

**Radiesse for Soft Tissue Augmentation for the Treatment of HIV-Associated Facial  
Lipoatrophy  
Panel Pack**

**I. EXECUTIVE SUMMARY**

Radiesse is a flexible, semi-solid, cohesive implant used as a space filling material for soft tissue augmentation, which has been commercially available in the United States, the European Union, Canada and other worldwide markets since 2001 for multiple soft tissue augmentation applications, with over 240,000 units distributed worldwide.

1. The primary component of Radiesse, calcium hydroxylapatite, is a biocompatible material that has been widely used for implant procedures for more than 20 years and has a well accepted and established safety profile for implant applications.
2. Radiesse has received FDA market clearance for multiple applications including soft tissue augmentation applications. U.S. approved indications include tissue marking, vocal fold insufficiency, oral maxillofacial defects. The BioForm product Coaptite is approved for use for the treatment of stress urinary incontinence. Coaptite is identical to Radiesse with the exception of CaHA particle size. In addition, Radiesse is approved worldwide, including Canada, the European Union and other markets for soft tissue augmentation applications, which include facial plastic and reconstructive surgery.
3. The underlying in vitro and in vivo testing confirms the well-known and established acute and chronic safety profile of the CaHA while establishing long-term durability and effectiveness of Radiesse.
4. The results of this FDA approved, IDE clinical study demonstrated that Radiesse remained effective as 100% of patients evaluated at each time point showed improvement from baseline on the Global Aesthetic Improvement Scale (GAIS) at 3, 6 and 12 months. The study met the primary and secondary GAIS effectiveness endpoints to a statistically significant level, as defined in the FDA approved protocol. Radiesse was determined to be safe as none of the adverse events were unexpected, all were transient in nature, and there were no Serious Adverse Events reported during the course of the study. Safety was demonstrated in this study was of a patient population that included a majority that was considered persons of color.
5. In a separate FDA approved, split face, IDE study of Radiesse for the treatment of nasolabial folds, all study endpoints were met with no unexpected or serious adverse events reported.

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**II. PRODUCT DESCRIPTION**

Calcium hydroxylapatite (CaHA), the principle component of Radiesse and a similar BioForm product, Coaptite, is a safe biomaterial with over twenty years of implantable use in orthopedics, neurosurgery, dentistry, otolaryngology, and ophthalmology. Radiesse and Coaptite are identical, except that the CaHA particles are smaller in Radiesse (25-45 microns) than the CaHA particles in Coaptite (75-125 microns).

Radiesse is a flexible, semi-solid, cohesive implant used as a space filling material for soft tissue augmentation, which has been commercially available in the United States, the European Union, Canada and other worldwide markets since 2001. Since that time, there have been over 240,000 units of Radiesse and 20,000 units of Coaptite distributed worldwide with a good safety history in commercial use.

CaHA is the principal inorganic constituent of human bones and teeth. The CaHA particles in Radiesse are manufactured synthetically and are chemically and biologically identical to the naturally occurring substance. Synthetically produced CaHA has been used as an implant material in other clinical applications that include dental ridge augmentation, bone augmentation, otology implants, and in other implantable devices. Radiesse is sterile, non-pyrogenic, supplied in a single syringe of 0.3cc, 1.0cc or 1.3cc, packaged in foil pouches and steam sterilized.

The CaHA particles are suspended in an aqueous based gel carrier composed of sodium carboxymethylcellulose (NaCMC), sterile water for injection, and glycerin. The NaCMC, sterile water for injection and glycerin have extensive use in pharmaceuticals and medical devices including intramuscular injection products and are classified as "Generally Recognized as Safe" (GRAS) as described in Title 21 CFR Part 182.1320 and Part 182.1745. The gel carrier suspends and allows delivery of the CaHA particles through injection needles. The gel carrier is then dissipated over time *in vivo*, while the CaHA particles remain and provide the durable bulking treatment. The CaHA particles act in two ways - by directly filling space in the soft tissue and by providing a scaffolding/microstructure for tissue infiltration.

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**III. WORLDWIDE REGULATORY HISTORY**

**United States**

BioForm's CaHA products (Radiesse and Coaptite) are commercially available in United States for multiple soft tissue augmentation applications, which follow.

- **Tissue Marker** (October 22, 2001 - 510(k) K012955): Intended to radiographically mark soft tissue during a surgical procedure or for future surgical procedures (Radiesse and Coaptite)
- **Laryngeal Augmentation** (January 9, 2002 - 510(k) K013243): Intended as an injectable, space-occupying implant for vocal fold medialization and augmentation (Radiesse and Coaptite)
- **Oral/Maxillofacial Defects** (June 27, 2003 - 510(k) K030682): Intended to fill or augment dental intraosseous and oral/maxillofacial defects including craniofacial augmentation, ridge augmentation, cystic defects, extraction sites, periodontal defects (Radiesse and Coaptite)
- **Stress Urinary Incontinence** (November 10, 2005 – PMA P040047): Intended for soft tissue augmentation in the treatment of stress urinary incontinence due to intrinsic sphincter deficiency (Coaptite)

**Rest of World**

Radiesse is also commercially available worldwide, including the European Union, Canada, and certain countries of Asia, Africa and South America for multiple soft tissue augmentation applications, which follow.

- **Facial Augmentation:** Intended for plastic and reconstructive surgery, including soft tissue augmentation of the facial area (Radiesse)
- **Laryngeal Augmentation:** Intended as an injectable, space-occupying implant for vocal fold medialization and augmentation (Radiesse and Coaptite)
- **Stress Urinary Incontinence:** Intended for soft tissue augmentation in the treatment of stress urinary incontinence due to intrinsic sphincter deficiency (Coaptite)
- **Vesicoureteral Reflux:** Intended for the treatment of children with vesicoureteral reflux Grades II-IV and Grade I associated with contralateral Grade II-IV (Coaptite)

BioForm CaHA products have undergone multiple clinical studies for multiple soft tissue augmentation applications. Those include the following:

- Treatment of Nasolabial Folds – U.S.A.: Radiesse

A 117-patient split face, IDE clinical trial was conducted to assess the safety and effectiveness of Radiesse compared to Cosmoplast for the treatment of nasolabial folds.

