

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

**I. GENERAL INFORMATION**

Device Generic Name:                   Injectable Calcium Hydroxylapatite Implant for Soft Tissue Augmentation for the Treatment of Nasolabial Folds

Device Trade Name:                   Radiesse

Applicant's Name and Address:       BioForm Medical, Inc.  
1875 South Grant Street  
Suite 110  
San Mateo, CA 94402

Pre-Market Approval  
Application Number:

Date of Good Manufacturing  
Practices Inspection:                   June 14-17, 2004

Date of Notice of Approval  
to the Applicant:

**II. INDICATIONS FOR USE**

Radiesse is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds such as nasolabial folds

**III. DEVICE DESCRIPTION**

Radiesse is a sterile, latex-free, non-pyrogenic, semi-solid, cohesive subdermal implant. The principle durable component of Radiesse is synthetic calcium hydroxylapatite, a biomaterial with over twenty years of use in orthopedics, neurosurgery, dentistry, otolaryngology and ophthalmology. Calcium hydroxylapatite is the primary mineral constituent of bone and teeth. The semi-solid nature of Radiesse is created by suspending calcium hydroxylapatite (CaHA) particles in a gel carrier that consists primarily of water (sterile water for injection USP) and glycerin (USP). The gel structure is formed by the addition of a small amount of sodium carboxymethylcellulose (USP). The gel is dissipated *in vivo* and replaced with collagen and other soft tissue ingrowth, while the CaHA remains at the site of injection to form a scaffold for the new tissue formation. The result is intended to be long-term soft tissue augmentation. Radiesse (0.3 cc and 1.3 cc) has a particle size range of 25-45 microns and should be injected with a 25 to 27 gauge needle.

**IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS**

Contraindications

- Radiesse is not to be used in patients with known hypersensitivity to any of the components.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

- Radiesse must not be injected into blood vessels. Introduction of Radiesse into the vasculature may occlude the vessels and could cause infarction or embolization.

Warnings

- Use of Radiesse in any person with active skin inflammation or infection in or near the treatment area should be deferred until the inflammatory or infectious process has been controlled.
- Injection procedure reactions to Radiesse have been observed consisting mainly of short-term bruising, redness and swelling. Refer to adverse events section for details.
- The safety and efficacy of Radiesse for use in the lips has not been established.

Precautions

- The calcium hydroxylapatite (CaHA) particles of Radiesse have been shown to be radiopaque. Studies have shown that the CaHA particles are clearly visible on CT Scans and may be visible in standard, plain radiography. The study did not provide any evidence of significant risk of the injected Radiesse potentially masking abnormal tissues or being interpreted as tumors in CT Scans. Patients need to be informed of the radiopaque nature of Radiesse, so that they can inform their primary care health professionals as well as radiologists.
- Radiesse is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged. Do not use if the syringe end cap or syringe plunger is not in place.
- Long-term safety and effectiveness of Radiesse beyond one year have not been investigated in clinical trials.
- The safety of Radiesse in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied. Radiesse should not be used in patients with known susceptibility to keloid formation or hypertrophic scarring.
- As with all transcutaneous procedures, Radiesse injection carries a risk of infection. Standard precautions associated with injectable materials should be followed. No infections have been reported in the clinical study. Refer to adverse events section for details.
- Safety of Radiesse for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- Patients who are using medications that can prolong bleeding, such as aspirin or warfarin, may, as with any injection, experience increased bruising or bleeding at the injection site.
- 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.

**V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

The safety of Radiesse in soft tissue augmentation of nasolabial folds is based upon a prospective randomized study in which 117 patients were treated with Radiesse and Control and evaluated through a 12-month assessment.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

Although there are additional potential risks with bulking agents identified in the literature, including hardening of the tissues at the injection site and/or allergic or autoimmune reactions, these were not reported in any patients.

**VI. ALTERNATE PRACTICES AND PROCEDURES**

The alternative treatments include permanent implants, other injectable dermal fillers or no treatment at all.

**VII. MARKETING HISTORY**

Radiesse is currently marketed worldwide including Europe, Canada and South America. Radiesse has not been withdrawn from marketing for any reason.

**VIII. SUMMARY OF PRECLINICAL STUDIES**

**A. Bench Testing**

Validation testing has been completed on the components (calcium hydroxylapatite, sterile water for irrigation, and sodium carboxymethylcellulose) and the packaging for Radiesse. The in process, as well as the final packaged and sterilized Radiesse was validated.

The following bench tests were conducted to evaluate the performance characteristics of final, packaged and sterilized Radiesse.

Injection Testing - Radiesse can be extruded in one minute with an average force of <15 lbf.

Syringe Leakage - Safety testing demonstrated that the syringe, injection needle or the syringe Luer cap would not rupture with the maximum hand pressure of 30 pounds force (133 Newtons) applied to the syringe push rod using the finger grips.

