator, where response was defined as at least 1 point improvement from baseline.

Secondary effectiveness endpoints assessed at Week 24 included the proportion of responders on the MAS Dynamic scale as assessed by a blinded evaluator, as well as the proportion of subjects with any improvement on the Global Aesthetic Improvement Scale (GAIS) as graded by treating investigators (iGAIS) and subjects themselves (sGAIS).

A secondary safety endpoint assessed the incidence of treatment emergent adverse events (TEAEs) related to treatment with diluted RADIESSE®, as reported by the treating investigator throughout the study. Adverse event data for the study is presented in **Section 6.3.1** above.

Study Population

A total of 152 subjects were enrolled in the study, with 116 randomized to the treatment group and 36 to the control / delayed treatment group. The safety evaluation set, which included all subjects who received treatment in the study, consisted of 137 subjects (90.1%).

Enrollment in the study was limited to patients who met the following inclusion criteria (this is an abbreviated list of inclusion criteria, as there were additional inclusion criteria considered):

- Female ≥ 30 and ≤ 65 years old at the time of screening.
- Subjects seeking improvement of décolleté wrinkles.
- Décolleté wrinkles with a rating of moderate to severe (grade 2 to 3) on the Merz Aesthetic Scales (MAS) Décolleté Wrinkles – At Rest, as determined live by a blinded evaluator.

Patients were not permitted to enroll in the study if they met any of the following key exclusion criteria (this is an abbreviated list of exclusion criteria, as there were additional exclusion criteria considered):

[1] Validated Assessment Scales for Décolleté Wrinkling and Pigmentation. Landau M, Geister TL, Leibou L, Blessmann-Gurk B, Gortelmeyer R, Frand J, et al. Dermatol Surg. 2016;42(7):842-52.

- Any previous surgery, including plastic surgery or permanent surgical implant in the treatment area.
- Previous treatment with collagen fillers, calcium hydroxylapatite, and/or long-lasting hyaluronic acid (HA) fillers in the décolleté within the previous 24 months, or with other HA fillers in the décolleté within the previous 12 months.
- Previous treatment with botulinum toxin, ablative or fractional laser, microdermabrasion, microneedling, chemical peels, and/or non-invasive skin tightening in the décolleté within the previous 6 months.

In the treatment group, the majority of subjects received all three scheduled treatments and the optional retreatment (65/107 subjects, 60.7%). In the delayed-treatment group, the majority of subjects received all three scheduled treatments (27/30 subjects, 90.0%; retreatment was not offered). Median injection volume was 4.50 mL for all treatment sessions.

Table 38: STUDY POPULATION

	Treatment (N=116)	Control/DT (N=36)	Total (N=152)
Sex (n (%))			
Female	116 (100.0)	36 (100.0)	152 (100.0)
Age [years]			
Mean (SD)	53.7 (7.05)	53.6 (8.08)	53.6 (7.28)
Age category I (n (%))			
≤ 54 years	62 (53.4)	17 (47.2)	79 (52.0)
> 54 years	54 (46.6)	19 (52.8)	73 (48.0)
Age category II (n (%))			
30-39 years	4 (3.4)	3 (8.3)	7 (4.6)
40-49 years	25 (21.6)	6 (16.7)	31 (20.4)
50-59 years	60 (51.7)	17 (47.2)	77 (50.7)
≥ 60 years	27 (23.3)	10 (27.8)	37 (24.3)
Ethnicity (n (%))			
Hispanic or Latino	18 (15.5)	7 (19.4)	25 (16.4)
Not Hispanic or Latino	98 (84.5)	29 (80.6)	127 (83.6)
Race (n (%))			
White	105 (90.5)	35 (97.2)	140 (92.1)
Asian	3 (2.6)	0 (0.0)	3 (2.0)
Black or African American	5 (4.3)	1 (2.8)	6 (3.9)
American Indian or Alaska Native	1 (0.9)	0 (0.0)	1 (0.7)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
More than one race	2 (1.7)	0 (0.0)	2 (1.3)
Fitzpatrick skin type category (n (%))			
I - III	85 (73.3)	31 (86.1)	116 (76.3)
IV - VI	31 (26.7)	5 (13.9)	36 (23.7)
Baseline MAS Décolleté Wrinkles At rest severity (n (%))[1]			
Moderate = 2	81 (69.8)	24 (66.7)	105 (69.1)
Severe = 3	35 (30.2)	12 (33.3)	47 (30.9)

DT = delayed treatment, Max = maximum, Min = minimum, N = total number of subjects in the corresponding treatment group, n = number of observations, SD = standard deviation
More than one response was allowed for race.
[1]As assessed for all subjects at screening, as part of the study inclusion criteria.
Percentages based on total number of subjects in intent to treat set; subjects analyzed as randomized.

