# 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 principal component is synthetic calcium hydroxylapatite suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. RADIESSE® injectable implant (1.5cc) 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 (0.0%) | 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 (0.0%) | 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%) | 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 (0.0%) | 0 (0.0%) |
| Nodule, Bumps/Lumps | 2 (1.8%) | (0.2-6.2) | 2 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Difficulty Performing Activities | 2 (1.8%) | (0.2-6.2) | 2 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Loss of Sensation | 0 (0%) | - | 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)**

| Adverse Event Type | All First Onset (N, % total) | Reported Adverse Events (N, % with event) | | | | |
|---|---|---|---|---|---|---|
| | | 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%) |
| 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)**

| Adverse Event Type | All First Onset (N, % total) | Reported Adverse Events (N, % with event) | | | | |
|---|---|---|---|---|---|---|
| | | 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%) |
| 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%) |
| 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)**

| Adverse Event Type | First Onset (N, % total) | Reported Adverse Events (N, % event type) | | | | |
|---|---|---|---|---|---|---|
| | | 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 Performing Activities | 36 (7.6%) | 32 (88.9%) | 2 (5.6%) | 1 (2.8%) | 1 (2.8%) | 34 (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)**

| Adverse Event Type | First Onset (N, % total) | Reported Adverse Events (N, % event type) | | | | |
|---|---|---|---|---|---|---|
| | | 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)

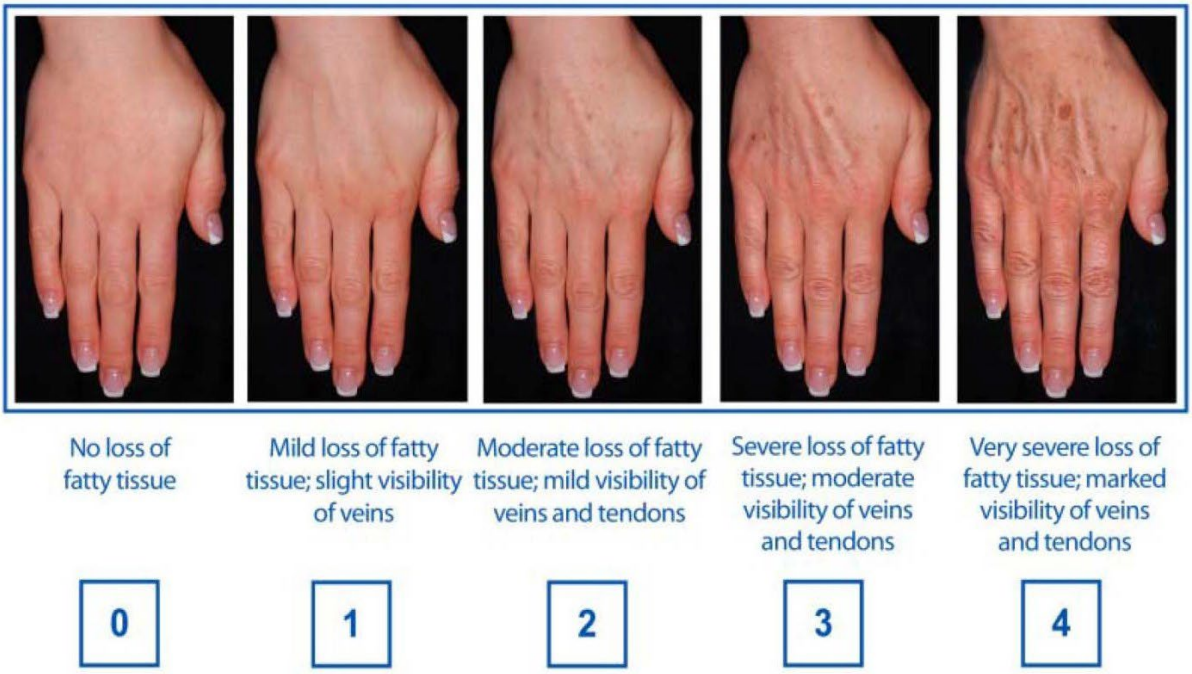



**Table 16. Global Aesthetic Improvement Scale (GAIS)**

| 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 ≥ 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 |
| ≥ 2 points | 0 (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 (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 (31.8%) |
| Much Improved | 75 (44.1%) |
| Improved | 37 (21.8%) |
| No Change | 4 (2.4%) |
| Worse | 0 (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%) |

**Side Effects Reported By Patients**

In a clinical study of RADIESSE® for hand injection, the majority of the patients, 79%, had side effects that were mild or moderate in nature. The most common side effects were related to the injection procedure itself and usually lasted less than or equal to 14 days. Based on the clinical study, the likelihood of experiencing a side effect after treatment with RADIESSE® reported by patients is shown in the table below.

