RADIESSE®

INJECTABLE IMPLANT

INSTRUCTIONS FOR USE FOR THE DORSUM OF THE HAND

℞ ONLY

DEVICE DESCRIPTION

RADIESSE® injectable implant is an opaque, 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 and 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.

INDICATION FOR USE

RADIESSE injectable implant is indicated for hand augmentation to correct volume loss in the dorsum of the hands.

RADIESSE injectable implant is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. It is also intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

Note: These instructions for use are specific for RADIESSE treatment in the dorsum of the hand. Please see alternate instructions for use for RADIESSE treatment for nasolabial folds and HIV lipoatrophy.

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

- Introduction of product 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 the product 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.

- 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. Refer to Individualization of Treatment section for additional details.

- Special care should be taken to avoid injection into veins or tendons in the hand. Injection into tendons may weaken tendons and cause tendon rupture. Injection into veins may cause embolization or thrombosis.

- Injection into the hand may cause adverse events that last for more than 14 days. Refer to adverse events sections for details.

- Injection in the dorsum of the hand may result in temporary difficulty performing activities (48% of study patients reported this adverse event). Fitzpatrick Skin Types IV-VI may have an increased risk in difficulty performing activities (68% of Fitzpatrick Skin Types IV-VI reported this event).

- RADIESSE may cause nodules, bumps or lumps in the dorsum of the hand (12% reported this event) and can last up to a 1 year.

- Injection into patients with very severe loss of fatty tissue with marked visibility of veins and tendons has not been studied. The safety and effectiveness in this patient population has not been established.

- Volumes over 3cc of RADIESSE per hand in a treatment session have not been studied. Increased bruising is associated with higher volume injection. Re-treatment with RADIESSE of volumes greater than approximately 1.6cc per hand in a treatment session can result in increased adverse events (redness, pain, swelling, and difficulty performing activities).

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by healthcare practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.

- In order to minimize the risks of potential complications, Healthcare practitioners should fully familiarize themselves with the product, the product educational materials and the entire package insert.

- 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. In a radiographic study of 58 faces, there was no indication that RADIESSE injectable implant potentially masked abnormal tissues or being interpreted as tumors in CT Scans. 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. Imaging studies have not been performed in the hand. It is presently unknown if RADIESSE could mask a hand injury on imaging studies.

- Healthcare practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that 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.

- Use of RADIESSE in the dorsum of the hand in patients with diseases, injuries or disabilities of the hand has not been studied. Care should be used in treating patients with autoimmune disease affecting the hand, hand implants, Dupuytren's contracture, history of hand tumor, vascular malformations, Raynaud's disease and patients at risk for tendon rupture.

- Use of RADIESSE in the dorsum of the hand may result in significant swelling of the dorsum of the hand. Patients should be instructed to remove jewelry (rings) before treatment and until swelling has resolved to avoid compromise of finger circulation.

- The effects of RADIESSE injection on hand function is uncertain.

- 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 1 year in the hand has not been investigated in clinical trials.

- Safety of RADIESSE injectable implant for use during pregnancy and in breastfeeding females has not been established.

- Safety of RADIESSE injected into the dorsum of the hand in patients under 26 years old and over 79 years old has not been studied.

- The safety of RADIESSE 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.

- The patient should be informed that he or she should minimize strenuous activity and exposure of the treated area to extensive sun or heat exposure for approximately 24 hours after treatment and until any initial swelling and redness has resolved.

- Universal precautions must be observed when there is a potential for contact with patient body fluids. The injection session must be conducted with aseptic technique.

- RADIESSE 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 re-shield used needles. Recapping by hand is a hazardous practice and should be avoided.

- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

HAND AUGMENTATION PRE-MARKET CLINICAL TRIAL

A. ADVERSE EVENTS

The information provided here contains the adverse events for the 113 subjects that completed a randomized, masked, controlled study at six US investigational sites. A total of 78 subjects were retreated after 6 months post-initial treatment. Adverse events were recorded in subject diaries (30 days post-treatment) as well as by physician evaluations.

RADIESSE was mixed with lidocaine HCl and then injected as small boluses of up to 0.5 cc into the dorsum of the hand. The RADIESSE/lidocaine was then massaged into the hand until the desired cosmetic effect was achieved.

Tables 1 and 2 summarize the adverse events reported by all subjects and physicians, respectively, over a 12 month period. The adverse events are presented by maximum severity (mild, moderate, or severe).

Table 1
Subject-Reported Adverse Events over a 12 month period
(N = 113 Subjects)

Adverse Event Type	# of Subjects With Event (% total)	Maximum Severity (N, % with event)		
		Mild	Moderate	Severe
Bruising	82 (72.6%)	48 (58.5%)	29 (35.4%)	5 (6.1%)
Swelling	112 (99.1%)	22 (19.6%)	74 (66.1%)	16 (14.3%)
Redness	92 (81.4%)	40 (43.5%)	48 (52.2%)	4 (4.3%)
Itching	52 (46.0%)	35 (67.3%)	17 (32.7%)	0 (0.0%)
Pain	104 (92.0%)	46 (44.2%)	51 (49.0%)	7 (6.7%)
Hematoma	1 (0.9%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	7 (6.2%)	2 (28.6%)	5 (71.4%)	0 (0.0%)
Difficulty Performing Activities	54 (47.8%)	30 (55.6%)	21 (38.9%)	3 (5.6%)
Loss of Sensation	17 (15.0%)	10 (58.8%)	7 (41.2%)	0 (0.0%)
Other	10 (8.8%)	4 (40.0%)	5 (50.0%)	1 (10.0%)
Total	113 (100.0%)	14 (12.4%)	78 (69.0%)	21 (18.6%)

* Other adverse events reported that were related to the device include vagal response, dry skin, hypersensitivity and needle pricks.

