

Panel Memo
P050052
Radiesse for Soft Tissue Augmentation
Nasolabial Folds

Sponsor: BioForm Medical

To: The Record
IDE number: G030221

Name of Study: Injectable Calcium Hydroxylapatite Implant for Soft Tissue Augmentation for the Treatment of nasolabial Folds.

Chemist Review: The data for this PMA is identical to that submitted for P050037-Radiesse for Facial Lipoatrophy.

Device Description:

Radiesse is a sterile, non-pyrogenic, flexible, semi-solid cohesive granular implant. The device contains calcium hydroxylapatite granules in a gel of glycerine, water and sodium carboxymethylcellulose. The final concentration of the ingredients are (by mass) XXX HA, XXX sterile water, XXX glycerine, and XX NaCMC. The implant is available in two versions, depending on the size of the hydroxyapatite particles. For this IDE, the sponsor is using only one size; the particle sizes for Radiesse are 25-45µm. The device comes in pre-filled syringes of 1.0 cc.

This PMA is being presented to panel because the device itself is new for this specific indication, and there are new questions of safety and/or effectiveness for this device. You will be asked several questions at the end of the panel meeting regarding some of these issues.

The **manufacturing** data was submitted in modules (M050012) for review. Several specifications were noted to be out of range and the sponsor addressed concerns of the reviewer satisfactorily. Noted in the review were issues related to device specifications, gel carrier specifications, CaHA specifications, process validation, packaging and package validation, sterilization, shelf life and quality systems.

Device History: The structure of Radiesse is identical to that of the cleared devices listed below, except for particle size (these particle sizes are larger- 75-125 microns).

K012955: Coaptite[®] Tissue Marker (soft tissue)

K013243: Coaptite[®] Laryngeal Augmentation System

K012955: Bone Filling Augmentation Material

The device for this PMA is identical to the device currently under investigation in G030221/P050037- Radiesse for the treatment of HIV associated lipoatrophy.

Clinical review:

The purpose of the study was to assess the safety and effectiveness of Radiesse for the correction of nasolabial folds. The comparator was Cosmoplast, a commercially available device labeled for this indication. The study was a prospective, randomized, controlled trial completing 6 month follow-up after optimal treatment had been achieved. Safety data on 47 patients were included to 12 months.

Clinical Trial Outline: Endpoints:

The **primary** effectiveness endpoint of the study was to evaluate, using the previously validated and published Lemperle Rating Scale (LRS), whether Radiesse was non-inferior to Control (COSMOPLAST) for the correction of nasolabial folds 3 months after final treatment by comparing the percentage of patients in whom Radiesse was superior to Control versus the percentage where Radiesse was inferior to Control.

The secondary effectiveness endpoints of the study were

- 1) To evaluate using the LRS scores whether Radiesse is superior to Control for the correction of nasolabial folds at 6 months after final treatment by comparing the percentage of patients where Radiesse was superior to Control versus the percentage where Radiesse was inferior to Control; and,
- 2) To evaluate, using blinded evaluator Global Aesthetic Improvement Scale (GAIS) ratings whether Radiesse is non-inferior to Control for the correction of nasolabial folds 3 and 6 months after final treatment by comparing the percentage where Radiesse was superior to Control versus the percentage where Radiesse was inferior to Control.

In addition, a superiority assessment in this study required a mean 1-point LRS difference between improvement on the Radiesse fold versus improvement on the Control treated fold and that in at least 50% of patients, the Radiesse treated fold be superior to Control treated fold.

Safety Endpoint

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

Study Highlights:

- Loss to follow-up was minimal. Of the 117 patients receiving treatment, 115 were available for the primary effectiveness measurements at three months, and 113 at 6 months. The safety analysis included all 117 patients, of whom 113 were available at 6 months.
- Adverse events were generally related to injections.
- Protocol deviations were few and minor.

Important Inclusion/Exclusion criteria:

Inclusion Criteria

- ◆ Had right and left nasolabial folds with a rating of 3 or 4 based on the LRS as determined by three blinded evaluators
- ◆ 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)
- ◆ 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
- ◆ 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

Study Synopsis:

- Enrollment visit- Pt. assessed to meet inclusion/exclusion criteria except NLF measurements, and females given pregnancy test. Standardized photos taken and assessed by 3 independent reviewers to assure a grade 3 or 4 (on the 6 point Lemperle scale) for inclusion

