

UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + + + +

65TH MEETING

+ + + + +

THURSDAY,
MARCH 25, 2004

+ + + + +

The panel met at 8:00 a.m. in Salons A-D of the Gaithersburg Hilton Hotel, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Michael Choti, Chairman, presiding.

PRESENT:

- MICHAEL A. CHOTI, M.D., Chairman
- GRACE T. BARTOO, Ph.D., RAC, Industry Representative
- BRENT A. BLUMENSTEIN, Ph.D., Voting Member
- PHYLLIS CHANG, M.D., Voting Member
- LEELEE DOYLE, Ph.D., Consumer Representative
- DOUGLAS G. FISH, M.D., Temporary Voting Member
- MICHAEL J. MILLER, M.D., Voting Member
- ROBERT J. MUNK, Ph.D., Patient Advocate
- AMY E. NEWBURGER, M.D., Voting Member
- MICHAEL J. OLDING, M.D., Temporary Voting Member
- NEAL S. PENNEYS, M.D.,
Ph.D., M.B.A., Temporary Voting Member
- DAVID KRAUSE, Ph.D., Executive Secretary

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P-R-O-C-E-E-D-I-N-G-S

(8:06 a.m.)

DR. KRAUSE: Good morning. Glad to see everybody could make it today. Were ready to begin this, the 65th Meeting of the General and Plastic Surgery Devices Panel. My name is David Krause. I'm the Executive Secretary of the panel. I'm also a biologist and a reviewer in the Plastic and Reconstructive Surgery Devices Branch, and the Division of General, Restorative and Neurological Devices. I would like to remind everybody that you are requested to sign in on the attendance sheets which are available at the tables just outside the door. You may also pick up an agenda, panel roster and information about today's meeting on that table. The information includes how to find out about future meeting dates through the advisory panel phone line, and how to obtain meeting Minutes or transcripts.

Before I turn the meeting over to Dr. Choti, I'm required to read a number of statements into the record. These are the Deputization of Temporary Voting Members and Conflict of interest.

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1 I'm going to start with the appointment to temporary
2 voting status. Today we have a number of panel
3 members who are from Center for Drug Panels, and I
4 need to read a different statement for them. That's
5 this statement here.

6 Pursuant to the authority granted under
7 the Medical Device Advisory Committee Charter of the
8 Center for Devices and Radiological Health dated
9 October 27, 1990, and amended August the 18th, 1999, I
10 appoint the following individuals as voting members of
11 the General and Plastic Surgery Devices Panel for the
12 meeting on March the 25th, 2004; Dr. Douglas Fish and
13 Dr. Neal S. Penneys. For the record, Dr. Fish is a
14 voting member of the Anti-Viral Drug Advisory
15 Committee, and Dr. Penneys is a consultant to the
16 Dermatologic and Opthamologic Drugs Advisory Committee
17 of the Center for Drug Evaluation and Research. They
18 are special government employees who have undergone
19 the customary conflict of interest review, and have
20 reviewed the material to be considered at this
21 meeting. This is signed by Mr. Peter Pitts, who is
22 the Associate Commissioner for External Relations.

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1 The second appointment to temporary voting
2 s status is for individuals who are consultants to
3 Center for Device Panels. Pursuant to the authority
4 granted under the Medical Device Advisory Committee
5 Charter dated October 27, 1990, and as amended August
6 the 18th, 1999, I appoint Steven Lee and Michael Olding
7 as Voting Members of the General and Plastic Surgery
8 Devices Panel for this meeting on March 25th, 2004.

9 For the record, these individuals are
10 special government employee and consultants to this
11 panel or other panels under the Medical Device
12 Advisory Committee. They have undergone the customary
13 conflict of interest review and have reviewed the
14 material to be considered at this meeting. This is
15 signed by Dr. David Feigel, who is the Director for
16 the Center for Devices and Radiological Health.