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The results of the study demonstrated that Radiesse was safe. The adverse events that were reported in the study were not unexpected nor serious and were generally short in duration. The safety profile of Radiesse was comparable to Control.

Radiesse was found to be effective. The primary endpoint of non-inferiority to Control was met ( $p < 0.0001$ ) and the secondary endpoint of superiority to Control was met ( $p < 0.0001$ ). Eighty-two percent of Radiesse treated nasolabial folds were improved at 6 months. The effectiveness of Radiesse was consistent as 84.6% of Radiesse treated nasolabial folds were judged to be superior ( $p < 0.0001$ ) to Control treated nasolabial folds at 3 months while 78.6% of Radiesse treated nasolabial folds were judged superior ( $p < 0.0001$ ) at 6 months.

There was significantly less ( $p < 0.0001$ ) volume of Radiesse used compared to the volume of Control used (1.2 mL and 2.4 mL, respectively).

Three independent, blinded evaluators rated all photos for the effectiveness endpoints. This method used a validated scale, preserved complete blinding, and provided for significant rigor in the analyses. Analysis by the validated LRS and the GAIS both showed Radiesse to be effective. Investigator and patient effectiveness evaluations confirmed these results with 96.5% of investigator evaluations and patient evaluations rating the Radiesse side as more satisfactory at 6 months.

The results in this study were consistent with the results reported in the HIV-associated facial lipoatrophy clinical study described immediately following.

- **Treatment of HIV-Associated Facial Lipoatrophy – U.S.A.: Radiesse**

A FDA approved, IDE 100-patient clinical study was completed to evaluate Radiesse for the treatment of HIV-associated facial lipoatrophy. The results of this study demonstrated that 100% of the patients met the primary endpoint of an improved aesthetic result at all time points (1 month, 3 months, 6 months and 12 months). Through the 12 month follow-up there were no unexpected adverse events, none of the patients required intervention for any of the adverse events, Radiesse did not exhibit adverse systemic effects and no serious adverse events were reported.

The safety of Radiesse in persons of color was also demonstrated as the majority of patients studied had a Fitzpatrick Skin score of  $\geq$  IV with no evidence of keloid formation. This was also true in this same patient sub-group that had CD4 counts within normal range for healthy adults.

- **Treatment of HIV-Associated Facial Lipoatrophy – Canada: Radiesse**

A similar clinical study that enrolled 30 patients was conducted in Canada. As with the U.S. clinical study, 100% of the patients met the primary efficacy endpoint. The number and type of adverse events that were reported were similar to those reported in the study in the United States. The data from this study provides additional evidence that Radiesse is safe and effective.

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- Radiographic Evaluation – Canada and U.S.A.: Radiesse

Radiesse was found to be radiopaque on both X-ray and on CT Scan, with it being more evident on CT Scan due to the sophistication of the CT Scan technology. Radiesse was seen on CT scan and the densities are greater than the surrounding soft tissue, but not as dense as seen in bony structures. The density and configuration of the CaHA particles remain constant over time. There is also no evidence of Radiesse being observed outside the injected area indicating that Radiesse had not migrated.

- Vocal Fold Medialization and Augmentation – U.S.A. and Europe: Radiesse

The use of CaHA for vocal fold augmentation and medialization has been described in two peer-reviewed articles one that has been accepted for publication and one that was presented at professional scientific session and subsequently submitted for publication.

A report of twenty-three patients with 39 vocal folds treated has been published. All individuals reported improvement on a self-administered outcome measure ( $p < 0.0001$ ). Pathology from a larynx donated from a terminally ill cancer patient 3 months after injection observed the CaHA still in position with minimal, inflammatory reaction and no evidence of rejection. Six-month data for 5 of 11 patients with unilateral vocal fold paralysis was reported. The Voice Handicap Index (VHI) improved for all 5 patients and four of the five achieved improvements in mean air flow rates. Two of the remaining patients were not seen in the physician's office, but in telephone follow-ups reported patient satisfaction.

- Treatment of Stress Urinary Incontinence – U.S.A.: Coaptite

Two hundred and ninety-six (296) patients were enrolled in an FDA approved, IDE study to evaluate Coaptite versus a collagen-based product for the treatment of stress urinary incontinence. One hundred fifty-eight patients were injected with Coaptite while 138 patients were injected with the collagen based control article. The injection of Coaptite resulted in equivalent rates for the study defined categories of "Improvement", "Substantial Improvement" and "Cure" for patients when compared to those patients injected with the control article. Coaptite met both the primary and secondary effectiveness endpoints as Coaptite was equivalent to the control article. Both Coaptite and collagen were well tolerated in study population. Eleven (11) Coaptite patients and 12 Control patients experienced serious adverse events (SAEs). There were no clinically significant laboratory findings that indicated Coaptite exhibited any systemic effects.

The equivalent results were achieved with a significantly less volume of Coaptite than collagen. There were also significantly fewer Coaptite patients undergoing additional injections than collagen patients to achieve the same result. Therefore, it was concluded that Coaptite is safe and effective for its intended use of soft tissue augmentation of the urethral sphincter in the treatment of stress urinary incontinence. Coaptite has received premarket approval for this indication in the United States.

This large body of experience confirms the previous 20 years experience with CaHA as a safe and effective implant material.

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**IV. PRE-CLINICAL STUDIES**

Radiesse has undergone extensive *in vitro* and *in vivo* testing confirming the material's biocompatibility and establishing its long-term safety profile and durability. The following is a summary of pre-clinical studies.