Simulated Use Testing - Radiesse, as prepared for injection in primed injection needles, remained functional after twelve hours at room conditions showing Radiesse is sufficiently resistant to dehydration.

Particle Durability - The particles of CaHA remained unchanged after being injected to all processing (including sterilization) and after implantation injection demonstrating that the particles are durable.

Environmental Exposure - Radiesse has been subjected to temperature extremes including multiple freezing cycles and heat exposures including two years at 45°C (113°F) without loss of functionality.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

**B. Sterilization and Shelf-life Testing**

Steam sterilization of Radiesse filled syringes was validated to provide a sterility assurance level (SAL) of  $10^{-6}$ . Testing performed on finished product verified that endotoxin levels are consistently maintained. The heat-sealing of the foil pouches has been validated and demonstrated to produce consistent seals with peel strengths of 5 pounds force. Real time and accelerated testing on Radiesse syringes support a shelf life claim of three years.

**C. Biocompatibility Testing**

Radiesse was subjected to *in-vitro* and *in-vivo* testing based on ISO10993 (Biological Evaluation of Medical Devices), using historically accepted test methods of biomedical materials or United States Pharmacopoeia references in accordance with GLP regulations. Test results indicate Radiesse is nontoxic and hemocompatible with no mutagenic response. Although there was a positive hemolytic result during testing, it has been shown this is attributed to the glycerin found in the aqueous gel vehicle.

*In-vivo* tests assessed sensitization, irritation, tissue reaction during short-term implantation, systemic reactions, and long-term safety. It was concluded that based on these tests Radiesse was nonantigenic, a nonirritant, and nontoxic with no concerns for long-term safety.

**D. Animal Studies**

A 36-month implant study was conducted with a calcium hydroxylapatite implant (identical to Radiesse, except the CaHA particles were larger) in canines. The objective of the study was to determine the biocompatibility and migration potential.

Using cystoscopic guidance, the implant was injected into the periurethral tissue of the bladder neck into twenty-four (24) female dogs. Twelve (12) additional dogs were similarly injected with the gel carrier (without the calcium hydroxylapatite particles). Dogs assigned to the 12, 24 and 36-month groups were re-injected six months after the initial injection. Blood and urine samples were collected from each animal for routine hematology, clinical chemistry and urinalysis prior to study initiation, at six-month intervals, and prior termination.

Designated dogs were terminated after 1, 3, 6, 12, 25 and 36 months after initial injection. Each was necropsied; injection sites and other tissue inspected grossly, and implant sites and selected tissues processed for microscopic examination. All of the dogs tolerated the procedure well and remained in good health during the course of the study except one that was euthanized for a reason unrelated to the Radiesse implantation.

The dog study reported the following significant findings:

- ◆ The hematology, clinical chemistry, urinalysis were acceptable throughout the study. All findings noted during necropsy were found to be within normal limits. There was

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

no clinical evidence that the injection procedure or the implant caused untoward effects in the dogs.

- ◆ Microscopic evaluations of the implant sites at 1, 3, 6 and 12 months revealed two mixed but separate responses. A simple macrophage clearing response was associated with the sodium carboxymethylcellulose in the gel carrier of the implant. A delicate fibrous encapsulation was associated with the calcium hydroxylapatite spherical particles. The implant at all time points was found to be biocompatible, forming a well-defined injection site. The calcium hydroxylapatite particles and the sodium carboxymethylcellulose carrier remained at the injection site with no evidence of migration. While some particles had undergone biodegradation into small particles that were engulfed and solubilized at the site by macrophages, most remained intact. Accidental deposits intraperitoneally or intravascularly caused by the dogs' anatomy, resulted in no clinical response or histomorphological cellular reaction unlike that found in the urinary bladder sites.
- ◆ The presence of the implant caused no reaction in the adjacent tissues.
- ◆ During the 36-month duration of the study, the CaHA particles in the implant were surrounded by a thin fibroplastic stroma and remained at the injection site without evidence of migration.

It was concluded that the implant was safe when injected into urinary bladder sites in dogs.

## **IX. SUMMARY OF CLINICAL STUDIES**

### **A. Study Objectives**

The purpose of the study was to assess the safety and effectiveness of Radiesse for the correction of nasolabial folds. The study compared nasolabial fold changes and incidence of adverse events in patients treated with Radiesse and treated contralaterally with Control, a commercially available product labeled for this indication.

### **B. Study Design**

The study was a prospective, randomized, controlled trial in 117 patients at four sites with 113 patients completing 6-month follow-up after optimal correction had been achieved. At the time of the analysis, twelve (12) month safety data of 47 patients were included.

Individual patient study participation lasted up to 12 months following the initial treatment. Patients were enrolled at the time of the patient informed consent.

Safety and effectiveness data included all applicable pre- and post-operative evaluations up to twelve months. Additional evaluations were performed if, in the opinion of the investigator, they were indicated.

