Panel Memo
P050037
Radiesse for Lipoatrophy of the Face

Sponsor: BioForm Medical

To: The Record
IDE number: G040068

Name of Study: Injectable Calcium Hydroxylapetite Implant for Soft Tissue Augmentation for the Treatment of Facial Lipoatrophy.

Chemist Review:

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, XX sterile water, XXX glycerine, and XXX 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.

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.

Clinical Study Summary: This is an open label, multicenter, non-randomized, non-comparator study to assess the safety and effectiveness of the device for the stated indication. Three hundred fifth four (354) patients were screened to enroll 100 into the study at three investigational sites.

Highlights:

- Loss to follow-up was excellent. All patients, except two who died during the study, were followed to the end of the trial
- Adverse events were generally as seen in previous filler studies; relatively minor events related to injections.
- Protocol deviations were few and minor.
- Protocol, CRF's, Informed Consent documents have all been reviewed in the IDE process.

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
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- Radiesse for the treatment of nasolabial folds.

Clinical Trial Outline:

Title: Evaluation of Radiesse for the treatment of HIV- Associated Facial Lipoatrophy

Objectives:

- The primary effectiveness endpoint of the study is to evaluate the correction of HIV associated facial lipoatrophy 3 months after the final treatment by comparing changes from baseline on the Global Aesthetic Improvement Scale (GAIS) with confirmation using standard photography.
- The secondary effectiveness endpoints of the study are to evaluate the correction of HIV associated facial lipoatrophy 6 months after the final treatment by comparing changes from baseline on the Global Aesthetic Improvement Scale (GAIS) with confirmation using standard photography and to evaluate the correction of HIV associated lipoatrophy 3 and 6 months after final treatment by comparing changes from baseline in cheek skin thickness measurements..
- The safety endpoint of the study is to record the incidence, severity, and duration of all local and systemic adverse events through 12 months.

Inclusion criteria:

1. Is HIV positive
2. Has a CD4 count >250/mm^3 and a viral load of <5000 copies/mL
3. Has been receiving HAART therapy for a minimum of 3 years
4. Has HIV-associated facial lipoatrophy that is a grade 2-4 on the Facial Lipoatrophy Severity Scale
5. Has a Fitzpatrick score of ≥4, if African American
6. Is at least 18 years old
7. Signs a written informed consent
8. Understands and accepts the obligation not to receive any other facial procedures or treatment affecting facial lipoatrophy through 12 month follow-up
9. Understands and accepts the obligation and is logistically able to present for all scheduled follow-up visits.

Exclusion criteria:

1. Has a known bleeding disorder

2. Has received or is anticipated to receive antiplatelet, anticoagulants, thrombolytics, vitamin E, anti-inflammatories, interferon, or prednisone from 1 week pre to 1 month post injection
3. Is receiving systemic corticosteroids or anabolic steroids
4. Has another medical condition that would preclude study participation or suggests an AIDS diagnosis (kaposi sarcoma, recurrent infection, recurrent pneumonia)
5. Has received silicone injections, facial tissue augmentation other than collagen, grafting, or any other surgery in the cheek area
6. Has received collagen in the cheek area within the last 6 months
7. Has received over-the-counter wrinkle products (alpha-hydroxy acids) or prescription treatments (Renova, Retin-A, microdermabrasion, chemical peels) within 4 weeks prior to study or intends to receive these products and/or treatments during the study
8. Has a history of keloid formation
9. Is pregnant or lactating or not using a reliable form of birth control, if female of child bearing potential
10. Is enrolled in an interfering study.

Study Synopsis:

- Enrollment Visit- must meet criteria for enrollment, sign Consent document, have photos taken, skin thickness measurements, treatment and initiation of diary.
- One month visit- re-treatment if necessary
- Two month visit- for pts receiving only treatment at enrollment visit. GAIS, photos, skin thickness measurements, adverse event reporting.
- Three month visit- same as two month visit for those with re-treatment at one month
- Four month visit- same as three month visit
- Six month visit- same as above plus CD4 counts, viral loads, relevant medications and adverse events. Evaluation for touch-up. A patient may receive a touch-up if they meet enrollment criteria again. ***Most did!***
- Seven month visit- for all patients having received treatment at 1 month and patients who received a touch-up at 6 months. GAIS, photos, skin thickness measurements, patient satisfaction assessments, CD4 and viral loads. Re-treatment for those patients who received a second initial treatment at one month.
- Eight month visit- patients who received touchup at 7 months will be evaluated
- Twelve month visit- patients who did not receive touchup after enrollment will be seen. GAIS, skin thickness, photos, patient satisfaction assessment, CD4 and viral loads, relevant medication changes and adverse events recorded.
- Thirteen month visit- for those patients receiving a touchup at one month visit.