17 The final statement which I will read into
18 the record is the conflict of interest statement. The
19 following announcement addresses conflict of interest
20 issues associated with this meeting, and is made a
21 part of the record to preclude even the appearance of
22 an impropriety.

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1 To determine if any conflict existed, the
2 agency reviewed the submitted agenda for this meeting,
3 and all financial interests reported by the committee
4 participants. The conflict of interest statute
5 prohibits special government employees from
6 participating in matters that could affect their or
7 their employer's financial interests. However, the
8 agency has determined that participation of certain
9 members and consultants, the need for whose services
10 outweighs the potential conflict of interest involved
11 is in the best interest of the government.

12 We would like to note for the record that
13 the agency took into consideration certain matters
14 regarding Dr. Leach and Dr. Miller. Each of these
15 panelists reported current and/or past interest in a
16 firm at issue, but in matters not related to today's
17 agenda.

18 The agency has determined, therefore, that
19 they may participate fully in today's deliberations.
20 In the event that the discussions involve any other
21 products or firms not already on the agenda for which
22 an FDA participant has a financial interest, the

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1 participant should excuse him or herself from such
2 involvement and the exclusion will be noted for the
3 record.

4 With respect to all other participants we
5 ask in the interest of fairness that all persons
6 making statements or presentations disclose any
7 current or previous financial involvement with any
8 firm whose products they may wish to comment upon.

9 Okay. Now that I've read the statements
10 into the record, I'd like to turn the meeting over to
11 Dr. Choti.

12 CHAIRMAN CHOTI: Thank you, Dr. Krause,
13 and good morning. My name is Michael Choti. I'm an
14 Associate Professor in the Department of Surgery, with
15 an interest in Surgical Oncology at Johns-Hopkins.
16 Today this panel will be making recommendations to the
17 Food and Drug Administration on the pre-market
18 approval application. The next item of business is to
19 introduce the panel members who are giving time to
20 help the FDA in these matters, and FDA Staff as well
21 at the table.

22 I'm going to ask each person to introduce

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1 him or herself stating his or her area of expertise,
2 position title, institution, and his or her status on
3 the panel, whether they're a voting member, industry
4 or consumer representative, or deputized voting
5 member. Why don't we start with Dr. Lee.

6 DR. LEE: Good morning. My name is Steven
7 Lee. I'm President of Medical Device Testing
8 Innovations in Sarasota, Florida, independent research
9 and testing lab. My areas of interest are
10 biomaterials and biomechanics, and I'm a deputized
11 voting member.

12 DR. OLDING: Michael Olding. I'm Chief of
13 Plastic Surgery at George Washington University. I'm
14 a deputized voting member, and David didn't mention
15 it, but I do have stock investment in what might be a
16 competing company, which is Medisys, which produces
17 Restylane, which is a filler. It's less than 5
18 percent of my income from stock.

19 DR. PENNEYS: Good morning. My name is
20 Neil Penneys. I'm a voting member. I'm a
21 dermatologist/dermatopathologist and I'm working at
22 Ameripath.

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1 DR. FISH: Good morning. I'm Douglas
2 Fish, a deputized voting member. I'm the Division
3 Head of the Division of HIV Medicine at Albany Medical
4 College in Albany, New York, and Assistant Professor
5 of Medicine there.

6 DR. MILLER: I'm Michael Miller. I'm a
7 Professor of Plastic Surgery at the University of
8 Texas MD Anderson Cancer Center. I do cancer-related
9 reconstructive surgery as a clinician primarily, and I
10 am a voting member.

11 DR. LEITCH: I'm Marilyn Leitch. I'm a
12 Professor of Surgery at the University of Texas
13 Southwestern Medical Center in Dallas. I deal
14 primarily with cancer surgery, and I am a voting panel
15 member.