- Initial injection- if all criteria met, randomized to side for study (split-face) device/comparator. Both sides treated to optimal correction. Volume of material recorded. Patient guess as to which devices injected on each side of face. Patient diary.
- Visit at 2 weeks- photos taken, touch-up allowed if optimal correction not achieved. Patient diary if retreated.
- Visit at 4 weeks- photos again taken. Third touch-up allowed in folds treated at week 2 (NOTE: three patients were treated at week four with out treatment at week 2, a protocol violation. See page 6-35, volume 2, section 6 for discussion)
- Visit at week 6- patients treated at week 2 or 4. No touch-up allowed. Photos taken and patient guess noted
- Visit at week 8- patients treated at week 4. Same as week 6.
- 3 month visit- from last injection in a given fold. Photos taken and patient guess.
- 6 month visit- from last injection in a given fold. Photos and patient guess. Patient satisfaction questionnaire, and each patient assessed by investigator in GAIS scale.
- After 6 months, patients could receive a touch-up with Radiesse on either side.
- 12 month visit- from injection of original Radiesse fold. Photos taken,

Note: Adverse events were recorded at each treatment and visit session.

Assessment tools:

Lemperle Rating Scale (LRS)

Classification	Description
5	Very deep wrinkle, redundant fold
4	Deep wrinkle, well-defined edges
3	Moderately deep wrinkle
2	Shallow wrinkles
1	Just perceptible wrinkle
0	No wrinkles

Global Aesthetic Improvement Scale (GAIS)

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.

Baseline Characteristics of Patient Population:

**Patient Demographics
N = 117**

Age	
Mean (Years)	
SD	
Min	
Max	
Gender	
Male	
Female	
Body	
Mass	
Index	
(BMI)	
Race	
White	
Black	
Hispanic	
Other	

Noted above is a small number of “persons of color”, and to address the issue, the sponsor has referenced the large number of patients with Fitzpatrick type IV-VI in their HIV lipoatrophy study. The sponsor notes that the adverse event profile for these patients was not a predictor of safety outcomes. However, it is obvious that the two patient populations are not homogeneous. The rationale for including “persons of color” is to assess the formation of skin changes (hypertrophic scars, discoloration, etc) and the patients in the lipoatrophy study were certainly immunosuppressed, or at best receiving immunosuppressive medications with diminished capacity to mount a hypersensitivity reaction. That would preclude assessing hypersensitivity reactions or skin changes and therefore would make the argument that we can infer no skin color issues mute. You will be asked a question at the end of panel discussion regarding this issue.

General Study Characteristics:

The sponsor has provided a table to demonstrate the distribution of the baseline nasolabial folds before treatment. This table showed that all patients met entry criteria for the study (table 2, page 2-9)

**Number of Patients Injected at Each Time Point During the Initial Injection Phase
N = 117**

Baseline			
Injection			
Baseline			
Only	2		
Baseline			
Week	4		
and			
Baseline,	4		
Week			
2-Week			
Injection	4		
and			
Week			
Injection			

	B		2		4	
	a	s)	W		W
V	e		e		e	
M	l		e		e	
S	i		k		k	
W	n		s		s	
M	e					
P	<		<		0	

The volume of Radiesse injected during the course of the study is detailed above. 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).

The majority of patients received anesthesia noted as “Block” during the baseline injection as well as during the 2 and 4-week injections. This was true for both Radiesse and Control. Local anesthesia use is common when injecting fillers, and has not been shown to affect clinical outcomes.

Statistical methods:

This was a split-face design in 117 patients comparing Radiesse to Cosmoplast, an approved human collagen product.

Sample Size

The sponsor's sample size calculation is based on 90% power and a 2.5% Type I error to detect a 15% absolute advantage assuming a 40% discordant rate for a one-sided hypothesis test. The non-inferiority margin was assumed to be 5%. With these parameters, the sponsor found a sample size of 99 evaluable patients would be needed. We have verified the sponsor's calculation using PASS 2005.

The sponsor also claims that the same sample size is robust for a number of scenarios of non-inferiority and superiority. The sponsor's calculations were relatively conservative in the assumptions made about the treatment compared to what was observed in the study. Therefore, the study was more than adequately powered.

Effectiveness Data:

The sponsor has presented summary tables (pages 51-70) to support the effectiveness endpoints, both primary and secondary.

Effectiveness Assessments:

Primary Effectiveness endpoint- LRS at 3 months:

A vast majority (84.6%) of Radiesse treated folds were determined by the blinded evaluators to be superior to the Control treated folds while 12.8% of Radiesse treated folds were determined to be equivalent at three months using the LRS. Non-Inferiority was 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 because the criteria set for this determination were met.

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

Radiesse¹ Compared to Control				Radiesse Superior Among Patients with Discordant Results		Radiesse Superior Among All Patients	
Superior	Equivalent	Inferior	p-Value	Point Estimate	Lower Limit One-sided 97.5% Exact CI	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%

Primary Effectiveness Endpoint – LRS at 3 Months: By Each Blinded Evaluator

All three blinded evaluators similarly determined that the vast majority of Radiesse treated folds were superior to the Control treated folds with few Radiesse folds being rated inferior to Control folds. The following table details the results of the LRS at three months for each blinder evaluator. Based on these determinations, Radiesse met the primary effectiveness endpoint.

