RADIESSE®

INJECTABLE IMPLANT

INSTRUCTIONS FOR USE

℞ ONLY

DEVICE DESCRIPTION

RADIESSE® injectable implant is a sterile, non-pyrogenic, semi-solid, cohesive implant, whose principle component is synthetic calcium hydroxylapatite suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. RADIESSE injectable implant (1.5cc, 0.8cc) has a CaHA particle size range of 25–45 microns and should be injected with a 25 gauge Outer Diameter (O.D.) to 27 gauge Inner Diameter (I.D.) needle.

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.

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.

WARNINGS

- 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.
- Special care should be taken to avoid injection into the blood vessels. An introduction into the vasculature may occlude the vessels and could cause infarction or embolism leading to ischemia, necrosis or scarring. This has been reported to occur in the lips, nose, glabellar or ocular area.
- 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.

PRECAUTIONS

- 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, there was no indication of RADIESSE injectable implant potentially masking abnormal tissues or being interpreted as tumors in CT Scans.
- Only health care providers with expertise in the correction of volume deficiencies in patients with human immunodeficiency virus should treat such patients with RADIESSE injectable implant after fully familiarizing themselves with the product, the product educational materials and the entire package insert.
- 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.
- Safety of RADIESSE injectable implant beyond 3 years 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.
- As with all transcutaneous procedures, RADIESSE injectable implant injection carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- Safety of RADIESSE injectable implant for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- 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.
- 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.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.
- The patient should be informed that he or she should minimize exposure of the treated area to extensive sun or heat exposure for approximately 24 hours after treatment or until any initial swelling and redness has resolved.
- Safety and effectiveness in the periorbital area has not been established.
- No studies of interactions of RADIESSE injectable implant with drugs or other substances or implants have been conducted.
- 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.

- 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.
- 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.
- Injection of RADIESSE injectable implant into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.

NASOLABIAL FOLDS

A. 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 Tables 1 and 2. Physician reported adverse events are those reported by Investigators and patients any time outside the 2 week diaries. Those adverse events are presented in Tables 3 and 4.

Table 1. **PATIENT DIARY ADVERSE EVENTS**

Reported Through Patient Diaries Number of Patients With at Least One Adverse Event
By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)
Ecchymosis	74 (63.2)	50 (42.7)
Edema	81 (69.2)	62 (53.0)
Erythema	78 (66.7)	84 (71.8)
Granuloma	0 (0.0)	0 (0.0)
Nodule	1 (0.9)	1 (0.9)
Pain	33 (28.2)	26 (22.2)
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 1.3cc of RADIESSE injectable implant mixed with 0.2cc 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)

B. 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 1.2mL and 2.4mL 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 1.3cc of RADIESSE injectable implant mixed with 0.2cc 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.

HIV-ASSOCIATED FACIAL LIPOATROPHY

A. 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 Tables 16 and 17. Physician reported adverse events (those reported by Investigators and patients any time outside the 2 week diaries) are presented in Tables 18 and 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 Tables 20 and 21. Physician reported adverse events (those reported by Investigators and patients any time outside the 2 week diaries) are presented in Tables 22 and 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 Tables 24 and 25. Physician reported adverse events (those reported by Investigators and patients any time outside the 2 week diaries) are presented in Tables 26 and 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)

B. 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 4.8mL for the initial treatment and 1.8mL at 1 month if necessary (85% of patients were treated at 1 month). At 6 months, the mean touch up volume was 2.4mL (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	4.7mm	7.3mm	2.6mm	<0.0001	7.1mm	2.4mm	<0.0001	6.9mm	2.2mm	<0.0001
Right Cheek	4.9mm	8.0mm	2.1mm	<0.0001	7.5mm	2.7mm	<0.0001	7.3mm	2.5mm	<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 4.4mL. At 30 months, 90% of patients received a mean touch-up volume of 2.8mL. 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.