16 DR. KRAUSE: I'm Dave Krause.

17 DR. CHANG: Good morning. I'm Phyllis
18 Chang. I'm an Associate Professor at the University
19 of Iowa, Carver College of Medicine. I am a Plastic
20 Surgeon with joint appointments in the Division of
21 Plastic Surgery, Department of Surgery, and the
22 Division of Hand and Microsurgery in the Department of

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1 Orthopedic Surgery. I am a voting member.

2 DR. BLUMENSTEIN: I'm Brent Blumenstein,
3 Biostatistician, Seattle, Washington. I'm a voting
4 member.

5 DR. NEWBURGER: I'm Amy Newburger. I'm a
6 Dermatologist in private practice in New York. I
7 teach at Roosevelt-St. Luke's Medical Center
8 Consortium. I'm a voting member.

9 DR. MONK: I'm Robert Monk with the
10 Department of Internal Medicine at University of New
11 Mexico, where I'm the coordinator of the New Mexico
12 AIDS Infonet. I am a patient representative, non-
13 voting member.

14 DR. BARTEAU: Good morning. My name is
15 Grace Barteau and I'm the General Manager of Decus
16 Biomedical. We are a medical device consulting firm
17 where my expertise is in regulatory affairs, designing
18 and executing clinical trials and quality systems. I
19 am an industry representative which is a non-voting
20 position.

21 DR. DOYLE: I'm LeeLee Doyle. I'm a
22 Professor Emeritus of Obstetrics and Gynecology, and

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1 currently the Assistant Dean for Faculty Development
2 at the University of Arkansas for Medical Sciences,
3 College of Medicine. I'm a consumer representative
4 and non-voting member.

5 DR. WITTEN: Celia Witten, FDA Division
6 Director of the Reviewing Division for these products.

7 CHAIRMAN CHOTI: Thank you. I'd like to
8 note for the record that the voting members present
9 constitute a forum as required by 21 CFR Part 14.

10 Now I'd like to introduce Commander
11 Stephen Rhodes, the Branch Chief of Plastics and
12 Reconstructive Surgery Devices Panel, who will update
13 the panel since the last meeting. Steve.

14 CDR RHODES: Thank you, Dr. Choti, and
15 good morning. I am Stephen Rhodes. I am the Branch
16 Chief here at the Plastic and Reconstructive Surgery
17 Devices Branch at the FDA. I want to welcome the
18 members of the panel, members of the public, and the
19 medical device industry to this one-day meeting of the
20 General Plastic Surgery Panel.

21 This panel last met on November 21st of
22 last year, at which time you recommended that two

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1 premarket approval applications for facial
2 augmentation devices, Restylane and Hylaform, be
3 approved with conditions.

4 In December, FDA approved the PMA for
5 Restylane and the firm Q-Med agreed to conduct a post
6 approval study in people of color to gain more safety
7 data for this population.

8 In January, FDA issued a draft revision of
9 the breast implant guidance document, which updated a
10 previous version issued in February, 2003. The
11 substantive new recommendations in this guidance
12 document involve mechanical testing, modes and causes
13 of rupture, clinical study information, post approval
14 studies and labeling.

15 Also in January, FDA determined that
16 Inamed's PMA application for their silicone gel-filled
17 breast implants was not approvable. The panel
18 reviewed the PMA during the October 14th and 15th panel
19 meeting last year and recommended that it be found
20 approvable with conditions.

21 Today you will make recommendations on a
22 premarket approval application from Dermik

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1 Laboratories for their Sculptra Augmentation Device.
2 Because of public interest in this application, the
3 agenda today includes two one-hour periods for public
4 comment, one in the morning, and one in the afternoon.

5 Panel Members, we appreciate your commitment to
6 members of the public who have requested time to
7 address the panel. We appreciate your comments. And
8 to the sponsor of this application, we appreciate your
9 participation in presenting the information you have
10 to the panel, and answering any questions that the
11 panel may have. Thank you.