**Primary Effectiveness Endpoint
Non-Inferiority - LRS
By Each Blinded Evaluator
3 Months
N = 117**

Blinded Evaluator	Radiesse Compared to Control				Radiesse Superior Among Patients with Discordant Results		Radiesse Superior Among All Patients	
	Superior	Equivalent	Inferior	p-Value	Point Estimate	Lower Limit One-sided 97.5% Exact CI	Point Estimate	Lower Limit One-sided 97.5% Exact CI
1	89 (76.1%)	24 (20.5%)	4 (3.4%)	<0.0001	95.7%	89.4%	76.1%	67.3%
2	90 (76.9%)	20 (17.1%)	7 (6.0%)	<0.0001	92.8%	85.7%	76.9%	68.2%
3	92 (78.6%)	18 (15.4%)	7 (6.0%)	<0.0001	92.9%	86.0%	78.6%	70.1%

Primary Effectiveness Endpoint – LRS at 3 Months: Race

The race of the patients in this study did not affect the outcome of the primary endpoint. The table below shows that there was no significant difference ($p = 1.0000$) between Caucasian patients non-Caucasian patients. As I stated previously, you will be asked a question regarding ethnicity of the patients enrolled in the study since the sponsor has noted throughout their submission that patients in their HIV lipoatrophy study (P050037) were included in their assessment of ethnicity evaluations.

Primary Effectiveness Endpoint – Race

**Non-Inferiority – LRS 3 Months
N = 117**

	Radiesse Superior	Radiesse Equivalent	Radiesse Inferior
Caucasian (N = 102)	86 (84.3%)	13 (12.7%)	3 (2.9%)
Non-Caucasian (N = 15)	13 (86.7%)	2 (13.3%)	0 (0.0%)
p-Value	1.0000		

Primary Effectiveness Endpoint – Change in LRS: Baseline to 3 Months

A significantly ($p < 0.0001$) higher number of Radiesse treated folds (87.2%) were reported as having a greater than a one-point improvement using the LRS than Control treated folds (27.4%) thereby Radiesse being determined as being superior to Control at 3 months.

**Primary Effectiveness Endpoint
Change in LRS
Baseline to 3 Months
N = 117**

	R	C	
\geq	86	3	
R	86	3	
W	86	3	

The mean change from baseline of the LRS for Radiesse was greater than one-point, at both 3 and 6 months, thereby meeting that requirement for superiority. Radiesse had a mean improvement of 1.50 and 1.23 points on the LRS over baseline at 3 and 6 months, respectively. As a comparison, Control had no improvement at 3 and 6 months (-0.09 and -0.05, respectively). Again, you will be asked a question regarding the lack of efficacy of the control in the final device efficacy determination.

Secondary Effectiveness Endpoint – LRS at 6 Months

The vast majority (78.6%) of Radiesse treated folds were determined to be superior to the Control treated folds while 16.2% were determined to be equivalent and 5.1% were determined to be inferior at six months using the LRS. Superiority was declared, as the lower limit of the one-sided 97.5% confidence interval was greater than 50%. It was determined that Radiesse met the secondary effectiveness endpoint of superiority using the LRS as established in the clinical protocol.

**Secondary Effectiveness Endpoint
Superiority – LRS at
6 Months
N = 117**

Radiesse Compared to Control				Radiesse Superior Among Patients with Discordant Results		Radiesse Superior Among All Patients	
Superior	Equivalent	Inferior	p-Value	Point Estimate	Lower Limit One-sided 97.5% Exact CI	Point Estimate	Lower Limit One-sided 97.5% Exact CI
92 (78.6%)	19 (16.2%)	6 (5.1%)	<0.0001	93.9%	87.1%	78.6%	70.1%

Secondary Effectiveness Endpoint – LRS – By Each Blinded Evaluator

At 6 months, all three blinded evaluators similarly determined that a significantly greater ($p < 0.0001$) number of Radiesse treated folds were superior to Control treated folds with few Radiesse treated folds being rated inferior to Control treated folds. The following table details the results of the LRS at six months for each blinder evaluator. Based on this data, Radiesse met this secondary effectiveness endpoint.