OTHER
SHORT TERM AND LONG TERM RADIOGRAPHIC EVALUATION

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.

POST MARKETING SURVEILLANCE

The following adverse events were received from post-marketing surveillance for the RADIESSE injectable implant in the US and outside the US and were not observed in the clinical trials with RADIESSE injectable implant: infection, over-injection, under-injection, loss of effect, product displacement, allergic reaction, necrosis, granuloma, exposed material, hair loss, tingling, ptosis, abscess, paralysis, superficial injection, herpetic infection, hematoma, blanching, blistering, bluish color, dark circles, did not like results, dizziness, double vision, festoons, flu-like symptoms, grey discoloration, Guillain-Barre syndrome, hyperventilating, inflammation, ischemic reaction, lymphoid hyperplasia, nausea, pallor to skin, prior medical condition worsened, pericarditis, possible blood clot, scarring, sensitivity to cold, skin texture changed, tissue mass developed, vascular compromise, and ocular ischemia.

The most commonly reported serious adverse events (with a frequency greater than 5 reported events) were necrosis, allergic reaction, edema, and infection. The following describes these serious adverse events:

- Necrosis was generally preceded by pain and blanching of the skin at the time of injection accompanied with stinging or tingling and bruising, redness, and swelling. Onset of necrosis ranged from immediately at time of injection to 12 days after injection. Treatment for necrosis generally consisted of a combination of nitroglycerin ointment/vasodilatation, ibuprofen, acetaminophen, or aspirin, antibiotics, steroids, non-steroidal wound treatment ointment and warm compresses. For cases where information was available, patients had recovered or were recovering with minimal to no scarring at last contact. Few cases required consultation with a plastic surgeon and possible excision and revision surgery to correct the defect resulting from the necrosis.
- Allergic Reaction was identified by itchiness and severe swelling, including swelling of the face and tongue. Onset ranged from immediately after injection to 2 days after injection. Allergic reaction was generally treated with anti-histamines and steroids. Some cases required hospitalization. All patients recovered from the allergic reaction with no permanent adverse outcome.

- Serious edema has been reported with an onset ranging from 1 day to 3 weeks (inflammation related to nodule formation). Treatment generally consisted of administration of antibiotics, anti-histamines and steroids. In some cases patients sought treatment in an emergency room or were hospitalized. Generally events resolved within 1 to 2 days but a few patients have been reported as having intermittent edema or persistent edema related to a reoccurring infection. For cases where information was available, most patients have recovered or are recovering.
- Infection, often identified as cellulitis, was accompanied by swelling, hardened areas, redness, pustules, and pain. Onset of infection ranged from 1 day to 2 months and generally lasted 2 days but, in one case, persisted for 6 months. Infections were generally treated with antibiotics. For cases where information was available, patients had recovered or were recovering. Few patients experienced scarring that may require corrective surgery or discoloration at the site of the infection.

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.

DIRECTIONS FOR USE

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.).
- 3.0cc sterile polypropylene luer-lock syringe (BD 309585)
- 0.2cc 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)
- 1.3cc syringe of RADIESSE injectable implant

The 3.0cc 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).

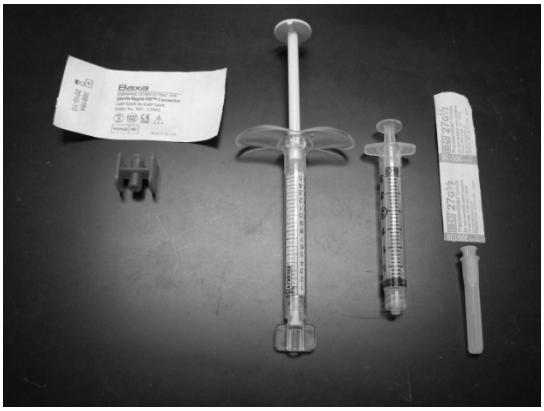

Figure 1: Left to right: Female-to-female luer lock connector, RADIESSE syringe, 3.0cc mixing syringe, sterile 27 gauge, 0.5" needle