12 CHAIRMAN CHOTI: Thank you, Commander
13 Rhodes. We'll now proceed with the open public
14 hearing session of this meeting, or the first one.
15 All persons addressing the panel are asked to speak
16 clearly into the microphone as the transcriptionist is
17 dependent on this in order to provide an accurate
18 record of the meeting.

19 I would like to have the attention of all
20 the individuals who are registered to speak to the
21 panel this morning and today. We have given you a
22 number corresponding to the order of appearance.

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1 Please come to the podium area in advance so that we
2 are not spending a great deal of time during the
3 transition period between speakers. The FDA panel
4 will direct you to the appropriate podium.

5 Please remain within your time constraints
6 as we have a timer going to help you follow this. And
7 also, let me address the issue regarding financial
8 disclosure. Both the Food and Drug Administration and
9 the public believe in a transparent process for
10 information gathering and decision-making. To ensure
11 such a transparency at an open public hearing session
12 of the advisory committee meeting, the FDA believes it
13 is important to understand the context of an
14 individual's presentation.

15 For this reason, the FDA encourages you,
16 the open public hearing speaker, to advise the
17 committee of any financial relationship that you may
18 have with the sponsor, its product, and if known, its
19 direct competitors. For example, this financial
20 information may include the sponsor's payment for
21 travel, lodging or other expenses in connection with
22 your attendance at this meeting.

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1 Likewise, the FDA encourages you at the
2 beginning of your statement to advise the committee if
3 you have any such financial relationships, or if you
4 have none. If you choose not to address this issue,
5 you will not be precluded from speaking.

6 Why don't we begin with speaker number
7 one. These are individuals who have notified the FDA
8 of their intent to testify during the open public
9 session. Remember to state your name clearly for the
10 record if you feel comfortable doing so.

11 MR. VIRGIL: Hello. Good morning. My
12 name is Nelson Virgil. I have no financial interest
13 or ties to Dermik or any other facial reconstruction
14 product company. I'm here representing the AIDS
15 Treatment Activist Coalition, ATAC, and also as a
16 founding member of facialwasting.org. I've been HIV
17 positive for 21 years, and I've had facial
18 reconstruction done on my face in the past, so I've
19 also suffered from facial wasting in the past five
20 years.

21 I'm honored to be here, and I'd like to
22 read a letter that the AIDS Treatment Activist

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1 Coalition wrote in support of this application.

2 "Dear Dr. Krause: With this letter, the
3 Drug Development Committee of the AIDS Treatment
4 Activist Coalition, ATAC, wishes to express its
5 support of Dermik Laboratories premarket approval
6 application, PMA, for Sculptra brand poly-L-lactic
7 acid, an injectable device intended for the use in the
8 correction of lipoatrophy of the face in HIV infected
9 patients.

10 The ATAC has closely followed the clinical
11 development and reporting of poly-L-lactic acid for
12 facial lipoatrophy most notably under the European
13 brand name New-Fill, and is extremely pleased that an
14 application seeking commercial availability in the
15 United States is now before the U.S. Food and Drug
16 Administration.

17 Based on our knowledge of the available
18 data and our communications with clinicians and HIV
19 infected people who have used this product, we would
20 like to see Sculptra approved.

21 As will clearly be highlighted in this
22 meeting, facial lipoatrophy, believed to be a side

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1 effect of antiretroviral therapy is a condition that
2 results in loss of fat in cheeks, temples and eye
3 sockets. While facial atrophy is not believed to be
4 associated with an increased risk of mortality and
5 morbidity, it can have devastating effects on self-
6 image and confidence, lead to anxiety around HIV
7 disclosure forced by hallmark body habitus changes and
8 significantly contribute to demoralization and
9 depression.

10 In turn, this can lead to reduced
11 adherence to antiretroviral medications. In fact, the
12 effects of facial wasting can be so severe that HIV
13 infected individuals may jeopardize their health by
14 refusing antiretroviral agents believed to be
15 associated with this condition, or worse,
16 discontinuing antiretroviral therapy all together.