All injections were performed by the investigators. Evaluations (baseline and post-procedure) that impacted the efficacy variables and safety profile as defined in the protocol were performed by or under the direction of the investigator at each site.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

**Primary Effectiveness Endpoint**

The primary effectiveness endpoint of the study was to evaluate, using the LRS, whether Radiesse was non-inferior to Control for the correction of nasolabial folds 3 months after final treatment by comparing the percent of patients where Radiesse was superior to Control versus the percent of patients where Radiesse was inferior to Control.

**Secondary Effectiveness Endpoints**

The secondary effectiveness endpoints of the study were:

- ◆ To evaluate, using the LRS, whether Radiesse is superior to Control for the correction of nasolabial folds 6 months after final treatment by comparing the percentage of patients where Radiesse was superior to Control versus the percentage of patients where Radiesse was inferior to Control.
- ◆ To evaluate, using the GAIS, whether Radiesse is non-inferior to Control for the correction of nasolabial folds 3 and 6 months after final treatment by comparing the percentage of patients where Radiesse was superior to Control versus the percentage of patients where Radiesse was inferior to Control.

**Safety Endpoints**

Safety was evaluated by the incidence and duration of local and systemic adverse events of both Radiesse and Control.

**C. Study Protocol**

**Patient Selection**

Inclusion Criteria

- ◆ Had right and left nasolabial folds with a rating of 3 or 4 based on the Lemperle Scale
- ◆ At least 18 years of age
- ◆ Signed a written informed consent
- ◆ Understood and accepted the obligation not to receive any other facial procedures through 6 month follow-up
- ◆ Understood and accepted the obligation and is logistically able to present for all scheduled follow-up visits
- ◆ Understood that during the study there may be unevenness in the nasolabial folds that will not be corrected until after the 6 month follow-up visit is completed

Exclusion Criteria

- ◆ Had curvilinear fold(s) (defined as perioral creases in continuity with the nasolabial fold(s))
- ◆ Had a known bleeding disorder (e.g., thrombocytopenia, thrombasthenia, or von Willebrand's disease)

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

- ◆ Had received or is anticipated to receive anti-platelets, anti-coagulants, thrombolytics, vitamin E or anti-inflammatories from 1-week pre to 1-month post injection
- ◆ Was receiving systemic corticosteroids or anabolic steroids (standard doses of inhaled or nasal corticosteroids are acceptable)
- ◆ Had a history of chronic or recurrent infection or inflammation that would preclude participation in the study
- ◆ Had received silicone injections, facial tissue augmentation other than collagen, grafting, or any other surgery in either nasolabial fold
- ◆ Had received collagen in either nasolabial fold within the past 6 months
- ◆ Had severe allergies manifested by a history of anaphylaxis
- ◆ Had a known lidocaine hypersensitivity
- ◆ Was pregnant, lactating, or not using acceptable contraception<sup>1</sup>
- ◆ Was enrolled in an interfering study
- ◆ Had history of keloid formation
- ◆ Had received over-the-counter wrinkle products (e.g., alpha-hydroxy acids) or prescription treatments (e.g., Renova, Retin-A, micro-dermabrasion, chemical peels) within 4 weeks prior to study or intended to receive those products and/or treatments during the study

Treatment Procedures

Each patient received Radiesse in one nasolabial fold and Control in the contralateral nasolabial fold. Treatment assignments were randomized side to side at the time of the injection<sup>2</sup>. The patient was not to be told their treatment assignments through 6 months. A nasolabial fold was defined as the fold extending from the corner of the nose to the corner of the mouth.

2 and 4 weeks from the initial injection, patients returned for an evaluation of their nasolabial folds. Photographs were taken of both folds using the same standardized photography procedure used for enrollment photographs. If, in the judgment of the treating physician using the enrollment photographs as a reference, one or both folds require a second or third treatment, respectively, the fold(s) that need to be corrected were injected as per the procedures identified in the protocol, ensuring that product randomization assignments are maintained.

6 and 8 weeks from the initial injection, patients who received treatment at Week 2 or Week 4 returned for evaluation of their nasolabial folds. Photographs were taken of both folds using the same standardized photography procedure used for enrollment photographs.

3 months from the last injection in a given fold, all patients returned for evaluation and photographs of their nasolabial folds using the same standardized photography

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<sup>1</sup> In-office urine test was administered under the direction of the investigator to assess pregnancy status.

<sup>2</sup> Computer generated randomization assignments were prepared and sealed in individual envelopes by patient ID# and opened at the time of treatment.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

procedure used for enrollment photographs. If the last treatment for the left fold occurred on a different visit than the right fold, the patient returned for two 3-month visits.

6 months from the last injection in a given fold, all patients returned for evaluation and photographs of their nasolabial folds using the same standardized photography procedure used for enrollment photographs. If the last treatment for the left fold occurred on a different visit than the right fold, the patient returned for two 6-month visits. Adverse events were recorded for all patients. Each investigator assessed each patient on the GAIS Rating Scale.