- Five year follow-up- Upon completion of the data analysis, it will be determined to what extent follow-up will be needed

Note: The sponsor has asked for, and received, a continued access protocol for following these enrolled patients in the event a post-market study is deemed necessary.

Patient Demographics
N = 100

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

Fitzpatrick Skin Types
N = 100

Fitzpatrick Type I	3 (3.0%)
Fitzpatrick Type II	13 (13.0%)

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

Lipoatrophy Severity Rating Scale:

Facial Lipoatrophy Severity Scale	
Grade	Description
1	Mild and localized facial lipoatrophy
2	Deeper and longer atrophy, with 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 muscle

Facial Lipoatrophy Severity Ratings
N = 100

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

Injection technique- Using a 25 gauge, 1½" needle, the material was injected into the subdermis using the linear threading technique. As many strands of material were injected to reach optimal correction. No overcorrection was permitted.

Measurement tools:

To assess the second endpoint, GAIS ratings, the following scale will be used:

Global Aesthetic Improvement Scale	
Rating	Description
Very Much Improved	Optimal cosmetic result for the implant in the 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

Photography is standard Canfield Scientific, Inc. equipment with training support.

Skin fold measurement was made with Lange Skin fold Caliper at bilateral fixed points located at the intersection of the vertical access through the lateral cantus of the eye and the horizontal axis of the nares.

Safety Results:

The five most common events reported were ecchymosis, edema, erythema, pain and pruritis. All of these were noted at the time or shortly after injection. The sponsor notes that none of these events were reported at the 6 or 12 month visits if re-treatment was not performed.

Table 2-30, A Summary of Severity of Adverse Events (page 2-43), indicates that there were 197 mild, 11 moderate, and 11 severe adverse events reported. The duration of the main events is: ecchymosis (1.0-27.0), edema (1.0- 63.0), erythema (1.0- 22.0), pain (1.0-26.0), and pruritis (1.0- 26.0). Of the eleven serious events, the patient's main event was ecchymosis and/or pain, generally lasting 2 weeks or less. There were 3 serious adverse events; two deaths and a patient treated for lung cancer. My review of the CRF's for the two deaths, and the patient treated for cancer demonstrates that none of the events were device related.

The 11 severe events reported were ecchymosis, edema or pain, lasting from 1-27 days post injection.

Table 2-30 (page 2-43) lists the severity of adverse events. Noted is that there were no "nodules" reported in any patients. Section 2-11 (Volume 2) is a listing of all "other" adverse events. The majority of these events are listed as "other" with a severity rating, but there are a number of "small lumps", contour deformities (including contour deficiencies and irregularities), thickening, etc. Table 2-31 (page 2-44) notes a list of "other" adverse events and nodules are not reported. No contour changes are noted.

Tab 2-11 is a line-listing of all patients with one of these "other" events, and the sponsor characterizes these in various ways; specifically as contour irregularities, nodules shrinkage, flattening, thickened areas, etc. That method of reporting makes it difficult to determine what, if any, effect the device has on these events. Some of these are "resolved" with another touch-up injection, some are gone by the time patients are seen for follow-up, and some apparently resolve spontaneously. There is no indication that the sponsor has any histology of these events, as no new procedures were reported. In the same listing there are time frames of the events to resolution, and for each type of event noted above the range is from 1-3 months to 6-12 months. Resolution at later time points apparently occurred secondary to touch-up treatments. In summary, we have reported a list of "other events" with no clear definitions, no indication of what the lumps or contour deformities were caused by and nothing to asses device/event relationship.

Table 2-29 (page 2-41) includes a listing of the timing of all adverse events over the course of the study. Noted are 1146 events spread through the 100 enrolled subjects. No event apparently was reported if there was no follow-up injection. The next table, 2-30, summarizes the severity of these reported events. This table changes the event reporting from number of events to number of patients experiencing these events. Therefore, the sponsor reports 339 patients experiencing the 5 main events and "other" events (this apparently demonstrates that each patient may have experienced more than 1 event).