Primary Effectiveness Evaluation

Treatment with diluted RADIESSE® provided a clinically and statistically significant improvement in the correction of décolleté wrinkles compared to the control / delayed treatment group. As summarized in **Table 39** below for the intent-to-treat population and using multiple imputation, the treatment response rate at Week 24 for the treatment group (n = 116) was 71.2% [95% CI: 61.4%, 79.4%], while that of the control group (n = 36) was 6.3% [95% CI: 1.5%, 22.9%]. The difference in estimated response rates between groups was 65.0% [95% CI: 45.6%, 74.4%], demonstrating a statistically significant, superior response rate in treated subjects compared to untreated controls.

Table 39: PRIMARY EFFECTIVENESS EVALUATION

	Treatment (N=116)	Control (N=36)
Number of subjects with imputed data (missing values)	21	5
Responder rate, n (%)[1]	83 (71.2)	2 (6.3)
95% CI[2]	[61.4, 79.4]	[1.5, 22.9]
Treatment – Control difference (%)	65.0	
95% CI[2]	[45.6, 74.4]	

CI = confidence interval, N = total number of subjects in the corresponding treatment group, n = number of observations
[1]Average number of responders (n) and average responder rate (%) over all imputations
[2]Hierarchical-testing procedure: A responder rate of ≥ 50% for treated subjects was demonstrated if the lower limit of the two-sided 95% Wilson CI for the treatment group was > 50%. Only then was a confirmatory comparison of treatment versus control performed. Superiority was concluded if the lower limit of the two-sided 95% Newcombe CI for the responder rate difference was > 0%.

The majority of treatment group subjects maintained a clinically significant improvement in skin in the correction of décolleté wrinkles (≥ 1-point improvement from baseline on the MAS Décolleté Wrinkles-At Rest) through 60 weeks post initial injection (**Table 40**).

Table 40: EFFECTIVENESS EVALUATION THROUGH 60 WEEKS

Treatment Group MAS Décolleté Wrinkles – At Rest Responder Rates on Observed Cases

	Treatment n/N (%)
24 weeks post initial injection (PII)	69/95 (72.6)
36 weeks PII	60/91 (65.9)
48 weeks PII	63/86 (73.3)
60 weeks PII	54/89 (60.7)
N = number of subjects with observed data	

Several subgroup analyses for the primary effectiveness evaluation were carried out. With respect to Fitzpatrick Skin Type (FST), 48/68 (70.6%, [58.9%, 80.1%]) subjects with FST I – III and 21/27 (77.8%, [59.2%, 89.4%]) subjects with FST IV – VI were responders on the MAS Décolleté Wrinkles-At Rest. For subjects with FST V – VI specifically, 5/6 (83.3%) subjects were responders at Week 24 (treatment group, observed cases). Comparable results were observed when stratifying MAS Décolleté Wrinkles-At Rest responder rates at Week 24 by baseline severity, median age, age group, investigational site, ethnicity, and race with responder rates favoring treatment with diluted RADIESSE® when compared to no treatment.

Secondary Effectiveness Evaluations

Analysis of the MAS Décolleté Wrinkles-Dynamic responder rate and the GAIS scores further supported the primary endpoint finding that treatment with diluted RADIESSE® resulted in overall aesthetic improvement of the décolleté at Week 24.

The estimated average MAS Décolleté Wrinkles-Dynamic responder rate at Week 24 was 65.8% [95% CI: 55.9%, 74.5%] among the treatment group (n=116). In the control group (n=36), the estimated average responder rate was 16.0% [95% CI: 6.8%, 33.1%].

In the Intent-to-Treat (ITT) population, 92.6% (88/95; observed cases) of subjects in the treatment group showed some level of improvement according to the iGAIS score.

Similarly, the majority of subjects (83/95, 87.4%; observed cases) in the treatment group self-reported some level of improvement on the sGAIS.

For subjects in the FST V – VI category, 4/6 (66.7%) were responders on the MAS Décolleté Wrinkles-Dynamic scale,6/6 (100%) showed some level of improvement according to the iGAIS score, and 5/6 (83.3%) self-reported some level of improvement on the sGAIS at Week 24 (treatment group, observed cases).

Breast Imaging Safety Evaluation

Following the conclusion of the pivotal trial described above, Merz conducted a retrospective addendum study on the same population to demonstrate the safety of treatment with diluted RADIESSE® in the décolleté and its lack of interference in mammograms and/or breast ultrasound images collected after treatment. The defined treatment area for diluted RADIESSE® injection in the décolleté does not overly breast tissue (see Injection Procedure Instructions, **Figure 16**); this retrospective study was initiated as a precautionary measure to provide further assurance of device safety.