**Table 22. Percent of Patient Reported Side Effects After Treatment**
**N = 113 Subjects**

| Side Effect | Number and Percent (%) of Patients Reporting Side Effects |
|---|---|
| | Number (N)<br>Percentage (%) |
| Swelling | N = 112; (99%) |
| Pain | N = 104; (92%) |
| Redness | N = 92; (84%) |
| Bruising | N = 84; (74%) |
| Difficulty Performing Activities | N = 52; (46%) |
| Itching | N = 52; (46%) |
| Loss of Sensation | N = 17; (15%) |
| Bumps/Lumps | N = 7; (6%) |
| Hematoma (blood clot in the tissue) | N = 1; (0.9%) |

**Post Approval**

**Radiological Evaluation of Implantation in the Hands Post-Approval Safety Study (PAS)**

**Study Objective**

A post-approval study was performed to provide an assessment of the radiographic appearance of RADIESSE® material that was injected into the dorsum of the hands with standard, plain radiography (X-rays).

**Study Design**

This was a single-center, open-label, PAS designed to provide an assessment of the radiographic appearance of RADIESSE® material that was injected into the dorsum of the hands. The hypothesis was that the radiographic appearance of RADIESSE® in the hands would not obscure the bones of the hands as seen on standard, plain radiography (X-rays) of the hand. All enrolled subjects received RADIESSE®, no controls procedures were used in this study.

The twenty subjects (40 hands) were enrolled at a single investigational site in the United States. All subjects (women) were new subjects who did not participate in the pre-market RADIESSE® hand treatment study (Merz #P110607). Subjects enrolled were at least 22 years of age and had hands ratings of 2, 3, or 4 on the validated MHGS, as determined live by a masked evaluator.

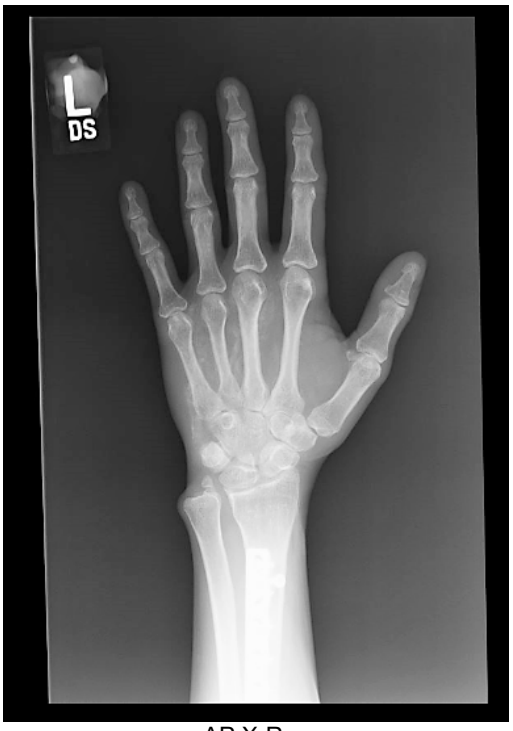
There were two study groups with 10 subjects enrolled in each group.

Group A subjects were required to present with MHGS grade 4 at baseline. Grade 4 hands were defined as, in the dorsal hand: very severe loss of fatty tissue and marked visibility of veins and tendons.

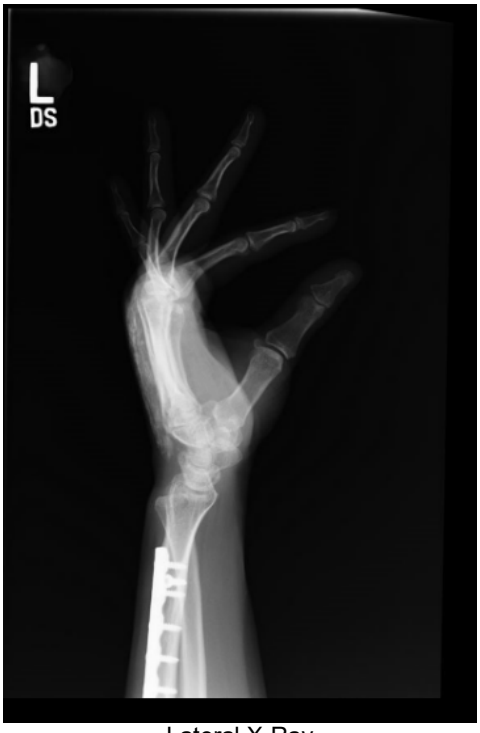
Group B subjects were required to present with MHGS grade 2 or 3 at baseline. Grade 2 and 3 were defined as, in the dorsal hand: moderate to severe loss of fatty tissue and mild to moderate visibility of veins and tendons as determined by the investigator based on the MHGS.