Biocompatibility testing was conducted in accordance with the ISO 10993 Standard (Biological Evaluation of Medical Devices), using accepted test methods for biomedical materials or United States Pharmacopoeia references. These studies were conducted in accordance with Good Laboratory Practice for Nonclinical Laboratory Studies (GLPs). The testing determined that the product was nonantigenic, a nonirritant, and nontoxic with no concerns for acute or chronic safety. The biocompatibility testing included:

- Acute Systemic Toxicity in Mice
- Intracutaneous Toxicity in Rabbits
- Systemic Antigenicity in Guinea Pigs
- 7-Day Muscle Implantation in Rabbits
- 28-Day Muscle Implantation in Rabbits
- Cytotoxicity (Agar Overlay Method)
- Ames Mutagenicity
- Lee-White Clotting Time
- Hemolysis

Various animal studies evaluating Radiesse in dermal soft tissue augmentation have been conducted that include the product injected into the dermis and subdermis in various animal models as well as a canine study involving soft tissue augmentation of the urinary sphincter. As expected, these studies provided acute and chronic results that demonstrated Radiesse was safe and remained durable without any evidence of particle migration.

- Subdermal Filler Materials in Yucatan Mini-Pig – 28 Days

Radiesse was injected subdermally at sites parallel to the lumbar region of the vertebral column of the animal. At 28 days, the animals were sacrificed and the subdermal tissue was visually examined and then prepared for histological examination. It was concluded that Radiesse performed as other currently marketed dermal fillers both histologically and macroscopically.

- Local and Systemic Effects in Rabbits – 6 Months

New Zealand White rabbits were injected subdermally with 0.25cc of Radiesse, Coaptite and the gel carrier component alone (same gel carrier for both Radiesse and Coaptite). Animals were evaluated at 3 and 6 months after injection, which included urinalysis, hematology, clinical chemistry, macroscopic observations, general health and histological evaluation. All animals were normal macroscopically with no evidence of migration or local reaction. No lymph nodes in the area draining the injection sites were enlarged or detected. None of the test articles including Radiesse showed evidence of migration, capsule formation or adverse reactions.

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- Durability and Absorption Profile in a Canine Model – 32 Weeks

The study evaluated the durability and absorption profile of Radiesse, when injected into the intradermal and subdermal tissues 12 canines. Animals were sacrificed and evaluated at 4, 8, 12, 16, 24 and 32 weeks after injection. The local reactions were transient and not considered unusual for an injected dermal filler material. At 32 weeks no erythema or edema was observed. Microscopically, the ingrowth of collagen in association at the injection sites was seen. There was no evidence of migration of Radiesse from the injection site and the lymphatic vessels were unremarkable.

- Durability and Absorption Profile in a Yucatan Mini-Pig Model – 32 Weeks

The study evaluated various dermal fillers in the swine model when injected intradermally and subdermally in the Yucatan Mini-Pig. Eleven animals were injected and animals were sacrificed and evaluated at 4, 8, 12, 16, 24 and 32 weeks after injection. The local reaction scores were transient and not considered unusual for injected dermal fillers. At 32 weeks no erythema or edema was observed for any of the test articles.

- Evaluation of Urinary Sphincter Augmentation Implantation in Dogs – 3 Years

The product<sup>1</sup> was injected the urinary bladder neck in 24 female mongrel dogs. Twelve additional female dogs were similarly injected with only the gel carrier component as the control. Blood and urine samples were collected from each animal prior to study initiation, prior to termination and at 6-month intervals for animals through the 36-month test period. Designated animals were removed from the study at 1, 3, 6, 12, 25 and 36 months. Each was necropsied, injection sites and other tissue inspected grossly, and implant sites and selected tissues processed for microscopic examination.

Microscopic evaluation of the implant sites at 1, 3, 6 and 12 months revealed a simple macrophage clearing response was associated with the gel carrier. The presence of the test article caused no reaction in the adjacent tissues. The CaHA particles from 1 through 36 months remained encapsulated with no evidence of migration from the injection site. The beginning of CaHA particle disintegration was present in several 25 and 36-month tissue specimens as the particles were being engulfed and solubilized 'in situ' by macrophages at the site. Many other particles remained intact.

At all time points throughout the three year study, the product was found to be tissue friendly and biocompatible forming a well defined injection site. The CaHA particles remained at the injection site with no evidence of particle migration.

### Pre-Clinical Study Conclusions

The battery of preclinical safety studies and the animal implant studies have shown that Radiesse is biocompatible when injected into various soft tissues of animals. The main cellular response to the test material is encapsulation of the CaHA particles and macrophage and

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<sup>1</sup> Please note that the product used in the canine study was Coaptite, which is identical to Radiesse, except for the size of the CaHA particles. The Coaptite particles are 75-125 microns in diameter, while the Radiesse particles are 25-45 microns.

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enzymatic biodegradation of the gel carrier. The CaHA particles have been shown to remain at the injection site with no evidence of particle migration.

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**V. CLINICAL STUDIES**

This section contains a summary of two clinical studies conducted in support of this PMA – Evaluation of Radiesse for the Treatment of HIV-Associated Facial Lipoatrophy and Radiological Evaluation of Short-Term and Long-Term Evaluation of Radiesse in the Face.

**PROTOCOL # 1003090**

**EVALUATION OF RADIESSE FOR THE TREATMENT OF HIV-ASSOCIATED  
FACIAL LIPOATROPHY**

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A 100-patient IDE clinical trial was conducted to assess the safety and effectiveness of Radiesse for treatment of facial lipoatrophy. The clinical protocol and evaluative endpoints and methods were approved by both FDA and the IRB prior to study initiation.

**CONCLUSIONS DRAWN FROM STUDY**

- Radiesse has been found to be safe. The adverse events were transient and expected (including swelling, redness and swelling at the injection site) and no patients required intervention for any of the adverse events. There were no clinically significant events that indicated Radiesse exhibited adverse systemic effects.
- Radiesse has been found to be effective. The study met the primary effectiveness endpoint on the Global Aesthetic Improvement Scale (GAIS) at 3 months. One-hundred percent (100%) of evaluable Radiesse patients also showed improvement on the GAIS at 6 and 12 months.
- Radiesse has been found to be safe and effective in persons of color as the majority of patients in this investigation (51%) had a Fitzpatrick Skin Score of  $\geq$  IV.

**STUDY DESIGN**

Objective

The purpose of this study was to assess the safety and effectiveness of Radiesse for the treatment of facial lipoatrophy. The study was designed to assess facial lipoatrophy changes and incidence of adverse events in patients receiving Radiesse treatment for the correction of facial lipoatrophy for 12 months after the initial treatment. The device used in this clinical study is identical to the commercially available device.