Participants who received treatment in the décolleté while in the pivotal study and completed the study were invited to participate in this retrospective study. Participants were contacted approximately 17-22 months after completing their participation in the pivotal study. A total of 81 participants provided informed consent for obtaining their medical records pertaining to mammograms and/or breast ultrasound images or reports taken before and after receiving treatment with diluted RADIESSE® in the décolleté. Of those who consented, a total of 71 participants provided at least one post-treatment mammography and/or breast ultrasound image and 4 participants provided at least one post-treatment mammography and/or breast ultrasound report (as the corresponding breast images could not be obtained). Available post-treatment images were taken as early as 3 days after first treatment with diluted RADIESSE® and up to 960 days after receiving optional retreatment.

All breast images and reports were evaluated by an Adjudication Committee, composed of two board-certified radiologists with a subspeciality in breast and body imaging and with at least five years of postgraduate training. The Adjudication Committee evaluated the breast images for any potential image interference after treatment of the décolleté with diluted RADIESSE®. When asked if the product is visible on the assessed images, evaluators answered “No” for 100.0% of the breast images and reports (71/71 participants). Additionally, for 4 participants, the Adjudication Committee evaluated mammography and/or breast ultrasound report. When asked if foreign material was reported as present in these reports, evaluators answered “No” for 100.0% of the reports (4/4 participants).

In summary, no product was observed in any of the assessed participant post treatment mammograms or breast ultrasounds and no foreign material was reported as present in any of the evaluated breast imaging reports. There were no instances of any interference of diluted RADIESSE® on mammogram or breast ultrasound images collected after treatment with diluted RADIESSE® in décolleté.

6.4 OTHER

6.4.1 SHORT TERM AND LONG TERM RADIOGRAPHIC EVALUATION

Facial Lipoatrophy and Facial Wrinkles and Folds

RADIESSE® injectable implant contains calcium hydroxylapatite particles (25-45 microns) that are radiopaque and suspended in a water based gel. Therefore, 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 for the CT Scan provided a superior image capability as compared to X-ray when visualizing RADIESSE® injectable implant.

Hands

A post-approval study was performed to provide an assessment of the radiographic appearance of RADIESSE® material that was injected into the dorsum of the hands with standard, plain radiography (X-rays). A total of 20 subjects (40 hands; all women) were enrolled and received treatment with RADIESSE® into the dorsum of the hands. Subjects were eligible for up to 3 retreatments over the 24-month study interval. Initial hands X-rays showed no foreign material in all subjects prior to RADIESSE® injection. Foreign material was present in all hands (100%) on Month 1 X-rays. At Month 6, foreign material was present in 85% of left hands and in 80% of right hands on the lateral view and in 85% of left hands and in 90% of right hands on the AP view. Among subjects who received all 4 available treatments, foreign material was present in 83.3% of hands at Month 24. Importantly, no obscuration of the bones was reported in either hand (left or right) for either view (anteroposterior or lateral view) at any evaluated time point.

Décolleté

As described in Section 6.3.2 above, a retrospective study was carried out to demonstrate the safety of treatment with diluted RADIESSE® in the décolleté and the potential risk of interference in mammograms and/or breast ultrasound images collected after treatment. As noted therein, in this study, available post-treatment images were taken as early as 3 days after first treatment with diluted RADIESSE® and up to 960 days after receiving a final, optional retreatment. No product was observed in any of the assessed participant post treatment mammograms or breast ultrasounds (71/71 participants) and no foreign material was reported as present in any of the evaluated breast imaging reports (4/4 participants). There were no instances of any interference of diluted RADIESSE® on mammogram or breast ultrasound images collected after treatment with diluted RADIESSE® in décolleté.

6.4.2 POST MARKETING SURVEILLANCE

The following adverse events have been identified during post-approval use of RADIESSE®. 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®. 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.

6.4.3 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® injectable implant 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.

7 DIRECTIONS FOR USE

The following subsections provide the procedural directions for use for the below approved indications associated with RADIESSE®.