Secondary Effectiveness Endpoint Superiority - LRS By Blinded Evaluator 6 Months N = 117

Blinded Evaluator	Radiesse Compared to Control				Radiesse Superior Among Patients with Discordant Results		Radiesse Superior Among All Patients	
	Superior	Equivalent	Inferior	p-Value	Point Estimate	Lower Limit One-sided 97.5% Exact CI	Point Estimate	Lower Limit One-sided 97.5% Exact CI
1	82 (70.1%)	25 (21.4%)	10 (8.6%)	<0.0001	89.1%	80.9%	70.1%	60.9%
2	84 (71.8%)	24 (20.5%)	9 (7.7%)	<0.0001	90.3%	82.4%	71.8%	62.7%
3	91 (77.8%)	21 (17.9%)	5 (4.3%)	<0.0001	94.8%	88.3%	77.8%	69.2%

Secondary Effectiveness Endpoint – Change in LRS: Baseline to 6 Months

The table below shows that a significantly greater number of Radiesse treated folds had a greater improvement with the LRS when compared to Control treated folds ($p < 0.0001$). Again, based on this data, FDA determined that Radiesse met this secondary effectiveness endpoint and that Radiesse was determined to be superior to Control at 6 months. Radiesse treated folds and Control treated folds were classified as “return to baseline” for the four missing patients (NL-02-098, NL-03-067, NL-04-037 and NL-04-112) in this analysis.

**Change in LRS
Baseline to 6 Months**

	Radiesse	Control	p-Value
≥ 1-Point Improvement	96 (82.1%)	32 (27.4%)	<0.0001
Return to Baseline or Worsen	20 (17.1%)	44 (37.6%)	
Worsen	1 (0.9%)	41 (35.0%)	

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

A secondary effectiveness endpoint was determining the effectiveness of Radiesse using the photograph-based GAIS evaluation.

**Photograph Based GAIS
3 Months
N = 115**

	Radiesse	Control	p-Value
Very Much Improved	23 (20.0%)	1 (0.9%)	<0.0001
Much Improved	46 (40.0%)	6 (5.2%)	
Improved	41 (35.7%)	22 (19.1%)	
No Change	5 (4.3%)	65 (56.5%)	
Worse	0 (0.0%)	21 (18.3%)	
Total Improvement	110 (95.7%)	29 (25.2%)	
Total No Change	5 (4.3%)	65 (56.5%)	
Total Worsening	0 (0.0%)	21 (18.3%)	

In addition 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
Non-Inferiority – GAIS
3 Months
N = 117**

Radiesse Compared to Control				Radiesse Superior Among Patients with Discordant Results		Radiesse Superior Among All Patients	
Superior	Equivalent	Inferior	p-Value	Point Estimate	Lower Limit One-sided 97.5% Exact CI	Point Estimate	Lower Limit One-sided 97.5% Exact CI
98 (83.8%)	16 (13.7%)	3 (2.6%)	<0.0001	97.0%	91.6%	83.8%	75.8%

Secondary Effectiveness Endpoint – Non-Inferiority with GAIS – 3 Months – By Each Blinded Evaluator

All three blinded evaluators similarly determined that significantly more ($p < 0.0001$) Radiesse treated folds were superior to Control treated folds with few Radiesse folds being rated inferior to Control folds.

**Secondary Effectiveness Endpoint
Non-Inferiority – GAIS
By Blinded Evaluator
3 Months
N = 117**

Blinded Evaluator	Radiesse Compared to Control				Radiesse Superior Among Patients with Discordant Results		Radiesse Superior Among All Patients	
	Superior	Equivalent	Inferior	p-Value	Point Estimate	Lower Limit One-sided 97.5% Exact CI	Point Estimate	Lower Limit One-sided 97.5% Exact CI
1	104 (88.9%)	10 (8.6%)	3 (2.6%)	<0.0001	97.2%	92.0%	88.9%	81.8%
2	96 (82.1%)	19 (16.2%)	2 (1.7%)	<0.0001	98.0%	92.8%	82.1%	73.9%
3	90 (76.9%)	22 (18.8%)	5 (4.3%)	<0.0001	94.7%	88.1%	76.9%	68.2%

Secondary Effectiveness Endpoint – Superiority Using GAIS – 6 Months

						CI		CI
1	94 (80.3%)	17 (14.5%)	6 (5.1%)	<0.0001	94.0%	87.4%	80.3%	72.0%
2	87 (74.4%)	27 (23.1%)	3 (2.6%)	<0.0001	96.7%	90.6%	74.4%	65.5%
3	84 (71.8%)	31 (26.5%)	2 (1.7%)	<0.0001	97.7%	91.9%	71.8%	62.7%

The GAIS results at 6 months are detailed in Table 6-48. As was seen with the 3-month GAIS, the 6-month GAIS resulted in Radiesse having a significantly better improvement than Control ($p < 0.0001$).