17 We take comfort in the extensive
18 experiences in poly-L-lactic acid injections in
19 Europe, where it was approved by the French Notified
20 Body G-Med in 1999 as a wrinkles filling product, and
21 has been marketed as New-Fill. It has been used by an
22 estimated 100,000 people in more than 30 countries

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1 through Europe and South America, and in Australia for
2 the treatment of a range of facial body imperfections,
3 including signs of aging, such as wrinkles, folds and
4 sunken cheeks.

5 We're also encouraged by the growing body
6 of preliminary data reported at various Medical
7 Congresses, and published in the November 21st, 2003
8 edition of AIDS. The study enrolled 50 patients with
9 a medium facial fat thickness of zero, and patients
10 were injected with poly-L-lactic acid every two weeks
11 for six weeks. The medientor or cutaneous thickness
12 increased by 5.1 millimeters at six weeks from
13 baseline, 6.4 millimeters at 24 weeks, 7.2 millimeters
14 at 48 weeks, 7.2 millimeters at 72 weeks, and 6.8
15 millimeters in 96 weeks.

16 The proportion of patients with cutaneous
17 thickness greater than 10 millimeters peaked at 61
18 percent at week 48, and ended the 96-week study at 43
19 percent. The only significant side effect noted in 44
20 percent of the patients was the appearance of palpable
21 but non-visible subcutaneous micro nodules with
22 spontaneous resolution in six patients at week 96. No

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1 side effects were serious enough to discontinue
2 injections.

3 Based on the safety and efficacy data
4 demonstrated at 72 and 96 weeks, we consider Sculptra
5 to be a device worthy of approval and commercial
6 availability in the United States. With this support,
7 however, we wish to raise four key issues, not only
8 with the General and Plastic Surgery Devices Panel,
9 the Medical Devices Advisory Committee, but with
10 Dermik Laboratories.

11 First, we sincerely hope that the FDA will
12 approve Sculptra as a reconstructive corrective
13 therapy, not simply as a cosmetic morality. Facial
14 lipoatrophy is very similar to the body habitus
15 altering effects of other therapies, including but not
16 limited to mastectomies and amputations. The
17 nomenclature of a device or surgical procedures
18 indication, particularly from the FDA, carries
19 significant weight when we negotiating with third-
20 party health care providers in seeking coverage for a
21 particular procedure, which will be vital for HIV
22 infected individuals with facial lipoatrophy.

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1 Second, for Sculptra and other facial
2 fillers, to yield safe and effective outcomes, it must
3 be administered by clinicians who are experienced in
4 using injectable devices of this nature. We as a
5 group of HIV/AIDS Treatment Activists are not in any
6 position to recommend minimum criteria that must be
7 met by clinicians.

8 However, we do recommend that Sculptra
9 only be available to and administered by clinicians
10 who have met specific training or experience criteria
11 specified by the FDA and Dermik Laboratories.

12 Three, long term safety and efficacy data
13 are limited, and most of the data relate to
14 applications of much lesser volumes of a product than
15 are anticipated for correction of facial wasting.
16 There are lingering questions regarding the durability
17 of Sculptra injections and the potential for long-term
18 complications.

19 In turn, we would like to see Dermik
20 Laboratories commit to a long-term follow-up study to
21 evaluate the durability of Sculptra injections. The
22 factors associated with premature reversal of

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1 treatment benefit, i.e., ongoing use of nucleoside
2 reverse transcriptase inhibitors like Zerit, and long-
3 term events.

4 Four, pricing and reimbursement concerns
5 are of significant importance to ATAC. We're aware of
6 the challenges that we, as consumer advocates, will
7 face in terms of achieving payment and reimbursement
8 from private and public health insurance.