Table 2
Physician-Reported Adverse Events over a 12 month period
(N = 113 Subjects)

Adverse Event Type	# of Subjects With Event (% total)	Maximum Severity (N, % with event)		
		Mild	Moderate	Severe
Bruising	21 (18.6%)	13 (61.9%)	6 (28.6%)	2 (9.5%)
Swelling	23 (20.4%)	7 (30.4%)	14 (60.9%)	2 (8.7%)
Redness	9 (8.0%)	5 (55.6%)	4 (44.4%)	0 (0.0%)
Itching	4 (3.5%)	3 (75.0%)	1 (25.0%)	0 (0.0%)
Pain	7 (6.2%)	4 (57.1%)	2 (28.6%)	1 (14.3%)
Hematoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nodule, Bumps/Lumps	7 (6.2%)	7 (100.0%)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	2 (1.8%)	2 (100.0%)	0 (0.0%)	0 (0.0%)
Loss of Sensation	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	13 (11.5%)	7 (53.8%)	5 (38.5%)	1 (7.7%)
Total	50 (44.2%)	24 (48.0%)	21 (42.0%)	5 (10.0%)

* Other adverse events reported that were related to the device include vagal response, dry skin, hypersensitivity and needle pricks.

Table 3 shows the duration of adverse events, reported by study subjects and/or physicians. A total of 24 out of 113 subjects (21%) experienced adverse events described as “severe.” All events resolved without sequelae.

Table 3
Duration of Severe Adverse Events over a 12 month period

Adverse Event Type	# of Subjects	Mean duration (days)	Median duration (days)	Range of days	Duration reported as “severe” in diary (days)
Swelling	18	17.5	12	3-57	1-8
Bruising	7	19.9	10.5	5-67	1-4
Pain	7	33.1	21.5	8-99	1-7
Difficulty in Performing Activities	3	41.8	15	3-97	1-11
Redness	4	18.5	14.5	3-37	1-2

Adverse Events with Duration Greater Than 14 Days

Events reported by subjects and/or physicians to last for longer than 14 days are listed below. The percentages are the number of subjects that experienced an adverse event for greater than 14 days out of 113 subjects that were treated in the study. All events resolved without sequelae.

- 29% swelling
- 25% pain
- 7% nodules/bumps/lump
- 6% difficulty performing activities
- 6% redness
- 3% bruising
- 1% hematoma

ADVERSE EVENTS AFTER INITIAL TREATMENT

Tables 4 and 5 present adverse events and maximum severity of those events following 6 months after initial treatment, as reported by subjects and by physicians, respectively.

Table 4
Subjects Experiencing Adverse Events, For First Six Months from Initial Treatment Reported in Subject Diaries
N = 113 Subjects

Adverse Event Type	# Subjects With Event		Maximum Severity		
	N	95% CI	Mild	Moderate	Severe
Bruising	73 (64.6%)	(55.0-73.4)	48 (65.8%)	22 (30.1%)	3 (4.1%)
Swelling	110 (97.3%)	(92.4-99.4)	28 (25.5%)	69 (62.7%)	13 (11.8%)
Redness	88 (77.9%)	(69.1-85.1)	46 (52.3%)	39 (44.3%)	3 (3.4%)
Itching	49 (43.4%)	(34.1-53.0)	36 (73.5%)	13 (26.5%)	0 (0.0%)
Pain	98 (86.7%)	(79.1-92.4)	48 (49.0%)	45 (45.9%)	5 (5.1%)
Hematoma	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)
Nodule, Bumps/Lumps	4 (3.5%)	(1.0-8.8)	1 (25.0%)	3 (75.0%)	0 (0.0%)
Difficulty Performing Activities	45 (39.8%)	(30.7-49.5)	26 (57.8%)	17 (37.8%)	2 (4.4%)
Loss of Sensation	11 (9.7%)	(5.0-16.8)	7 (63.6%)	4 (36.4%)	0 (0.0%)
Other	9 (8.0%)	(3.7-14.6)	4 (44.4%)	5 (55.6%)	0 (0.0%)
Total	112 (99.1%)	(95.2-100.0)	21 (18.8%)	75 (67.0%)	16 (14.3%)

Table 5
Subjects Experiencing Adverse Events, For First Six Months from Initial Treatment
Reported by Physician Assessment
N = 113 Subjects

