UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

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MEETING

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Thursday, August 24, 2006

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The meeting came to order at 8:00 a.m. in the Grand Ballroom of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, MD. Dr. Joseph LoCicero, III, Chairman, presiding.

PRESENT:

JOSEPH LOCICERO, III, MD, Chairman
BRENT BLUMENSTEIN, PhD, Voting Member
A. MARILYN LEITCH, MD, Voting Member
FRANK R. LEWIS JR., MD, Voting Member
AMY E. NEWBURGER, MD, Voting Member
MICHAEL J. OLDING, MD, Voting Member
STEPHEN LI, PhD, Temporary Voting Member
MICHAEL J. MILLER, Temporary Voting Member
CONNIE WHITTINGTON, MSN, RN, Patient Advocate
GRACE T. BARTOO, PhD, RAC, Industry Representative
ROBERT J. MUNK, PhD, Consumer Representative
DAVID KRAUSE, PhD, Executive Secretary
MARK MELKERSON, FDA

I-N-D-E-X

M-O-R-N-I-N-G S-E-S-S-I-O-N

8:08 a.m.

EXEC. SEC. KRAUSE: On the record. Good morning again. We have a different kind of microphone system than we normally have. Normally, the microphones are just on all the time. These microphones have a little button on them as you'll see in front of you. So when you want to say something, you push that little button so the red light comes on.

Then you say what you want to say and then you push the little button and the mike goes off and then you can say things that nobody can hear. If somebody else is saying something you don't like, you can whisper to your neighbor you know "What's that moron saying" and nobody will hear it. So it's okay. Just thought I'd let you all know that.

I think everybody is here. People are kind of getting coffee and stuff and what we usually do first is not that big a deal anyway. So I'll get started and then we can get on with the meeting when everybody has their coffee and is sitting down.

Good morning, everyone. We're ready to begin this, the 68th Meeting of the General and Plastic Surgery Devices Panel. My name is David Krause and I'm the Executive Secretary of this panel and I'm also a biologist and a reviewer in the Plastic and Reconstructive Surgery Devices branch in the division of General, Restorative and Neurological Devices.

I would like to remind everyone that you're required to - or requested to sign in on the attendance sheets which are available at the tables just outside the doors. There is also copies of the agenda. There's a copy of the panel roster and other information about today's meeting. You can also find out about future meetings and how you can get meeting minutes or transcripts.

Before I turn the meeting over to Dr. LoCicero, I'm required to read two statements into the record, the Deputization of Temporary Voting Member Statement and the Conflict of Interest Statement. "Pursuant to" - This is the Appointment to Temporary Voting Status. "Pursuant to the

authority granted under the Medical Devices Advisory Committee Charter dated October 27,1990, as amended August 18, 1999 and November 16, 1999, I appoint Stephen Lee and Michael Miller as Voting Members of the General and Plastic Surgery Devices Panel for this meeting on August 24, 2006."

For the record, these individuals are special Government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. And this statement is signed by Dr. Dan Schultz who is the Director of the Center for Devices and Radiological Health.

The second statement is the Conflict of Interest Statement. It goes as follows: "The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry

Representative, all members and consultants of the panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations. The following information on the status of this panel's compliance with Federal Ethics and Conflict of Interest laws covered by but not limited to those found at 18 USC 208 are being provided to participants in today's meeting and to the public."

The FDA has determined that members and consultants of this panel are in compliance with Federal Ethics and Conflict of Interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Members and consultants of this panel who are special Government employees at today's meeting have been screened for potential financial conflicts of interest of their own as well as those imputed to

them including those of their employer, spouse or minor child related to the discussion of today's meeting. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the review of two premarket approval applications for the correction of facial lipoatrophy and subdermal implantation for the correction of moderate to severe facial wrinkles and folds such as nasolabial folds. This is a particular matters meeting during which specific matters related to the PMAs will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 USC Section 208(b)(3) for Dr. Michael Olding for a stock holding in a direct competitor valued at between $50,000 and $100,000. The waiver allows this individual to participate fully in today's deliberations. Copies of this waiver may be obtained

by visiting the Agency's website or by submitting a written request to the Agency's Freedom of Information Office, Room 630 of the Park Lawn Building. A copy of this statement will be available for review at the registration table during this meeting, will be included as part of the official transcript.

Dr. Grace Bartoo is serving as the Industry Representative acting on behalf of all related industry and is employed by Decus Biomedical. We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the panel of any financial relationships that they may have with any firms at issue. Thank you.

I would now like to turn the meeting over to Dr. LoCicero.

CHAIRMAN LoCICERO: Good morning. We're all going to get used to these mikes. I'm Dr. Joseph LoCicero III. I am a Thoracic Surgeon. I'm currently the Chief of Surgical Oncology at Maimonides Medical Center in Brooklyn.

Today we will be making recommendations to the Food and Drug Administration on two premarket approval applications. The next item of business is to introduce the panel members who are giving of their time to help the FDA on these matters and the FDA staff here at this table. I'm going to ask each person to introduce himself or herself and to state his or her area of expertise, position, title, institution and his or her status on the panel, that is voting member, industry, consumer representative, deputized voting member. If we could begin at the end of the table please.

DIRECTOR MELKERSON: I'm Mark Melkerson. I'm the Director of the Division of General, Restorative and Neurological Devices.

MEMBER OLDING: Michael Olding, I'm Chief of Plastic Surgery at George Washington University

and I'm a permanent member of the Panel.

MEMBER LEWIS: Frank Lewis, Surgeon, Executive Director of The American Board of Surgery and a regular member of the Panel.

MEMBER MILLER: Michael Miller. I'm the Deputy Chairman of Plastic Surgery at the University of Texas, MD Anderson Cancer Center and I'm a temporary member of the Panel.

MEMBER LI: My name is Stephen Li. I'm President of Medical Device Testing Innovations of Sarasota, Florida and I'm a temporary voting member.

MEMBER LEITCH: Marilyn Leitch. I'm a Surgical Oncologist and Professor of Surgery at UT Southwestern in Dallas. I'm a voting member.

MEMBER NEWBURGER: Amy Newberger. I'm a dermatologist in private practice, Director of Dermatology Consultants of Westchester Scarsdale, New York and I have a teaching appointment at St. Luke's Roosevelt Medical Center in New York City.

CONSUMER REP. MUNK: I'm Robert Munk. I'm the Coordinator of the AIDS Infonet website and I'm a Consumer Representative on the Panel.

MEMBER BLUMENSTEIN: I'm Brent Blumenstein, a biostatistician in private practice working out of Seattle.

PATIENT ADVOCATE WHITTINGTON: I'm Connie Whittington. I'm the Director for Nursing Systems at Piedmont Health Care in Atlanta, Georgia. I'm a permanent member of the Orthopaedic and Rehabilitation Devices Panel and I've been invited to be the Patient Advocate on this Panel today.

INDUSTRY REP. BARTOO: I'm Grace Bartoo and I'm the General Manager of Decus Biomedical which is a medical device regulatory and clinical consulting firm. I'm the Industry Representative for this panel.

CHAIRMAN LoCICERO: Thank you. I would like note for the record that the voting members present today constitute a quorum as required by 21 CFR Part 14. Now I'm going to introduce Captain Stephen Rhodes, the Branch Chief of the Plastic and Reconstructive Surgery Devices branch who will update the Panel since the last meeting.

CAPT. RHODES: Thank you, Dr. LoCicero

and good morning. I am Stephen Rhodes, Chief of the Plastic and Reconstructive Surgery Devices branch. Welcome members of the Panel, members of the public and manufacturers to this two-day meeting of the General and Plastic Surgery Devices Panel.

Today you will make recommendations and vote on two premarket approval applications submitted by BioForm Medical for their Radiesse dermal filler. And tomorrow, you will make recommendations and vote on the reclassification petition submitted by the Regulatory and Clinical Research Institute to down-classify cyanoacrylate tissue adhesives for topical skin approximation.

This panel met almost one year ago to the day for a two-day meeting at which you recommended to classify five device categories: bone wax, medical maggots, medicinal leeches, tissue expanders and wound dressings with a drug. We are continuing to work on the classification of these five device categories.

Also last year, FDA issues a Public Health Notice to alert users of serious complications

associated with the use of metallic stents in patients with benign airway disorders. Since the issuance of the Public Health Notice, we have been working with manufacturers to ensure that the labeling for these stents adequately conveys the risks associated with their use in patients with benign airway disorders, and we are in the process of issuing an updated guidance document which includes additional testing and labeling concerns.

On June 2nd of this year, FDA approved Inamed Corporation's Juvederm dermal filler premarket approval application for use in moderate to severe facial wrinkles and folds.

The Agency appreciates the commitment of the Panel members to keep coming back to Gaithersburg, Maryland in August and we also appreciate the PMA sponsor and the Petitioner for their participation and the members of the audience for their interest in this public meeting. That concludes my panel update. Thank you for your attention. Dr. LoCicero.

CHAIRMAN LoCICERO: We will now proceed

to the Open Public Comment sections. All persons addressing the Panel are asked to speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate record of this meeting. Both the FDA and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee

if you do not have financial relationships. If you choose not to address this issue in financial relationships at the beginning of your statement, it will not preclude you from speaking.

Since no individuals have notified the FDA of their interest to testify during the open public comment session, we will begin with a show of hands of any individuals who wish to testify before the Panel. Are there any?