9 In turn, what is needed from the FDA is
10 the strongest possible labeling language, indicating
11 the reconstructive corrective nature of Sculptra.
12 What is needed from Dermik Laboratories is a strong
13 patient assistance program commitment which must
14 include steadfast support and advocacy to secure
15 treatment reimbursement from public and private health
16 insurance. And when necessary, free or low-cost
17 therapy administered by clinicians with consultation,
18 administration, and follow-up fees contracted through
19 the IP.

20 Respectfully, we submit this letter to the
21 FDA and hopefully we'll get some approval of this
22 first of its kind facial wasting reconstructive

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1 product. Thank you.

2 CHAIRMAN CHOTI: Thank you very much. The
3 next scheduled speaker.

4 DR. KRAUSE: I have a few testimonies that
5 were sent in to be read. I can read these now while
6 we're waiting for the other speakers.

7 "Dear Esteemed Members of the FDA Advisory
8 Committee: I truly wish that I could testify in person
9 to the panel. Unfortunately, given the presence of
10 the media and the taping of the hearing, I am unable
11 to do so as it would more than likely jeopardize my
12 position at my firm.

13 I want you to know how very difficult of a
14 decision this has been for me. Given the overwhelming
15 benefits of Sculptra, I wanted to testify in-person to
16 let you know it has changed my life. Unfortunately,
17 in balancing this desire with my need for anonymity, I
18 concluded that it would be impossible for me to
19 testify in-person.

20 However, given the importance of Sculptra,
21 I felt that it was imperative to, at a minimum,
22 provide you my testimony in writing. Of note, I have

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1 not received compensation in any form with respect to
2 Sculptra as a whole, or my testimony in the specific.

3 Who am I? I am a 42-year old Caucasian
4 male. I am a senior partner in an international
5 professional services firm which has in excess of 700
6 offices worldwide. I have been HIV positive for
7 approximately 22 years, and I'm currently healthy with
8 T-cells in excess of 1,200, and a very low viral load.

9 My current regimen of antivirals consists of four
10 Class I drugs, which include Zerit.

11 I have been on antiviral therapy for nine
12 years. Due to adverse reactions, I have been unable
13 to successfully change my regimen to other antivirals
14 that are perceived to be less detrimental with respect
15 to fat depletion and facial wasting.

16 Why did I receive treatment?
17 Unfortunately, the life-saving antivirals have caused
18 significant fat depletion and facial wasting
19 specifically. I have loss of fat in my arms and legs,
20 and have begun to have significant facial wasting. I
21 sought treatment in the hopes of restoring my face.

22 Treatment results. The results of the

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1 treatment have been nothing less than miraculous. I
2 have the following to report. I have full facial
3 restoration. Friends and family who know my condition
4 are amazed at the success of the product and the
5 complete facial restoration that has been
6 accomplished. Business associates and friends that do
7 not know my condition have provided numerous
8 unsolicited comments ranging from what you have done,
9 you look fantastic, to you look so rested and healthy,
10 what is your trick?

11 The process is fast. The treatments are
12 done in less than 30 minutes. Although they are not
13 pain-free, the discomfort is tolerable. With the use
14 of ice to keep the swelling down, I return to work
15 either the next day or the day after. Other than
16 facial fullness which I commented was as a result of
17 allergies, there were not telltale signs that
18 treatment had been performed. The process has been
19 side effect free. I am not aware of any negative side
20 effects from the treatment.

21 My conclusions. The product has been
22 miraculous. Previously, I was concerned that I would

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1 be in my position for no more than another year before
2 the facial wasting was so obvious that I would have to
3 retire early or choose another profession. With the
4 restoration that has taken place, I no longer have
5 concerns about my visual appearance. As long as I am
6 wearing long-sleeved shirts, which is always, there
7 are no telltale signs that I have fat depletion issues
8 as a result of the medicine I am taking.

9 Personally, my views about my physical
10 appearance have improved substantially. It is very
11 depressing to use medicine that allows me to remain
12 healthy internally with the knowledge that it is
13 creating such physical distortions and it will make me
14 look unhealthy externally.