The volume of RADIESSE® required to correct the baseline hand condition was expected to be lower for moderate volume loss and higher for very severe volume loss. Maximum injection volume was two 1.5 cc RADIESSE® syringes per hand (i.e., up to 3 cc total), per treatment visit. Although no touch-up injections were administered during the study, subjects were eligible for up to 3 retreatments over the 24-month study interval.

Initial hands X-rays showed no foreign material in all subjects. Foreign material was present in all hands (100%) on Month 1 X-rays. At Month 6, foreign material was present in 85% of left hands and in 80% of right hands on the lateral view and in 85% of left hands and in 90% of right hands on the AP view. Among subjects who received all 4 available treatments, foreign material was present in 83.3% of hands at Month 24. Importantly, no obscuration of the bones was reported in either hand (left or right) for either view (AP or lateral view) at any evaluated time point. Refer to X-ray images below.



AP X-Ray



Lateral X-Ray

Representative Anteroposterior (AP) and Lateral X-rays of the left hand at the one month time point after treatment with RADIESSE®. Note the faintly radiopaque material in the soft tissue on both views.

**Extent of exposure**

**Table 23 Summary Extent of Exposure**

| | Group A (N = 10) | | Group B (N = 10) | | Total (N = 20) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Initial Treatment Only | 1 | (10.0) | 1 | (10.0) | 2 | (10.0) |
| 2 Treatments | 0 | (0.0) | 4 | (40.0) | 4 | (20.0) |
| 3 Treatments | 5 | (50.0) | 3 | (30.0) | 8 | (40.0) |
| 4 Treatments | 4 | (40.0) | 2 | (20.0) | 6 | (30.0) |

Note: 100% base = subjects enrolled

**Volume Injection**

Injection volumes were recorded as the sum of total volumes of RADIESSE® and lidocaine injected.

**Table 24 Summary Volume Injection**

| | **Group A (N=10)** | **Group B (N=10)** | **Total (N=20)** |
|---|---|---|---|
| | | | |
| Number of Hands | 20 | 20 | 40 |
| | | | |
| Baseline | | | |
| n | 20 | 20 | 40 |
| Mean (SD) | 3.34 (0.361) | 2.64 (0.404) | 2.99 (0.520) |
| Median (Q1, Q3) | 3.52 (3.52, 3.52) | 2.64 (2.64, 2.64) | 2.64 (2.64, 3.52) |
| Min, Max | 2.64, 3.52 | 1.76, 3.52 | 1.76, 3.52 |
| | | | |
| Month 6* | | | |
| n | 14 | 8 | 22 |
| Mean (SD) | 2.26 (0.452) | 2.36 (0.528) | 2.30 (0.470) |
| Median (Q1, Q3) | 2.64 (1.76, 2.64) | 2.64 (2.07, 2.64) | 2.64 (1.76, 2.64) |
| Min, Max | 1.76, 2.64 | 1.50, 2.64 | 1.50, 2.64 |
| | | | |
| Month 12* | | | |
| n | 16 | 16 | 32 |
| Mean (SD) | 2.86 (0.394) | 1.87 (0.545) | 2.37 (0.687) |
| Median (Q1, Q3) | 2.64 (2.64, 3.08) | 1.76 (1.76, 2.20) | 2.64 (1.76, 2.64) |
| Min, Max | 2.64, 3.52 | 0.88, 2.64 | 0.88, 3.52 |
| | | | |
| Month 18* | | | |
| n | 14 | 8 | 22 |
| Mean (SD) | 2.89 (0.639) | 2.20 (0.470) | 2.64 (0.665) |
| Median (Q1, Q3) | 2.64 (2.64, 3.52) | 2.20 (1.76, 2.64) | 2.64 (1.76, 3.52) |
| Min, Max | 1.76, 3.52 | 1.76, 2.64 | 1.76, 3.52 |
| | | | |
| Cumulative Volume | | | |
| n | 20 | 20 | 40 |
| Mean (SD) | 9.24 (3.108) | 5.96 (2.514) | 7.60 (3.248) |
| Median (Q1, Q3) | 9.24 (7.92, 12.32) | 5.59 (3.52, 7.04) | 7.48 (5.28, 10.12) |
| Min, Max | 2.64, 13.20 | 2.64, 10.56 | 2.64, 13.20 |
| * Repeat treatment | | | |

**MHQ (Merz Hand Outcome Questionnaire)**

Overall, mean MHQ function scores at the end of the study (Month 24, left hand: 99.8 and right hand: 100) were higher than baseline,(initial scores which were 95.3 and 97.8 for left and right hand respectively). MHQ pain scores (Month 24, left hand: 0.0 and right hand: 0.5) were lower than baseline. Similar results were obtained by those subjects who received four treatments through the study (Function, left hand: 99.2 and right hand: 100; and Pain, left hand: 0.0 and right hand: 1.7). MHQ pain scores (Month 24, left hand: 0.0 and right hand 0.5) were lower than baseline (prior to injection, left hand 3.0 and right hand 2.3) **Hand Function Test**

Hand-function testing was evaluated by range of motion, functional dexterity, touch sensation, grip strength, tip pinch strength, key pinch strength and palmar pinch strength at the study site at baseline and at 24 months.