Seeing no one wishing to address the Panel at this time, we are now ready to begin with the Applicant's presentation.

DR. BASTA: Good morning, Members of the Panel. I'm Stephen Basta. I am President and Chief Executive Officer of BioForm Medical. It's a pleasure to be here with you this morning and thank you very much for your time to assist us in the review of the premarket approval applications for Radiesse.

The morning session obviously will review the HIV lipoatrophy indication, but some of the general introductory comments that I will make will

apply broadly to the product and its multiple applications to give you a little bit of background and context on that.

BioForm Medicals, so that you have some context of who we are as an organization, is a privately-held medical device company developing on a worldwide basis tissue augmentation materials based upon the technology that underlies our two lead products, Coaptite and Radiesse. Radiesse is the product which is the subject of today's panel review obviously.

Radiesse and Coaptite are similar technology materials with a distinction of particle size, but otherwise fundamentally the same tissue augmentation technology that supports both products. Radiesse is designed for applications where a smaller gauge needle may be needed. Coaptite, requires a larger bore needle and it's designed specifically for urology applications. Coaptite has been approved through a PMA process reviewed by FDA for urology applications particularly stress urinary incontinence for women. That approval occurred in

November of 2005 and it has been launched through our partner, Boston Scientific Corporation.

The technology that underlies both Radiesse and Coaptite and broadly our tissue augmentation products in development was originally developed by a research team at Bristol-Myers Squibb. It was acquired by BioForm Medical in late 1999 and formed the basis or formation of the company. We have approximately 170 employees worldwide with operations in the United States and Europe.

The Radiesse product is delivered to physicians in a prefilled syringe format in a sterile pouch. Single unit boxes are shipped to each physician. Product is available in a range of sizes. Because this material contains no animal products, it requires no skin testing for potential allergic reaction and the material is stable at room temperature, can be immediately removed from the pouch and used for injection which provides an ease of use that is advantageous for a number of applications.

The product is commercially available

worldwide including in the U.S. as I'll show you in a moment for several applications. The two indications which are being reviewed today are additional indications for the already commercially-available medical device and it is approved internationally for facial soft tissue aesthetics applications.

The slide which you're looking at is broken into three sections. The bottom two sections describe our approvals on a commercial basis in the United States and internationally and we've only chosen internationally to discuss CE marking which is for the European indications and Canadian clearances. You will see that Radiesse is a commercially-available material on a worldwide basis through three 510K clearances which have been received for a number of indications including oral maxiofacial/craniofacial augmentation, a reconstructive plastic surgery or facial application and available for vocal fold augmentation and tissue marking.

Internationally, the product is cleared for facial soft tissue augmentation including

nasolabial fold and HIV associated facial lipoatrophy and is used commonly for those applications in Europe. Also has those clearances in Canada and Latin American and in certain countries of Asia.

BioForm has a long standing commitment to rigorous and thorough clinical research of these materials. The technology as I described earlier was acquired by the company from Bristol-Myers. Originally the technology was developed for stress urinary incontinence bulking. So the first clinical trials done with this material were in the urology application.

You will note the time line for the stress urinary incontinence application and clinical study. We've done a clinical study in the United States of 296 patients for stress urinary incontinence use. That material has been approved.

The use of this material in facial aesthetics application emerged after Radiesse was first developed for the vocal fold applications and in response to the significant interest that we've seen in the aesthetics community we engaged in a

rigorous clinical program conducting two facial studies, one for nasolabial folds, one for HIV associated lipoatrophy. We worked with the FDA to define these protocols, complete the clinical studies and those clinical studies are being presented today.

We also have noted - Sorry, I apologize. I'm pressing the wrong button on the pointer. - the lipoatrophy study, one of the notes that we will discuss is that that study actually has been amended so that we are providing a long-term safety followup anticipating that one of the questions that the FDA Panel has asked about each of these products is to have longer-term safety data beyond the data which is originally submitted for approval, and so we've proactively taken the step of engaging in that longer-term followup as patients have already come in for their 18 month visit and are scheduled to come in for a 30 month followup visit to provide that long-term safety data as well.

The Radiesse material flows like a gel and the flow characteristics are really driven by the carrier gel and the material, but the product

consists of two components. Thirty percent of the material by volume is calcium hydroxylapatite (CaHA) particles. Seventy percent of the material is a gel carrier which is composed of standard pharmaceutical excipients, water, cellulose, glycerine.

These materials have been classified as generally regarded as safe by FDA classifications and calcium hydroxylapatite, the component which is in the particles, has an extensive clinical safety history in use in a variety of applications. I'll tell you a little bit more about the history of it, but I'm sure that each of you as practicing physicians is well aware of calcium hydroxylapatite use in orthopaedics applications and through your training have likely used several of these materials.

CaHA was first used in 1920 in bone healing applications. In 1970s, it gained significant interest associated with the biocompatibility characteristics. Calcium hydroxylapatite itself is a synthetic form of a naturally occurring material that occurs in bone tissue, and so the body views it as a natural

biomaterial that provides a biocompatibility profile that is quite appealing and there is significant long-term safety experience with this material.

I won't walk through every one of these applications, but this listing just describes for you the breadth of uses of CHA. What we are presenting to you today is a new use of a biomaterial that has been used for more than 20 years actively in a variety of surgical procedures, has a very long safety history in the body in a range of tissue types, in a range of forms. It has been used in block forms. For example, in the ENT vocal fold applications, you can use a solid block form of calcium hydroxylapatite or you can use Radiesse which is an injectable form containing calcium hydroxylapatite. Both work well. Both have long-term followup information available.

The calcium hydroxylapatite material is one of the safest biomaterials available with an extensive history and knowledge that makes it appropriate for these applications and what we are doing here is extending those applications to facial

soft tissue with a demonstration of safety and effectiveness in our studies.

The components of the gel carrier as I described earlier are water, sodium carboxymethylcellulose and glycerine, all commonly used agents in pharmaceutical and medical device preparations again with extensive safety experience and history.

When the material is injected, the combination of gel plus particles acts to provide a space-filling augmentation immediately upon injection. Radiesse provides immediate filling effect and immediate benefit as do other immediate fillers. This material does provide longer-lasting effects than some of gel based fillers, hyaluronic acid or collagen products because over time as you get resorption of the gel component you start with a fill that consists of gel plus particles. The gel resorbs over time and you have collagen ingrowth around the particles that provides a mechanism for more durable augmentation. This describes the theory of how the product works.

This next slide is actually a histology image from one of our preclinical studies with a stain that specifically demonstrates that collagen formation. What you see in this slide are three components. The white spaces, in order to do this histology slice, we have to decalcify the materials because otherwise you would be slicing through hard particles. So what you see are white spaces where the particles were. Every white space that you see is where one of the Radiesse calcium hydroxylapatite particles was in this tissue, but it's been decalcified.

The gray is the residual gel. So again when you inject the material, you get a fill due to both particles and gel. Over several months, the gel resorbs, new collagen forms to fill some of that space and we have here a picosirius red stain for collagen, 16 weeks post implantation. The red fibers are collagen formation that is coming in to fill that space so that the gel plus particles has been replaced with collagen plus particles.

I won't go through every one of the

preclinical studies, but we have rigorous preclinical work that demonstrates consistently the gel resorbs within approximately three to six months. Over a longer period of time, we see particle degradation, but the particles last longer than the gel to provide the scaffold for the collagen integration and that's how we get longer-term effects than some of the shorter-term, temporary filler materials. And our preclinical work in multiple tissues, spaces in the body, dermal, subdermal and urology applications as well as fecal incontinence applications, gastroesophageal reflux, a variety of tissue types. We have done an extensive amount of clinical work that demonstrates the same pattern of gel resorption, collagen integration and eventual particle degradation.

In conclusion to the introductory portion, calcium hydroxylapatite is a well-known biomaterial with a long clinical history of safe use in a variety of tissue types throughout the body. Our gel carrier consists of well-known pharmaceutical excipient materials that have been used in

pharmaceuticals, in medical devices, in foods and a variety of applications with an excellent safety history.

Radiesse provides longer-term correction than many of the short-term fillers that have been commonly used in practice, but not permanent correction because the particles will be in fact be resorbed through the same biological processes that will turn over bone in the body. The particles themselves will break down and will be metabolized into calcium and phosphate ions and we have demonstrated that in our studies.

There are extensive worldwide market clearances and clinical experience for this material. The worldwide market clearances include three applications cleared in the United States, facial soft tissue augmentation applications cleared in Europe, in Canada, in Latin America and parts of Asia and the product has been used for many years in facial soft tissue applications. We also do know that in the United States physicians have used this product because it's commercially available for other

indications, have used it in facial soft tissue applications. The material has a long-standing experience of safe clinical use in a range of applications. Thank you.

To begin the clinical portion of the presentations, I will introduce Dr. Stacey Silvers. Dr. Silvers was an investigator in the clinical study testing facial lipoatrophy associated with HIV antiretroviral therapy and she will walk you through the clinical data and present that information to you. Thank you.

DR. SILVERS: Good morning. My name is Stacey Silvers. I'm a practicing ear, nose and throat and facial plastic surgeon in New York. I've been honored to ask by BioForm to participate in this study. I have been paid to participate in this study and I'm paid to be here today to present to you and it's an honor to be here to present to you today.