**Photograph-Based GAIS
6 Months
N = 113**

	Radiesse	Control	p-Value
Very Much Improved	16 (14.2%)	1 (0.9%)	<0.0001
Much Improved	34 (30.1%)	5 (4.4%)	
Improved	40 (35.4%)	20 (17.7%)	
No Change	23 (20.4%)	67 (59.3%)	
Worse	0 (0.0%)	20 (17.7%)	
Total Improvement	90 (79.6%)	26 (23.0%)	
Total No Change	23 (20.4%)	67 (59.3%)	
Total Worsening	0 (0.0%)	20 (17.7%)	

The sponsor has presented a series of tables for correlation of intra-observer and inter-observer correlations for LRS based on photographic GAIS at varying time points during the study.

Patient Guess of Treatment Received

The patients were asked at each visit to guess which product was injected into each of their treated folds. The table below details the results of the patient guesses 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.

Patient Guess of Treatment Received

E	C
B	0
a	0
t	6
W	e
0	0
t	0
n	2
e	8

Her		0	0
mat		0	0
Inte		0	0
oma		0	0
Nec		0	0
Nose		1	0
Nled		0	0
Pain		0	0
Prior		0	0
Ush		0	0

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

Adverse Event	AR	CR	P
Her	0	0	0
mat	0	0	0
Inte	0	0	0
oma	0	0	0
Nec	0	0	0
Nose	1	0	0
Nled	0	0	0
Pain	0	0	0
Prior	0	0	0
Ush	0	0	0
3-6 Months	0	0	0

Systemic Adverse Events

Patient Number	Systemic Adverse Event
NL-01-013	Emergency gallbladder surgery
NL-02-054	Breast pain
	Infected and exposed right breast implant
NL-02-128	Vomiting, dehydration and intravenous fluids. Possibly due to Gastroenteritis
NL-02-161	Uterine fibroids, D&C
NL-02-184	Headache, Tylenol
NL-03-015	Headache
NL-03-065	Headache
	Headache
NL-04-037	Burning sensation in tongue and lips
	Numbness in tongue and lips
	Tongue ulceration
NL-04-124	Fatigue

Adverse Events through 12 Months

As described in the protocol, only Radiesse was offered for touch-up after the six-month evaluation and not Control for one or both folds. At the time of PMA submission, 47 Radiesse patients have their 12-month follow-up data included. The rate of adverse events for Radiesse patients was generally not different when comparing the 0-6 month follow-up time period to the 6-12 month follow-up time period, with the one exception of more “Other” adverse events at <6 months when compared to the “Other” adverse events at 6-12 months. The rate and type of adverse event reported for folds that received Radiesse at some point during the study remain consistent. It is important to note that 47 folds received Control during 0-6 months and then received Radiesse after the 6-month evaluation, which can be viewed as a worst-case scenario.

**Adverse Events
Radiesse Injections
Comparison of 0-6 Months to 6-12 Months**

Adverse Event	0-6 Months (n)	6-12 Months (n)	p-value
None	0	0	0.000
Redness	7 (14.0%)	2 (4.0%)	0.000
Swelling	0	2 (4.0%)	0.000
Pain	5 (10.0%)	0	0.000
Itching	82	2	0.000
Other	0	0	0.000
Total	0	0	0.000
Total	0	0	0.000

Adverse Events
 Comparison of 0-6 Months to 6-12 Months
 p-value

7
4
%

3

N	0	0	N
1	(1	/
1	0	0	N
34		7	4
22	0	2	0
36	%	0	2
336)	0	N

The sponsor provided a detailed summary table of the adverse events from this PMA application as well as their HIV Lipoatrophy study. No comparisons can be made as these are two distinct patient populations, and the events may or may not be related to these differences.

And finally, a concern of the review staff was the radiologic appearance of CaHA crystals injected in the face of individuals, specifically related to its appearance as a possible tumor, or its ability to hide a tumor beneath the injection site. The sponsor was asked to perform a radiographic evaluation of patients receiving Radiesse injections at several time points, specifically before, immediately after and several months after injection.

The sponsor has presented complete sets of radiographs and CT scans of the 48 patients studied in their Canadian radiographic study. This protocol was reviewed by FDA prior to initiation. The study enrolled 15 patients who were de novo for Radiesse injections in the NLF, 15 patients de novo for HIV lipoatrophy, and 28 lipoatrophy patients who were at least 12 months out from their initial injection. The purpose of the study was to obtain an assessment of the appearance of Radiesse that had been injected into the face immediately after injection and 12 months after the initial injection. The study was designed to evaluate patients at variable time points and with variable volumes of material injected. Specifically, patients with short term follow-up (immediately after injection) and long-term follow-up (at least 12 months after initial injection) as well as patients with smaller volumes of Radiesse injected (nasolabial patients) and larger volumes of Radiesse injected (facial lipoatrophy patients) were assessed. You will be asked a question at the end of panel discussion regarding the radiographic evaluations performed.