In this study, there was no signal of loss of sensation, no deterioration on functional dexterity and no loss of flexion on the range of motion testing in the fingers at Month 24 when compared to baseline in either group. For extension tests, there was a slightly reduced extension in the right hands after treatment that was not observed in the left hands.

Strength tests revealed no appreciable loss of strength for the tip, key and palmar pinch tests and only slight reductions on grip strength (change from baseline at Month 24, left hand: -6.6 and right hand: -7.4). The study was not powered to statistically analyze differences in hand function between groups.

**Study Population**

All 20 subjects enrolled were female. The patient population included subjects of at least 22 years of age that were allocated to one of two study groups based on baseline MHGS ratings, as determined live by a masked evaluator. Patient demographics are provided in Table 25.

Table 25. Patient Demographics N=20

| | Group A (N = 10) | Group B (N = 10) | Total (N = 20) |
|---|---|---|---|
| Sex (n (%)) | | | |
| Male | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Female | 10 (100.0) | 10 (100.0) | 20 (100.0) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Age [years] | | | |
| n | 10 | 10 | 20 |
| Mean (SD) | 61.6 (7.40) | 53.3 (9.83) | 57.5 (9.48) |
| Median (Q1, Q3) | 62.5 (57.0, 65.0) | 52.5 (52.0, 61.0) | 59.0 (52.0, 64.5) |
| Min, max | 48, 75 | 32, 66 | 32, 75 |
| Race (n (%)) | | | |
| White | 9 (90.0) | 10 (100.0) | 19 (95.0) |
| American Indian or Alaskan Native | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Native Hawaiian or other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Black or African-American | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other (Two or more races) | 1 (10.0) | 0 (0.0) | 1 (5.0) |
| Fitzpatrick Skin Type (n (%)) | | | |
| I | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| II | 6 (60.0) | 4 (40.0) | 10 (50.0) |
| III | 3 (30.0) | 6 (60.0) | 9 (45.0) |
| IV | 1 (10.0) | 0 (0.0) | 1 (5.0) |
| V | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| VI | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Note: SD = standard deviation, Q1 = first quartile, Q3 = third quartile, n = number of observations, N = number of subjects in corresponding group

**Data Source**

The data source is the post market approval study required by FDA as a condition of approval for the PMA for hand augmentation to correct volume loss in the dorsum of the hands (P050052/S049). It was a single center, open label, descriptive study with 20 subjects with medium to severe volume loss in both hands conducted to evaluate the radiographic appearance of RADIESSE® in the hands under X-Ray.

**Total Number of Enrolled Study Sites and Subjects, Follow-up Rate**

The study enrolled adults at least 22 years of age at a single center site. There were two study groups, with 10 subjects enrolled in each group.

Group A subjects were required to present with MHGS grade 4 at baseline. Grade 4 hands were defined as, in the dorsal hand: very severe loss of fatty tissue and marked visibility of veins and tendons.

Group B subjects were required to present with MHGS grade 2 or 3 at baseline. Grade 2 and 3 were defined as, in the dorsal hand: moderate to severe loss of fatty tissue and mild to moderate visibility of veins and tendons as determined by the investigator based on the MHGS.

**Table 26. Number of hands treated**

| | Group A (N = 20) | | Group B (N = 20) | | Total (N = 40) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| MHGS Grade 4 hands | 16 | (80.0) | 0 | (0.0) | 16 | (40.0) |
| MHGS Grade 3 hands | 4 | (20.0) | 14 | (70.0) | 18 | (45.0) |
| MHGS Grade 2 hands | 0 | (0.0) | 6 | (30.0) | 6 | (15.0) |
| Note: 100% base = hands enrolled | | | | | | |

**Study Visits and Length of Follow-up**

Subjects were required to present for a total of up to 15 visits and 4 follow-up phone calls. Of these visits, 7 to 10 were in-office investigational site visits; an additional 3 to 5 were X-ray visits at a licensed radiology center and 1 to 4 were follow-up phone calls during their 24-month study participation.