Patient Population

The study was a prospective, open label clinical trial in 100 subjects that met the inclusion and exclusion criteria at three (3) investigational sites. The study sites and number of patients treated by site are provided in the table below. Of the 100 patients receiving treatment, all 100 were available for the primary effectiveness endpoint at 3 months. Ninety-eight (98) patients were available for 6 and 12 month evaluations.

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<b>STUDY SITES AND NUMBER OF PATIENTS TREATED</b>	
Principal Investigator	Number Patients Enrolled
Joseph Eviatar, MD New York, NY	34
Stacey Silvers, MD New York, NY	60
Michael Echavez, MD San Francisco, CA	6

At the time that the patient presented for inclusion in the study, an assessment was made to determine whether the patient met the study inclusion/exclusion criteria. Patients enrolled in the trial were required to have a facial lipoatrophy rating grade of 2, 3, or 4 on the Facial Lipoatrophy Severity Scale<sup>2</sup> below.

<b>FACIAL LIPOATROPHY SEVERITY SCALE</b>	
GRADE	DESCRIPTION
1	Mild and localized facial lipoatrophy
2	Deeper and longer atrophy, with the facial muscles beginning to show through
3	Atrophic area is even deeper and wider, with the muscles clearly showing through
4	Lipoatrophy covers a wide area, extending up toward the eye sockets, and the facial skin lies directly on the muscles

Patients were also required to be HIV positive, have a CD4 count  $\geq 250$  /mm<sup>3</sup>, viral load  $\leq 5000$  copies/ml, and have been receiving HAART therapy for a minimum of 3 years.

Treatment and Follow Up Visit Schedule

All patients had baseline facial cheek thickness measurements taken. The same standardized measurement procedure was used for these and all subsequent measurements. All patients also had baseline photographs taken of their facial lipoatrophy using standardized photography.

Patients then received Radiesse treatment for their facial lipoatrophy. The lipoatrophy was treated until, in the judgment of the treating physician, the lipoatrophy was corrected.

One month after initial injection, patients returned for an assessment of their lipoatrophy. If, in the judgment of the treating physician, a second treatment was required, the injection was

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

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performed. Three, six and twelve months after last injection, patients again returned for an evaluation of their lipoatrophy. This included a Global Aesthetic Improvement Scale (GAIS) assessment, standard photographs and a cheek thickness measurement. In addition, at the 6 month visit, a touch up treatment was performed if clinically indicated. All patients were to return one month after any injection for a safety assessment.

### Effectiveness Endpoints

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

The secondary effectiveness endpoints of the study were to evaluate the correction of facial lipoatrophy at 6 months by comparing changes from baseline using the Global Aesthetic Improvement Scale (GAIS) with confirmation using a standardized photograph and to evaluate the correction of facial lipoatrophy 3 and 6 months after final treatment by comparing changes from baseline in cheek thickness measurements.

<b>Global Aesthetic Improvement Scale <sup>3</sup></b>	
Rating	Description
Very Much Improved	Optimal cosmetic result for the implant in this patient
Much Improved	Marked improvement in appearance from initial condition, but not completely optimal for this patient. 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 is worse than the original condition

The figures below are photographs of patients for each of the three GAIS ratings as seen in the clinical study.

### Safety Endpoint

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

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3 Narins R, et al., "A randomized, double blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg*, 29:6, Jun 2003.

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## **RESULTS**

### Patient Demographics

Patients participating in the investigation had a mean age of 48.2 years and 94% were male. Forty-four percent (44%) of patients were Non-Caucasian and a majority of patients (51.0%) reported a Fitzpatrick Skin Type IV or greater.

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. 48%, 39%, and 13% of patients had severity ratings of 2, 3 and 4, respectively.

### Injection Procedure / Exposure to Study Devices

Patients were to receive Radiesse at baseline, 1 month after initial injection and at 6 months after final injection, if study criteria were met. Eight-five patients (85.0%) received an additional injection at 1 month and 89 of the 98<sup>4</sup> patients (90.8%) received an additional injection at 6 months. One patient (Patient Number LA-3-003) met the exclusion criteria (he had taken aspirin) and therefore was not eligible to receive the 6 month touch up. One patient elected not to receive the 6 month touch up (LA-1-033), due to pain at previous injections.

All injections during the course of the study (baseline, 1 month and 6 months) were performed using a 25 gauge, 1½" needle.

The baseline injection and the 1 month injection (if necessary) were considered as being necessary to reach optimal correction. The mean total volume for the initial and 1 month injection was 6.6 ml. The mean total volume injected through 6 months was 8.4 ml.

Most patients (78.0%) received three injections, while 4.0% of the patients received only the baseline injection.