2. Draw the lidocaine into a 3.0cc 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 Figures 2 and 3).

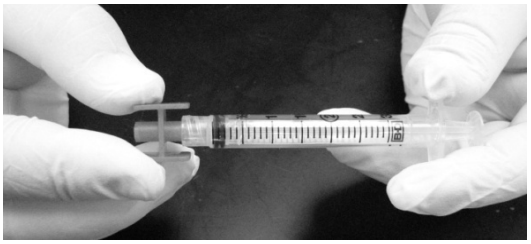

Figure 2

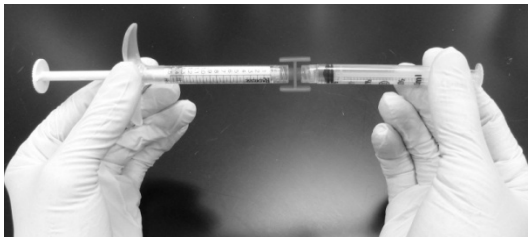

Figure 3

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.

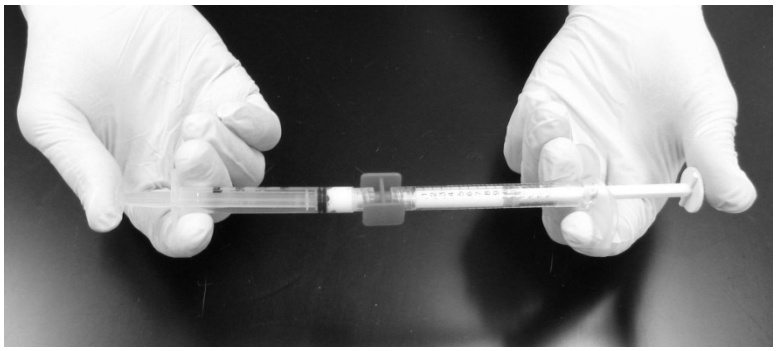

Figure 4

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 0.2cc of 2% lidocaine with 1.3cc of RADIESSE injectable implant in the 3.0cc 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 3.0cc BD mixing syringes (see Table 34).

Table 34**. LIDOCAINE CONCENTRATION**

RADIESSE® (cc)	2% Lidocaine (cc)	Resulting Lidocaine Concentration (w/v%)
0.8	0.11	0.31% - 0.32%
1.5	0.26	0.31% - 0.32%

PATIENT COUNSELING INFORMATION

Refer to RADIESSE injectable implant Patient Information Guide.

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 1.5cc syringe volume. The expiration date, when stored in these temperatures, is two years from date of manufacture for the 0.8cc syringe volume. Do not use if the expiration date has been exceeded.

DISPOSAL

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

WARRANTY

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

THIS WARRANTY IS IN LIEU OF AND EXCLUDES ALL OTHER WARRANTIES NOT EXPRESSLY SET FORTH HEREIN, WHETHER EXPRESSED OR IMPLIED BY OPERATION OF LAW OR OTHERWISE, INCLUDING BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR ITS PARTICULAR PURPOSE.

Handling and storage of this product, as well as factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond the control of Merz North America, Inc. directly affect the product and the results obtained from its use. Merz North America, Inc.'s obligation under this warranty is limited to the replacement of this product and Merz North America, Inc. shall not be liable for any incidental or consequential loss, damage, or expense, directly or indirectly, arising from the use of this product. Merz North America, Inc., neither assumes, nor authorizes any person to assume for Merz North America, Inc., any other or additional liability or responsibility in connection with this product.

MANUFACTURED BY

Merz North America, Inc.
4133 Courtney Road, Suite #10
Franksville, WI 53126 U.S.A.
Fax: 262-835-3330
Telephone: 262-835-3300
E-Mail: info@merzaesthetics.com

EM00543-02/DEC 2013