Adverse Event Type	# Subjects With Event		Maximum Severity		
	N	95% CI	Mild	Moderate	Severe
Bruising	20 (17.7%)	(11.2-26.0)	14 (70.0%)	4 (20.0%)	2 (10.0%)
Swelling	23 (20.4%)	(13.4-29.0)	7 (30.4%)	14 (60.9%)	2 (8.7%)
Redness	9 (8.0%)	(3.7-14.6)	5 (55.6%)	4 (44.4%)	0 (0.0%)
Itching	4 (3.5%)	(1.0-8.8)	3 (75.0%)	1 (25.0%)	0 (0.0%)
Pain	7 (6.2%)	(2.5-12.3)	4 (57.1%)	2 (28.6%)	1 (14.3%)
Hematoma	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)
Nodule, Bumps/Lumps	2 (1.8%)	(0.2-6.2)	2 (100.0%)	0 (0%)	0 (0%)
Difficulty Performing Activities	2 (1.8%)	(0.2-6.2)	2 (100.0%)	0 (0%)	0 (0%)
Loss of Sensation	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)
Other	10 (8.8%)	(4.3-15.7)	6 (60.0%)	3 (30%)	1 (10%)
Total	44 (38.9%)	(29.9-48.6)	20 (45.5%)	19 (43.2%)	5 (11.4%)

Tables 6 and 7 represent the onset of adverse events after initial treatment, as reported by subjects and physicians, respectively

Table 6
Subject-Reported* Adverse Events Onset after Initial Treatment
(n = 914 Events)

		Reported Adverse Events (N, % with event)				
Adverse Event Type	All First Onset (N, % total)	Week 1	Week 2	Week 3	Week 4 and Beyond	Week 1 and 2 Combined
Bruising	133 (14.6%)	124 (93.2%)	5 (3.8%)	3 (2.3%)	1 (0.8%)	129 (97.0%)
Swelling	218 (23.9%)	218 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	218 (100.0%)
Redness	166 (18.2%)	163 (98.2%)	3 (1.8%)	0 (0.0%)	0 (0.0%)	166 (100.0%)

		Reported Adverse Events (N, % with event)				
Adverse Event Type	**All First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Pain	192 (21.0%)	180 (93.8%)	4 (2.1%)	6 (3.1%)	2 (1.0%)	184 (95.8%)
Itching	83 (9.1%)	60 (72.3%)	16 (19.3%)	6 (7.2%)	1 (1.2%)	76 (91.6%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	7 (0.8%)	2 (28.6%)	4 (57.1%)	0 (0.0%)	1 (14.3%)	6 (85.7%)
Difficulty Performing Activities	82 (9.0%)	71 (86.6%)	7 (8.5%)	4 (4.9%)	0 (0.0%)	78 (95.1%)
Loss of Sensation	16 (1.8%)	8 (50.0%)	5 (31.3%)	3 (18.8%)	0 (0.0%)	13 (81.3%)
Other	17 (1.9%)	13 (76.5%)	4 (23.5%)	0 (0.0%)	0 (0.0%)	17 (100.0%)
Total	914 (100.0%)	839 (91.8%)	48 (5.3%)	22 (2.4%)	5 (0.5%)	887 (97.0%)

* Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

Table 7
Physician-Reported Total Number of Adverse Events Onset after Initial Treatment
(n = 117 Events)

		Reported Adverse Events (N, % with event)				
Adverse Event Type	**All First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Bruising	26 (22.2%)	23 (88.5%)	0 (0.0%)	0 (0.0%)	3 (11.5%)	23 (88.5%)
Swelling	39 (33.3%)	28 (71.8%)	10 (25.6%)	1 (2.6%)	0 (0.0%)	38 (97.4%)
Redness	15 (12.8%)	14 (93.3%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	15 (100.0%)
Pain	11 (9.4%)	5 (45.5%)	2 (18.2%)	1 (9.1%)	3 (27.3%)	7 (63.6%)
Itching	7 (6.0%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	5 (71.4%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	3 (2.6%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	2 (66.7%)
Difficulty Performing Activities	4 (3.4%)	2 (50.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	4 (100.0%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

		Reported Adverse Events (N, % with event)				
Adverse Event Type	**All First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Other	12 (10.3%)	4 (33.3%)	0 (0.0%)	0 (0.0%)	8 (66.7%)	4 (33.3%)
Total	117 (100.0%)	83 (70.9%)	15 (12.8%)	2 (1.7%)	17 (14.5%)	98 (83.8%)

Recurrent Adverse Events

An adverse event was considered a recurrent adverse event, if an adverse event of the same type was reported again after greater than 3 days. A total of 58% subjects (66 out of 113) had a recurrent adverse event after initial treatment. Table 8 provides the number of recurrent adverse events reported by subjects after initial treatment. Physicians reported recurrent swelling adverse events after initial treatment from 14-19 days (2 events) and from 60 or more days (1 event).

Table 8
Total Number of Recurrent AEs after Initial Treatment
Reported in Subject Diaries*
(n=239 events)

	Less Than 14 Days	**14-19 Days**	**20-29 Days**	**30-59 Days**	**Total Adverse Events per Event Type**
Bruising	4 (28.6%)	4 (28.6%)	6 (42.9%)	0 (0.0%)	14 (5.9%)
Swelling	44 (64.7%)	17 (25.0%)	6 (8.8%)	1 (1.5%)	68 (28.5%)
Redness	16 (40.0%)	10 (25.0%)	11 (27.5%)	3 (7.5%)	40 (16.7%)
Pain	43 (65.2%)	6 (9.1%)	14 (21.2%)	3 (4.5%)	66 (27.6%)
Itching	17 (54.8%)	7 (22.6%)	7 (22.6%)	0 (0.0%)	31 (13.0%)
Nodule, Bumps/Lumps	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	3 (1.3%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	11 (68.8%)	1 (6.3%)	3 (18.8%)	1 (6.3)	16 (6.7%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Total	137 (57.3%)	46 (19.2%)	48 (20.1%)	8 (3.3%)	239 (100.0%)

*Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

ADVERSE EVENTS REPORTED AFTER RE-TREATMENT

Tables 9 and 10 present adverse events and maximum severity of those events following initial treatment and following re-treatment, as reported by subjects and by physicians, respectively.