### Effectiveness Endpoints

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

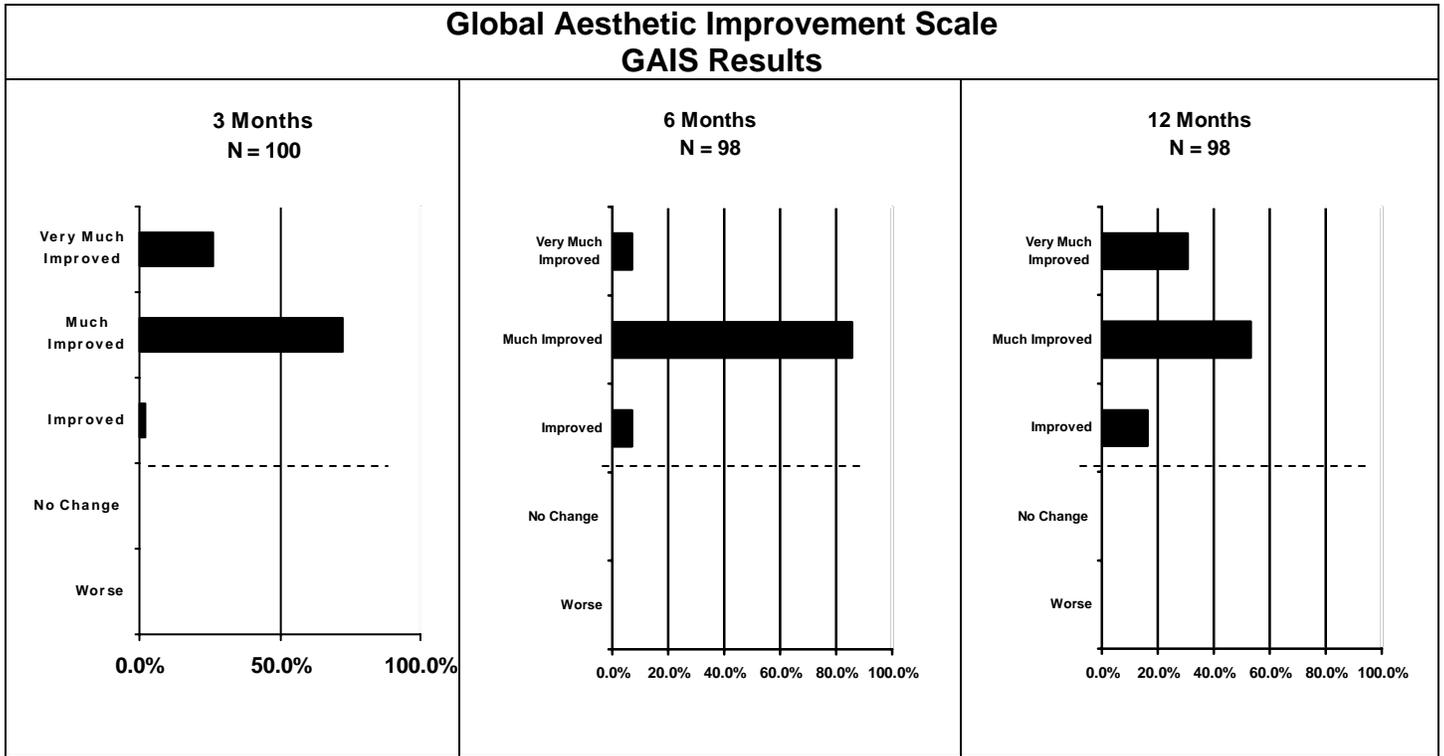
The secondary endpoint was to evaluate the correction of facial lipoatrophy at 6 months by comparing changes from baseline using the Global Aesthetic Improvement Scale (GAIS) with confirmation using a standardized photograph and to evaluate the correction of facial lipoatrophy 3 and 6 months after final treatment by comparing changes from baseline in cheek thickness measurements.

As can be seen in the figure immediately following, 100% of patients showed improvement from baseline on the GAIS at 3, 6 and 12 months. All patients met the primary and secondary GAIS endpoints.

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4 Two patients deaths occurred, unrelated to the study device, prior to the six-month follow-up

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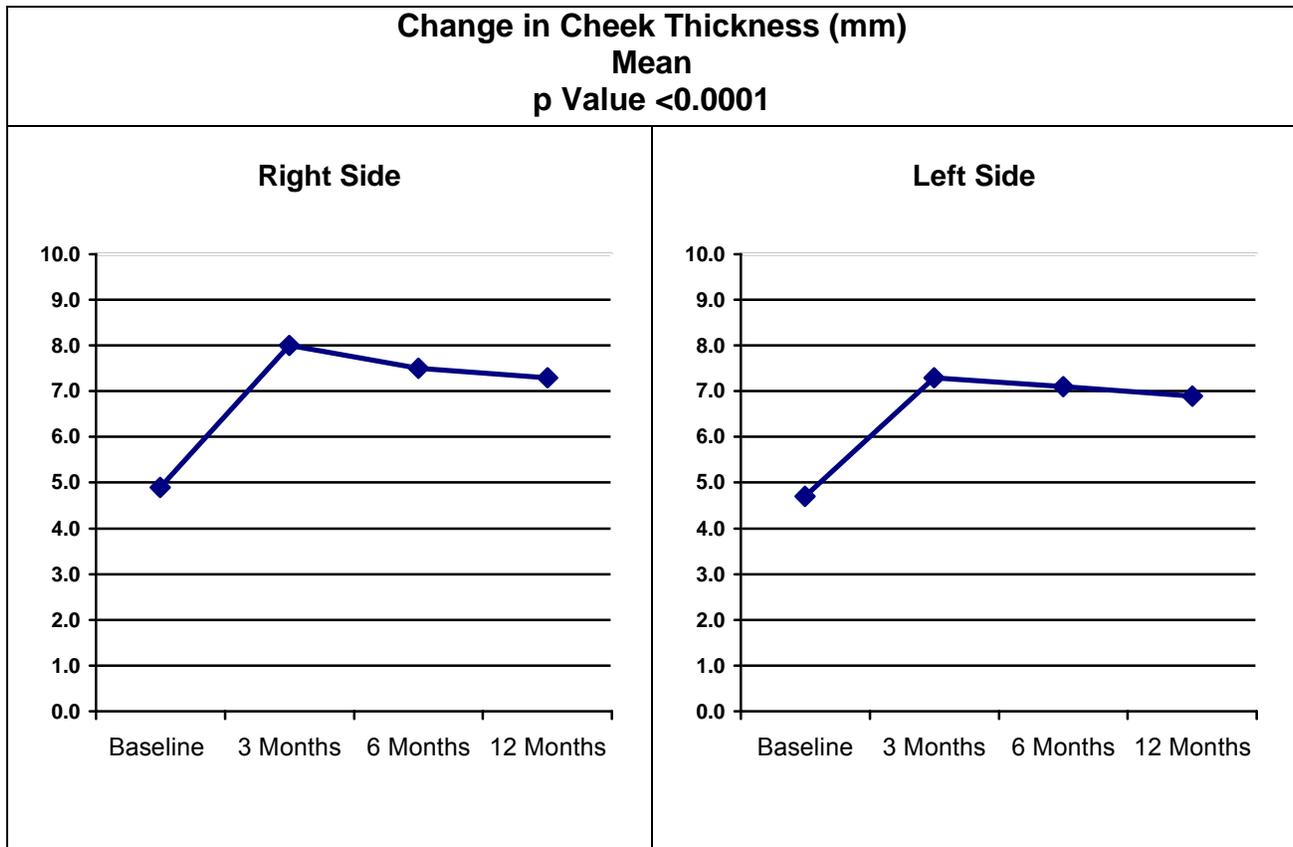


The table and figure immediately following show changes from baseline in cheek thickness at 3, 6, and 12 months. A statistically significant increase in cheek thickness was demonstrated at all time points.