Table 41: DIRECTIONS FOR USE SECTION

Section	Indication	Starting Page #
7.1	DIRECTIONS FOR USE: FACIAL WRINKLES AND FOLDS, SUCH AS NASOLABIAL FOLDS AND/OR SIGNS OF FACIAL FAT LOSS (LIPOATROPHY) IN PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS)	42
7.2	DIRECTIONS FOR USE: DÉCOLLETÉ	45

7.1 DIRECTIONS FOR USE: FACIAL WRINKLES AND FOLDS, SUCH AS NASOLABIAL FOLDS AND/OR SIGNS OF FACIAL FAT LOSS (LIPOATROPHY) IN PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS)

General

The following is required for the percutaneous injection procedure:

- RADIESSE® injectable implant syringe(s)
- 25 gauge OD - 27 gauge ID needle(s) with Luer lock fittings

1. Prepare patient for percutaneous injection using standard methods. The treatment injection site should be marked and prepared with a suitable antiseptic. Local or topical anesthesia at the injection site should be used at the discretion of the physician.
2. Prepare the syringes of RADIESSE® injectable implant and the injection needle(s) before the percutaneous injection. A new injection needle may be used for each syringe, or the same injection needle may be connected to each new syringe.
3. 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.*
4. Peel or twist apart the needle packaging to expose the hub. For use of needles other than the needle(s) provided with this package, follow the directions provided with the needle(s).
5. Remove the Luer syringe cap from the distal end of the syringe prior to attaching the needle. The syringe of RADIESSE® injectable implant can then be twisted onto the Luer lock fitting of the needle taking care not to contaminate the needle. Discard needle package. **The needle must be tightened securely to the syringe and primed with RADIESSE® injectable implant.** 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® injectable implant extrudes from the end of the needle. If leakage is noted at the Luer fitting, it may be necessary to tighten the needle, or to remove the needle and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle.
6. 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.
7. The amount injected will vary depending on the site and extent of the restoration or augmentation desired. RADIESSE® injectable implant should be injected subdermally.
8. Use a 1:1 correction factor. No overcorrection is needed.
9. 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.
10. If significant resistance is encountered when pushing the plunger, the injection needle may be moved slightly to allow easier placement of the material or it may be necessary to change the injection needle. One needle jam occurred in the nasolabial fold clinical study. Needle jams are more likely with use of needles smaller than 27gauge ID.
11. Advance the needle into the subdermis to the starting location. Carefully push the plunger of the RADIESSE® injectable implant syringe to start the injection and slowly inject the implant material in linear threads while withdrawing the needle. Continue placing additional lines of material until the desired level of correction is achieved.

12. Apply slow continuous even pressure to the syringe plunger to inject the implant as you withdraw the needle. The implant 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.

13. Use once and discard in accordance with local safety standards.

Technique for Mixing RADIESSE® injectable implant and 2% Lidocaine HCl

CAUTION: Do not use the RADIESSE® injectable implant and 2% lidocaine mixture later than 2 hours after mixing.

CAUTION: The assembled components are intended for one-time use only.

Within the clinical study, the following components were used:

- Sterile 27 gauge, 0.5" regular-wall needle with Luer lock connector (not supplied by Merz North America, Inc.).
- 3.0 mL sterile polypropylene luer-lock syringe (BD 309585)
- 0.2 mL of Hospira, Inc. (NDC 0409-4277-02) 2% lidocaine HCl for injection, USP solution (not supplied by Merz North America, Inc.)
- Sterile Female-to-female luer lock connector (Braun FDC1000 or Baxa 13901)
- 1.3 mL syringe of RADIESSE® injectable implant

The 3.0 mL sterile polypropylene mixing syringe (BD 309585) and the female-to-female luer lock connector (Baxa 13901) are separately available in the Merz North America Accessory Kit. Neither the lidocaine nor the sterile 27 gauge, 0.5" needle are supplied by Merz North America, Inc.

Component Assembly and Mixing Instructions

1. Assemble the components and perform the mixing using sterile technique (see **Figure 1**).

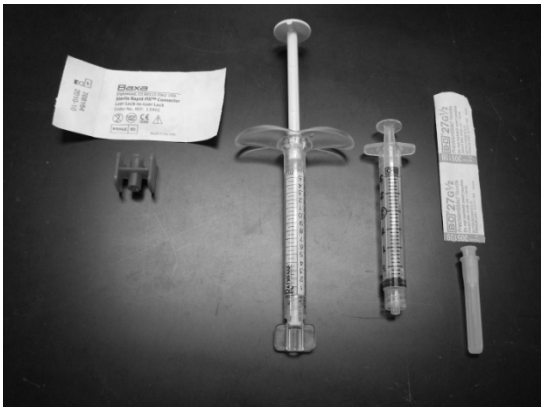

Figure 1: Left to right: Female-to-female luer lock connector, RADIESSE® syringe, 3.0 mL mixing syringe, sterile 27 gauge, 0.5" needle

2. Draw the lidocaine into a 3.0 mL sterile polypropylene mixing syringe fitted with a sterile 27 gauge, 0.5" needle.
3. Tap the mixing syringe, containing lidocaine and depress its push rod to remove all excess air.
4. Remove the sterile 27gauge, 0.5" needle.