If a subject only received the initial treatment, there were a total of 7 in-office clinic visits, 3 X-ray visits, and 1 follow-up phone call. For each of the 3 optional retreatments received, there was an additional follow-up phone call (72-hours post injection). The fourth X-ray visit was only required at Month 12 if obscuration was present in the 6 month X-ray, and the fifth X-ray visit was only conducted if a subject received all 4 total treatments of RADIESSE® in this study.

**Primary Safety endpoint**

The primary safety endpoint was the number and percent of subjects with an X-ray of either hand with obscuration of the bones of the hand at 1, 6, 12, and 24 months following injection of RADIESSE® in the dorsum of the hand.

**Effectiveness Endpoints**

Secondary effectiveness endpoints were assessed using the Merz Hand Grading Scale (Please refer to MHGS, Figure 1), which were validated for live assessments. Secondary effectiveness additionally was assessed by subject reported assessment of a non-validated Global Aesthetic Improvement Scale (GAIS).

**Bone Obscuration**

Results of the core lab radiologists' blinded assessment of bone obscuration and prominence of any foreign material to that of the previous X-ray for that subject on each hand (right and left) at Month 1, Month 6, and Month 24 are displayed in Table 27.

**Table 27. Bone Obscuration**

| | Foreign Material Present with 95% CI | | Any Bone Obscuration with 95% CI | |
|---|---|---|---|---|
| | n/N | (%) [CI] | n/N | (%) [CI] |
| Month 1 | | | | |
| Left hand | | | | |
| AP view | 20/20 | (100.0) [83.2,100.0] | 0/20 | (0.0) [0.0, 16.8] |
| Lateral view | 20/20 | (100.0) [83.2,100.0] | 0/20 | (0.0) [0.0, 16.8] |
| Right hand | | | | |
| AP view | 20/20 | (100.0) [83.2,100.0] | 0/20 | (0.0) [0.0, 16.8] |
| Lateral view | 20/20 | (100.0) [83.2,100.0] | 0/20 | (0.0) [0.0, 16.8] |
| | | | | |
| Month 6 | | | | |
| Left hand | | | | |
| AP view | 17/20 | (85.0) [62.1, 96.8] | 0/17 | (0.0) [0.0, 19.5] |
| Lateral view | 17/20 | (85.0) [62.1, 96.8] | 0/17 | (0.0) [0.0, 19.5] |
| Right hand | | | | |
| AP view | 18/20 | (90.0) [68.3, 98.8] | 0/18 | (0.0) [0.0, 18.5] |
| Lateral view | 16/20 | (80.0) [56.3, 94.3] | 0/16 | (0.0) [0.0, 19.5] |
| | | | | |
| Month 24 | | | | |
| Left hand | | | | |
| AP view | 5/6 | (83.3) [35.9, 99.6] | 0/5 | (0.0) [0.0, 52.2] |
| Lateral view | 5/6 | (83.3) [35.9, 99.6] | 0/5 | (0.0) [0.0, 52.2] |
| Right hand | | | | |
| AP view | 5/6 | (83.3) [35.9, 99.6] | 0/5 | (0.0) [0.0, 52.2] |
| Lateral view | 5/6 | (83.3) [35.9, 99.6] | 0/5 | (0.0) [0.0, 52.2] |

Note: X-ray at Month 12 was to be conducted only for subjects who had obscuration present at Month 6. X-ray at Month 24 was only conducted for subjects who received 4 total treatments (initial and 3 retreatments). Further, only those hands with foreign material present in the X-ray were evaluated for any bone obscuration. AP = anteroposterior.

Initial hands X-rays showed no foreign material in all subjects. Foreign material was present in all hands (100%) on Month 1 X-rays. At Month 6, foreign material was present in 85% of left hands and in 80% of right hands on the lateral view and in 85% of left hands and in 90% of right hands on the AP view. Among subjects who received all 4 available treatments, foreign material was present in 83.3% of hands at Month 24. Importantly, no obscuration of the bones was reported in either hand (left or right) for either view (AP or lateral view) at any evaluated time point.

**Adverse events**

Reported AEs were local in nature, mostly mild or moderate in severity, and were generally unrelated to the treatment procedure, with the exception of administration-site conditions. The only AE reported as severe was swelling. AEs considered possibly or definitely related to the study device or injection procedure and present in 30% of subjects were injection-site abnormalities of mild to moderate severity, including injection-site swelling, injection-site nodule, and injection-site pain. No serious AEs were reported, and no subject withdrew from the study because of an AE.

Adverse events occurring from the time the subject signed the informed consent through study completion were reported by the investigator or other study staff and by the subjects (30-day diaries).