Change in Cheek Thickness (mm)							
	Baseline N = 100	3 Months N = 100		6 Months <sup>5</sup> N = 97		12 Months N = 98	
	mm	mm	Change From Baseline	mm	Change from Baseline	mm	Change From Baseline
<b>Left Side</b>							
Mean	4.7	7.3	2.6	7.1	2.4	6.9	2.2
p Value			<0.0001		<0.0001		<0.0001
<b>Right Side</b>							
Mean	4.9	8.0	3.1	7.5	2.7	7.3	2.5
p Value			<0.0001		<0.0001		<0.0001

<sup>5</sup> One patient did not have a cheek thickness recorded at the 6 month time period; therefore the N for the 6 month cheek thickness is 97.

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Patient satisfaction was assessed at 3, 6 and 12 months by asking patients a series of questions that were modeled after the Freiburg Questionnaire on Aesthetic Dermatology and Cosmetic Surgery (FQAD).<sup>6</sup> The responses at each time point demonstrated overwhelming patient satisfaction. Not only was the patient satisfaction very positive, the patient satisfaction remained consistent to the 12 month time period.

<sup>6</sup> Sommer, et al, "Satisfaction of Patients After Treatment with Botulinum Toxin for Dynamic Facial Lines," *Dermatol Surg*, 2003, 29:456-460.

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

<b>Patient Satisfaction Results</b>						
<b>Question</b>	<b>3 Months N = 100</b>		<b>6 Months N = 98</b>		<b>12 Months N = 98</b>	
	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%)

Safety Endpoint

The clinical trial established Radiesse as being a safe medical device for soft tissue augmentation for the treatment of facial lipoatrophy. 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, nodules, necrosis, infection or hematomas at any time during the course of the study.

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

<b>Adverse Events Over the Course of the Study</b>						
	<b>Number of Events</b>	<b>Baseline to 1 Month</b>	<b>1 to 3 Months</b>	<b>3 to 6 Months</b>	<b>6 to 12 Months</b>	<b>12 Months</b>
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%)
Erythema	214	64 (29.9%)	69 (32.2%)	0 (0.0%)	81 (37.9%)	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. The table below 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

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(3.3%). The severe events were not unexpected, were short in duration, were typical of injection procedures and had no impact on patient outcomes.

<b>Severity of Adverse Events</b>				
<b>Adverse Event</b>	<b>Number of Patients With Event</b>	<b>Maximal Severity</b>		
		<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Echymosis	65	34 (52.3%)	26 (40.0%)	5 (7.7%)
Edema	99	46 (46.5%)	49 (49.5%)	4 (4.0%)
Erythema	57	34 (56.7%)	23 (40.4%)	0 (0.0%)
Pain	39	25 (64.1%)	13 (33.3%)	1 (2.6%)
Pruritis	21	18 (85.7%)	3 (14.3%)	0 (0.0%)
Other	58	40 (69.0%)	17 (29.3%)	1 (1.7%)
<b>Total</b>	<b>339</b>	<b>197 (58.1%)</b>	<b>131 (38.6%)</b>	<b>11 (3.2%)</b>

“Other” adverse events that were reported captured those that did not fit into the categories detailed the table above. The most common report was that of uneven contours and irregularities early in the treatment and resolved with additional injections. The majority were reported as being mild in nature (69.0%).

One patient reported a systemic adverse event (blood in urine) that was short in duration (1 day), mild in severity, and not related to the device.

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 was determined to be related to either the procedure or the device.

With respect to safety in persons of color, an analysis was also performed comparing Fitzpatrick Skin Scores to adverse events. The analysis revealed that the Fitzpatrick Skin Score was not a predictor ( $p = 0.9736$ ) for the occurrence of adverse events.

## **SUMMARY AND 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 endpoints at 3 and 6 months (Improved, Much Improved or Very Much Improved on the GAIS). In addition, all patients reported GAIS improvement 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 to a statistically significant level 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.

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Safety

Results of this clinical study indicate that Radiesse was safe in that it was well tolerated in the study population. The adverse events were associated with the injection procedure 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.

Therefore, it has been concluded that Radiesse is safe and effective for its intended use of soft tissue augmentation in the treatment of facial lipoatrophy. The clinical trial confirmed that Radiesse clearly met all the primary and secondary endpoints of the study as defined in the clinical protocol with an acceptable level of risk.

Immediately following are baseline, 3 month, 6 month and 12 month photographs for 5 representative patients that participated in this clinical study.

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**PROTOCOL #s 1205191 and 0106198  
RADIOLOGICAL EVALUATION OF  
SHORT-TERM AND LONG-TERM IMPLANTATION OF RADIESSE IN THE FACE**

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A 58 patient clinical trial was conducted to assess the radiographic appearance of Radiesse in patients with both short-term and long-term follow-up after injection for the treatment of HIV-associated facial lipoatrophy and nasolabial folds. The study was designed to ensure that a broad range of treatment conditions was evaluated. Patients were imaged immediately after initial injection, at least 12 months after initial injection and following treatment with both small and large Radiesse volumes.

**CONCLUSIONS DRAWN FROM STUDY**

- Radiesse is seen on both X-ray and CT Scan; however the CT Scan provides a much clearer and more consistent image.
- There is virtually no risk that the presence of Radiesse will mask underlying structures or abnormal growths in the areas in which it is injected.
- There is no evidence that Radiesse migrates.
- The presence of Radiesse as a radiographic material does not pose a safety concern. Injecting physicians and other medical professionals are to be made aware of the radiographic appearance of Radiesse when injected in the facial area.