5. Firmly connect the mixing syringe to the RADIESSE® syringe using the female-to-female luer lock connector (see **Figure 2** and **Figure 3**).

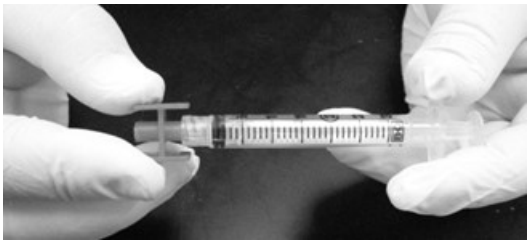

Figure 2

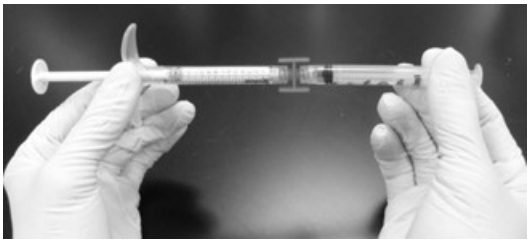

Figure 3

6. Mix the lidocaine and RADIESSE® injectable implant by alternately depressing the plungers, first on the mixing syringe and then on the RADIESSE® syringe for ten mixing strokes (each mixing stroke is one complete compression of the mixing syringe plunger followed by one complete compression of the RADIESSE® syringe plunger). Plungers are compressed firmly and quickly, at about two compressions per second.

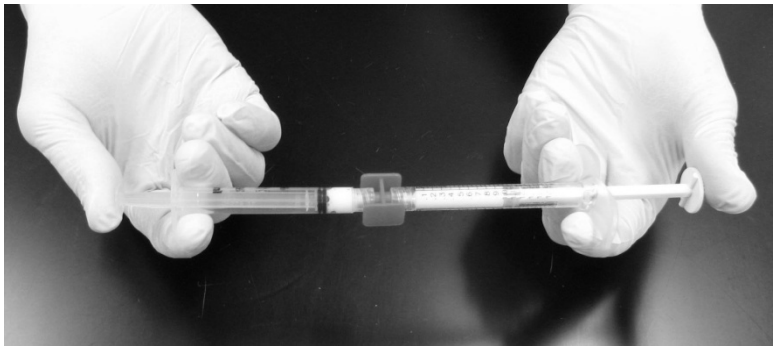

Figure 4

7. After mixing, remove the mixing syringe and the female-to-female luer lock connector and discard.
8. Fit the syringe containing the lidocaine and RADIESSE® mixture with an injection needle.
9. Proceed with the injection of the RADIESSE® injectable implant.

The clinical study was conducted by mixing 0.2 mL of 2% lidocaine with 1.3 mL of RADIESSE® injectable implant in the 3.0 mL BD syringe. The table below provides the ratio of 2% lidocaine to be mixed with the various syringe volumes of RADIESSE® injectable implant. These ratios result in the same concentration of 2% lidocaine (w/v%) in RADIESSE® injectable implant that was mixed in the clinical study after accounting for the dead space in the RADIESSE® and 3.0 mL BD mixing syringes (see **Table 42**).

Table 42: LIDOCAINE CONCENTRATION

RADIESSE® (mL)	2% Lidocaine (mL)	Resulting Lidocaine Concentration (w/v%)
1.5	0.26	0.31% - 0.32%

7.2 DIRECTIONS FOR USE: DÉCOLLETÉ

CAUTION: Only use diluted RADIESSE® Injectable Implant within 30 minutes after preparation. It is recommended to inject the diluted product immediately when feasible.

CAUTION: Check diluted RADIESSE® injectable implant for absence of foreign particles before use and discard the product if foreign particles are visible.

CAUTION: Use product once and discard in accordance with local safety standards.

Assembly and Dilution Instructions

CAUTION: RADIESSE® must be diluted 1:2 with sterile saline solution (0.9% NaCl) before injecting as detailed within all of the steps in this section.

The following components listed below in **Table 43** and depicted in **Figure 5** were utilized for the dilution and percutaneous injection procedures in the pivotal premarket clinical trial. Note that Merz North America Inc. does not offer the components for dilution and injection commercially; the user must obtain dilution and injection components separately prior to the procedure. All components are sterile and for single use only and should be labeled as such. Any saline solution remaining after the procedure should be discarded after use.