Facial lipoatrophy is a loss of subcutaneous fat from the cheeks which produces an emaciate appearance in the face. An estimated 150,000 to 350,000 patients could potentially benefit

from this new treatment.

The psychological and social impact of lipoatrophy on HIV positive patients is significant. The potential impact on compliance with medication and antiviral medications, I have patients who tell me they would rather be sick than look sick. Many patients will discontinue their medications not to have a look of lipoatrophy. The potential impact on the social workplace and workplace acceptance, many patients can't even get jobs because of the way they look. And the significant quality of life reduction, many patients haven't even seen their families in many years and won't even leave the house and be social because of the look of lipoatrophy.

This is a typical image of what a lipoatrophy patient will look like. You can see the significant tissue loss, the loss of the buccal fat pad, the facial musculature showing through.

In our study, we did an prospective, open-label, clinical trial with 100 patients at three investigational sites. We found Radiesse to be safe. We found it to be effective. One hundred percent of

our patients were improved through 12 months. All primary and secondary endpoints were met and we found a greater than 90 percent satisfaction through 12 months.

Our objective was to assess the safety and effectiveness of radius for the treatment of HIV associated facial lipoatrophy. A prospective, open-label, IDE clinical trial with 100 patients and three investigational sites in the U.S., the facial lipoatrophy improvement and incidence of adverse events were assessed through these 12 months. The device used in the clinical trial was identical to the commercially-available device which is Radiesse.

The primary effectiveness endpoint was to compare changes in facial lipoatrophy on the Global Aesthetic Improvement Scale (GAIS) at three months from the last injection when compared to baseline and the secondary effectiveness endpoint was to compare changes in facial lipoatrophy on the Global Aesthetic Improvement Scale at six months from the last injection when compared to baseline, to compare changes in cheek thickness and three at six months

from last injection when also compared to baseline.

This GAIS Improvement Scale is a published improvement scale where patients that are very much improved show an optimal cosmetic result for the implant in the patient, patients much improved showing a marked improvement in their appearance from initial condition but not completely optimal and a touch-up would slightly improve the results, improved showing an obvious improvement in the appearance but a touch-up or retreatment being indicated, no change as listed here, and worse, the appearance being worse than the original condition.

The cheek thickness measurement methodology was used using a Lange caliper system where we took the inner section between the vertical axis through the lateral canthus and the horizontal axis of the nares. The one tip of the caliper was placed inside of the mouth. One tip of the caliper was placed outside the patient's cheek. This kept us consistent throughout our investigational sites and also consistent with our patients throughout the 12 month study.

The incidence, severity and duration of all local and systematic adverse events were recorded through 12 months and they were captured through a 72-hour phone call that was made after each injection. The patients kept a diary for twelve weeks - Sorry, for two weeks after each injection and they were instructed to write down the date, the side of any adverse event, the severity and a description of that adverse event. Each patient had a one month safety visit after each injection and a physician evaluation each scheduled visit. The patients were observed at any point over the 12 months. If they felt that something needed to be looked at, they were welcome to come into the office.

This slide simply shows the study design and treatment, followup schedule, over the 12 month period where at baseline patients received their initial photograph and their initial injection along with their 72-hour phone call and their two week patient diary. Patients also were opted for a one-month touch-up to complete the optimal first injection.

Their three-month visit was either three months after their first injection or three months after the first touch-up was needed and a second set of photographs were taken. A third set of photographs were taken at six months along with a touch-up injection if needed, again 72-hour phone call, two week patient diary. At 12 months, a fourth set of photographs were taken.

The study, arrow indicates that the study is continuing and I've had the benefit of seeing these patients at 18 months which is one year post injection and these patients are still looking excellent.

The inclusion criteria for the study design, patients needed to be HIV positive, have a CD4 count of greater than 250 and a viral load less than 5,000 copies. They have to be receiving highly active, antiretroviral therapy for a minimum of three years, be Grade 2, 3 or 4 on the Carruthers Facial Lipoatrophy Severity Scale, be over 18 years of age, have signed a written consent form, understand and accept the obligations not to receive any other

facial procedures or treatments affecting facial lipoatrophy throughout the 12 month followup, understand and accept the obligations and logistically be able to present for all followed schedule-up visits.

The exclusion criteria were provided to you. You can take your time to look over some of these. Some of the key ones, known bleeding disorders and patients, of course, could not have received any prior treatments for lipoatrophy that would affect our study.

The Carruthers Facial Lipoatrophy Severity Scale is as you see before you with a Grade 1 showing mild to localizing facial lipoatrophy with some loss of tissue; in Grade 2, deeper, longer atrophy, muscle of the face are starting to show through; with grade 3 you can certainly see much deeper pitting of the face with significant muscles clearing showing through in these pictures; and with Grade 4, there's a much wider extension of lipoatrophy with facial wasting extending up to the eye sockets. These patients also have loss of fat

around the temples, the scalp over their eyes and really look fairly skeletonized.

The three investigational sites, 94 of the patients were in New York. Sixty of them were at my site in my office. Dr. Eviatar had 34 patients and Dr. Eschavez had six in San Francisco.

We had a variety of ethnicity with one-quarter of our patients being Hispanic, 18 percent African-American. We had one Asian patient and the rest were Caucasian. Six out of 100 patients were women. Our age range was 34 to 69 years with a median of 48.2 years.

We had a nice distribution of severity with Type 2s, Type 3s and Type 4s and we had all skin types represented here.

The next six slides I'm going to show you are patients throughout the study with before and after photographs during and after their injections. All patients received different volumes on injections based on need to receive optimal results.

This 38-year-old male, you can see his pre-injection photographs and photographs throughout

three months, six months and one year. At baseline, he received 4.1 ccs of injection. At six months, he only received a touch up of 0.7 and what I think that clearly indicates is that a majority of what he received at baseline has still stayed with him at 12 months with an excellent natural result.

Again, you can see the pitting and the loss of facial fat here, the natural results post injection. At six months, very little touch up needed here and excellent results at 12 months.

A more severe stage of lipoatrophy with facial muscles showing through. This patient received a larger volume of injection with 13 ccs at baseline to achieve these results. But even after 13 ccs, he's got excellent results at six months, receiving less than half of that with an excellent maintenance at 12 months indicating that quite a bit of the volume that he received at baseline has stayed with him at 12 months.

Again, pre-injection and excellent results throughout the study.

Another patient, just life changing

images.

Again you can see this deep pitting and facial loss and the natural look post injection.

This slide indicates that 100 percent of the patients were injected at baseline. Eighty-five percent received a touch-up at one month. At six months, 89 percent of patients received a touch-up of injection. The average injection volume at the first injection was 4.8. The average touch-up injection at the second visit or one month was 1.8 ccs and at six months was 2.4. So it took 75 percent of the whole volume to achieve the optimal injection at the initial visit and about a quarter of that to maintain them for a full one year followup with excellent results.

The GAIS ratings, what jumps out here is that all patients at all times during the study show improvement. The vast majority were at least much improved at all times during the study. At the three month followup, most patients were either much improved or very much improved. Prior to the touch-up at six months, most patients remained at much

improved. And at 12 months, patients again still remained in the much improved and very much improved range and this was consistent throughout the study.

The next five slides I'm going to show you were the patients satisfaction questionnaires and these were yes and no questions that we asked the patients. Oops sorry skipped a slide. This slide indicates the cheek thickness and basically shows that cheek thickness was maintained throughout the study. The baseline thickness averaged about five on each side, the right and left, and was maintained through much of the study up until about 12 months and this does mimic GAIS rating.

Okay. Now my next five slides. Questions asked of the patients, would you recommend Radiesse treatment? Ninety-nine percent of them at each visit, three, six and twelve months, said yes.

Has the treatment been beneficial to you? One hundred percent of the patients at three, six and twelve months said yes.

Do you feel more attractive after receiving Radiesse and 98 to 99 percent said yes.

They were asked if their emotional well-being was better since receiving Radiesse and again greater than 90 percent of the patients throughout the study said yes.

When asked if they felt more confident in their appearance, again 98 to 99 percent of the patients said yes.

And this is basically a summary of the proceeding bar graphs.

I'm going to go through just a couple more photographs, before and after photographs, of our patients, again, before, after injections and the natural look of the face and the skin is significant.

Another one of my patients just with some deep pitting and post injections.

And still holding excellent fullness and the material is able to bring the skin out with a natural fullness of the cheeks.

This next patient came in and told my office a story. She used to lecture in London and when she'd walk in the room and get on the stage everybody would avert their eyes because she looked

so frightening. Her son is a model and never really brought his friends home and after she had her injections, he just swept her up in his arms and swung her around the room and they were crying and it was just so heartwarming.

And she came in and said she never realized how much her appearance affected him in his life and he was just too ashamed to say something to her. And after receiving treatment, she came in. She fixed her hair, got new clothes and it was just an incredible story in just how much this product has changed her life and just how treating these patients changes the lives of so many and she's had a wonderful result.

We have found Radiesse to be safe. We have found no unanticipated adverse device effects. Any adverse events were transient. Injection related adverse events were typical of dermal fillers. There were no nodules, no granulomas or device related adverse events.

The most common results that we found were after injection. So you can see the yellow

lines here along all the zeros. Patients weren't receiving any injections. Patients after receiving injections commonly got a little swelling, a little bit of redness, a little bit of echymosis and the larger amounts of these happened when they received larger volumes. After any intradermal filler, patients usually will get some swelling.