For 6 (60.0%) subjects in Group A and 8 (80%) subjects in Group B, physicians reported at least one treatment emergent adverse event (TEAE). Of the 14 subjects with at least one physician-reported TEAE over the course of the study, only 6 (30%) subjects had a TEAE that was deemed, by the physician, to be related to the device. There was only one subject for whom the physician reported device-related severe TEAEs. The Subject of Group B experienced related severe swelling in both hands at 15 days after the initial injection with RADIESSE® and again at 29 days after Month 18 re-treatment.

**Duration**

**Table 28 Summary of Physician-Reported TEAEs over the course of the study by duration**

| **MedDRA SOC**<br>**Preferred Term** | **Maximum duration**<br>**n (% of subjects with event)** | | | | |
|---|---|---|---|---|---|
| | 1-3 days | 4-7 days | 8-14 days | 15-30 days | >30 Days |
| General Disorders and administration- site conditions | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) | 2 (33.3%) |
| Nodule | 0 | 0 | 0 | 0 | 1 (100.0%) |
| Pain | 0 | 0 | 0 | 0 | 1 (100.0%) |
| Swelling | 1 (25.0%) | 1 (25.0%) | 1 (25.0%) | 1 (25.0%) | 0 (0.00%) |
| Infections and Infestations | 0 | 0 | 0 | 1 (50.0%) | 1 (50.0%) |
| Injury, poisoning and procedural complications | 0 | 2 (33.3%) | 1 (16.7%) | 0 | 3 (50.0%) |
| Musculoskeletal and connective tissue disorders | 1 (50.0%) | 0 | 0 | 0 | 1 (50.0%) |
| Surgical and medical procedures | 2 (100.0%) | 0 | 0 | 0 | 0 |

**Table 29 Subject-reported TEAEs following initial treatment by maximum duration**

| Side effect | Maximum Duration n (% of subjects with event) | | | | |
|---|---|---|---|---|---|
| | 1-3 Days | 4-7 Days | 8-14 Days | 15-30 Days | >30 Days |
| Swelling | 3 (15.0%) | 10 (50.0%) | 2 (10.0%) | 4 (20.0%) | 1 (5.0%) |
| Redness | 12 (66.7%) | 4 (22.2%) | 0 (0.0%) | 2 (11.1%) | 0 (0.0%) |
| Bruising | 12 (70.6%) | 4 (23.5%) | 1 (5.9%) | 0 (0.0%) | 0 (0.0%) |
| Pain | 6 (37.5%) | 4 (25.0%) | 2 (12.5%) | 3 (18.8%) | 1 (6.3%) |
| Difficulty performing activities requiring the hands | 5 (55.6%) | 2 (22.2%) | 1 (11.1%) | 1 (11.1%) | 0 (0.0%) |
| Itching | 5 (62.5%) | 3 (37.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Loss of ability of hands to sense hot, cold, or touch | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Other | 5 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

**Table 30 Number (%) of subjects with physician-reported TEAEs by System Organ Class and Preferred Term**

| MedDRA System Organ Class Preferred Term | Group A (N=10) | | Group B (N=10) | | Group C (N=10) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Subjects with at least one TEAE | 6 | (60.0) | 8 | (80.0) | 14 | (70.0) |
| **General Disorders and administration site disorders** | 2 | (20.0%) | 4 | (40.0%) | 6 | (30.0%) |
| Nodule | 1 | (10.0%) | 0 | (0.0%) | 2 | (20.0%) |
| Pain | 0 | (0.0%) | 1 | (10.0%) | 1 | (10.0%) |
| Swelling | 1 | (10.0%) | 3 | (30.0%) | 1 | (10.0%) |
| **Infections and infestations** | 2 | (20.0%) | 0 | (0.0%) | 2 | (20.0%) |
| Herpes zoster | 1 | (10.0%) | 0 | (0.0%) | 1 | (10.0%) |
| Upper respiratory tract infection | 1 | (10.0%) | 0 | (0.0%) | 1 | (10.0%) |
| **Injury, poisoning and procedural complications** | 1 | (10.0%) | 5 | (50.0%) | 6 | (30.0%) |
| Animal scratch | 0 | (0.0%) | 1 | (10.0%) | 1 | (5.0%) |
| Contusion | 1 | (10.0%) | 1 | (10.0%) | 2 | (10.0%) |
| Fibula fracture | 0 | (0.0%) | 1 | (10.0%) | 1 | (5.0%) |
| Limb injury | 0 | (0.0%) | 1 | (10.0%) | 1 | (5.0%) |
| Tendon rupture | 0 | (0.0%) | 1 | (10.0%) | 1 | (5.0%) |
| Thermal Burn | 0 | (0.0%) | 1 | (10.0%) | 1 | (5.0%) |
| **Musculoskeletal and connective tissue disorders** | 1 | (5.0%) | 1 | (5.0%) | 2 | (10.0%) |
| Osteoarthritis | 0 | (0.0%) | 1 | (10.0%) | 0 | (0.0%) |
| Synovial cyst | 1 | (10.0%) | 0 | (0.0%) | 1 | (10.0%) |
| **Surgical and medical procedures** | 2 | (20.0%) | 0 | (0.0%) | 2 | (10.0%) |
| Dental implantation | 1 | (10.0%) | 0 | (0.0%) | 1 | (5.0%) |
| Oral surgery | 1 | (10.0%) | 0 | (0.0%) | 1 | (5.0%) |
| Rotator cuff repair | 1 | (10.0%) | 0 | (0.0%) | 1 | (5.0%) |