Between completion of the patient's last 6-month visit and their 12-month visit, if a patient desired a touch up in one or both folds with Radiesse, within one month of the planned touch up, it was administered by the investigator.

12 months from the last injection in the original Radiesse fold, all patients were scheduled to return for evaluation of their nasolabial folds. Photographs were to be taken of both folds using the same standardized photography procedure used for enrollment photographs.

Patients were able to receive Radiesse at baseline, 1 month after initial injection and 6 months after last injection, if study criteria were met. Fifty-two percent patients received 1 injection, while the remaining patients had two or more injections. A majority of patients underwent the procedure with block anesthesia. This was the case not only at the time of the initial injection but for follow-up injections.

## **Study Variables**

### **D. Description of Study Population**

Five hundred sixty-three (563) patients had informed consent obtained for inclusion into the study, of which 117 patients were injected with both Radiesse and Control. Of the 117 receiving treatment, all patients were included in the primary efficacy analysis as any patients missing assumed no change from baseline for both Radiesse and Control. Safety data was analyzed for all injected patients to their last known follow-up.

All 117 injected patients at 4 investigational sites were included in the safety analysis. Safety data was analyzed for all injected patients to their last known follow-up time-period.

Protocol deviations were minor and did not exclude any subjects in either the safety or effectiveness analysis.

### **Baseline Patient Characteristics**

The Table 1 contains the patient demographic characteristics.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds  
Original Premarket Approval Application  
Section 2 – Summary of Safety and Effectiveness**

**Table 1  
Patient Demographics  
N = 117**

<b>Age (Years)</b>	
Mean	54.7
Standard Deviation	8.9
Minimum	31.0
Maximum	76.0
<b>Gender</b>	
Female	105 (89.7%)
Male	12 (10.3%)
<b>Body Mass Index (BMI)<sup>3</sup></b>	
Mean	24.3
Standard Deviation	3.8
Minimum	17.1
Maximum	37.9
<b>Race</b>	
American Indian	0 (0.0%)
Asian	0 (0.0%)
Black	2 (1.7%)
Caucasian	102 (87.2%)
Hispanic	11 (9.4%)
Other	2 (1.7%)

Table 2 details the paired distribution of the LRS for both Radiesse and Control for the 117 patients. Most patients (47.0%) had an LRS of 3 in both nasolabial folds.

**Table 2  
Distribution of LRS  
Pre-Treatment  
N = 117**

<b>Radiesse</b>	<b>Control</b>	<b>Number (Percent)</b>
3	3	55 (47.0%)
3	4	20 (17.1%)
4	3	21 (17.9%)
4	4	21 (17.9%)

Treatment Information

The volume of Radiesse injected during the course of the study is seen in Table 3. The total mean volume for Radiesse was 1.2ml and was 2.4ml for the Control. There was significantly less Radiesse injected when compared to the amount of Control injected ( $p < 0.0001$ ). Volume of injected material was compared at initial injection, 2 weeks, and 4 weeks for the two products. A t-test was used to evaluate the difference and the

<sup>3</sup> BMI = 703(Weight in pounds/Height in inches<sup>2</sup>)

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds  
Original Premarket Approval Application  
Section 2 – Summary of Safety and Effectiveness**

resultant p values. Please note that volumes of '0' were inserted in order to create the delta volume variable when a value was not available for a given observation. For example, if a patient received an injection of one material and not of another, the missing data point was substituted with a value of '0' in order to be able to create the delta variable used in the t-test.

Even though the protocol allowed continuous injections until optimal correction was achieved, all patients (for both Radiesse and Control) achieved the optimal correction with no more than three injections. See Table 3 for the volume of material injected for both Radiesse and the Control in the Initial Injection Phase and Table 4 for the total amount of material injected.

**Table 3  
Volume of Material Injected (ml)**

	Baseline		2 Weeks		4 Weeks	
	<b>Radiesse N = 117</b>	<b>Control N = 117</b>	<b>Radiesse N = 54</b>	<b>Control N = 76</b>	<b>Radiesse N = 7</b>	<b>Control N = 12</b>
<b>Volume</b>						
Mean	1.0	1.7	0.4	0.9	0.5	0.7
Standard Deviation	0.4	0.6	0.2	0.3	0.2	0.3
Minimum	0.3	0.8	0.2	0.4	0.2	0.2
Maximum	1.8	3.6	1.0	1.9	0.8	1.2
p Value	<0.0001		<0.0001		0.0975	

**Table 4  
Total Volume of Material Injected (ml)  
N = 117**

	<b>Radiesse</b>	<b>Control</b>	<b>Difference</b>	<b>p-Value</b>
Mean	1.2	2.4	1.1	<0.0001
Median	1.1	2.2	1.1	
Standard Deviation	0.5	0.9	0.8	
Minimum	0.3	0.8	-0.4	
Maximum	2.7	4.7	3.0	

**E. Effectiveness Endpoint Results**

The primary effectiveness endpoint of the study was to evaluate, using the Lemperle Scale (LRS), whether Radiesse is non-inferior to Control for the correction of nasolabial folds 3 months after final treatment by comparing the percentage where Radiesse was superior to Control versus the percentage where Radiesse was inferior to Control.