Table 9
Subject-Reported* Adverse Events
Following Initial Treatment v. Re-treatment
Reported in Subject Diaries* (N = 78 Retreated Subjects)

Adverse Event Type	# Subjects							
	Following Initial Treatment				Following Re-Treatment			
	N (%)	Max Severity			N (%)	Max Severity		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Bruising	52 (66.7%)	34 (65.4%)	16 (30.8%)	2 (3.8%)	45 (57.7%)	27 (60.0%)	16 (35.6%)	2 (4.4%)
Swelling	75 (96.2%)	23 (30.7%)	44 (58.7%)	8 (10.7%)	68 (87.2%)	31 (45.6%)	33 (48.5%)	4 (5.9%)
Redness	60 (76.9%)	34 (56.7%)	24 (40.0%)	2 (3.3%)	42 (53.8%)	26 (61.9%)	15 (35.7%)	1 (2.4%)
Itching	33 (42.3%)	23 (69.7%)	10 (30.3%)	0 (0.0%)	16 (20.5%)	7 (43.8%)	9 (56.3%)	0 (0.0%)
Pain	65 (83.3%)	34 (52.3%)	28 (43.1%)	3 (4.6%)	47 (60.3%)	28 (59.6%)	17 (36.2%)	2 (4.3%)
Nodule, Bumps/Lumps	2 (2.6%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	3 (3.8%)	1 (33.3%)	2 (66.7%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (100.0 %)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	26 (33.3%)	15 (57.7%)	10 (38.5%)	1 (3.8%)	21 (26.9%)	15 (71.4%)	5 (23.8%)	1 (4.8%)
Loss of Sensation	8 (10.3%)	6 (75.0%)	2 (25.0%)	0 (0.0%)	6 (7.7%)	3 (50.0%)	3 (50.0%)	0 (0.0%)
Other	7 (9.0%)	3 (42.9%)	4 (57.1%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (100.0 %)
Total	77 (98.7%)	17 (22.1%)	50 (64.9%)	10 (13.0%)	73 (93.6%)	28 (38.4%)	39 (53.4%)	6 (8.2%)

*Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

Table 10
Physician-Reported Adverse Events
Following Initial Treatment v. Re-treatment
(N = 78 Retreated Subjects)

Adverse Event Type	# Subjects							
	Following Initial Treatment				Following Re-Treatment			
	N (%)	Max Severity			N (%)	Max Severity		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Bruising	11 (14.1%)	9 (81.8%)	1 (9.1%)	1 (9.1%)	5 (6.4%)	3 (60.0 %)	2 (40.0%)	0 (0.0%)
Swelling	12 (15.4%)	5 (41.7%)	6 (50.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Adverse Event Type	# Subjects							
	Following Initial Treatment				Following Re-Treatment			
	N (%)	Max Severity			N (%)	Max Severity		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Redness	6 (7.7%)	3 (50.0%)	3 (50.0%)	0 (0.0%)	1 (1.3%)	1 (100.0 %)	0 (0.0%)	0 (0.0%)
Itching	2 (2.6%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	4 (5.1%)	3 (75.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (6.4%)	5 (100.0 %)	0 (0.0%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	1 (1.3%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	4 (5.1%)	3 (75.0%)	1 (25.0%)	0 (0.0%)	3 (3.8%)	1 (33.3 %)	2 (66.7%)	0 (0.0%)
Total	24 (30.8%)	14 (58.3%)	9 (37.5%)	1 (4.2%)	14 (17.9%)	10 (71.4 %)	4 (28.6%)	0 (0.0%)

Tables 11 and 12 represent the onset of all adverse events after re-treatment, as reported by subjects and physicians, respectively.

Table 11
Subject Reported* Total Number of Adverse Events
Onset after Re-treatment
(n = 473 Events)

		Reported Adverse Events (N, % event type)				
Adverse Event Type	**First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Bruising	82 (17.3%)	82 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	82 (100.0%)
Swelling	133 (28.1%)	133 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	133 (100.0%)
Redness	83 (17.5%)	82 (98.8%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	83 (100.0%)
Pain	91 (19.2%)	91 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	91 (100.0%)
Itching	30 (6.3%)	30 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	30 (100.0%)
Hematoma	1 (0.2%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Nodule, Bumps/Lumps	5 (1.1%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	3 (60.0%)	2 (40.0%)
Difficulty	36	32	2	1	1	34