Finally, Table 2-27 (page 2-39) separates adverse events by Fitzpatrick skin scores. Contrary to the statisticians comment that 68% of patients had a moderate or severe event, I feel this table demonstrates that, of all the reported events, the number of events was not predictive based on skin color. There does not appear to be a clinical association between the percent of each skin type and number of events reported.

The sponsor was asked to provide an analysis of Adverse Events and Viral Load. On page 2-45 there are tables indicating that there was no statistically significant correlation between changes in viral load or CD4 counts and reported severity of events.

Baseline CD4 Counts and Moderate/Severe Intensity N = 100

CD4 Count	Mild Adverse Event	Moderate or Severe Adverse Event	Total	p Value
<250 mm^3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.1693
250-500 mm^3	13 (13.0%)	37 (37.0%)	50 (50.0%)	
501-1000 mm^3	19 (19.0%)	28 (28.0%)	47 (47.0%)	
>1000 mm^3	0 (0.0%)	3 (3.0%)	3 (3.0%)	

Baseline Viral Loads and Moderate/Severe Adverse Events N = 100

Viral Loads	Mild Adverse Event	Moderate or Severe Adverse Event	Total	p Value
< 400 copies/mm	28 (28.0%)	49 (49.0%)	77 (77.0%)	0.2196
400-1000 copies/mm	2 (2.0%)	6 (6.0%)	8 (8.0%)	
1000-5000 copies/mm	2 (2.0%)	13 (13.0%)	15 (15.0%)	

Summary: Adverse events are generally the same as those reported for other filler studies, and the severity is reported as mostly mild or moderate. Few of these events last longer than several days. It appears that no surgical interventions, or other treatments other than re-treatment with the study device, were needed. My only concern is that there are no events listed as "nodules" except as noted above.

There were no associations reported between adverse events and change in HAART (see table 2-26, page 2-39).

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 about the adequacy of this study at the end of the panel discussion.

Study Results- Radiologic Evaluation

The data in the clinical report (blinded radiologist investigator) demonstrated 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 study 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.

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 from the radiographic evaluators 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.

Efficacy Results:

The primary effectiveness endpoint of the study is to evaluate the correction of HIV associated facial lipoatrophy 3 months after the final treatment by comparing changes from baseline on the Global Aesthetic Improvement Scale (GAIS) with confirmation using standard photography. The following table illustrates that, on the five point severity scale, all patients rated their correction as 1-3 (very much improved to improved). There were no reports of "no change" or worse.

Global Aesthetic Improvement Scale (GAIS) Results

GAIS Rating	3 Months N = 100	6 Months N = 98	12 Months N = 98
Very Much Improved (1)	26 (26.0%)	7 (7.1%)	30 (30.6%)
Much Improved (2)	72 (72.0%)	84 (85.7%)	52 (53.1%)
Improved (3)	2 (2.0%)	7 (7.1%)	16 (16.3%)

No Change (4)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worse (5)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANY IMPROVEMENT	100 (100.0%)	98 (100.0%)	98 (100.0%)
95% Confidence Interval	96.4% - 100.0%	96.3% -100%	96.3% -100.0%

The secondary endpoint is to evaluate the correction of HIV associated facial lipoatrophy 6 months after the final treatment by comparing changes from baseline on the Global Aesthetic Improvement Scale (GAIS) with confirmation using standard photography and to evaluate the correction of HIV associated lipoatrophy 3 and 6 months after final treatment by comparing changes from baseline in cheek skin thickness measurements. The sponsor has presented, in section 9.3 (page 2-35) an analysis of measured skin changes, and concludes that there is a statistically significant change in skin thickness to 12 months.

Change in Skin Thickness (mm)

	Baseline N = 100	**3 Months N = 100**		**6 Months[1] N = 97**		**12 Months N = 98**	
	mm	mm	Change From Baseline	mm	Change from Baseline	mm	Change From Baseline
Left Side							
Mean	4.7	7.3	2.6	7.1	2.4	6.9	2.2
Standard Deviation	0.9	1.7	1.9	1.7	1.6	1.6	1.5
Minimum	3.0	4.7	-1.7	4.0	-1.0	4.0	-0.7
Maximum	7.0	11.3	7.3	12.3	6.3	10.3	6.0
p Value			**<0.0001**		**<0.0001**		**<0.0001**
Right Side							
Mean	4.9	8.0	3.1	7.5	2.7	7.3	2.5
Standard Deviation	1.0	2.1	2.1	2.2	2.1	2.0	1.9
Minimum	3.0	4.3	-1.3	4.0	-0.7	3.7	-1.0
Maximum	8.0	13.0	8.0	13.3	7.7	12.3	7.3
p Value			**<0.0001**		**<0.0001**		**<0.0001**

It should be noted that, in Appendix 2-7- the listing of facial thickness and volume injected, there are a majority of patients having correction both at one and six months post initial injection, that the amount of material injected was quite variable between patients, and that it appears that the duration of effect is predictably just a few months, event though the material is considered a permanent implant.