Per the protocol, missing data would be treated as no advantage for either Radiesse or Control. Therefore, the effectiveness analysis is based on N = 117 patients for both the three and 6-month periods in all the analyses. The number of patients missing for those follow-ups was very limited (1.7% at 3 months and 3.4% at 6 months), there was no affect on the study results or the conclusions drawn from those study results.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

Primary Effectiveness Endpoint – LRS at 3 Months

A vast majority (84.6%) of Radiesse treated folds were determined to be superior to the Control treated folds while 12.8% were determined to be equivalent at three months using the LRS. Non-Inferiority is declared if the lower limit of the one-sided 97.5% confidence interval is greater than 45%. This criterion is equivalent to a 5% disadvantage for Radiesse. It was determined that Radiesse exceeded the primary endpoint of non-inferiority as established in the clinical protocol.

**Table 5**  
**Primary Effectiveness Endpoint**  
**Non-Inferiority - LRS**  
**3 Months**  
**N = 117**

Radiesse <sup>4</sup> Compared to Control				Radiesse Superior Among Patients with Discordant Results		Radiesse Superior Among All Patients	
Superior	Equivalent	Inferior	p-Value <sup>5</sup>	Point Estimate	Lower Limit One-sided 97.5% Exact CI <sup>6</sup>	Point Estimate	Lower Limit One-sided 97.5% Exact CI
99 (84.6%)	15 (12.8%)	3 (2.6%)	<0.0001	97.1%	91.6%	84.6%	76.8%

**Secondary Effectiveness Endpoint Results**

The secondary effectiveness endpoints of the study were:

1. To evaluate, using the LRS, whether Radiesse is superior to Control for the correction of nasolabial folds 6 months after final treatment by comparing the percentage of patients where Radiesse was superior to Control versus the percentage of patients where Radiesse was inferior to Control, and;
2. To evaluate, using the GAIS, whether Radiesse is non-inferior to Control for the correction of nasolabial folds 3 and 6 months after final treatment by comparing the percentage of patients where Radiesse was superior to Control versus the percentage of patients where Radiesse was inferior to Control.

<sup>4</sup> Two patients did not have a three-month evaluation.

<sup>5</sup> McNemar's Test

<sup>6</sup> CI = Confidence Interval

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

Secondary Effectiveness Endpoint – Non-Inferiority with GAIS – 3 Months

A secondary effectiveness endpoint was determining the effectiveness of Radiesse using the GAIS evaluation. As with the LRS, a significantly greater number of Radiesse treated folds (83.8%) were determined to be superior to Control treated folds, 13.7% of the Radiesse treated folds were determined to be equivalent to the Control treated folds while 2.6% were determined to be inferior ( $p < 0.0001$ ). It was determined that Radiesse met this secondary effectiveness endpoint.

Secondary Effectiveness Endpoint – Superiority Using GAIS – 6 Months

Radiesse treated folds were determined to be superior to Control treated folds at 6 months using GAIS. Superiority was declared, as the lower limit of the one-sided 97.5% confidence interval was greater than 50%.

Assessment of Inter-Observer Agreement on Change in Photograph-Based LRS and GAIS at 3 and 6 Months

An analysis of inter-observer agreement the photo-based LRS and GAIS results at 3 and 6 months demonstrated that all three evaluators consistently rated folds using either the photo-based LRS or GAIS at 3 or 6 months.

An analysis of the three methods of effectiveness was performed. With the establishment that the LRS and the Photo-based GAIS at 3 and 6 months provided reliable and consistent analyses from the three blinded evaluators, those results were tested to determine if there could be a correlation drawn between the observations using the two photo-based methods by the blinded evaluators as well as the observations of the investigators that had performed the Live-GAIS evaluation. The analyses revealed that that was a high correlation ( $p < 0.0001$ ) between the three methodologies.