**STUDY DESIGN**

Methods and Materials

A study was conducted to assess the radiographic appearance of Radiesse in patients with both short-term and long-term follow-up after injection for the treatment of HIV-associated facial lipoatrophy and nasolabial folds.

Short-term eligible patients were to participate in two imaging sessions – one prior to Radiesse treatment and the other within 12 weeks after Radiesse treatment. Patients were eligible to participate if they met the following selection criteria:

- Had not received any facial surgery or facial silicone injections and agreed not to receive any such procedures until the radiology study was complete.
- Had not received collagen or hyaluronic acid injections in the face within the past 6 months and agreed not to receive any such procedures until the radiology study was complete.
- If a female of child bearing potential, was using birth control methods that were either barrier methods (condom or diaphragm) plus spermicide starting at least 14 days prior to entry into the study, or starting at least 4 weeks prior to entry into the study and agreed to continue these methods of birth control until 14 days after last imaging.

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Long-term patients were selected from those who had received Radiesse for the treatment of HIV-associated facial lipoatrophy and had Radiesse material in their face for a minimum 12 months. These patients were drawn from the clinical trial entitled, “Protocol for the Evaluation of Radiesse in the Treatment of HIV-Associated Facial Lipoatrophy” that was conducted in Canada conducted by Alistair Carruthers, MD. Eligible patients could participate in up to two imaging sessions.

All X-rays and CT Scans were assessed by two blinded, licensed radiologists. Based upon his/her review, each radiologist completed a Blinded Evaluator Case Report Form for each image.

**Results**

Three patient categories were possible and are detailed below in the table immediately following.

**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, 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. Of the 28 long-term lipoatrophy patients, 23 underwent imaging sessions prior to the 12-month injection and 27 underwent imaging sessions after the 12 month injection. All 30 short term patients underwent imaging sessions before and after injections. This resulted in 110 images (55 CT scans and 55 x-rays) being evaluated by each the two blinded evaluators for a total of 220 imaging data points.

**X-Ray Analysis**

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

## **Radiesse for Soft Tissue Augmentation for the Treatment of HIV-Associated Facial Lipoatrophy Panel Pack**

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 Radiesse in a group (N = 3) that had not yet undergone any injections.

Both evaluators identified x-rays for which they believed Radiesse could be falsely interpreted as a malignant or benign tumor or could mask a tumor. This is most likely due to the lower sensitivity of the X-ray when compared to the CT Scan. Those concerns were not expressed when the CT Scans for these same patients were evaluated. In standard clinical practice, if a suspect finding was seen on X-ray, a CT Scan would typically then be ordered. A suspect finding would then most likely be favorably resolved upon the reading of the CT Scan. An x-ray would rarely, if ever, be used as the final diagnostic tool.

### CT Scan Analysis

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 seen when imaging was done several months out from an injection (approximately 70% of time by each evaluator). As expected, the results for the CT Scan provided a superior image capability as compared to X-ray.

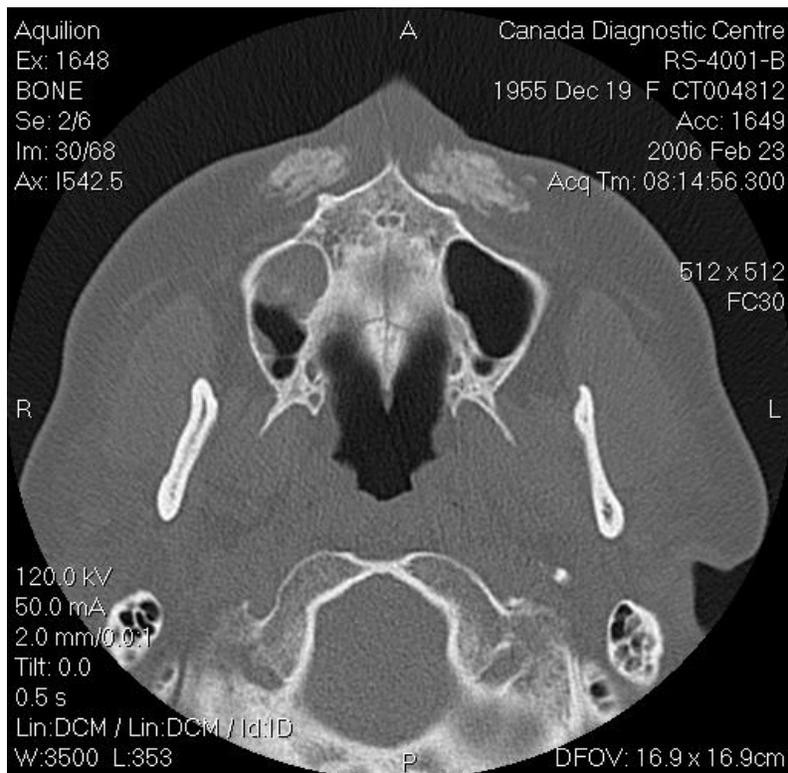
Even though the evaluators determined that Radiesse as seen in the CT Scans may be similar to the appearance of a tumor, those masses were generally identified by both evaluators as being “unlikely” to be falsely interpreted as a tumor. The appearance of Radiesse bilaterally is not typical for either benign or malignant tumors and the presence of a mass of this type in the area in which Radiesse was seen is extremely rare. The most common cancer in the facial area is skin cancer and that is not typically a radiographic diagnosis but the result of an excisional biopsy.

### Discussion

Radiesse was found to be radiopaque on both X-ray and on CT Scan, with it being more evident on CT Scan due to the sophistication of the CT Scan technology. Radiesse was seen on CT scan and the densities are greater than the surrounding soft tissue, but not as dense as seen in bony structures. Figure A is representative of Radiesse in the soft tissue of the facial area.