		Reported Adverse Events (N, % event type)				
Adverse Event Type	**First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Performing Activities	(7.6%)	(88.9%)	(5.6%)	(2.8%)	(2.8%)	(94.4%)
Loss of Sensation	11 (2.3%)	9 (81.8%)	0 (0.0%)	2 (18.2%)	0 (0.0%)	9 (81.8%)
Other	1 (0.2%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Total	473 (100.0%)	461 (97.5%)	5 (1.1%)	3 (0.6%)	4 (0.8%)	466 (98.5%)

* Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

Table 12
Physician Reported Total Number of Adverse Events Onset after Re-treatment
(n = 21 Events)

		Reported Adverse Events (N, % event type)				
Adverse Event Type	**First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Bruising	8 (38.1%)	7 (87.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	7 (87.5%)
Swelling	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	2 (9.5%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)
Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Itching	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	7 (33.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	6 (85.7%)	1 (14.3%)
Difficulty Performing Activities	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	4 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (100.0%)	0 (0.0%)
Total	21 (100.0%)	10 (47.6%)	0 (0.0%)	0 (0.0%)	11 (52.4%)	10 (47.6%)

Table 13 shows the total number of recurrent adverse events after re-treatment, as reported by subjects. No recurrent adverse events after re-treatment were reported by physicians.

Table 13
Total Number of Recurrent Adverse Events after Re-treatment Reported in Subject Diaries*
(n = 31 events)

Adverse Event Type	Less Than 14 Days	14-19 Days	20-29 Days	30-59 Days	60 or More Days	Total Adverse Events per Event Type
Bruising	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	4 (33.3%)	1 (8.3%)	5 (41.7%)	2 (16.7%)	0 (0.0%)	12 (38.7%)
Redness	1 (20.0%)	2 (40.0%)	1 (20.0%)	1 (20.0%)	0 (0.0%)	5 (16.1%)
Pain	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (9.7%)
Itching	0 (0.0%)	0 (0.0%)	4 (66.7%)	2 (33.3%)	0 (0.0%)	6 (19.4%)
Nodule, Bumps/Lumps	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (9.7%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	5 (16.1%)	9 (29.0%)	12 (38.7%)	5 (16.1%)	0 (0.0%)	31 (100.0%)

*Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

B. PIVOTAL HAND CLINICAL TRIAL

Study Design

A prospective, randomized, masked, controlled study in 114 subjects at six investigational sites in the United States was conducted to evaluate the safety and effectiveness of RADIESSE injectable implant for the treatment of volume loss in the hands. Eighty-five (85) subjects were randomized to a treatment group (immediate treatment) and twenty-nine (29) subjects were randomized to an untreated control group (delayed treatment) through 3 months from enrollment. One hundred-thirteen (113) of the 114 subjects (99%) completed the study through 3 months. After collection of the required data for the analysis between these two groups, the control group was crossed over and received treatment. All subjects were eligible for re-treatment 6 months after initial treatment. Seventy-eight of the 113 subjects (69%) received re-treatment. From enrollment to 12 months, one hundred eleven out of 113 subjects (98%) subjects completed study follow-up.

Subject Demographics

Table 14 summarizes the demographics for the 114 subjects who participated in the investigation. Statistical analysis for the comparison between the treatment group and the control group showed there were no statistical differences between the groups in any of the demographics categories.

Table 14.
Subject Demographics
N = 114 Subjects*

	Treatment Group (Immediate) (N=85)	**Control Group (Delayed) (N=29)**
Age (years)		
Mean	52.8	54.8
SD	8.0	10.6
Median	52.0	57.0
Range	(26 - 75)	(34 - 79)
Gender – n (%)		
Female	81 (95.3%)	28 (96.6%)
Male	4 (4.7%)	1 (3.4%)
Race – n (%)		
Caucasian	66 (77.6%)	21 (72.4%)
African American	3 (3.5%)	3 (10.3%)
Hispanic	12 (14.1%)	3 (10.3%)
Asian	3 (3.5%)	1 (3.4%)
Other	1 (1.2%)	1 (3.4%)
Fitzpatrick Skin Type – n (%)		
I	3 (3.5%)	0 (0.0%)
II	45 (52.9%)	11 (37.9%)
III	19 (22.4%)	11 (37.9%)
IV	13 (15.3%)	4 (13.8%)
V	4 (4.7%)	2 (6.9%)
VI	1 (1.2%)	1 (3.4%)
Hand Dominance – n (%)		
Right	79 (92.9%)	26 (89.7%)
Left	6 (7.1%)	3 (10.3%)

*Including a subject withdrawn prior to treatment

Injection Volume

Subjects received Radiesse injectable implant mixed with 2% lidocaine HCl (final concentration 0.3% as per mixing protocol detailed in Section *Component Assembly and Mixing Instructions*) in the dorsum of both hands (defined as the space bound laterally between the first and fifth metacarpals, proximally by the dorsal wrist crease, and distally by the metacarpophalangeal joints) using a 27 gauge needle. The number of injection points varied and was left to the discretion of the treating investigator. Injected aliquots had volumes of a maximum of 0.5 cc each.

The volumes of Radiesse (including the volume of added lidocaine) that were injected are detailed in Table 15. The data are presented by initial treatment, re-treatment, and by the combined amount of both treatments.