Patient Guess of Treatment Received

The patients were asked at each visit to guess which product was injected into each of their treated folds. Table 6 details the results of the patient guess from the initial baseline injection through the 6 month follow-up. It can be seen that patients increasingly guessed correctly as the study progressed. This is not an unexpected result as Radiesse provided the longer lasting treatment. The patient guess was not used as a blinded measure of effectiveness, as that was provided by the three blinded evaluators.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds  
Original Premarket Approval Application  
Section 2 – Summary of Safety and Effectiveness**

**Table 6  
Patient Guess of Treatment Received**

<b>Evaluation</b>	<b>Correct</b>	<b>Incorrect</b>
Baseline	70 (59.83%)	47 (40.17%)
2 Weeks	73 (62.93%)	43 (37.07%)
4 Weeks	67 (59.29%)	46 (40.71%)
6 Weeks	48 (59.26%)	33 (40.74%)
8 Weeks	9 (75.00%)	3 (25.00%)
3 Months	87 (75.65%)	28 (24.35%)
6 Months	107 (94.69%)	6 (5.31%)

Most Satisfactory Nasolabial Fold at 6 Months

Both the investigator and the patient were asked to judge the most satisfactory treated fold at the 6 month follow-up visit prior to patient unblinding. A vast majority of both the patients and the investigators (96.5%) judged the Radiesse treated fold to be the most satisfactory. See Table 7.

**Table 7  
Most Satisfactory Nasolabial Fold  
6 Months**

	<b>Patient</b>		<b>Physician</b>	
	<b>Radiesse</b>	<b>Control</b>	<b>Radiesse</b>	<b>Control</b>
Number of Patients	109 (96.46%)	4 (3.54%)	109 (96.46%)	4 (3.54%)

**F. Safety Results**

**Adverse Events**

The clinical trial established Radiesse as being a safe medical device for soft tissue augmentation for the treatment of nasolabial folds. The adverse events that were reported were not unexpected with most being mild in nature and short in duration. It can be seen that the adverse events are a result of the injection procedure, which is not unusual for dermal filler products and is not a result of Radiesse being injected. It is important to note that there were no reports of granulomas, allergic reaction, erosion, necrosis, infection or hematomas at any time during the course of the study. The rate and duration of the adverse events of Radiesse were not significantly different from those reported for Control, except for ecchymosis and edema. This is also not unexpected, as it was concluded that these are a result of the larger and longer needles used with Radiesse when compared to the needles used with Control. There were no serious adverse event or patient deaths reported during the course of the study.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

**Table 8**  
**Adverse Events**  
**Patients With at Least One Adverse Event per Treatment Side**  
**N = 117**

Adverse Event			p-Value
	Radiesse N(%)	Control N(%)	
Allergic Reaction	0 (0.0%)	0 (0.0%)	N/A
Ecchymosis	74 (63.2%)	51 (43.6%)	0.0038
Edema	86 (73.5%)	66 (56.4%)	0.0090
Embolization	0 (0.0%)	0 (0.0%)	N/A
Erosion	0 (0.0%)	0 (0.0%)	N/A
Erythema	82 (70.1%)	88 (75.2%)	0.4636
Extrusion	0 (0.0%)	0 (0.0%)	N/A
Granuloma	0 (0.0%)	0 (0.0%)	N/A
Hematoma	0 (0.0%)	0 (0.0%)	N/A
Infection	0 (0.0%)	0 (0.0%)	N/A
Necrosis	0 (0.0%)	0 (0.0%)	N/A
Needle Jamming	1 (0.9%)	0 (0.0%)	1.0000
Nodule	1 (0.9%)	3 (2.6%)	0.6218
Pain	34 (29.1%)	27 (23.1%)	0.3717
Pruritis	22 (18.8%)	26 (22.2%)	0.6275
Other	36 (30.8%)	28 (23.9%)	0.3046

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

**Table 9**  
**Initial Injection Phase**  
**Duration of Adverse Events (Days)**  
**Number of Events, Mean, Std, (Range)**

<b>Adverse Event</b>	<b>Radiesse</b>	<b>Control</b>	<b>p-Value</b>
Allergic Reaction	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Ecchymosis	N = 89 8.44, 11.44 (1 – 96)	N = 57 7.49, 12.31 (2 – 96)	0.6365
Edema	N = 107 7.21, 8.31 (1 – 47)	N = 90 6.01, 7.80 (1 – 60)	0.3025
Embolization	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Erosion	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Erythema	N = 109 14.82, 29.41 (1 – 177)	N = 135 19.99, 41.98 (1 – 336)	0.2597
Extrusion	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Granuloma	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Hematoma	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Infection	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Necrosis	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Needle Jamming	N = 1 1.00 (1 – 1)	N = 0 0.0, 0.0 (0 – 0)	N/A
Nodule	N = 1 195.00 (195 – 195)	N = 4 34.00, 38.43 (8 – 91)	0.0332
Pain	N = 39 4.79, 5.56 (1 – 32)	N = 30 4.07, 3.56 (1 – 17)	0.5115
Pruritis	N = 24 4.21, 3.89 (1 – 17)	N = 28 9.39, 22.50 (1 – 122)	0.2403
Other	N = 52 12.17, 22.15 (1 – 155)	N = 39 15.74, 19.12 (1 – 74)	0.4126