Table 43: DÉCOLLETÉ CLINICAL TRIAL COMPONENTS

# in Figure 5	Component	Model Used in Pivotal Clinical Trial	
		Manufacturer	Manufacturer Part Number
1	One (1) 1.5 mL RADIESSE® injectable implant syringe	Merz North America, Inc.	N/A
2 & 3	Two (2) 5 mL sterile polypropylene Luer-Lock syringes	BD	309649
3 (bottom portion)	One (1) 18G 1” blunt needle	N/A	N/A
4	One (1) female-to-female Luer lock connector	Baxter Healthcare Corp.	H93813901
5	Sterile physiological saline solution (0.9% NaCl)	N/A	N/A
N/A (not depicted)	22G 2” (50 mm) blunt-tipped cannula with 21G 1″ introducer needle	TSK Laboratory	PRC-22050ISG

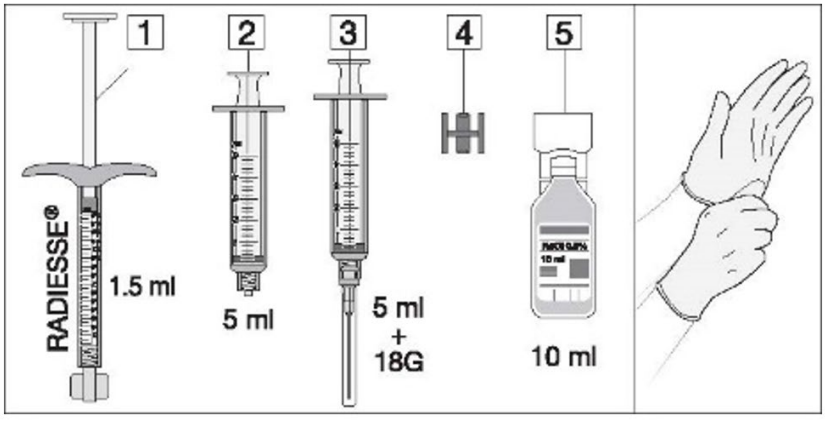

Figure 5

1. Assemble the components as displayed in **Table 43** and **Figure 5**. To unpack the RADIESSE® syringe, remove the 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*. Perform dilution using aseptic technique detailed in the following steps.
2. Attach the Luer-lock connector to an empty 5 mL syringe and remove the protective cap from the RADIESSE® syringe (**Figure 6**).

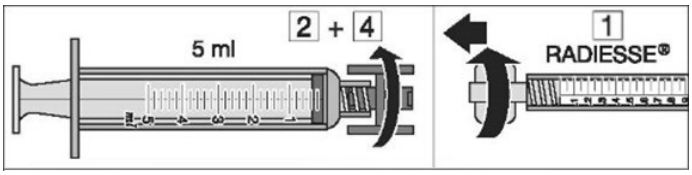

Figure 6

3. Attach the RADIESSE® syringe to the opposite side of Luer lock (**Figure 7**).

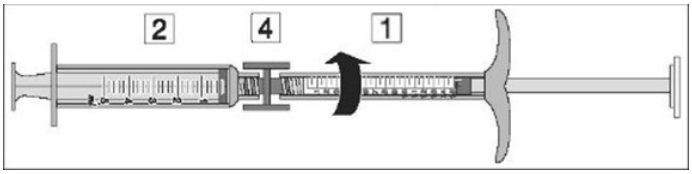

Figure 7

4. Transfer the entire RADIESSE® Injectable Implant (1.5 mL) into the 5 mL syringe by depressing the RADIESSE® plunger (**Figure 8**). Once complete, place the interconnected syringes on a cleaned and disinfected surface.

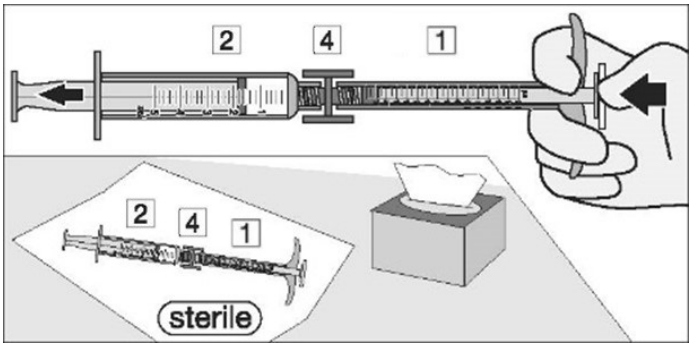

Figure 8

5. Draw up 3 mL of saline in a **new, empty 5 mL syringe** using a blunt needle (**Figure 9**). Remove all excess air. Discard needle.