Note: Treatment emergent adverse events are defined as adverse events with on-set or worsening on or after date of first RADIESSE® injection up to and including study completion. Note: A subject with more than one TEAE within a SOC/Preferred Term was counted once in the SOC/Preferred Term.

**Table 31 Summary of physician-reported TEAEs over the course of the study by duration**

| | Maximum Duration n (% of subjects with event) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| MedDRA SOC Preferred Term | 1-3 Days | | 4-7 Days | | 8-14 Days | | 15-30 Days | | >30 Days | |
| General disorders and administration-site conditions | 1 | (16.7%) | 1 | (16.7%) | 1 | (16.7%) | 1 | (16.7%) | 2 (33.3%) | 2 (33.3%) |
| Nodule | | 0 | | 0 | | 0 | | 0 | 1 | (100%.0) |
| Pain | | 0 | | 0 | | 0 | | 0 | 1 | (100%.0) |
| Swelling | 1 | (25.0%) | 1 | (25.0%) | 1 | (25.0%) | 1 | (25.0%) | | 0 |
| Infections and Infestations | | 0 | | 0 | | 0 | 1 | (50.0%) | 1 | (50.0%) |
| Injury, poisoning and procedural complications | | 0 | 2 | (33.3%) | 1 | (16.7%) | | 0 | 3 | (50.0%) |
| Musculoskeletal and connective tissue disorders | 1 | (50.0%) | | 0 | | 0 | | 0 | 1 | (50.0%) |
| Surgical and medical procedures | 2 | (100.0%) | | 0 | | 0 | | 0 | | 0 |

**Table 32 Subject reported adverse events**

| **Event** | **# of subjects with event** | **% of subjects treated** |
|---|---|---|
| Swelling | 20 (100.0%) | 100.0% |
| Redness | 18 (90.0%) | 90.0% |
| Bruising | 17 (85.0%) | 85.0% |
| Pain | 16 (80.0%) | 80.0% |
| Difficulty performing activities requiring the hands | 9 (45.0%) | 45.0% |
| Itching | 8 (40.0%) | 40.0% |
| Loss of ability of hands to sense hot, cold, or touch | 1 (5.0%) | 5.0% |
| Other | 5 (25.0%) | 25.0% |

**Table 33. Summary of physician-reported TEAEs over the course of the study by severity**

| | Maximum Severity n (% of subjects in the study with event) | | |
|---|---|---|---|
| MedDRA SOC Preferred Term | Mild | Moderate | Severe |
| General disorders and administration-site conditions | 4 (20%) | 1 (5%) | 1 (5%) |
| Nodule | 1 (5%) | 0 | 0 |
| Pain | 0 | 1 (5%) | 0 |
| Swelling | 3 (15.0%) | 0 | 1 (5.0%) |
| Infections and infestations | 2 (10.0%) | 0 | 0 |
| Injury, poisoning and procedural complications | 6 (100.0%) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 2 (30.0%) | 0 | 0 |
| Surgical and medical procedures | 0 | 2 (10.0%) | 0 |

**Merz Hand Grading Scale (MHGS)**

At baseline and subsequent designated visits, a blinded, masked evaluator conducted a live assessment of both hands for each subject enrolled in the study. At Month 1, all hands for all subjects showed a ≥ 1-point improvement from baseline. Summary MHGS results are reported in Table 26.