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

**Table 10**  
**3-6 Months**  
**Duration of Adverse Events (Days)**  
**Number of Events, Mean, Std, (Range)**

<b>Adverse Event</b>	<b>Radiesse</b>	<b>Control</b>	<b>p-Value</b>
Allergic Reaction	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Ecchymosis	N = 2 3.50, 0.71 (3 – 4)	N = 5 6.4, 5.08 (3 – 15)	0.4809
Edema	N = 2 5.00, 2.83 (3 – 7)	N = 4 4.5, 1.91 (3 – 7)	0.8042
Embolization	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Erosion	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Erythema	N = 5 26.00, 25.80 (3 – 56)	N = 5 24.80, 26.27 (3 – 55)	0.9437
Extrusion	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Granuloma	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Hematoma	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Infection	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Necrosis	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Needle Jamming	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Nodule	N = 0 0.0, 0.0 (0 – 0)	N = 0 0.0, 0.0 (0 – 0)	N/A
Pain	N = 4 4.00, 1.83 (2 – 6)	N = 4 3.25, 1.26 (2 – 5)	0.5239
Pruritis	N = 1 10.00 (10 – 10)	N = 1 10.00 (10 – 10)	N/A
Other	N = 4 7.50, 3.87 (4 – 13)	N = 5 29.40, 50.20 (2 – 119)	0.3854

**G. Short Term and Long Term Radiographic Evaluation of Radiesse**

Radiesse contains calcium hydroxylapatite particles (25-45 microns) that are radiopaque and are suspended in a water based gel therefore a radiographic study was conducted to assess the radiographic appearance of Radiesse in patients with both short-term and long-term follow-up after injection for HIV-associated facial lipoatrophy and treatment of nasolabial folds. The radiographic assessment consisted of standard, plain radiography and CT scanning. All X-rays and CT Scans were assessed by two blinded, licensed radiologists. The inclusion of these patients allowed assessment of patients immediately

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds  
Original Premarket Approval Application  
Section 2 – Summary of Safety and Effectiveness**

after initial injection, at least 12 months after initial injection and patients with varying volumes of Radiesse implanted.

A total of 58 patients in three patients groups were enrolled into the study. A description of the patient groups is provided in Table 11 below.

**Table 11  
Description of Patient Groups**

	<b>Description</b>	<b># Patients</b>
Long-Term Lipoatrophy	Patient who received up to 4 Radiesse injections for the treatment of HIV-associated facial lipoatrophy prior to imaging – at baseline, 1 months, 6 months, and post-12 months. These patients participated in either 1 or 2 imaging sessions.	28
Short-Term Lipoatrophy	Patients who received imaging prior to receiving their initial Radiesse injection for the treatment of HIV-associated facial lipoatrophy and imaging immediately after treatment.	15
Short-Term Nasolabial	Patients who received imaging prior to receiving their initial Radiesse injection for the treatment of nasolabial folds and imaging immediately after treatment.	15
Total		58

Based on the three patient groups described in Table 11 above, 6 “imaging groups” were identified, as patients in each of the three patient groups may or may not have undergone imaging both before and after injections of Radiesse. This resulted in 110 imaging sessions (55 CT scans and 55 x-rays) being evaluated by each the two blinded evaluators for a total of 220 imaging data points. Table 12 below is a summary of the imaging groups. Also included in the table below is the average volume of Radiesse injected for each of the groups and the average time from injection to the time of the imaging sessions.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

**Table 12**  
**Description of Imaging Groups**

Patient Group	Long-Term Lipoatrophy N=28		Short-Term Lipoatrophy N=15		Short-Term Nasolabial N=15	
	Prior to 12 Month Injection	Immediately After 12 Month Injection	Prior to Initial Injection	Immediately After Initial Injection	Prior to Initial Injection	Immediately After Initial Injection
<b>Group Number</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
Number of Patients Imaged	23	27	15	15	15	15
Average Time from Initial Injection to Imaging	405 days 384-425	404 378-427	N/A	2.5 Days (0-6)	N/A	4.8 Days (1-7)
Average Time from Last Injection to Imaging	324 Days 175-399	11.7 Days (0-40)		N/A		N/A
Average Total Volume Radiesse Injected (ml)	12.2 (6.7 -25.0)	16.5 (7.8-34.1)		10.3 (4.9 – 17.9)		2.1 (1.3 -3.6)

Radiesse was determined to be visualizable in the X-rays by both evaluators, but the X-ray readings were not conclusive for the presence of Radiesse, when in fact it was present. This is not a surprising finding, as the volume of Radiesse in some patients was small and the sensitivity of X-ray may not be sufficient to detect these smaller volumes of Radiesse. Both evaluators noted the presence of material in Group 5 (N = 3), even though these patients not yet received injections.

When there was a larger volume of material injected, it was more often observed on the X-ray. Groups 2 and 4 represented patients just treated for facial lipoatrophy at high volumes explaining why Radiesse was more often identified as being present by both evaluators. See Table 13 for details.