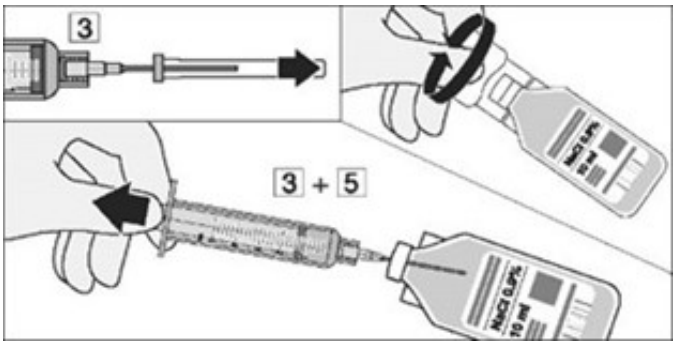

Figure 9

6. Remove the attached RADIESSE® syringe from the Luer lock (**Figure 10**). Do not discard the RADIESSE® syringe.

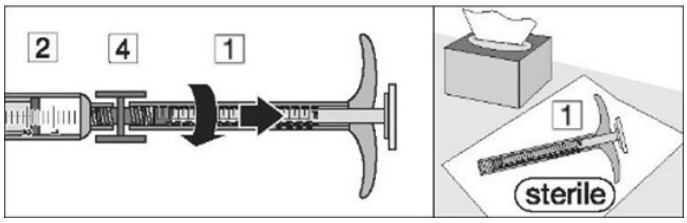

Figure 10

7. Attach the second 5 mL syringe (containing saline) to the open end of Luer lock (**Figure 11**).

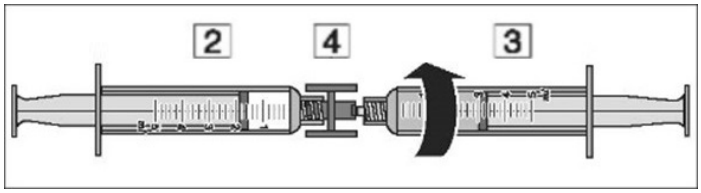

Figure 11

8. Transfer product back and forth between both 5 mL syringes until product is homogeneous, completing at least 20 back-and-forth passes (**Figure 12**). Verify that the product is mixed homogenously – if necessary, mix again.

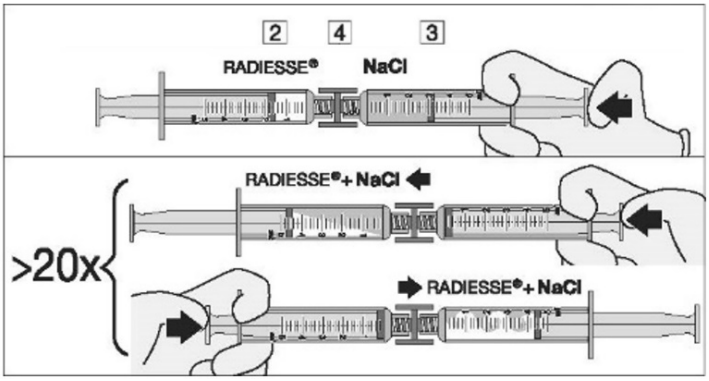

Figure 12

9. Transfer all product into one of the 5 mL syringes. Leave the Luer lock on the syringe with the product and remove the empty 5 mL syringe, placing it on a sterile surface (**Figure 13**).

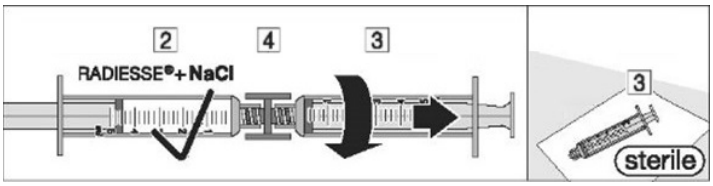

Figure 13

10. Attach the empty RADIESSE® syringe to the open end of the Luer lock and transfer 1.5 mL of product into the RADIESSE® syringe (**Figure 14**).

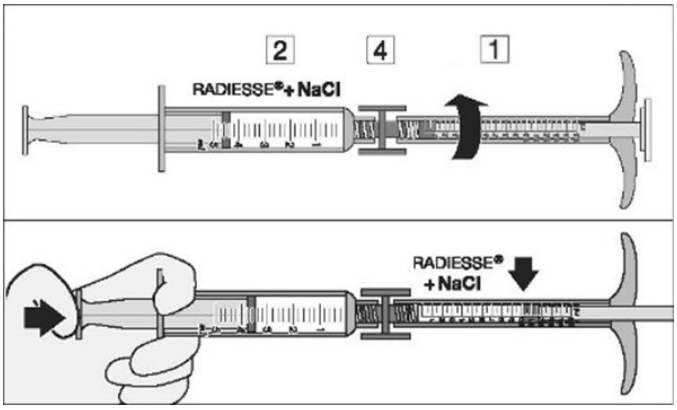

Figure 14

11. Disconnect the RADIESSE® syringe from the Luer lock and attach the cannula to the RADIESSE® syringe. The cannula must be tightened securely to the syringe. Do not over-tighten as this may break the cannula and/or dislodge the syringe. Be careful not to bend the cannula. Prime the cannula by depressing plunger until product is visible at the tip of cannula. If leakage is noted at the Luer fitting, it may be necessary to tighten the cannula, remove the cannula and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the cannula. To avoid contamination and dry out of the remaining product, attach the empty 5 mL dilution syringe again to the Luer lock to close the 5 mL syringe with the remaining product and place it on a clean and disinfected surface (**Figure 15**).