The other on the bottom consists on contoured irregularities, a little bit of lumpiness, some discoloration. A rare patient complained of a headache, a little facial tightness, a little soreness, scab and a whole list of a variety of things, but very uncommon things, all of which were transient and all of which quickly resolved.

Commonly when we do inject this filler, any contour irregularities and lumpiness which I do tell patients they're going to get, that they're going to be lumpy for a couple of weeks, the material has settle, has to soften and is gone by two weeks and I've found that in all of my patients and even patients that I've been treating subsequently.

In summary with - and our product

endpoint has been met, one hundred percent of our patients have shown improvement on our Global Aesthetic Improvement Scale over three, six and twelve months. Our secondary endpoint, we've had an increase skin thickness at three, six and twelve months and a greater than 90 percent satisfaction rate in our satisfaction questionnaire at three, six and twelve months.

In conclusion, Radiesse is a safe for facial lipoatrophy treatment. Radiesse is effective for facial lipoatrophy at three, six and twelve months by the three distinct evaluation methods which is the Global Aesthetic Improvement Scale, the Skin Thickness Method and the patient questionnaire.

As a practicing physician who has been blessed to work with these lipoatrophy patients for many years, I'm thrilled to find a product like Radiesse and I have no financial tie to this company. I find that its ease of use is wonderful compared to other things on the market and I've used cheek implants which when they work are wonderful but can be difficult. I could stand here and tell you all of

the heartfelt stories and the tears and the hugs and the cards and the flowers and it's just truly been an honor to work with these patients and work with this product and I thank you for the opportunity and thank you all for the opportunity to present to you today. Thank you.

DR. LIEBESKIND: Good morning. My name is Marc Liebeskind. I'm a radiologist in private practice. I'll be presenting the radiographic appearance of Radiesse and following me, Dr. Carruthers who conducted a simultaneous protocol in Canada will present his clinical correlation of both his and my findings.

Our radiographic study was a separate evaluation according to a protocol that was previously reviewed by the FDA in consultation and designed to answer questions about the radiographic appearance of Radiesse. We evaluated both CT and x-ray images of 58 patients who were treated in Vancouver by Dr. Carruthers. Twenty-eight of the patients were seen more than twelve months following therapy for facial lipoatrophy. Fifteen patients

were seen both before and then less than one month following treatment for lipoatrophy. Fifteen patients were seen both before and immediately following treatment for nasolabial fold thickening.

All of the imaging was performed at an independent clinical center in Vancouver. The images were then sent to us and I oversaw the review by two blinded, independent evaluators. The evaluators were both Board certified radiologists. They reviewed the images independent of each other. The radiologists were blinded not only to the study purpose but to the product and the underlying patient condition. We did this in order to create the most challenging scenario for possible radiographic misinterpretation.

We looked at a broad range of clinical situations, a broad range of treatment volumes. Patient received anywhere from 1.3 milliliters of Radiesse up to 34 milliliters. There was a broad range of time from the initial injection of material, in other words, immediately afterwards or zero days up to 427 days. This included both nasolabial fold and facial lipoatrophy patients.

This graph gives you an idea of the two separate groups that we looked at looking at CT and x-ray greater than 12 months following treatment for facial lipoatrophy and then in the short term groups looking at the lipoatrophy and nasolabial fold patient populations both before and then following the injection.

Most of the images that I'm going to present are images of CT scans because of the much better ease with which radiologists can see Radiesse by CT scan as opposed to x-ray. Here is a first example of more than twelve months following injection of 25 milliliters of Radiesse and this is a bone window CT from the level of the mandible and we can see in the subcutaneous fat bilaterally in a relatively symmetric fashion calcium density. The same patient demonstrates some degree of flattening of the facial contour interiorly after the short-term treatment, after the followup treatment, excuse me, of nine more milliliters of Radiesse. You can clearly see the Radiesse in the short term as calcium density in the same region and you can clearly see

the convexity of the facial contour as opposed to the adjacent image.

This second example was also seen. It is also an example of a patient seen more than twelve months following treatment with Radiesse of 15.7 milliliters. You can see that there's a minimal amount of residual calcium within the subcutaneous fat bilaterally. It's very faint.

Following the twelve month injection, in other words, we had 6.5 milliliters of Radiesse that was injected additionally and you can clearly see the Radiesse in the subcutaneous soft tissues. You also see some additional bulking of the skin surface on the axial image just at the level of the nose.

This is a patient from the short-term cohort. So this example here is the normal appearance of the subcutaneous fat in this particular patient before therapy. In the short-term following therapy with 15.6 milliliters, we can see some Radiesse calcium density within the subcutaneous fat and we see the marked convexity of the cheeks on the axial images. We see that the Radiesse does not

interfere with the adjacent structures and has a density similar to underlying bone.

This is another patient who received short-term followup after Radiesse treatment for lipoatrophy. Again we can see the concavity of the face on the pre-injection image and the marked convexity following the post injection image. We can see the distribution of Radiesse that it's clearly within the anatomic region where it was injected. It doesn't appear elsewhere within the facial soft tissues and it's distinct separation from bone on the CT images.

The nasolabial fold patients received far less material overall, but this did not interfere with visualization by CT scan. We can still see the Radiesse even though only 2.6 milliliters are injected in this patient. We can see the deep nasolabial folds on the axial image pre-injection and post injection we can see the change in contour.

This is another example of a short-term followup after treatment of the nasolabial folds and again even though only 2.3 milliliters were injected,

we clearly see the Radiesse, we see the effect and we see that the material remains where it was injected.

I'm going to show a few images from this patient. This by contrast is a soft tissue window of a CT of the sinuses and we're able to highlight muscles of mastication, the soft tissues on this filter. Radiesse is clearly seen within the subcutaneous fat. This is a patient who was treated more than twelve months before the image was taken and we can see that the calcium that was deposited remains where it was placed, that there is no calcium extending posteriorly into the musculature into the other portions of the face.

This is two separate images below the level of the mandible in the same patient and we can see that following 7.8 milliliter total volume injected of Radiesse normal appearing lymph nodes in this patient that are nicely highlighted by surrounding fat in the jugular chains and submandibular chains don't demonstrate that calcium, that marked calcium, that we just saw in the last slide of Radiesse. So we don't see any CT evidence

that Radiesse is migrating to regional lymph nodes even twelve months following injection.

One of the concerns that prompted the radiology study to be separately performed for this product was that injecting something radiopaque might interfere with the radiographic evaluations of these patients. This is an interesting example because again we have a soft tissue window through the level of the mandible, excuse me, the maxilla and we can see the Radiesse quite clearly. We see that immediately inferiorly the dental hardware that this patient just happens to have causes so much more effect than any potential interference by the Radiesse. So Radiesse compared to dental hardware produces virtually no radiographic interference.

As I said initially, most of the images that I'm going to present, most of the discussion, will involve the CT examinations even though all patients had x-ray studies at every time point where they had a CT scan and this is because Radiesse is not consistently evident on x-ray studies. After twelve months, only 6.5 percent of the time did

evaluators respond yes to whether a foreign mass was visualized by x-ray after the patient had been injected with Radiesse.

By contrast, the lipoatrophy patients overall received generally larger volumes than the nasolabial fold patients. At most this was seen half of the time on plain-film x-rays. The important thing was that Radiesse was not considered concerning for possible tumor by our evaluators on x-ray.

The same question when asked by CT scan, is there a foreign mass present on these images, evaluator, excuse me, both evaluators felt that after about twelve months that one-third of the time they did not see a foreign body. So there is some evidence of resorption radiographically at twelve months. However, following treatments, virtually 100 percent of the time the evaluators were able to identify a foreign mass present on CT scans.

As to the question of whether a foreign mass obstructed and underlying structure on CT scan, the evaluators responded almost entirely negatively, that only less than one percent of the time did we

get a positive answer and I will demonstrate that example next.

This is the case where the evaluator felt that there was a foreign body that masked an underlying structure. We feel that the way we posed the questions prompted the response because if you look on this patient there's marked dental hardware. So there clearly is a foreign mass obstructing underlying structures in this image and it is just not Radiesse.

So in summary, Radiesse while radiopaque is not consistently evident by plain-film x-ray. Radiesse is clearly visualized by CT scan. It's seen separate from the bone and it's seen clearly within the subcutaneous fat in the areas where it was injected.

Radiesse is also -- Importantly, as a radiologist, I can tell you it's visualized bilaterally because of its cosmetic and aesthetic use which is very atypical for any sort of malignancy and should not prompt any form of a work-up even if the radiologist looking at a CT scan was not familiar

with this use of a calcium containing gel.

As a result of the study, however, and the fact that Radiesse is visualized very clearly by CT scan the instructions for use that are being requested would ask patients to notify their physicians that they have had this procedure and that the material injected does contain calcium.

We found no CT evidence that Radiesse migrated from point of injection. Overall as a radiologist, I can say I feel that there is no safety concern that Radiesse should not prompt work-ups, biopsies, etc., based on its appearance even in the uninformed radiologist. I think the bilateral symmetry, the location, give it an overall very benign radiographic appearance. Thank you.

I should also mention and I should have mentioned at the beginning of this talk that I was an investigator clearly in this clinical study and I've been compensated for my time at this meeting and my travel and lodging.