**Table 34. MHGS ≥1-point improvement in both hands**

| | Group A n/N (%) | Group B n/N (%) | Total n/N (%) |
|---|---|---|---|
| 1-Point Improvement from Baseline | | | |
| Month 1 | 10/10 (100.00%) | 10/10 (100.00%) | 20/20 (100.00%) |
| Month 6 | 8/10 (80.00%) | 9/10 (90.00%) | 17/20 (85.00%) |
| Month 12 | 6/10 (60.00%) | 7/10 (70.00%) | 13/20 (65.00%) |
| Month 18 | 8/10 (80.00%) | 7/10 (70.00%) | 15/20 (75.00%) |
| Month 24 | 8/10 (80.00%) | 5/10 (50.00%) | 13/20 (65.00%) |
| 1-Point Improvement from Month 6 Retreatment | | | |
| Month 7 | 7/7 (100.00%) | 4/4 (100.00%) | 11/11 (100.00%) |
| Month 12 | 5/7 (71.43%) | 3/4 (75.00%) | 8/11 (72.73%) |
| 1-Point Improvement from Month 12 Retreatment | | | |
| Month 13 | 7/8 (87.50%) | 8/8 (100.00%) | 15/16 (93.75%) |
| Month 18 | 6/8 (75.00%) | 7/8 (87.50%) | 13/16 (81.25%) |
| 1-Point Improvement from Month 18 Retreatment | | | |
| Month 19 | 7/7 (100.00%) | 4/4 (100.00%) | 11/11 (100.00%) |
| Month 24 | 5/7 (71.43%) | 3/4 (75.00%) | 8/11 (72.73%) |
| Note: N = number of subjects treated/retreated at corresponding injection visit | | | |

**POST MARKETING SURVEILLANCE**

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

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

## INDIVIDUALIZATION OF TREATMENT

Before treatment, the patient's suitability for the treatment and the patient's need for pain relief should be assessed. The outcome of treatment with RADIESSE® 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.
3. A new injection needle may be used for each syringe, or the same injection needle may be connected to each new syringe.
4. 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.
5. 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.
6. 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.
7. 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.
8. Immediately after injection, cover the injection site with a sterile 4x4 gauze and have patient sit on this hand while the contralateral hand is being injected. This warms the RADIESSE® injectable implant making it more malleable for later massaging.
9. Treat the contralateral hand in the same manner as described in steps 2 through 7 above.
10. Immediately after injection of the contralateral hand, cover the injection site with a sterile 4x4 gauze and have the patient sit on this hand.
11. 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.
12. 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).

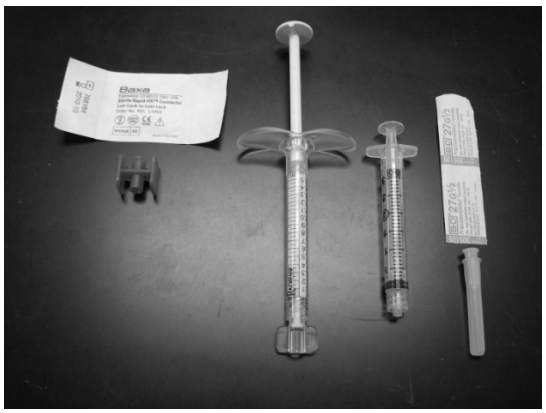


**Figure 2:**

**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).

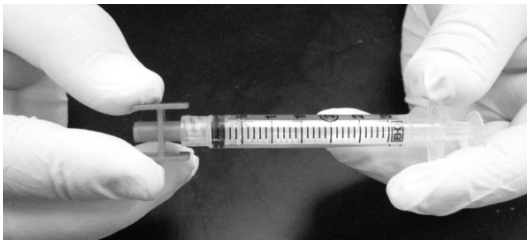


**Figure 3**

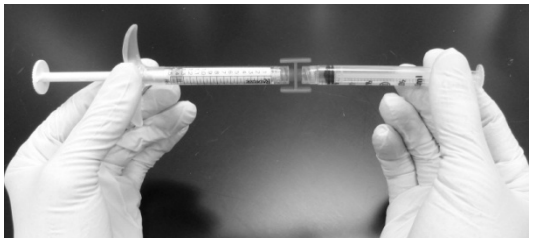


**Figure 4**

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).

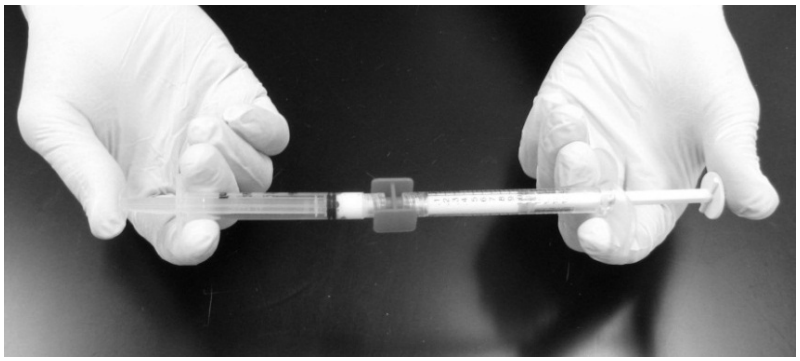


**Figure 5**

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%) |
|---|---|---|
| 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.. 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.

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