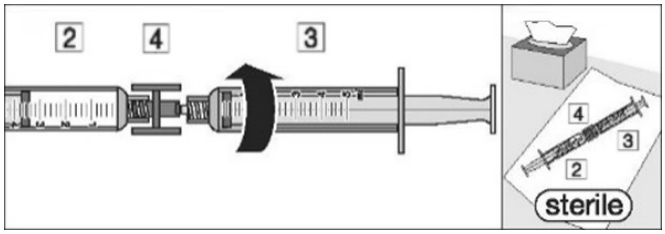

Figure 15

12. If more product is needed, repeat mixing steps 8 to 12. As noted in **Table 44** below, 1.5 mL of RADIESSE® when diluted with saline in a 1:2 dilution factor will result in 4.5 mL total volume of diluted product.

Table 44: DILUTION OF RADIESSE®

Dilution factor	Amount of RADIESSE® Injectable Implant (mL)	Amount of saline (mL)	Total volume of implant (mL)
1:2	1.5	3.0	4.5

Injection Procedure Instructions

1. Prepare patient for percutaneous injection using standard methods. The treatment injection site should be marked and prepared with a suitable antiseptic. Local or topical anesthesia at the injection site should be used at the discretion of the physician. **Figure 16** illustrates the décolleté treatment region that comprises approximately 100 cm^2, and is delineated superiorly by the sternoclavicular notch, laterally by the midclavicular line, and inferiorly by the superior point of the intermammary cleft. No injections should be made in the area overlying or including breast tissue.

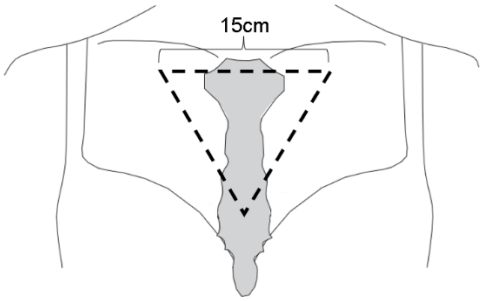

Figure 16

2. 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 cannula. Using the introduction needle, skin punctures should be made at the desired injection point(s). The cannula will be inserted through the established skin puncture.
3. Using the syringe of RADIESSE® injectable implant that has been diluted 1:2 with saline per the procedure described in the “Assembly and Dilution Instructions” section, advance the cannula down to the desired depth. Insert cannula at approximately a 30° angle to the skin. Cannula should slide under the dermis to the point you wish to begin the injection. This should be easily palpable with the non-dominant hand. Apply slow, continuous, even pressure when pushing the plunger of the syringe to start the injection and place the product subdermally using a linear threading and/or fanning retrograde technique (**Figure 17**). Care must be taken to avoid intravascular injection regardless of technique used.

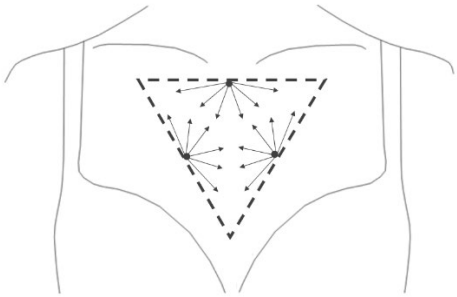

Figure 17

4. Continue placing additional lines of product until the desired level of correction is achieved. The amount injected will vary depending on the site and extent of correction desired. Use a 1:1 correction factor. No overcorrection is needed. The implant 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.

Note: If significant resistance is encountered when pushing the plunger, the injection cannula may be moved slightly to allow easier placement of the material or it may be necessary to change the injection cannula. Be careful not to bend the cannula. Cannula blockage is more likely with use of cannulas with an internal diameter smaller than 22G.

8 PATIENT COUNSELING INFORMATION

Refer to RADIESSE® injectable implant Patient Information Guide.

9 STORAGE

RADIESSE® injectable implant 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 three years from date of manufacture for the 1.5 mL syringe volume. Do not use if the expiration date has been exceeded.

10 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.

11 WARRANTY

Merz North America, Inc. warrants that reasonable care has been exercised in the design and manufacture of this product.

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IN00244-00/April 2026