

Radiesse for Soft Tissue Augmentation for the Treatment of Facial Lipoatrophy
Original Premarket Approval Application
M050012 - Module 3: Clinical
Section 1 – Summary of Safety and Effectiveness

I. GENERAL INFORMATION

Device Generic Name: Injectable Calcium Hydroxylapatite Implant for Soft Tissue Augmentation for the Treatment of Facial Lipoatrophy

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: M050012

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 the correction of facial lipoatrophy (facial fat loss).

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 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 calcium hydroxylapatite 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

A. Contraindications

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

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B. 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.
- Special care should be taken to avoid injection into the blood vessels. An introduction into the vasculature may occlude the vessels and could cause infarction or embolism.

C. 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.
- 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.
- Universal precautions must be observed when there is a potential for contact with patient body fluids. The injection session must be conducted with aseptic technique.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

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- The patient should be informed that he or she should minimize exposure of the treated area to extensive sun or heat exposure for approximately 24 hours after treatment.

V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of Radiesse in soft tissue augmentation of facial lipoatrophy is based upon a prospective open label study in which 100 patients were treated and evaluated through a 12-month assessment.

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 lbsf.

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.

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Particle Durability - The particles of calcium hydroxylapatite 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.

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

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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 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 study was designed to assess facial lipoatrophy changes and incidence of adverse events in patients receiving Radiesse treatment.

B. Study Design

The study was a prospective, controlled trial of 100 subjects injected with Radiesse at three investigational sites in the United States. Three hundred fifty-four (354) patients were screened which resulted in 100 patients being treated.

Individual patient study participation lasted 12 months following the initial treatment. Patients were enrolled at the time of the patient informed consent. After informed consent was obtained, 254 patients did not receive injections.

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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.

Primary Effectiveness Endpoint

The primary endpoint of the study was to evaluate the correction of lipoatrophy 3 months after treatment by comparing changes from baseline on the GAIS. The GAIS is a 5-category scale (Very much improved, much improved, improved, no change and worse).

Secondary Effectiveness Endpoints

The secondary endpoints of the study were to evaluate the correction of facial lipoatrophy 6 months after treatment by comparing changes from baseline on the GAIS and 3 and 6 months after treatment by comparing changes from baseline in cheek skin thickness measurements.

Safety Endpoints

The safety endpoint of the study is to record the incidence, severity and duration of all local and systemic adverse events through 12 months.

C. Study Protocol

Patient Selection

Inclusion criteria were defined as:

- ◆ Patient is HIV positive¹
- ◆ Has a CD4 count ≥ 250 /mm³ and viral load ≤ 5000 copies/ml²
- ◆ Has been receiving HAART therapy for a minimum of 3 years³
- ◆ Has HIV-associated facial lipoatrophy that is a grade 2, 3, or 4 on the Facial Lipoatrophy Severity Scale⁴
- ◆ Is at least 18 years of age
- ◆ Signs a written informed consent

¹ As documented in writing by study candidate's primary care physician within 30 days prior to visit date.

² As documented in writing by most recent lab reports.

³ As documented in writing by study candidate's primary care physician within 30 days prior to visit date.

⁴ James, et al. HIV-associated facial lipoatrophy. *Dermatol Surg*, 28:11, Nov 2002, p. 979-986.

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- ◆ Understands and accepts the obligation not to receive any other facial procedures or treatment affecting facial lipoatrophy through 12 month follow-up
- ◆ Understands and accepts the obligation and is logistically able to present for all scheduled follow-up visits

The exclusion criteria were defined as

- ◆ Has a known bleeding disorder (e.g., thrombocytopenia, thrombasthenia, or von Willebrand's disease)
- ◆ Has received or is anticipated to receive antiplatelets, anticoagulants, thrombolytics, vitamin E, anti-inflammatories, interferon, or prednisone from 1 week pre to 1 month post injection
- ◆ Is receiving systemic or topical corticosteroids or anabolic steroids
- ◆ Has another medical condition that would preclude study participation or suggests an AIDS diagnosis (e.g., kaposi sarcoma, recurrent infection, and recurrent pneumonia).⁵
- ◆ Has received silicone injections, facial tissue augmentation other than collagen, grafting, or any other surgery in the cheek area.
- ◆ Has received collagen in the cheek area within the past 6 months.
- ◆ Has received over-the-counter wrinkle products (e.g., alpha-hydroxy acids) or
- ◆ Prescription treatments (e.g., Renova, Retin-A, microdermabrasion, chemical peels) within 4 weeks prior to study or intends to receive these products and/or treatments during the study.
- ◆ Has facial hair that would preclude ability to assess facial lipoatrophy.
- ◆ Has a history of keloid formation.
- ◆ Is pregnant or lactating or not using a reliable form of birth control, if female of child bearing potential⁶
- ◆ Is enrolled in an interfering study