I'd now like to introduce Dr. Carruthers who conducted the Canadian examination.

DR. CARRUTHERS: Dr. LoCicero, panel members, I am Alastair Carruthers. I'm a dermatologist in Vancouver, British Columbia, Canada. I was an investigator in this study. I am a consultant to the company and I have been compensated for my time here today and for my expenses in being here.

This was a fascinating opportunity because we had all heard about Radiesse. It's approved as a radiological marker. Therefore, there were rumors as to whether it interfered with x-ray or radiological evaluation and the opportunity to look at this problem as well as to have a look at an implant which is something that's my life if you like was a very unusual opportunity. So I'm happy to be able to supplement Dr. Liebeskind's remarks.

You have already seen the overview of the long-term study that we performed in Canada. This is not part of the PMA because this data completed following the submission, but this is essentially an identical protocol to the 100-patient U.S. study. The addition to this slide from the one that Dr.

Liebeskind showed you is the amount and you'll see that we were a bit more aggressive than Dr. Silvers that her colleagues, so that the amount that we injected in the touch-up visits which we've labeled here zero months because we started counting with the second or with the last of the initial injections.

And also the amount that we put in, the number of individuals that we injected out here at six months, we only injected 31 percent of individuals. Is less than in the United States.

As practicing clinicians, many of you will be aware that we have an obligation to do the very best for our patients at all times and when you get to the opportunity to treat individuals with a severe condition for free you'd like to take advantage of it and so that the amounts that I have injected you'll see are larger probably than would be generally used in a clinical practice. In other words, this data is based on a very challenging clinical situation. And the other two studies, basically we got the 15 individuals with lipoatrophy and injected them and then took the radiological

evaluation within a few days and the same with the 15 nasolabial fold patients.

So here is one of our long-term facial lipoatrophy patients. You'll see that this is very similar to the patients that Dr. Silvers already showed you. Baseline amounts basically 7 ml. Very small touch-up at six months.

Another individual, again relatively small amounts at the potential touch-up and at six months.

This shows an interesting observation, this individual, which was not present in all, but was certainly something that we saw quite often and that is I think that you will agree that at six months he actually looks fuller than at three months. This is the fibroplasia, the collagen synthesis that is induced by the presence of the beads producing this increase in response between three months and six months.

One of the fascinating things reinjecting these individuals at twelve months, here for example, was that although none of them complained about it

there was a firmness to the tissues in the skin where this material had been injected, mainly twelve months previously, and as the needle goes in, I find the needle encountering hard collagen and I'm attempting to inject around this collagen which has been induced by the presence of the material.

Another individual. These are representative individuals from our study and you can see that we had more severely effected subjects but again relatively small amounts at touch-up and at six months.

Because we were a little more aggressive, we had a greater number of individuals here in the very much improved category, but out here at twelve months, our results were relatively similar to Dr. Silver's.

You may wonder, like I did, at the differing shape of the CT scans here and of course, when we're evaluating the CTs we're looking at the area where the material was injected. In this individual, you can see how his lipoatrophy is relatively low. This is the twelve month picture, so

that I would be injecting down (Indicating) here so that you would expect the slice to be through here and sure enough, we can see his teeth here and his mandible and here is the material.

Whereas, this individual has much more superior loss of material, so that you would expect the slice to go through here (Indicating) and sure enough, you can see his nose here, so that we have adapted the radiological demonstration here to show where the material was injected.

This is one of the short-term lipoatrophy individuals and again you can see that I'm using relatively large volumes so as to challenge Dr. Liebeskind to try and occlude the clinical, the evaluation, of the radiological evaluation.

And this is one of the nasolabial fold individuals. Much smaller volumes and you can see this is a different location. Another nasolabial fold patient.

Showing the material right here and the change in the contour again.

So our conclusions from this radiological

from this radiological study just to repeat really what Dr. Liebeskind has already said that they confirm our clinical evaluation of these patients that you can see the material and it does not cause any problems with evaluation of radiological evaluation.

For me as a clinician, this was very interesting that one-third of the individuals did not receive a touch-up at six months, but 100 percent were improved and only approximately two-thirds of the individuals who were treated actually showed sufficient calcium for it to be visualized on the CTs. In other words, it looks to me as though this material is going away more rapidly than we had thought from the animal studies. The calcium seems to be gone in many of these individuals by twelve months.

The long-term effect is not due to the continued presence of the material. We also -- So we did show in the study that the material although not permanent it does provide long-term duration of the augmentation.

So this is the final slide of the sponsor's presentation and in summary, the study which Dr. Silvers has presented to you has demonstrated we believe both safety and efficacy through twelve months. The radiopacity of Radiesse does not present any safety concerns and our findings were an interesting support for those of the pivotal study.

And Dr. Silver began by talking about the management of these individuals. I spent over eight years looking after individuals with facial lipoatrophy. They are indeed a very rewarding group of individuals to manage. One of the interesting things coming out of studies like this is you saw in Dr. Silver's material how most of their responses to the questions plateaued. They were 98 and 99 percent.

But the feeling of wellness was the one difference insofar as it increased over the twelve months of the study. It is a frequent observation that individuals such as the individuals in these studies have been very sick, have been on long-term

disability, are now well but haven't realized it and improving their facial appearance, many of them go out, get a job, become productive members of society again, get integrated into society. It's a very moving experience to be involved with these individuals. Thank you for your attention.

CHAIRMAN LoCICERO: Thank you. Does the sponsor have any other comments to make at this time?

DR. BASTA: We do not. That's our presentation.

CHAIRMAN LoCICERO: Thank you. It is now time for the Panel to ask questions of the sponsor to clarify any points that they have based on the presentation and if we can start with Dr. Olding.

MEMBER OLDING: I have a couple of questions and probably too many. One is the size of the calcium hydroxylapatite. The material that's used in Europe that you were talking about, is it the same size particles that are used here with the Radiesse and I think you said in your presentation that the choice of the particle size had something to do with injectability, ease of injectability.

However, given the relatively small particle size, that doesn't make a lot of sense to me that it would actually be that much more difficult to inject and does the differing particle size have to do - have something to do with the amount of time that it remains? Because presumably in this patient population, you would like it to remain longer than one year.

And for Dr. Silvers, you said that your patients had lumps afterwards and that you cautioned them that they would and yet in the study there was no nodule. Can you tell me the difference between a lump and a nodule? I think that's it.

DR. BASTA: Dr. Olding, there are obviously several parts to your questions. So let me take pieces of it and then for the final portion of it, I'll let Dr. Silvers address the question of lumps and nodules and what her clinical observations were.

Your question was just about whether or not the product in the U.S. and the product in Europe based upon particle size are the same material.

Radiesse is in fact the same product distributed commercially worldwide. So the product used for facial aesthetics indications in Europe is the same product that was tested in the clinical studies presented today to the Panel and is the same product that is used for vocal fold augmentation in the United States under a 510k clearance. So the 25 to 45 micron particle size product is identical on a worldwide basis under the name Radiesse.

MEMBER OLDING: And always has been, the material that's been injected years ago before Radiesse was actually out, that's the same material?

DR. BASTA: Well, the history of the material, the technology was originally developed for urology bulking agents. The first product produced is the product that we named Coaptite which has 75 micron to 125 micron products. That was in 2000 and 2001, the original product that was introduced and introduced in Europe.

The first use that occurred in facial applications actually was used in Italy that resulted from plastic surgeons who knew our Italian

distributor who asked to be able to access the material and test it in facial applications. We also had emerging interest at that time in vocal fold applications of the material. For both of those applications, the large particle sizes required a needle gauge that would be undesirable for those applications. A smaller particle size product was developed, launched for vocal fold applications on a worldwide basis and commercialized internationally for aesthetics applications and began clinical testing in the U.S. for aesthetics applications.

But that smaller particle size product is in fact designed -- The 25 to 45 micron size range and this is the second half of your question is intended to address two key needs. One is the minimum size is set to make the products large enough that they won't be engulfed by a macrophage. Much of the scientific literature discusses the particles of a 10 micron size or smaller, could be taken up in a macrophage and so in order to provide for durability, we wanted to have particles that were a significant distance from that range; hence the 25 micron lower

size limit for production of these particles.

The 45 micron upper limit is designed to create a consistent material with a consistent range of particle sizes that are small enough relative to the diameter of the needle through which they will be placed, that they will have appropriate flow characteristics. When particle sizes begin to approximate the needle diameter or even if they're not at the same level of the needle diameter, as they become larger the risk of multiple particles hitting the needle opening simultaneously as you're putting force on a syringe to try to push the materials through that needle increases and that increases the propensity for needle jams. We have designed this product such that with the characteristics of the gel you will get a low rate of needle jams with the appropriate needles that would be used in the vocal fold or facial aesthetics indications.

MEMBER OLDING: Durability comparison.

DR. BASTA: Exactly. The third component of your question was related to durability and size and it is at least theoretically reasonable to

believe that the smaller particles will in fact degrade faster than the larger particles. It's very difficult to precisely quantitate that because when you inject the material you see particle degradation and we do see evidence of particle degradation that occurs with both the small particles and the large particles.

Quantitating the exact rate of that degradation will vary by species, vary by tissue in which you inject it and so the expectation that you make at somewhat faster resorption of the smaller particles than large particles is possible but we have not demonstrated that there is a quantitative difference in the resorption rate of the two materials.