Table 15
INJECTION VOLUMES (cc)
n = 226 Hands (All Subjects)

	Initial Treatment n = 226 Hands			Re-treatment n = 156 Hands			Combined n = 226 Hands		
	Right Hand	Left Hand	Total	Right Hand	Left Hand	Total	Right Hand	Left Hand	Total
Mean	2.58	2.60	5.18	1.64	1.61	3.25	3.72	3.71	7.43
Standard Deviation	0.68	0.69	1.37	0.52	0.61	1.08	1.16	1.15	2.29
Median	2.64	2.64	5.28	1.76	1.76	3.52	3.52	3.54	7.20
Range	1.50 - 3.60	1.40 - 3.60	2.90 - 7.20	0.70 - 2.64	0.00 - 3.00	1.40 - 5.30	1.50 - 6.16	1.40 - 6.16	2.90 - 12.32

Study Endpoints

Primary effectiveness was assessed using the Merz Hand Grading Scale (MHGS, Figure 1), which was validated for live assessments. Secondary effectiveness was assessed by subject reported assessment of a non-validated Global Aesthetic Improvement Scale (GAIS, Table 16).

Figure 1 – Merz Hand Grading Scale (MHGS)

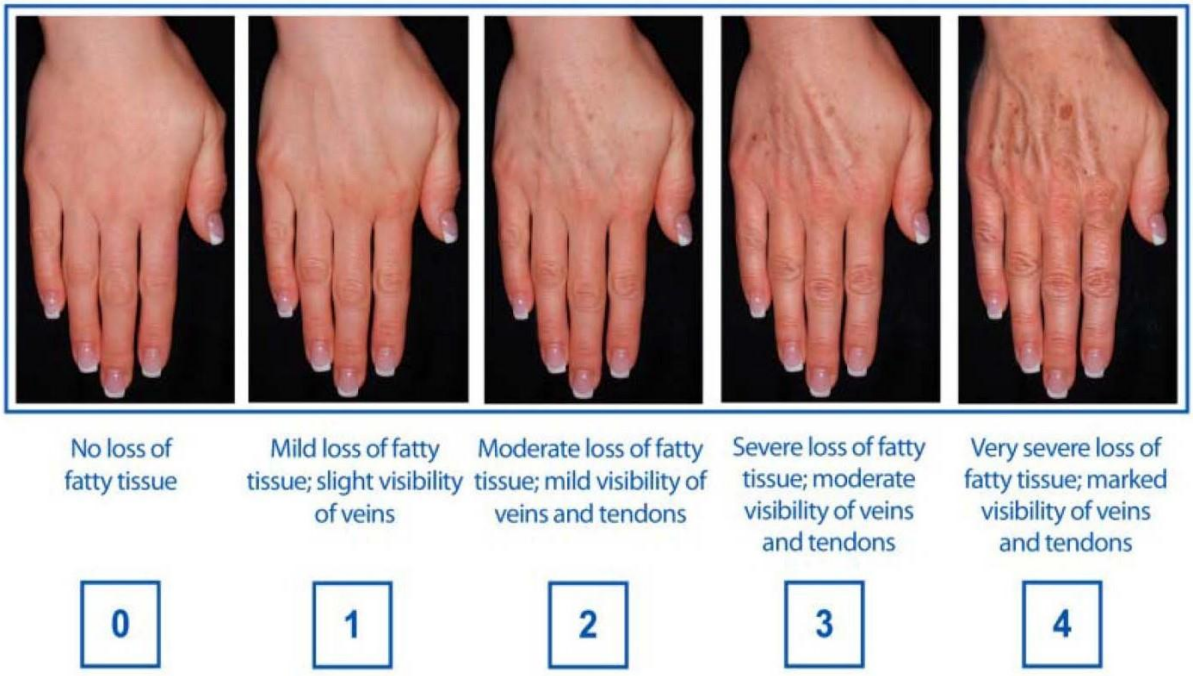

Table 16–
Global Aesthetic Improvement Scale (GAIS)

Rating	Description
Very Much Improved	Optimal cosmetic result for the implant in this subject.
Much Improved	Marked improvement in appearance from initial condition, but not completely optimal in this subject. A touch-up would slightly improve the result.
Improved	Obvious improvement in appearance from the initial condition, but a touch-up or re-treatment is indicated.
No Change	The appearance is essentially the same as the original condition.
Worse	The appearance worse than the original condition.

The primary efficacy variable was the improvement of ≥ 1 point on the MHGS between baseline and 3 months in both hands for the treatment group versus the control group. The MHGS live assessments were performed by a masked non-physician evaluator at each site who was blinded to randomization assignments of the subjects. The GAIS assessments were performed by the subjects, comparing their live hand appearance to pre-treatment hand photographs.

Safety Assessments

The safety endpoint of the study was to assess the incidence, severity, duration, relationship to study device and treatment, if any, of all adverse events observed by subjects and treating investigators. Safety was also evaluated using a series of real-time hand function tests which assessed range of motion, sensation, dexterity, and grip and pinch strength.

Primary Effectiveness Endpoint Results

Table 17 shows that the MHGS, improvement in hand appearance in the treatment group compared to the control group at 3 months was statistically significant and 75% of the treated subjects had both hands showing a ≥ 1 point improvement on the MHGS.