Study Results- Radiographic Study

The sponsor concluded that Radiesse did not pose a significant risk of either masking an existing benign or malignant tumor in the facial area or that it could be interpreted as a tumor, when seen with CT Scans.

The sponsor concluded that Radiesse was radiopaque on X-rays and CT Scans however, there was not a significant risk for Radiesse to either mask a benign or malignant tumor or that it would be interpreted as a benign or malignant tumor. The study also determined that Radiesse was not as consistently visible on X-ray as it was on CT Scan.

Typically, the presence of Radiesse would first be observed on an X-ray. If that were the case, the patient would then undergo a CT Scan, which has become the primary radiographic imaging methodology, due to the inconclusive nature of X-rays. If after the CT Scan there was still a concern, and after consultation with the patient and the other referring medical professionals, the worse case scenario would be a fine needle aspiration biopsy. The biopsy is minimally invasive and is typically performed with a needle of the same size as the needle used to inject Radiesse (25 or 27 gauge). With each step in the process, the chance of the worst case minimally invasive procedure occurring is diminished dramatically.

The conclusions that were drawn from the study (radiologic evaluator) by the sponsor were:

- 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.

The sponsor concluded the safety data section with a review of the published literature of the use of Radiesse worldwide. There are numerous anecdotal reports of use, including use in the lips, nasolabial folds, cheeks, mental crease, buccal region and tear trough. To support the worldwide safety profile the sponsor reports the following:

There have been approximately 160,425 units of Radiesse distributed worldwide. It can be seen that the complaint rate for Radiesse is extremely low and there are no indications that the product is not performing as intended. It is important to note that the complaints

described below are as received. In many cases, it was not possible to confirm that the incident occurred and/or if the incident was related to the product.

Radiesse Units Shipped vs. Complaints Received

Complaint	Number of Complaints	% of Shipped N = 160425
Allergic Reaction	4	0.002%
Dry Product	14	0.009%
Erythema	13	0.008%
Gel Separation	1	0.001%
Lip Nodules	49	0.030%
Lost Effect	72	0.040%
Necrosis	3	0.002%
Needle Jam	26	0.015%
Other Nodules	51	0.032%
Over Injection	4	0.002%
Pain	1	0.001%
Swelling	26	0.015%
Systemic Reaction	15	0.009%
Uneven Contour	9	0.006%

*The above results were based on a passive voluntary reporting system; therefore, FDA is uncertain as to how one interprets these results.

Statistical Review:

The control product was not effective at either the 3 or the 6 month time point. However, Radiesse showed both statistical and clinical superiority at both of these time points, where clinical superiority was pre-specified as at least a 1 point difference in mean improvement in LRS scores, and Radiesse being judged superior in at least 50% of patients. With respect to safety, the adverse event profiles of the two treatments were mostly not significantly different, with the exception of greater incidence of ecchymosis and edema and possibly longer duration of nodules in the Radiesse treatment.

Patient Follow-Up

Patients received up to three treatments two weeks apart. Following each treatment patients received a two-week diary and a 72 hour telephone call to elicit adverse events. Follow-up occurred at 2 weeks and 4 weeks after each treatment application, and 3 and 6 months after the last injection. If the last treatment date differed for each side of the face, the patient returned for two 3 and 6-month visits.

Hypotheses Tested

The primary non-inferiority hypothesis is based on a matched pair design where the percent of patients with Radiesse advantage is compared to the percentage with Control advantage. The hypotheses are as follows:

$$H_0: \Delta < -\delta$$

$$H_A: \Delta > -\delta$$

Where Δ is the difference in percentages with advantage for each treatment and δ was taken to be 5%.

Randomization

The sponsor did not give details of their randomization procedure. In a footnote on page 6-21 of the clinical report you state, "Computer generated randomization assignments were prepared and sealed in individual envelopes by patient ID# and opened at the time of treatment." Not detailed is what occurred when patients who had received a patient ID number were later found to be ineligible for the study.

Blinding

For the primary and secondary effectiveness assessments, the sponsor relied on photographic assessment by three blinded physicians "who were board certified dermatologists or plastic surgeons familiar with the clinical use of cosmetic dermal fillers" [Clinical Report, p. 6-20] However, effectiveness of the blinding of the physician evaluators was not assessed.

Patients were also blinded. However, the sponsor does not include any patient based measures of product effectiveness, other than patient reporting of which was the most satisfactorily treated fold at the 6 month follow-up visit. Effectiveness of patient blinding was assessed and showed that at baseline, only slightly more patients guessed the assignment than would have been expected by chance. However, by 6 months, nearly all patients correctly guessed the assignment. This is probably due to the known greater durability of the Radiesse treatment.