We do know that both are durable for a significant period of time. In fact, in our animal studies, the particles are durable for beyond twelve months, although we begin to see some particle degradation. Many of the particles are there. Quantitating the exact rate of that resorption is difficult to do. It also varies by whether you

inject a bolus of material or you inject threads of material because you have surface area phenomena associated with gel resorption and how quickly you get collagen integration in the metabolic activity at the site. So it's just been hard for us to quantitate the exact rate of resorption of each of the two particles and how they change.

MEMBER OLDING: Thank you.

DR. BASTA: I'll have Dr. Silvers address the question of lumps.

DR. SILVERS: Thank you. Hi. Nodules would be long-lasting, visual, almost scar like material which we've not seen. The lumpiness is the material that's settling in the skin while the material settles. So it's something that's more palpable.

The thickening of the material as it's injected, that's really more descriptively what it is. The two of them are entirely different. It's actual material but not scar tissue that the patient will build up as a result of injection.

MEMBER OLDING: I'm trying to sort of

figure out what Dr. Carruthers said that when he injected and I've also used the product when you inject after a certain amount of time. It is difficult to inject in the same place and there's obviously a difference between a granuloma and a nodule, but a nodule in my opinion is something that is palpable, visible.

DR. SILVERS: Right.

MEMBER OLDING: And so I'm just trying to justify that because a lot of the other products that have been presented do in fact result in nodularity.

DR. SILVERS: Right.

MEMBER OLDING: Is it a question of technique then?

DR. SILVERS: Well, it could be. I mean as an ENT surgeon I see them all the time on the vocal cords which are basically a build up of scar tissue. Visible nodules, we haven't seen and we haven't seen any of them in the study. We haven't seen any bumps on the skin. We haven't seen any -- And you could see them in a lot of our photographs. We haven't seen any outgrowths on the skin or any

asymmetries in that way.

The thickening that you may find under the skin, some of that is material that's still there after twelve months that we may be further injecting into which makes a virgin injection a little different than a twelve month injection. Some of that is the collagen regrowth and fibrosis. The subsequence injections a little more difficult, but the injections are still not difficult to do, but it's something as physicians that do the product and as dermatologists and facial plastic surgeons and people that use any fillers get comfortable doing.

MEMBER OLDING: In general, do you inject the site a deeper level than you do say the intradermal -

DR. SILVERS: I'm sorry.

MEMBER OLDING: In general, do you inject this at a deeper level, i.e. not so close to the dermis or in the deep dermis?

DR. SILVERS: Subdermally.

MEMBER OLDING: Always subdermally.

DR. SILVERS: Yes.

MEMBER OLDING: Never intradermal.

DR. SILVERS: Never.

MEMBER OLDING: Okay. Thank you.

DR. SILVERS: Thanks.

CHAIRMAN LoCICERO: Dr. Lewis.

MEMBER LEWIS: Thank you. I have actually several questions. So I'm not sure who would most appropriately answer them, but let me address them one by one. The first issue is that it would appear to me that if you over-injected it would be impossible to remove the material. So what is the -- Maybe Dr. Silvers, what is the protection against that? You just intentionally always tend to error on the low side so that you can touch it up later and have you had any instances in which there was over-injection for any reason?

DR. SILVERS: There -- I have never had that. There has never been a reported, at least, in the face of anyone having had their material removed except for a couple of instances in the lips which is why we don't use it in the lips. The material when larger volumes are injected in the face, we always do

a lot of facial massage to distribute the material in the face.

It can be massaged and manipulated to be extract out the initial injection site. So that also can be done at the time of injection if recognized by the physician initially. But I have not seen it and it's again another reason why I tell patients "I'd like to see you back in few weeks. You may need a little touch up and more just for symmetry."

MEMBER LEWIS: Okay. The second question and I'm slightly confused about differing evidence that's been presented about either the metabolism or disappearance of the product. The nasolabial fold thickness measurements that you provided suggest that they go down by about 20 percent at twelve months. So there is a slight decrease, but really not very great and yet Dr. Carruthers said that a third of the patients at twelve months have no evidence of the material present.

It's puzzling to me that one-third of the people should have the calcium completely disappear without the other two-thirds having fairly uniform

evidence of decreasing amounts and I find all of that hard to reconcile. So I wonder if you could tell me what you think.

DR. CARRUTHERS: I agree. I mean it was something that we did not expect because from the animal studies we expected the beads to be still very present at one year and yet we couldn't see the beads in 30 percent of the individuals. But it's the collagen formation which is induced by the presence of the beads early on which produces the long-term correction. So as a clinician, I'm looking at this and I'm thinking well that means the material that you're injecting goes away earlier than we thought. Well, that's good because the correction is still there.

And just to go back to Dr. Olding's question, this material is not difficult to inject. It flows very smoothly. It doesn't have a lumpy flow as you are aware out of the syringe. We are injecting at a relatively deep plane. People who inject this sort of thing routinely will be doing some massage which is all you need to do.

But it is very common to get with this particular material, and it's distinct from other things, all of these fillers have their own characteristics, it's very common to get a feeling, not an appearance but a feeling, of lumpiness which lasts for two weeks and that sort of self-corrects, so that like Dr. Silvers, we would agree. We've never seen over correction. If anything, you're tending to under correct these people, although as you can see from our data, I sure tried hard not to and so that there may be a feeling of a little bit of irregularity.

We tell people two weeks it's going to feel a little bit lumpy underneath there and then it'll all be nice and smooth and that's what happens. Whereas the nodules that you are discussing which are much more common with let's call another product don't occur with this. You end up with a nice smooth appearance and that was, I think, well shown by all the clinical data that we've shown you. We would be happy to show you all 130 individuals, but I don't think it's necessary. What you saw was

representative.

MEMBER LEWIS: But if one-third of the people have total disappearance of the calcium, how -- You've shown that it does not go to the lymph nodes. How is it metabolized and removed?

DR. CARRUTHERS: Firstly, the one-third that we did not demonstrate total disappearance of the calcium. We would just fail to demonstrate it on CT scan which is a relatively good way of assessing its presence. But I would suspect that there is actually quite a bit of the beads there and we're just not seeing it and obviously it's just metabolized just as our bones are metabolized on a regular basis. There is turnover.

MEMBER LEWIS: Do you think there's insight to your resorption of calcium?

DR. CARRUTHERS: Yes, we're full of the cells and enzymes, etc., necessary to break down calcium hydroxylapatite and that's what we do and so the material is gone. The surprising thing from our study was that so much of it had gone, I think.

MEMBER LEWIS: Your presumption would be

that if you had 24 month data you would find that significantly more than two-thirds or even more of the calcium would be gone in the patients.

DR. CARRUTHERS: I'd hate to presume, but probably you're correct.

MEMBER LEWIS: Okay. The last question I have is that you have, for a number of you have, basically shown that the initial material is replaced by collagen. The plasticity or pliability of collagen is very different than fat, so and obviously in your face, you want something to be pliable and plastic. So what is the consequence in these people of having in essence collagen formation in their face which is presumably permanent in terms of flexibility, smiling, other characteristics? I would think that would become a fairly significant factor either subjectively that they would feel as they attempt to go through the various facial gestures or it might be noticeable cosmetically.

DR. CARRUTHERS: Maybe I'll say a word and then Dr. Silvers can talk from her experience. There is a firmness there for awhile and then that

seems to largely disappear so that the feeling of the tissues are maybe a little firmer than normal but not dramatically so and that's why when I stuck the needle in and was trying to inject in that area I was surprised at how firm the tissue was, so that these individuals described their faces as being back to normal. They don't have a feeling of an abnormal sensation. Their faces move quite normally by comparison, for example, in the past I've used Gore-Tex implants and those really produce an abnormal appearance. And that's not the case with this where it's a very normal appearance. Dr. Silvers.

DR. SILVERS: I also find it amazing how natural it does feel and again the less lipoatrophy they have, the more natural it feels. The more if they have a little bit of fat, if they are more of a Grade 2, they do have a better result in anything that we do. The patients with a Stage 3 and 4 with really severe lipoatrophy are just happy to have a look of a filler. It's not going to feel like natural fat. Their faces no matter what we do move naturally. When they smile you can see some of the

material move up with them.

I used to do a lot of, as I said before, cheek implants that would set right to the bone and I would tell patients even now we could do implants but then we would need to do some fillers around there because we can't use implants on mobile areas of the face. I just find it amazing of everything that I've used, injectable, how natural it does feel.

MEMBER LEWIS: Okay. Dr. Silvers, one last question for you.

DR. SILVERS: Yes.

MEMBER LEWIS: You've made a point of the injection being subdermal, not intradermal. The plane between subdermal and intramuscular is narrow. What level of -- Or how experienced and practiced does the practitioner need to be doing these injections to ensure they're at the right level and to what extent would this preclude the product from being available for general use for people who unlike yourselves are not doing this on a regular basis?

DR. SILVERS: Right. To address, first of all, for any of us that do use injectable fillers,

it's very easy. For teaching purposes, I find it very easy because that plane as you know is very smooth. There's no resistance in the subdermal plane at all. So if doctors are getting resistance, they're in the wrong plane. The subdermal plane, is the needle tip is easy to visualize. There is no resistance to the needle whatsoever and I have taught a couple people how to do it. It is so easy to teach and easy for them to do for that reason. I find it a very easy product to use and teach.