Table 17
MHGS ≥ 1 Point Improvement
Both Hands at 3 months
(n = 114 Subjects)**

n (%)		p – value*
Treatment Group n = 85	Control Group n = 29	
64 (75.3%)	1 (3.4%)	<0.0001

* Fisher's exact test

** Including a subject withdrawn prior to treatment

Table 18 shows the MHGS results, by hand, for both the treatment and control groups at 3 months. In the treatment group there was a statistically significant improvement at 3 months when compared to the control. In addition, the treatment group showed a statistically significant improvement from baseline condition, whereas, the control group did not.

Table 18
MHGS By Hand
(n = 228 Hands*)**

	Baseline	3 Month	Change

	Treatment Group n = 170	Control Group n = 58	Treatment Group n = 170	Control Group n = 58	Treatment Group n = 170	Control Group n = 58
Mean	2.6	2.6	1.5	2.6	-1.1	-0.1
Median	3.0	3.0	1.0	3.0	-1.0	0
Standard Deviation	0.5	0.5	0.8	0.5	0.9	0.2
Range	2 - 3	2 - 3	0 - 3	2 - 3	-3 , 1	-1 , 0
Mean Difference	0		-1.1		-1.0	
p-value - Treatment vs. Control*	0.56		<0.0001		<0.0001	
p-value - vs. Baseline**					<0.0001	0.25

* Wilcoxon Rank-Sum Test
**Wilcoxon Signed-Rank Test
*** Including the subject withdrawn prior to treatment

A sensitivity analysis per site was performed and it was found that one site (Site 7) had effectiveness scores significantly higher than all other sites. When effectiveness was evaluated excluding Site 7, the mean MHGS improvement was 0.7. When effectiveness was evaluated excluding Site 7, 65.5% of subjects showing at least a 1 point improvement on the MHGS in both hands as compared to 75.3% when site 7 was included. The percent of subjects that showed $\geq$ 1 point improvement at 3 months by investigational site is provided in Table 19.

Table 19
MHGS ≥ 1 Point Improvement at 3 months – By Investigational Site
n = 114 subjects

Improvement From Baseline	n (%)			
	Site 1, 2, 3	Site 4	Site 6	Site 7
	n=16	n=44	n=17	n=37
$\geq$ 2 points	0 (0%)	1 (2%)	5 (29%)	25 (68%)
1 point	8 (50%)	27 (61%)	10 (59%)	11 (30%)
0 point	7 (44%)	15 (34%)	2 (12%)	1 (3%)
< 0 point	1 (6%)	1 (2%)	0 (0%)	0 (0%)

Secondary Endpoint Results
Table 20 describes the Global Aesthetic Improvement Scale (GAIS) results for the treatment group as rated by the subjects at 3 months. Evaluation of the subject-reported results demonstrated that 166/170 hands (97.6%) were improved compared to baseline. Only 4 hands (2%) were reported as unchanged and no hands rated as being worse.

Table 20
GAIS By Hand
(n = 170 Hands for 85 subjects)

Rating	n (%)
Very Much Improved	54

Rating	n (%)
	(31.8%)
Much Improved	75 (44.1%)
Improved	37 (21.8%)
No Change	4 (2.4%)
Worse	0 (0%)
TOTAL - At Least "Improved"	**166 (97.6%)**

Table 21 provides long term effectiveness data of Radiesse injected into the dorsum of the hand after initial treatment (single treatment) and re-treatment of subjects that had ≥ 1 point improvement in the MHGS at 3, 6, 9 and 12 months.

Table 21
MHGS Ratings: ≥ 1 Point Improvement at 3, 6, 9 and 12 Months After Initial Treatment and After Re-treatment (n=113 Subjects)

Number (N) or Percentage (%) of Subjects					
Time After Initial Treatment				Time After Re-Treatment	
3 months N=113	6 months N=113	9 months N=35	12 months N=22	3 months N=78	6 months N=61
87 (77%)	82 (72.6%)	25 (71.4%)	15 (68.2%)	64 (82.1%)	54 (88.5%)

POST MARKETING SURVEILLANCE

The following adverse events were received from post-marketing surveillance for the RADIESSE injectable implant, regardless of the indication, 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, blanching, blistering, bluish color, dark circles, did not like results, dizziness, double vision, festoons, flu-like symptoms, grey discoloration, inflammation, ischemic reaction, lymphoid hyperplasia, pallor to skin, possible blood clot, scarring, sensitivity to cold, skin texture changed, tissue mass developed, vascular embolus resulting in tissue compromise, and visual loss or blindness

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. Jewelry should be removed prior to injection and until post-procedure swelling has resolved.

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.

Injection Procedure for Hand Augmentation

1. Prepare patient for percutaneous injection using standard methods. Have the patient wash both hands with soapy water producing friction for 5-10 minutes and then prepare hands with suitable antiseptic. The treatment injection site may be marked for planned injection sites. Jewelry should be removed prior to injection and until post-procedure swelling has resolved.
2. Using the syringe of RADIESSE® injectable implant that has been mixed with Lidocaine using the procedure described in “Mixing Instructions” below, and fitted with the injection needle, slowly push the syringe plunger until RADIESSE® injectable implant extrudes from the end of the needle performing aspiration before bolus injection to avoid intravascular injection. If leakage is noted at the Luer fitting, wipe it clean with sterile gauze. It may be necessary to tighten the needle, remove the needle and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle. A new injection needle may be used for each syringe, or the same injection needle may be connected to each new syringe.
3. Locate the initial site for injection. Patients are to receive injections in the dorsum of the hands between the 1st and 5th metacarpals. Injection should initially occur between the 2nd and 4th metacarpals, taking care not to inject close to the metacarpophalangeal joints. If necessary to achieve optimal correction, injection is also allowed between the 1st and 2nd and 4th and 5th metacarpals.