Treatment Procedures

Patients were able to receive Radiesse at baseline, 1 month after initial injection and 6 months after last injection, if study criteria were met. Eight-five (85.0%) of patients received an additional injection 1 month after baseline and 89 of the 98⁷ patients (90.8%) received an additional injection 6 months after the last injection. One patient did not meet all the exclusion criteria (he had taken aspirin) and therefore was not eligible to receive the 6 month touch up. One patient elected not to be injected again (LA-1-033), due to pain at previous injections.

A majority of patients underwent the procedure with local anesthesia. This was the case not only at the time of the initial injection but for the 1 month and 6 month injections.

⁵ As documented in writing by study candidate's primary care physician within 30 days prior to visit date

⁶ In-office urine test to be administered to female candidates of child bearing potential under the direction of the investigator to assess pregnancy status

⁷ Two patients died prior to the six-month follow-up period.

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Study Variables

D. Description of Study Population

Three hundred fifty-four (354) patients were screened for inclusion into the study, of which 100 patients received Radiesse. Of the 100 receiving treatment, all patients reported a GAIS at the three-month period and were therefore included in the analysis for the primary efficacy endpoint.

All 100 injected patients at 3 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

**Table 1
Patient Demographics
N = 100**

Age (Years)	
Mean	48.2
Standard Deviation	7.2
Minimum	34.0
Maximum	69.0
Gender	
Female	6 (6.0%)
Male	94 (94.0%)
Race	
American Indian	0 (0.0%)
Asian	1 (1.0%)
Black	18 (18.0%)
Caucasian	56 (56.0%)
Hispanic	25 (25.0%)
Other	0 (0.0%)

As required in the clinical protocol, patients were to have a Lipoatrophy Severity Scale rating of 2, 3, or 4 to be included in the clinical study. Table 2 details the distribution of the lipoatrophy severity scale ratings for the 100 study subjects.

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Table 2
Facial Lipoatrophy Severity Ratings
N = 100

Lipoatrophy Severity 1	0 (0.0%)
Lipoatrophy Severity 2	48 (48.0%)
Lipoatrophy Severity 3	39 (39.0%)
Lipoatrophy Severity 4	13 (13.0%)

As seen in Table 3, a majority of patients (51.0%) reported a Fitzpatrick Skin Type IV or greater. The data generated in this clinical study establishes a high level of assurance that patients susceptible to keloid formation/hypertrophic scarring can be treated safely and effectively with Radiesse for facial lipoatrophy.

Table 3
Fitzpatrick Skin Types
N = 100

Fitzpatrick Type I	3 (3.0%)
Fitzpatrick Type II	13 (13.0%)
Fitzpatrick Type III	33 (33.0%)
Fitzpatrick Type IV	21 (21.0%)
Fitzpatrick Type V	13 (13.0%)
Fitzpatrick Type VI	17 (17.0%)

Treatment Information

The volume of Radiesse injected during the course of the study is shown in Table 4. The baseline injection and the 1-month injection were considered as potentially being necessary to reach optimal correction. The mean volume for both the initial and 1-month injection was 6.6 ml. The mean total injected through 6 months was 8.4 ml/

Table 4
Volume of Radiesse Injected (ml)

	Baseline N = 100	1 Month N = 85	6 Months N = 89	Total N = 100
Mean	4.8	1.8	2.4	8.4
Standard Deviation	1.9	1.1	1.5	3.6
Minimum	1.8	0.3	0.2	2.0
Maximum	14.0	6.0	6.0	20.4

E. Effectiveness Endpoint Results

The primary effectiveness endpoint of the study was to evaluate the correction of facial lipoatrophy 3 months after last injection by comparing changes from baseline on the Global Aesthetic Improvement Scale (GAIS) with confirmation using a standardized photograph.

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The 6 month GAIS is for 98 patients. All patients are accounted for at 6 months, as no patients were lost to follow-up. Two (2) patients died before the 6 month GAIS secondary efficacy endpoint but were available for the primary efficacy endpoint (3 month GAIS). Therefore, the section of the protocol that describes patients as being “lost to follow-up” would be analyzed, as “No Change” does not apply.