MEMBER LEWIS: So you would not feel that any restriction in the product is necessary in terms of usage by or that any particular training is necessary for the practitioner.

DR. SILVERS: I think I personally would not. I think like with anything you need proper training, but I think it's a very simple material to use.

MEMBER LEWIS: Thank you.

DR. SILVERS: Thank you.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: Thank you. Thank you for

the presentation and discussion up to this point. Dr. Lewis touched on many of the thoughts that came to my mind. You know I think what this material does is make a scar. I mean you can call it collagen ingrowth and fibroplasia, but basically what you're describing is a scar and so you're injecting a material that induces a volume filling scar and it would seem that all the concerns that are related to scar formation would have some bearing on these patients like, for example, a patient who tends to form a hypertrophic scar. Would that patient have a possibility of having an adverse result with this? You may not see that in these lipoatrophy patients, but is that a concern? I know you excluded keloid formers but what about hypertrophic scar formers?

DR. CARRUTHERS: Scar is a pejorative term and so we've tended to talk more about fibroplasia and collagen deposition because I think that the process that we see in the subdermal area where we're discussing is different from the process that we see when you involve the dermis and the epidermis and from your experience, you will know

that hypertrophic scars on the face are relatively uncommon and not unknown, but relatively uncommon. In Dr. Silvers' study, a large number of darker skin types were included, some of whom likely might have been keloid formers. I mean so far it's not been an issue and it may become an issue, but I don't think so from the evidence that we've seen so far.

And the - going back to the fascination with the radiological studies, you can see that the material was deposited not just at a subdermal level, but principally subdermal in the nasolabial fold patients. But in the lipoatrophy patients, you could see it from the dermis down to the bone or certainly some of it, I think, was relatively close to the periosteum.

PARTICIPANT: I thought it was separate.

DR. CARRUTHERS: But separate from it. But as you're injecting this matter in these individuals with lipoatrophy, there is very little subdermal space and it's common to see twitching and you know that you have the needle in the muscle and you then need to go either superficial or deep

depending on where you want to deposit it.

But there is nothing that I have seen so far to suggest that you should not deposit it between the periosteum and the muscle or at other layers. Clearly, we don't want it too superficial and the more material that you have between the Radiesse and the skin, the smoother will be the outcome, so that often we do inject relatively deeply.

CHAIRMAN LoCICERO: Dr. Silvers, could you please describe what you've seen referenced to this question since you're the principal investigator in a pivotal trial.

DR. SILVERS: In reference to the scar question?

CHAIRMAN LoCICERO: Yes.

DR. SILVERS: Yes. Again, I haven't seen scarring per se. I suppose every time we inject multiple needles we're going to get some scarring. I know these patients pay for scarring or anything that's going to leave their face full and again as Dr. Carruthers said, I imagine that as we call some of this fibrosis and collagen formation, some of this

is going to be the development of scar tissue which hopefully does give them some long-lasting benefits.

MEMBER MILLER: Yes. It's not superficial scarring I was thinking of but just what happens to the material.

DR. SILVERS: Sure.

MEMBER MILLER: Are there any longer term histology on it? You showed some nice histology early on of the void spaces with the decalcified material. But what about long term? Does the tissue look much different than a scar? A deep scar I'm talking about.

(Discussion off the microphone.)

DR. SILVERS: Right. Well again, I can just describe clinically at 18 months again the material in the face and how the face is palpable. Again the face still feels soft and just the way it did at twelve months. So really there's no clinical difference in how the patient does feel. There is still a little bit of loss of material relative, but again, they still have a nice fill and the face still does feel soft. There's no firmness to it and no

evidence of a significant build-up of scar tissue under the skin.

MEMBER MILLER: It would have been nice to have seen some animated views because I think especially with some of the larger injections, I saw some with 30 ccs injected in some of these patient's cheeks, a large plaque of scar in their cheek and I would think possibly with animation you would see this less pliable area, less mobile area.

But the other question, you mentioned injecting it in a muscle. What happens if you inject it in a muscle or what happens if you get an intravascular injection?

DR. SILVERS: You get a bruise. I mean we -- The echymosis is one of the temporary adverse events which is very short lived, but we - bruising is not uncommon. But there's nothing permanent that happens. It doesn't get into the blood stream and cause any systemic adverse events. But a small vascular injury can happen.

MEMBER MILLER: Okay. What's the worst thing that can happen with this material? I mean if

you take somebody who's never injected it and you hand them a syringe and say, "Go and put this in this patient" what would you worry about because it seems like you have few worries with this.

DR. SILVERS: Sure. I mean a couple things I would worry about is safety for the physician. I mean you're dealing with HIV patients and good practice and caution is very important. We take it for granted. I deal with these patients all the time. I don't even think twice about and my staff is very cautious. So on the physician's side, you want to be very careful. If the patient moves, it's not difficult to get a needle stick.

From the patient's side also, I tend to do a local block for these patients. I try to make them nice and numb because I don't want the patient to move. So I'll do a local block with a infraorbital nerve block and then a little wheel where I'm going to do my injection site. Many physicians don't do that. We're around the orbit, so there can be complications there. Again, I think this is where proper training comes in with anything.

I mean all injectable fillers are done, all facial injectable fillers are done around the face. So we're dealing with needles around the face and all precautions have to be taken near vital facial structures.

CHAIRMAN LoCICERO: Dr. Li.

MEMBER LI: I'm not sure who best to answer this question. I just have -- If you could briefly describe to me exactly the nature of the calcium hydroxylapatite you're using. I come from a largely orthopaedic background, but in our history, there has been several versions of hydroxylapatite. So could you tell me exactly what your source is of hydroxylapatite and just briefly describe, for instance, its calcium phosphorate ratio and crystalinity?

DR. BASTA: Dr. Li, we would be happy to discuss the details of the manufacturing process of the material. I would want to confer with my colleagues for a few moments first to determine that there's not going to be any disclosure of proprietary information regarding the compositions of our

material in that context. But one assurance which I can, one sort of general description which I can provide to you which won't provide all the detail that you've asked for is that our material is derived from a synthetic process, not animal derived components.

Involved in the production of the calcium hydroxylapatite the synthesis comes from a calcium source material that is produced through chemical reaction processes to pull it out, I believe, from a calcium carbonate source, but I will discuss the exact ratio of the materials and the composition with my colleagues and then get back to you in more detail on that just because I want to make sure we're not disclosing in a public session any proprietary information that's not otherwise publicly available.

Also while I'm up just very briefly, Dr. Miller, per your questions on histology, we have extensive preclinical studies in multiple animal models in dermal applications that go out for beyond a year. In urology applications, our longest animal study goes out for three years. There is

significant histology data from all of that.

We can show you the histology images from that, although I'm not sure that it's going to answer your question about palpability because what you'll see on the histology image is resorption of gel over time, ingrowth of collagen around the particles and then the existence of particles and the breakdown of particles gradually. But the histology images may not answer your palpability question which is probably best addressed by your colleagues as to exactly how this feels in the face of the patients and they could discuss it with more clinical experience.

And Dr. Silvers as she had mentioned also now has 18 month followup on all of the patients from the U.S. pivotal study or her patients at least and we have data from the full cohort and had not observed any of that in the clinical reports. But she has obviously given you her clinical perspective. If you would like to go through some of the preclinical data, we can again pull up some of that material, but I'm not sure it will answer the

palpability question that you're looking at.

MEMBER MILLER: Well, it's more than just the palpability. It's you know scars are active pieces of tissue that contract and they can do all kinds of things and depending on the patient. In a place like an all scar tissue, for a vocal cord or for an urology application, it almost doesn't matter what three dimensional thing happens to the scar as long as it's filling the void and providing the function. But in the face, I could envision some set of patients having scar contracture or especially with a large plaque of scar resulting from this material. So what I'm doing is trying to search for the type of patient who this would possibly be a problem in because in your set, I didn't see them. These were wonderful results and very impressive, but there are enough patients who have this that we'll begin to see patients who have problems related to the type of thing I'm thinking of I think.

DR. BASTA: And the best response to that would come from the clinicians as to what they've actually seen in their clinical observations and if

you'd like more discussion, I'm sure that Dr. Silvers or Dr. Carruthers could provide their own clinical experience with that. Dr. Li, would it be acceptable for me to confer with my colleagues and then get back to you with an answer to your question?

MEMBER LI: Certainly because I think it's -- Why I'm harping on this is you gave a long list of the history of hydroxylapatite in medical devices, but if you're not - those you are not familiar with it, they are not all the same hydroxylapatite and resorption rates and tissue responses are very dependent on specifically what hydroxylapatite you're using and I didn't get anything in my panel pack that described that.

DR. BASTA: Understandable because some of the manufacturing information is proprietary. It's been discussed and disclosed with FDA.

MEMBER LI: Yes. I don't really need to know how you make it. I'd just like to know what we're sticking in there, putting in there.

DR. BASTA: Okay. I will get you the response to that question.

MEMBER LI: And also while you're looking that up, you give the particle size as 25 to 45 micron. Is that the actual -- Is that the desired particle size range or is that the actual particle size range of your product? In other words, if I got some and I did a size determination, would I find particles less than 25 and greater than 45 in the syringe?