Patient Accountability

Five hundred sixty-three (563) patients were consented for inclusion into the study. Four hundred nineteen (419) of these did not meet the inclusion/exclusion criteria for their nasolabial folds, and an additional 27 withdrew their consent. The remaining 117 patients received treatment.

Of the 117 patients receiving treatment, only 2 were missing for the primary effectiveness evaluation at 3 months. At 6 months there were 4 patients without data. Thus follow-up in the study was quite good. As of the date of the submission, 47 patients had 12 month data and 66 had not yet been seen.

Protocol Deviations

There were a few minor deviations involving 1 patient with a violation of exclusion criteria (had received Restylane prior to the study), 4 patients with non-critical missing photographs, 3 patients with non-allowed concomitant medications, 3 patients where correct procedure was not followed for touch-up injections, 2 patients receiving expired Radiesse, and 18 patients with randomization errors. In addition, there were many patients (53) seen outside of the assessment time windows. Also, there was a problem with patient pregnancy tests not being performed prior to 6 month touch up as described in the protocol. However, none of these protocol violations is critical to the study results. This is mostly because they occurred in few patients or were not severe in their impact. In particular, the 18 randomization errors only determined the side of the face for each treatment, and this was most likely not critical to the results.

The sponsor also presents a statistical analysis of patients with protocol violations versus patients without. This analysis shows that the presence of violations did not significantly affect the observed results.

Intent-to-Treat

The sponsor states that the intent-to-treat (ITT) population was defined as all patients who received both randomized treatments as planned. Missing data were to be counted as no change for either treatment. Note that an ITT analysis is not conservative for non-inferiority. However, the sponsor demonstrated superiority in addition to non-inferiority at both time points. Moreover, there was less than 2% of data missing at 3 months and less than 4% at 6 months. Thus the sponsor's analysis approach is acceptable.

Patient Demographics

The study population was primarily female (90%) with a mean age of 54.7 years. The study was also primarily Caucasian (87%) with some Hispanic patients (9%), few African American patients (2%) and some "Other" patients (2%). Thus, it was not possible for the sponsor to fully evaluate safety and effectiveness in patients with darker skin types (Fitzpatrick Types IV, V and VI). The sponsor presents the results of another Radiesse trial to support safety and effectiveness in these patients. However, the cited trial is for a completely different indication (facial lipoatrophy), with different device usage, in a different population (immuno-compromised patients with HIV infection).

Other baseline variables which were considered in the analysis were history of smoking and sun exposure. Approximately 29% of patients were either current smokers (7%) or former smokers (22%), and 71% of patients reported that they had never smoked. With regard to sun exposure, 22% had no history of sun exposure and 78% reported some sun exposure. For those patients with sun exposure, the mean number of hours of weekly exposure was 7.6 hours with a standard deviation of 7.1 hours. The sponsor also collected information on prior collagen procedures, which were the only prior soft tissue

augmentation allowed in the study. Approximately 9.4% of patients had had these procedures.

Statistical Evaluation of Primary Endpoint

The sponsor's primary endpoint is change in LRS scores as assessed by three blinded evaluators. It is not clear how the three independent assessments were combined to yield one summary result. In addition, note that the assessments by the three blinded evaluators were performed from patient photographs, not live assessment, although there was one live assessment as a secondary endpoint.

It is clear that the sponsor met the statistical criteria for non-inferiority at 3 months, i.e. the p-value from McNemar's test was <0.0001 , and the lower limit of the confidence interval for the percent with Radiesse superior was 76.8%. The Control did not show any improvement over baseline at 3 months. This can be seen in the sponsor's Figure 5, on page 6-6 of the Clinical Report. Fortunately for the sponsor, the treatment also demonstrates statistical and clinical superiority at 3 months. That is, greater than 50% of subjects rated Radiesse superior, and the mean difference in change in LRS scores between treatment and control was -1.59 (95% CI -1.70, -1.48), which is larger in magnitude than the required 1-point difference. We do have a question about the model used to calculate this "least squares mean difference" between the treatments.

Statistical Evaluation of Secondary Endpoints

The sponsor has also demonstrated statistical and clinical superiority of the treatment at 6 months, as measured by independent evaluator LRS scores. Namely, the lower confidence limit for the percent of folds where Radiesse was superior was 70.1%, which is greater than the required 50%, and the mean difference in change in LRS scores between treatment and control was -1.28 (95% CI -1.38, -1.18), which is larger in magnitude than the required 1-point difference.