Number of Injections per Time Point

Baseline Injection Only	4 (4.0%)
Baseline and 1 Month Injection	7 (7.0%)
Baseline, 1 Month, and 6 Month Injection	78 (78.0%)
Baseline and 6 Months Injection	11 (11.0%)

There were several patients who did not receive any retreatment, and it appears that there was some sustained "improvement" at 12 months with a GAIS score of improved or much improved, and cheek thickness still above baseline (although in some cases only tenths of a mm.)

Photographic Assessment: Section 2-8 of the submission contains the pre-treatment and 3 month photographs of all patients enrolled in the study. Four patients did not have the 3 month photo, and 11 did not have the pre-treatment photo. Eliminating those patients without comparative photos, there does appear to be correction of the facial lipoatrophy at 3 months. It is difficult for me to assess the listed "patient GAIS ratings"; there are photos that I would not rank as noted on the photos.

Taking note of the photographic assessments, the patients were also asked to note how satisfied they were with their treatment. Patient satisfaction was high, and constant throughout the 12 month evaluation period.

Patient Satisfaction Results

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

The sponsor has provided data to assess the safety and efficacy of their device. Follow-up was excellent, with 98% of the subjects enrolled completing the study (there were two patient deaths).There appear to be few significant adverse events.

Statistical Review

The sponsor states that, "The purpose of this study is to assess the safety and effectiveness of Radiesse for the treatment of HIV-associated facial lipoatrophy." [Protocol, p.2] This is a one arm study with an OPC criterion. Namely, if 50% or more of patients showed improvement at 3 months (defined as a GAIS score ≤ 3) this would be considered clinically significant for the primary endpoint.

Design

This was a one arm study in 100 patients. The primary effectiveness endpoint was improvement at 3 months as assessed by the Global Aesthetic Improvement Scale (GAIS). This scale rates patients as 1- "Very Much Improved", 2- "Much Improved", 3- "Improved", 4- "No Change", or 5- "Worse". It appears that the GAIS assessments were done in-person, "with confirmation using a standardized photograph." [Clinical Report, p. 2-8] However, there are no details of how the assessments were performed.

The sponsor states their secondary endpoints as improvement in the GAIS at 6 months, and cheek skin thickness measurements at 3 and 6 months.

Sample Size

The sponsor's sample size calculation is based on a Chi-Square test of the percentages of patients in each GAIS category at 3 months. The null hypothesis was that the procedure would be only marginally effective, defined as 20% of patients with GAIS ≤ 3. (This includes the categories "Improved", "Much Improved", and "Very Much Improved".) The alternative is that the procedure would be significantly effective, defined as at least 50% of patients with GAIS ≤ 3. The sponsor found that a study with 100 patients had over 90% power to discriminate between these null and alternative hypotheses, when the one-sided type I error was held fixed at 0.025. We have verified this sample size calculation, finding study power with these parameters to be approximately 94%.

However, we found that the sponsor's sample size calculation for the secondary endpoint of GAIS at 6 months was not correct. Using the sponsor's assumptions, we found study power for this secondary endpoint to be only 56%. Note, however, that the post-hoc power is not an issue, because actual improvement on the GAIS was far larger than anticipated in the sample size calculations. Moreover, the primary questions regarding this study are not whether results of the GAIS and skin thickness are significant, but rather whether these endpoints capture all of the relevant aspects of device effectiveness.

Patient Treatment and Follow-Up

Patients were followed for 12 months after the last initial treatment application. There were up to three possible treatments with the device, one at the first study visit, one at the 1 month follow-up visit (if deemed necessary), and 1 additional injection at 6 months. After each treatment application, patients received a two week diary to record adverse events, and a phone call 72 ± 24 hours post-injection for early detection of adverse events.