DR. BASTA: You should find that virtually all the particles are between 25 and 45 microns. We run through a rigorous process of multiple washing stages, multiple sieving stages through filters that filter out material above 45 microns and below 25 microns. It's actually an extensive multi-step process with rigorous repeat evaluations and then we do size distribution testing by scanning electron microscopy and other means to determine that we are in fact within that size range.

MEMBER LI: Thank you. I have a couple of other questions. One, I'm a little bit confused over this issue of nodules and perhaps it's semantics or perhaps it's something else. But on one hand, you

report that there were no nodules in your clinical trial. Yet I think it's Table 235 in your clinical report the list - that you provide a list of complaints and that if you add the lip nodule complaint and the other nodule complaint, those two add up to be the largest source of complaints in that table.

So is it a semantic difference for nodules in that complaint list versus what you saw in your clinical trials or do your clinical trials for some reason maybe because of the expertise of your surgeons or for some other reason they don't manifest themselves in the clinical trial but they would in a larger population? Could you comment on that?

DR. BASTA: I will comment on part of it and then part of it I will defer to my clinical colleagues to talk about the clinical observations in this study. Regarding complaint rates and nodule formation, particularly the most common site of nodule formation with Radiesse that's been reported to us is in lip augmentation. As I mentioned earlier, Radiesse is a commercially-available

material approved for facial aesthetics applications internationally and also in the United States for vocal fold applications, but we do know that it's being used for facial aesthetics applications. Many physicians have published reports on facial aesthetics applications or other aesthetics applications of this material. It is commonly being used as other materials have been on an off-label basis prior to approval for these indications.

What we have heard regarding nodule formation most commonly occurs in lip injections. It is an immediate accumulation of the material in the days post injection when a physician injects a large amount of material into the mobile parts of the lip. The muscle motion of the label can physically cause this material to accumulate at the weak point of the lip.

So the most common discussion of the terms "nodules" or the most common use of the word "nodules" associated with Radiesse appears in that context. That's not one of the indications we are seeking in today's review and the two clinical

studies that have been submitted. It is the site where you have the most mobility and clearly the viscosity of this material is somewhat greater than the viscosity of other agents that have been approved some of the aesthetics applications or that are being used off-label for lip augmentation because many of these agents are, in fact, being used off-label for lip augmentation.

All of them have a propensity for forming nodules in the lips. Because this is a longer lasting material, those nodules tend to last a bit longer with Radiesse than with other materials and hence the reported events. But the rate would be very low in terms of, from my understanding of our complaints files, the rate would be very low outside of the lip applications and that's the most common site of nodule discussions.

MEMBER LI: Actually the reports for other nodules was really one or two different from lip nodules if I remember the table correct.

DR. BASTA: I don't have that table in front of me.

MEMBER LI: Could you check that?

DR. BASTA: I will do that.

MEMBER LI: Because the number was about -- They're about the same. So again, this just caused some confusion in my mind of whether or not we're talking about the same nodules or if there's a good compelling reason like you just stated for the lips.

DR. BASTA: Okay, and part of the understanding of that may come from the discussion that the clinicians may offer regarding what they saw early in the clinical experience with this material and how that resolved over a matter of weeks because you do get lumpiness whenever you inject the material and then there's a phenomenon where that seems to smooth over the course of the first week or two as the swelling from the injection procedures subsides and others. But clinicians, Dr. Silvers or Dr. Carruthers, may provide you more insight on that. Did you have any other questions before I turn the podium over them to discuss that issue and I can get the background information.

MEMBER LI: No, I think you've answered actually those questions sufficiently.

DR. BASTA: Okay.

MEMBER LI: Thank you.

DR. BASTA: Let me get you the background information on your other questions, Dr. Li, and I will have Dr. Silvers or Dr. Carruthers address the clinical observations.

MEMBER LI: I just have two other questions if I may. One is regarding the radiographic review. It's been stated that there's no evidence from migration but that -- Actually, I'm a little confused over how you can actually state that so categorically, given that Dr. Carruthers actually said at some time period the hydroxylapatite is probably still there. You just can't see it. So given the limitations of the resolution for both CT and x-ray, do you actually have any evidence that there's no migration or are you simply saying if it moves you can't see it?

DR. LIEBESKIND: What I was trying to say as a radiologist I can't see any of this material

accumulating. I can see the material even at small volumes very conspicuously by CT scan, but that I don't see it anywhere else.

MEMBER LI: Okay. So you're --

DR. LIEBESKIND: There's no radiographic evidence for migration.

MEMBER LI: So your comments about where you actually said very clearly there's no migration, there's really no evidence of migration.

DR. LIEBESKIND: Correct.

MEMBER LI: But it could be moving and you just can't see it.

DR. LIEBESKIND: Right. On a molecular basis, clearly. I mean on a microscopic basis we can't see, but macroscopically, by CT scan we can see it.

MEMBER LI: And what is the smallest particle that you could reliably see with CT?

DR. LIEBESKIND: The analogy I would probably give you that's probably the easiest as a radiologist is a kidney stone because those are small bits of largely calcium although they have different

chemical compositions and we routinely see down to 0.1, maybe just under 0.1, millimeters size, excuse me, 0.1 centimeter size, so about a millimeter.

MEMBER LI: Because that's substantially larger though than the particles we're talking about.

DR. LIEBESKIND: We're not looking at individual particles actually.

MEMBER LI: Right. And the other question is what's the chance that the injection of this material would just block a regular dental x-ray and we're kind of looking at a single plane here and if you interview the dentist, the dentist doesn't normally look at. But certainly in large volumes, would they interrupt with the risk of normal dental x-ray?

DR. LIEBESKIND: Actually, I wanted to show you one of the x-ray images just to show you how difficult this material is to see on a plain-film x-ray and several of these patients have dental hardware. So I think it's very good. Bear with us one second while we pull up that slide.

So as you can see here, there is very

faint -- The dental hardware is quite obvious on all three of these individuals. This is the outline for instance on the right of the maxillary sinus, the antrum on this patient, and you can see Radiesse faintly on the left.

There actually, if I could blow this image up, there actually is a very cloudy appearance in the medial wall of that right antrum and that is Radiesse projected. But as you can see as relative density to dental hardware or to the teeth themselves even though this is a projection image and hard to see, the Radiesse is barely visible.

MEMBER LI: Thank you. I have a question on the skin thickness measurement. If I understood your diagram and the protocol, I'm not a dermatologist, so please excuse me on the questions, I'm just too naive, are these single point measurements? In other words, you just go in and take a single point measurement in one repeatable location?

DR. SILVERS: Yes.

MEMBER LI: But often though, it seems

like from the different views that actually may be some varying distances from where you actually inject the material. So this is a single point skin measurement at a very repeatable point, but perhaps not the most, the point where the skin thickness may, for instance, change more.

DR. SILVERS: That's correct, but it does give us consistency again across the board and throughout the patients. It also does cover where the buccal fat pad is where most of the patients are losing much of their fat.

MEMBER LI: No, I understand why you did it. I'm just trying to get a sense for how far I can carry that measurement forward. Okay, and the other thing is do you have any correlation between the change in the skin thickness you measure and the volume of material injected.

DR. SILVERS: The patients that are Grade 4 and 3 tended to have a lower skin thickness measurement in the beginning. So that definitely would correlate. Patients with a higher grade of severity of facial wasting would have a thinner skin

thickness measurement. Patients with a higher - better grade or Grade 2 would have a thicker skin thickness as our baseline. Once we then did our injections we would try to get them all to an optimal injection which would then bring us up to that level in the higher sevens and the eights.

MEMBER LI: Were there any patients that had what I'll call an unusual response to the material either you injected just a little bit of material and there was a large skin thickening or you injected a lot of material and there was just a little skin thickening.

DR. SILVERS: No.

MEMBER LI: So is it pretty direct correlation?

DR. SILVERS: Yes.

MEMBER LI: Okay, and my last question for now is I guess back to the histology question. I just find that there is remarkably little histology being presented here. You referenced a couple of publications in your panel packet, but looking up those publications, even those publications only have

a handful of micrographs in very kind of small locations. So what is your sense of the histology that's going on in these patients. And again in the orthopaedic area, when we inject hydroxylapatite, of the kind we use, there's an immediate inflammatory response, macrophages come, giant cells come. It's a little war going on wherever you put the hydroxylapatite in. So the histology that's shown is almost remarkably clear versus my general experience with hydroxylapatite. Could you comment on that?

DR. BASTA: I can certainly comment on that. I also have some further information for you on your prior questions and so we can work through that.

We have not made efforts today to go through in any meaningful fashion all of the underlying basic science. Part of it is just the time constraints of a presentation in a forum such as this. If we have one hour to make a presentation, it's hard to go through all the basic science at the same time that one goes through all of the clinical data as well as the supplementary data from the

radiology study that was requested by the Agency. So time constraints limit how much one presents in that process.

We have provided as I mentioned earlier a much more complete set of histology and preclinical findings to FDA that's been reviewed by FDA. We've addressed questions on it and we've worked through a rigorous review process regarding all of the basic science work on the manufacturing and the preclinical components of Radiesse.

Most of the histology data that we have or most of the histology images come from animal studies rather than from human studies. With facial injection procedures such as this, one does not typically do biopsies in patients who are having aesthetic procedures in the face for obvious reasons of a patient morbidity and so forth. But we have a significant body of data.

If you would like to see serial collagen production images over the course of several time periods out to a year and a half, we can work through that information. We have some of that in backup