In Table 5, all patients reported GAIS ≤ 3 at all time periods, through the 12 month follow-up, the primary endpoint for efficacy has been met and the results have been determined to be clinically meaningful for the 3 month, 6 month and 12 month time periods.

Table 5
Global Aesthetic Improvement Scale (GAIS) Results

GAIS Rating	3 Months N = 100	6 Months N = 98	12 Months N = 98
Very Much Improved (1)	26 (26.0%)	7 (7.1%)	30 (30.6%)
Much Improved (2)	72 (72.0%)	84 (85.7%)	52 (53.1%)
Improved (3)	2 (2.0%)	7 (7.1%)	16 (16.3%)
No Change (4)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse (5)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANY IMPROVEMENT	100 (100.0%)	98 (100.0%)	98 (100.0%)
95% Confidence Interval	96.4% - 100.0%	96.3% -100%	96.3% -100.0%

Secondary Effectiveness Endpoint Results

The secondary endpoint (GAIS ≤ 3 at 6 months) was met by 100% of patients available for that evaluation. In addition, even though the 12 month GAIS was neither a primary or secondary endpoint, 100% of all patients (N = 98) continued to report a successful efficacy outcome (GAIS ≤ 3).

Patient Satisfaction

The questions comprising the patient satisfaction assessment were provided on the CRFs. Those questions were modeled after the Freiburg Questionnaire on Aesthetic Dermatology and Cosmetic Surgery (FQAD), Sommer, et al, “Satisfaction of Patients After Treatment with Botulinum Toxin for Dynamic Facial Lines,” *Dermatol Surg*, 2003, 29:456-460. The responses at each time point demonstrated overwhelming patient satisfaction. Not only was the patient satisfaction very positive, the patient satisfaction remained consistent out to the 12 month time period.

The patient satisfaction at 3 and 6 months appears to reflect the GAIS scores for those same time periods. Table 6 contains the details of the Patient Satisfaction results.

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Table 6
Patient Satisfaction Results

Question	3 Months N = 100		6 Months N = 98		12 Months N = 98	
	Yes	No	Yes	No	Yes	No
Would you recommend Radiesse treatment?	99 (99.0%)	1 (1.0%)	97 (99.0%)	1 (1.0%)	97 (99.0%)	1 (1.0%)
Has the Radiesse treatment been beneficial to you?	100 (100.0%)	0 (0.0%)	98 (100.0%)	0 (0.0%)	98 (100.0%)	0 (0.0%)
Do you feel more attractive since receiving Radiesse treatment?	98 (98.0%)	2 (2.0%)	96 (98.0%)	2 (2.0%)	97 (99.0%)	1 (1.0%)
Is your emotional wellbeing better since receiving Radiesse?	91 (91.0%)	9 (9.0%)	94 (95.9%)	4 (4.1%)	95 (97.0%)	3 (3.0%)
Do you have more confidence in your appearance since receiving Radiesse?	98 (98.0%)	2 (2.0%)	96 (98.0%)	2 (2.0%)	97 (99.0%)	1 (1.0%)

F. Safety Results

Adverse Events

The adverse events reported were ecchymosis, edema, erythema, pain and pruritis, all commonly seen at the time of any injection procedure. None of these five adverse events were reported when there no injections were performed (3 to 6 Months and 12 Months follow-up visits). Table 7 details the number of events and at what time point during the study that the events occurred.

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Table 7
Adverse Events
Over the Course of the Study

	Number of Events	Baseline to 1 Month	1 to 3 Months	3 to 6 Months	6 to 12 Months	12 Months
Allergic Reaction	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Echymosis	147	63 (42.9%)	40 (27.2%)	0 (0.0%)	44 (29.9%)	0 (0.0%)
Edema	443	179 (40.4%)	135 (30.5%)	0 (0.0%)	129 (29.1%)	0 (0.0%)
Embolization	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erosion	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema	214	64 (29.9%)	69 (32.2%)	0 (0.0%)	81 (37.9%)	0 (0.0%)
Extrusion	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Granuloma	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematoma	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infection	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Necrosis	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Needle Jam	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	114	56 (49.1%)	31 (27.2%)	0 (0.0%)	27 (23.7%)	0 (0.0%)
Pruritis	54	32 (59.3%)	15 (27.8%)	0 (0.0%)	7 (13.0%)	0 (0.0%)
Other	174	74 (42.5%)	52 (29.9%)	2 (1.2%)	46 (26.4%)	0 (0.0%)

At the time of the adverse event, the severity was determined by the investigator. Table 8 details the maximal severity for each the adverse events. A majority of the events were determined to be Mild (58.1%) with the remaining being either Moderate (38.6%) or Severe (3.3%). The table also contains the 95% confidence intervals.