## Radiesse for Soft Tissue Augmentation for the Treatment of HIV-Associated Facial Lipoatrophy Panel Pack

Figure A

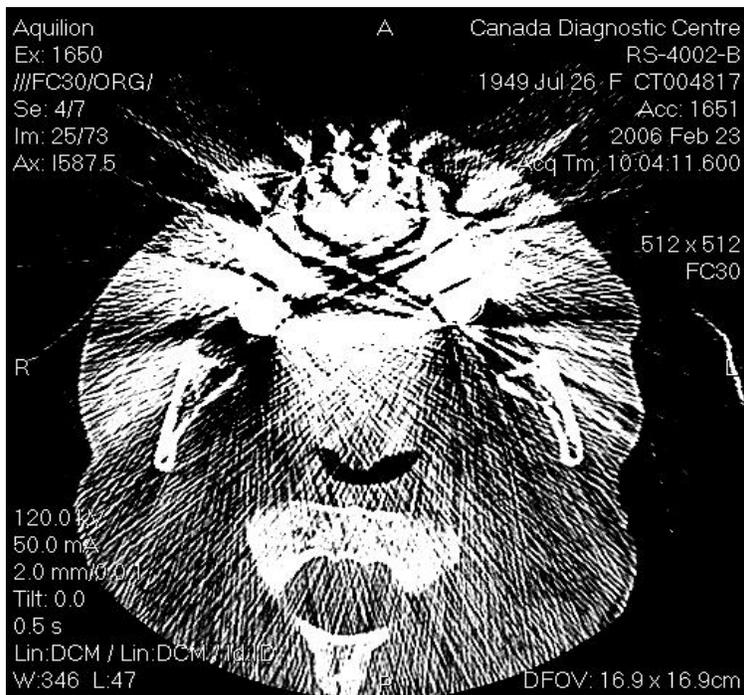


Since Radiesse is injected in the soft tissues of the face it does not interfere with radiologic interpretation of cranial and facial structures. It does not create artifacts that would cause it to mask other structures, which would result in the misdiagnosis relating to a tumor. Unlike a tumor, because Radiesse is injected symmetrically on both sides of the face, it appears as two equally distributed masses. This dual, evenly distributed pattern would be highly unusual for a tumor. In addition, the most likely facial tumor would be a bone tumor that would radiate from the facial bone.

As demonstrated in the image above, Radiesse is clearly separated from the bone. It was also observed that Radiesse does not result in scattering in the CT Scan image, as seen with dental work that contains metal. The scattering that is produced by dental work is much more pronounced and causes large interference patterns making diagnosis in these areas difficult. Figure B below is representative of this phenomenon. The density and configuration of Radiesse appears to remain constant over time.

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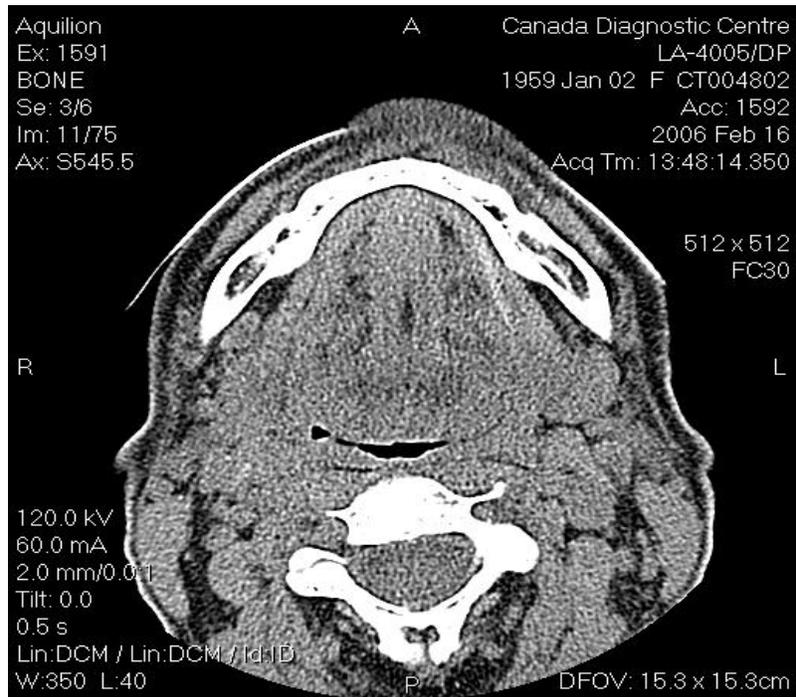
**Figure B  
CT Scattering Due to Dental Work**



There is no evidence in the CT Scans or in the X-rays for Radiesse being observed outside the area where it was injected. The 2 “yes” responses were due to intentional injections outside the cheek area. Figure C is a typical CT Scan that shows no evidence of material that could be considered Radiesse in areas in which it was not injected. The lymph nodes appear clear of material that would be typical of Radiesse as seen in a CT Scan. These results are consistent with the results reported in the PMA as well as seen in animal studies.

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**Figure C  
CT Scan of Lymph Node Area**



If in a rare case Radiesse were to be falsely interpreted as a tumor, the radiologist would follow a clinical course to ensure that his/her interpretation of the image was accurate and that a proper course of action could be employed. If a suspect finding was seen on X-ray, a CT Scan would typically then be ordered. Based upon the results of this study, a suspect finding would most likely be favorably resolved upon the reading of the CT Scan. If the CT Scan was still inconclusive, then the communication between the patient and the referring physician would occur in an attempt to clarify the issue.

Given the extremely rare incidence of masses and tumors in this area, the risk of a patient undergoing further invasive procedures would be low. It is also important to note that the Radiesse that would be seen in an X-ray or a CT Scan would present as bilateral, unlike a tumor. Typically, tumors do not present as two distinct symmetric masses and the occurrence of a tumor in the facial area is rare.

If in the rare instance that these steps did not provide satisfactory closure, the worst-case scenario would be a minimally invasive fine needle (25-27 gauge) aspiration biopsy. The needle used in this biopsy is of the same or smaller gauge needle used for the injection of a dermal filler. The possibility of this procedure occurring would be quite low as there would be many steps that would be taken by the radiologist, the primary care professional and the patient prior to a biopsy. The risk of any intervention more significant than a fine needle biopsy is negligible, as the biopsy report would rule out further action.