**Table 13**  
**Mass of Material Visualizable**  
**X-Rays**

		Group 1 N = 23	Group 2 N = 27	Group 3 N = 15	Group 4 N = 15	Group 5 N = 15	Group 6 N = 15
Evaluator 1	Yes	1 (4.4%)	16 (59.3%)	0 (0.0%)	6 (40.0%)	1 (6.7%)	1 (6.7%)
	No	22 (95.7%)	11 (40.7%)	15 (100.0%)	9 (60.0%)	14 (93.3%)	14 (93.3%)
Evaluator 2	Yes	2 (8.7%)	14 (51.9%)	0 (0.0%)	4 (26.7%)	2 (13.3%)	3 (20.0%)
	No	21 (91.3%)	13 (48.1%)	15 (100.0%)	11 (73.3%)	13 (86.7%)	12 (80.0%)
Combined N = 2X	Yes	3 (6.5%)	30 (55.6%)	0 (0.0%)	10 (33.3%)	3 (10.0%)	4 (13.3%)
	No	43 (93.5%)	24 (44.4%)	30 (100.0%)	20 (66.7%)	27 (90.0%)	26 (86.7%)

Radiesse was more readily visualizable by CT Scan when compared to X-ray and the CT Scan results were read more consistently between two evaluators. Radiesse was

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

easily seen when imaging was done soon after an injection and was also seen when imaging was done several months out from an injection (approximately 70% of time by each evaluator in Group 1 patients). As expected, the results for the CT Scan provided a superior image capability as compared to X-ray. See Table 14 below for details.

**Table 14**  
**Foreign Mass of Material Visualizable**  
**CT Scan**

		Group 1 N = 23	Group 2 N = 27	Group 3 N = 15	Group 4 N = 15	Group 5 N = 15	Group 6 N = 15
Evaluator 1	Yes	15 (65.2%)	27 (100%)	0 (0.0%)	15 (100.0%)	0 (0.0%)	15 (100.0%)
	No	8 (34.8%)	0 (100%)	15 (100.0%)	0 (0.0%)	15 (100.0%)	0 (0.0%)
Evaluator 2	Yes	17 (73.9%)	27 (100%)	0 (0.0%)	15 (100.0%)	0 (0.0%)	14 (93.3%)
	No	6 (26.1%)	0 (0%)	15 (100.0%)	0 (0.0%)	15 (100.0%)	1 (6.7%)
Combined N = 2X	Yes	32 (69.6%)	54 (100%)	0 (0.0%)	30 (100.0%)	0 (0.0%)	29 (96.7%)
	No	14 (30.4%)	0 (0%)	30 (100.0%)	0 (0.0%)	30 (100.0%)	1 (3.3%)

Based on the results of the radiographic study, the following conclusions can be drawn:

- Radiesse is seen on both X-ray and CT Scan; however the CT Scan provides a much clearer and consistent image.
- Radiesse could be seen as the shape and size of either a benign or malignant tumor with similar edges of tumors however, there is virtually no risk of Radiesse being interpreted as either a benign or malignant tumor.
- There is virtually no risk that the presence Radiesse will mask underlying structures or abnormal growths in the areas in which it is injected.
- There is no evidence that Radiesse migrates.
- As with any course of medical care, the Radiologist, the referring physician and the patient need to communicate when an unexpected finding is seen. There is a minimal chance that patient would undergo the worst case scenario (fine needle aspiration biopsy) and the benefit outweighs the small risk of that procedure occurring.
- The presence of Radiesse does not pose a safety concern and patients, injecting physicians and other medical professionals are to be made aware of the radiographic appearance of Radiesse when injected in the facial area.

**Radiesse for Soft Tissue Augmentation for the Treatment of Nasolabial Folds**  
**Original Premarket Approval Application**  
**Section 2 – Summary of Safety and Effectiveness**

**X. CONCLUSIONS**

**Effectiveness**

Radiesse met the primary effectiveness endpoint of non-inferiority when compared to Control using the LRS. Radiesse also met all the secondary endpoints determining that Radiesse was superior and non-inferior to Control using both the LRS and GAIS as the measurement tools. Each of the three-blinded evaluators independently rated Radiesse in the same manner that resulted in the non-inferior and superior conclusions. The photographic-based GAIS was shown to have a significant correlation to LRS.

The amount of Radiesse injected was significantly less than the amount of Control injected at each injection session. In addition, Radiesse was significantly less likely to require an injection after the initial treatment when compared to the Control.

**Safety**

The adverse events reported in this study were similar in rate and duration for Radiesse and Control, with the exception of edema and ecchymosis. The higher rate of edema and ecchymosis for Radiesse was attributed to the larger and longer needle used with Radiesse when compared to the needle size and length used for Control. There were no serious adverse events or patient deaths reported during the course of the study.

**XI. PANEL RECOMMENDATIONS**

**XII. CDRH DECISION**

**XIII. APPROVAL SPECIFICATIONS**