4. Skin tenting should be performed to separate the skin from vascular and tendinous structures by using the thumb and forefinger of the non-injecting hand to lift skin over the dorsal aspect of the hand being treated.
5. Advance the needle between the subcutaneous layer and superficial fascia with the syringe parallel to the dorsum of the hand. Carefully push the plunger of the RADIESSE® injectable implant syringe to start the injection and inject the RADIESSE® injectable implant material in small boluses, 0.2 – 0.5cc/bolus. No more than 0.5cc should be injected per bolus. The number of boluses will vary depending on the extent of treatment desired. No more than 3cc of RADIESSE® injectable implant (2 syringes) will be injected per hand.
6. 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.
7. Immediately after injection, cover the injection site with a sterile 4x4 gauze and have patient sit on the this hand while the contralateral hand is being injected. This warms the RADIESSE injectable implant making it more malleable for later massaging.
8. Treat the contralateral hand in the same manner as described in steps 2 through 6 above.
9. Immediately after injection of the contralateral hand, cover the injection site with a sterile 4x4 gauze and have the patient sit on this hand.
10. While the contralateral hand is warming, remove the gauze from the hand that was initially injected, have the patient make a fist with this hand, and gently massage the dorsum of the hand until RADIESSE injectable implant has been evenly spread across the dorsum remaining distal to the wrist crease and proximal to the metacarpophalangeal joints.

11. Use a 1:1 correction factor. No overcorrection is needed.

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 2).

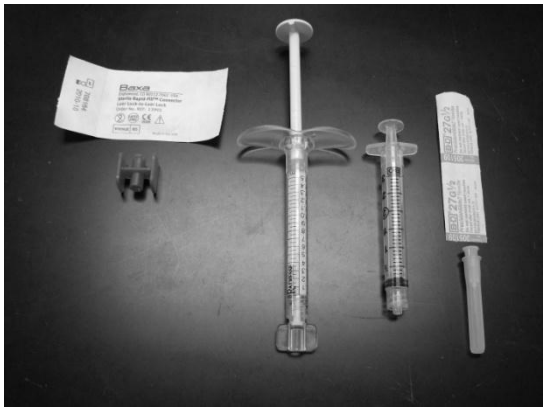

Figure 2:

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 3 and 4).

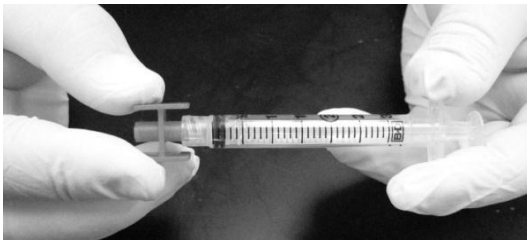

Figure 3

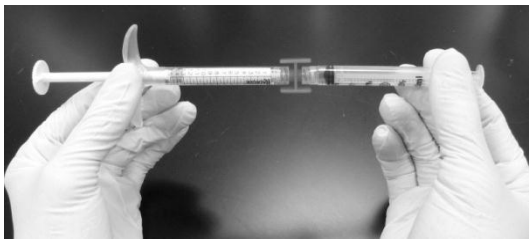

Figure 4

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 5).

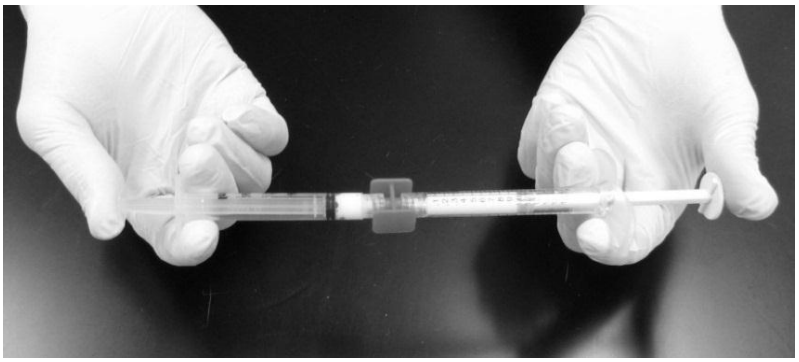

Figure 5

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. Table 20 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 22).

Table 22**. LIDOCAINE CONCENTRATION**

RADIESSE® (cc)	2% Lidocaine (cc)	Resulting Lidocaine Concentration (w/v%)
0.3	0.02	0.30% - 0.33%
0.8	0.11	0.31% - 0.32%
1.3	0.20	0.31% - 0.32%
1.5	0.26	0.31% - 0.32%
3.0	0.45	0.32% - 0.34%

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 two years from date of manufacture. Do not use if the expiration date has been exceeded.

DISPOSAL

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

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MERZ AESTHETICS™

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@merz.com

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