The 3 and 6 month photographic assessments with the GAIS scale were also favorable to the treatment. Namely, a large percentage of assessments showed Radiesse superior to the control, i.e. 83.8% of patients at 3 months and 75.2% of patients at 6 months showed this result. In addition, there were live GAIS assessments by the principal investigator in 74 of the 117 patients. These results were also favorable to the treatment. Namely, 94.6% of Radiesse folds were rated improved to some degree at 6 months while only 2.7% of control folds received this rating.

At 6 months, both the patients and investigators were asked to judge which was the most satisfactory treated fold. Among patients, 96.5% favored the Radiesse treated fold and, among physicians, the same percentage (96.5%) did the same.

Statistical Consistency of Results: Inter and Intra-Evaluator agreement

The sponsor presents many tables attempting to demonstrate consistency between the three blinded evaluators. First they present effectiveness results at both 3 and 6 months separately for each evaluator. These results are remarkably consistent, with each evaluator rating Radiesse superior in approximately the same percentage of patients for each 3 and 6 month endpoint. The sponsor also presents the statistical agreement between pairs of evaluators in the form of weighted Kappa statistics. These results are not as impressive, with most of the weighted Kappa statistics ranging from about 0.4 to 0.6. Note that the relatively low Kappa could be partly a statistical artifact due to agreement tables which are somewhat symmetrically unbalanced.

The sponsor also explores agreement between the photographic LRS, photographic GAIS, and live GAIS assessments. Here the weighted Kappa ranges from about 0.45 to 0.60, again indicating moderately acceptable agreement.

In each photographic assessment, the sponsor attempted to capture intra-observer agreement by embedding duplicate photographs in the set of photographs being evaluated. The results for intra-observer agreement were better than those between investigators. Here the weighted Kappa ranged from about 0.55 to 0.85, indicating relatively good agreement.

Subgroup and Covariate Results

The sponsor performed several statistical tests for association between covariates and the LRS outcomes. They found no statistical association between the two treatments and the covariates of history of smoking, history of sun exposure, and Caucasian vs. non-Caucasian. The p-values for these comparisons were all non-significant and the percentage of folds rated Radiesse superior, equivalent or inferior was highly similar for the various levels of the above covariates.

Data Pooling and Analyses by Site

The sponsor provides results of formal statistical tests of site by treatment interaction for LRS and GAIS assessments at both 3 and 6 months. None of these tests for site by treatment interaction were statistically significant. The sponsor argues that thus the data are suitable for pooling

Safety

In a comparison of Radiesse to the Control, the occurrence of local adverse events was similar with the exception that patients experienced significantly more edema and ecchymosis on the Radiesse side. However, the duration of adverse events was mostly not significantly different between the treatments, including the durations of ecchymosis and edema. One exception is that there may have been a difference in the duration of nodules with each treatment. Specifically, the Radiesse treatment resulted in one nodule,

which had a duration of 195 days, while the Control resulted in 4 nodules with a mean duration of 34 days and a range of 8 to 91 days.

There were 12 systemic adverse events, none of which were attributed to Radiesse or Control. These included vomiting, headache, fatigue and one patient with numbness and a burning sensation on the tongue and lips. The sponsor also presents a comparison of adverse events occurring in all patients during months 0-6 to adverse events experienced during months 6-12 by 47 patients who have 12 month data after a 6 month touch up injection. There were no significant differences except that significantly fewer patients in months 6-12 experienced adverse events in the "Other" category.

An examination of the category of "Other" adverse events shows that there were numerous events related to implant feel. Specifically there were 21 patients in the Radiesse side and 17 patients in the Control side who experienced events such as "lumpy" or "bumps". The difference between Radiesse and Control in this case was not statistically significant by McNemar's test. In addition there were 6 patients in the Radiesse side and 2 patients in the Control side who experienced "hardness", "tightness" or other events related to implant feel. However, differences between Radiesse and Control were again not statistically significant by McNemar's test.

The sponsor presents additional evidence to support the safety of Radiesse. This evidence includes a comparison of the safety of Radiesse in the current indication to that of Radiesse when used to treat facial lipoatrophy. This comparison shows a similar safety profile for both indications, with the notable difference that nasolabial fold patients were significantly more likely to experience erythema and for a longer duration. In contrast, lipoatrophy patients were more likely to report "edema" and "other" adverse events. The duration of "other" adverse events was also significantly longer for lipoatrophy patients.

The sponsor also presents the number of complaints received as a percentage of the number of units of Radiesse shipped. These are all below 0.04%. There is also brief mention of other clinical experience with Radiesse, including a number of studies for facial reconstruction and augmentation, and studies of monopolar radiofrequency treatment, vocal fold mediation, stress urinary incontinence, and nipple areolar reconstruction. Not much detail is provided for each of these studies. However, it does appear that there are few reports of any severe adverse events associated with the use of Radiesse.