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Table 8
Severity of Adverse Events

Adverse Event	Number of Patients With Event	95% Confidence Interval	Maximal Severity			Duration ⁸ (Days)
			Mild	Moderate	Severe	
Allergic Reaction	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0, 0 (0.0-0.0)
Echymosis	65	(54.8% - 74.2%)	34 (52.3%)	26 (40.0%)	5 (7.7%)	7.7, 4.8 (1.0 -27.0)
Edema	99	(94.6% - 100.0%)	46 (46.5%)	49 (49.5%)	4 (4.0%)	5.0, 5.4 (1.0 - 63.0)
Embolization	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0, 0 (0.0-0.0)
Erosion	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0, 0 (0.0-0.0)
Erythema	57	(46.7% - 66.9%)	34 (56.7%)	23 (40.4%)	0 (0.0%)	4.4, 3.0 (1.0 – 22.0)
Extrusion	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0, 0 (0.0-0.0)
Granuloma	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	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)
Infection	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0, 0 (0.0-0.0)
Necrosis	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0, 0 (0.0-0.0)
Needle Jam	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0, 0 (0.0-0.0)
Nodule	0	(0.0%– 0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0, 0 (0.0-0.0)
Pain	39	(29.4% - 49.3%)	25 (64.1%)	13 (33.3%)	1 (2.6%)	5.2, 4.5 (1.0 – 26.0)
Pruritis	21	(13.5% - 30.3%)	18 (85.7%)	3 (14.3%)	0 (0.0%)	6.9, 6.9 (1.0 – 26.0)
Other	58	(47.7% - 67.8%)	40 (69.0%)	17 (29.3%)	1 (1.7%)	31.3, 49.8 (1.0 – 208.0)
Total	339		197 (58.1%)	131 (38.6%)	11 (3.2%)	

There were no Serious Adverse Events reported during the course of the study. There were 2 patient deaths and one report of a patient being treated for lung cancer. None of those events were determined to be related to either the procedure or the device. The details for those three patients follow. Please note that “Serious” Adverse Events are not the same as adverse events reported as “severe”.

⁸ Mean, Standard Deviation, Minimum and Maximum

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There were two patient deaths during the course of the study. Both patients were available for the 3-month efficacy endpoint, but did not have the 12-month evaluation. The deaths were not related to either the device or the procedure.

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 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 patient groups were enrolled into the study. A description of the patient groups is provided in Table 9 below.

Table 9
Description of Patient Groups

	Description	# Patients
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 9 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 10 below is a summary of the imaging groups. Also included in the table below is the average volume of Radiesse

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injected for each of the groups and the average time from injection to the time of the imaging sessions.

Table 10
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
Group Number	1	2	3	4	5	6
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 131for details.

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Table 11
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 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 12 below for details.

Table 12
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:

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- 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, Radiesse was not 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.
- 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 that 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.

X. CONCLUSIONS

Effectiveness

Injection of Radiesse for soft tissue augmentation for the treatment of facial lipoatrophy resulted in all patients meeting the primary and secondary efficacy (GAIS ≤ 3) endpoint. In addition, all patients reported GAIS ≤ 3 at 12 months. The analyses clearly demonstrate that Radiesse is effective for soft tissue augmentation for the treatment facial lipoatrophy. Radiesse was determined to have met both the primary and secondary endpoints. The patient satisfaction ratings revealed that all patients were highly satisfied with the results through the 12-month follow-up.

Safety

Results of this clinical study indicate that Radiesse was safe in that it was well tolerated in study population. The adverse events were associated with the injection procedure and the device and were transient in nature. There were no clinically significant findings that indicated Radiesse exhibited any systemic effects confirming what BioForm has observed with other marketed hard and soft tissue clinical indications of this material over an extended period of time.

XI. PANEL RECOMMENDATIONS

XII. CDRH DECISION

XIII. APPROVAL SPECIFICATIONS