The sponsor also states that there was a protocol amendment that provided for longer term follow-up of patients of 18 and 30 months. However, they state that currently none of the patients has reached the 18 month follow-up time point. Therefore, there is no follow-up data beyond 12 months in this submission.

Patient Accountability

354 patients were screened, resulting in 100 enrolled patients. There were two patient deaths between the 3-month and 6-month visit, leaving 98 patients with 12 month follow-up. Of these, the sponsor claims that 100% were seen at every follow-up visit as required by the protocol, although some of these visits were outside the prescribed window. This is very good patient follow-up.

The sponsor reports that of the 100 patients treated, 85 received the touch-up injection at 1 month. In addition, 89 of 98 patients received a touch-up injection at 6 months.

Patient Demographics

The study sample was predominantly male (94.0%), with mean age of 48.2. Out of 100 patients, there was 56.0%, Caucasians, 25.0% Hispanic, 18.0% Black, and 1.0% Asian. A majority of patients (51.0%) reported darker Fitzpatrick skin type (Type IV or greater). The sponsor claims that the distribution of skin types establishes a high level of assurance that patients susceptible to keloid formation/hypertrophic scarring can be treated safely and effectively with Radiesse.

Protocol Violations

Protocol violations included 11 patients not having a baseline photograph, 3 patients taking contraindicated medications such as aspirin, 3 patients with misplaced diaries, 4 minor lab work violations, and several patients with follow-up visits outside the prescribed window.

The only serious violations are the 11 patients without baseline photographs. It appears that the standard procedure for the 3-month and 6-month effectiveness evaluation was to compare the patient to the baseline photograph to determine improvement with the GAIS

scale. This was unavailable for these 11 patients. Therefore, the sponsor states, "the GAIS for those 11 patients was determined by comparing the live appearance of the patient at the time of the follow-up visit to the Lipoatrophy Severity Rating instead of the baseline photograph." It is assumed that these patients did have a baseline Lipoatrophy Severity Rating. At 3-months, all 11 patients were rated "Much Improved" or "Very Much Improved". At 6-months 9 of the 11 were rated "Much Improved", 1 was rated "Improved" and 1 of the patients died before the 6-month visit. The sponsor claims that even if these 11 patients were excluded from the analysis, this would not change the statistical conclusions. This is correct in terms of the clinical significance of the GAIS assessments. (The cheek thickness measures are not missing.) However, note that there are other questions about effectiveness.

Statistical Evaluation of Primary and Secondary Effectiveness Endpoints

As measured by the GAIS scale, the treatment would appear to have been highly effective. At 3 months, 26.0% of patients were rated "Very Much Improved" and 72.0% of patient were rated "Much Improved". The remaining 2.0% were rated "Improved". Thus, 100% of the study population achieved some degree of improvement. At 6 months, 7.1% were rated "Very Much Improved", 85.7% were rated "Much Improved" and the remaining 7.1% were rated "Improved". There was then an intervening additional touch up injection at 6 months. Following that procedure, the month 12 results were slightly more variable but still quite good. Namely, 30.6% of patients were rated "Very Much Improved", 53.1% were rated "Much Improved", and the remaining 16.3% were rated "Improved".

The GAIS scores are supported by the measurements of change in skin thickness. The mean change at 3 months was 2.6 mm for the left cheek and 3.1 mm for the right. At 6 months, this was 2.4 mm and 2.7 mm for the left and right cheeks, respectively. At 12 months, there was still a change of 2.2 mm for the left cheek and 2.5 mm for the right. The standard deviation of the change from baseline ranged from 1.5 mm to 2.1 mm. All of the mean changes from baseline were highly statistically significant. (p-value < 0.0001). In addition, the sponsor has provided the photographs for baseline and 3 months for all patients.

The sponsor also presents patient satisfaction results. These are favorable to Radiesse, with no fewer than 98% of patients at the 3-month, 6-month and 12-month assessments answering "Yes" to the questions "Would you recommend Radiesse treatment?", "Has the Radiesse treatment been beneficial to you?", "Do you feel more attractive since receiving Radiesse?", and "Do you have more confidence in your appearance since receiving Radiesse?" In addition, 91.0% at 3 months, 95.9% at 6 months and 97.0% at 12 months answered "Yes" to the question "Is your emotional wellbeing better since receiving Radiesse?" The satisfaction questions do not appear to be a validated instrument. Importantly, the patients appear to have only given a yes or no choice, instead of being allowed to rate their satisfaction on some ordinal scale. Moreover, patient satisfaction with the physical "feel" of the implant is an important question which

has not been directly addressed. Thus, the favorable patient satisfaction questions are not as strong a result as might at first appear.

Subgroup analyses and covariates

The sponsor examined the following covariates for an association with change in skin thickness: age, gender, BMI, race, initial Lipoatrophy Severity, Fitzpatrick Skin Scores, history of smoking, sun exposure, prior collagen use, cheek side, study site (site 1 vs. sites 2 and 3 pooled). The sponsor's analysis showed that for the change from baseline to month 3, the factors of initial Lipoatrophy Severity, cheek side, and study site were statistically significant. Specifically, as the initial Lipoatrophy Severity increased, so did the change in skin thickness. This would not be unexpected. Also, the change from baseline was larger in the right cheek, and was also larger in pooled sites 2 and 3 as compared to site 1. For the change from baseline to 6 months, only the factor of study site reached statistical significance. In addition, however, history of smoking became marginally significant (p-value = 0.0708). We would like to verify the sponsor's analyses. See below.

Safety

The adverse events reported by the sponsor are echymosis, edema, erythema, pain and pruritis. The sponsor notes that there were "no reports of granulomas, allergic reaction, erosion, nodules, necrosis, infection, or hematomas…" [Clinical Report, p. 2-41] However, the sample size would be a limiting factor for detecting these adverse events. Specifically, 100 patients are only enough to state that these adverse events do not have occurrence rates greater than 3%. In addition, although the sponsor lists "nodules" as not having occurred, there were many adverse event reports of "lumps" or "mass of material" and even "pt has nodule, R cheek" [Appendix 2-11, p. 12]

With respect to adverse event severity, the sponsor states that the majority of events were Mild (58.1%), with the remainder being Moderate (38.6%) or Severe (3.3%). However, from other tables it can be discerned that 68% of total patients experienced an adverse event which was at least Moderate in severity. There were 11 severe adverse events. These consisted of echymosis, edema, pain and one report of bloodshot eyes.

There were also several possibly systemic adverse events. These included one report of "blood in urine", and several such as "headache", "feverish", "runny ear". None of these adverse events were judged to be related to the procedure or device.

Because the treatment is in the cheek area, there may be a concern about adverse events involving the eyes. From Appendix 2-11, it can be observed that there were four of these events. As mentioned previously, one of these was described as "eyes very bloodshot and irritated". There was also one "black eye" and two reports of "lumps below the eye."

The sponsor examined the distribution of adverse events by CD4 counts and baseline viral load. These results are presented in tables 2-32 and 2-33. The tables present the percents within each category of disease severity rather than the overall percents.

As noted in the tables, there does not appear to be a strong association between baseline CD4 count or baseline viral load and adverse event severity. The sponsor states that the p-values for tests of association are 0.1693 for baseline CD4 and 0.2196 for baseline viral load, both of which are not significant.

The sponsor also examined adverse events by Fitzpatrick Skin Score and by change/no change in HAART therapy. Again, there is not much variation in the severity of adverse events when results are stratified by these two covariates.

Statistical Conclusions

The sponsor has met their primary effectiveness endpoints.

With regard to safety, there do not appear to have been any of the more serious anticipated adverse events. However, most (68%) of patients experienced an adverse event which was at least "Moderate" in severity.

CDER HIV Team Review

The CDER HIV experts added the following to the IDE process, and the sponsor has addressed their concerns appropriately. The stated:" In the initial IDE consult we recommended the following:

> "Although opportunistic infections (OIs) typically develop in subjects with CD4 cell counts < 200, OIs can develop at higher CD4 cell counts or during immune reconstitution following HAART. The protocol includes subjects with CD4 cell counts > 250. Therefore for the safety analysis the sponsor should attempt to correlate AEs, particularly injection site reactions, nodules etc with CD4 cell counts. As a result a revision to the safety monitoring scheme is needed to include additional CD4 and HIV RNA measurements, for example every 4-6 months and/or at the time of event."

As requested the sponsor included CD4 and HIV RNA measurements at baseline and at month 6 and 12. The sponsor concluded no significant difference in CD4 cell counts between the patients that experienced a severe or moderate AE and those that did not ($p=0.1693$) was observed. Therefore, the occurrence of moderate or severe intensity was not influenced by CD4 cell counts.

There were no other issues from that group.