15 I am personally aware of individuals who
16 are HIV positive that have chosen to go off their
17 medication because they cannot handle the resulting
18 physical distortions. This product will alleviate the
19 need to make that decision.

20 Panel members, I cannot imagine a valid
21 reason not to approve this product. Please know that
22 my experience has been nothing less than life-

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1 changing. Respectfully, a Sculptra patient."

2 I have a second one that I'm also going to
3 read anonymously.

4 "I am a recipient of New-Fill treatments
5 performed through the organized FDA testing study in
6 the United States. There hasn't been a day go by that
7 I haven't appreciated how very fortunate I have been
8 to participate in the review process for this product.

9 At times, it seems as though the reality of my
10 illness was more than I could deal with. Without many
11 choices, I was faced with many life-altering
12 experiences. I made many trips to the doctor,
13 consumed thousands of pills, but the most devastating
14 effect of all was watching myself take on disfiguring
15 changes in my facial appearance.

16 It was my opinion that image cast back
17 from my reflection was death. I lost all self-esteem
18 and confidence. I had no desire to leave the house.
19 My will to fight the disease was exhausted. I was
20 prepared to discontinue all medication regime and
21 accept the course and consequences of the disease.

22 All of my concerns were discussed with my

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1 physician. It was suggested that I research
2 information and alternative treatments regarding
3 facial wasting on the Internet before making any
4 decisions of this magnitude.

5 That is when I made the discovery of the
6 product New-Fill. I consulted with a local cosmetic
7 surgeon about the product and he said it wasn't
8 approved by the FDA for distribution in the United
9 States. However, he was interested in performing
10 another procedure, an invasive type of correction
11 using cheek implant devices. Unfortunately, there was
12 a huge downside to this procedure. There was a
13 possibility the syndrome of facial wasting may cause
14 outlines of the cheek implant device to show through
15 my skin. I quickly declined the option.

16 I went to great lengths to find out where
17 I could receive treatments of New-Fill. That's when I
18 stumbled upon information concerning a trial study and
19 product review of the New-Fill for FDA consideration.

20 I was quick to call and ask if I met the protocol to
21 participate.

22 Once accepted, I invested a great deal of

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1 time, effort and expense in this study, affected by a
2 job lay-off and very limited income. I was persistent
3 to stay in this study not only for my benefit but the
4 future benefit of this product in regards to others.
5 The effectiveness of these treatments on my facial
6 wasting has given me personal satisfaction, self-
7 confidence and a greater state of overall well-being.

8 I have a desire to lead a productive life, and to do
9 that I know the importance of staying on track with my
10 healthcare and medication regime.

11 I have great respect for my physicians and
12 the results that this product has given me. These
13 treatments are directly responsible for my renewed
14 feeling of confidence and emotional strength. I hope
15 my contributions to this study enables others to
16 benefit from this product as I have, without enduring
17 the excessive hardships and expense.

18 I offer my thanks to the Committee for the
19 opportunity I have been given to submit this written
20 testimony. Sincerely, a Sculptra patient."

21 CHAIRMAN CHOTI: Yes.

22 MR. LAND: Good morning. My name is

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1 Bradley G. Land, and I am HIV positive, Fifth District
2 Commissioner for the Los Angeles County Commission on
3 HIV Health Services, serving the Honorable Supervisor,
4 Michael Antonovich and the Los Angeles County Board of
5 Supervisors.

6 Dermik Laboratories has paid for my
7 travel, accommodations and expenses for my trip to
8 this hearing. I have no additional financial
9 relationship with the company.

10 The statement I am providing today is my
11 own opinion, and Dermik has not advised me what to say
12 to the panel. I am also here today to offer my
13 personal testimony as a private citizen in support of
14 New-Fill, not as commissioner. I am here today thanks
15 to a new lease on life called New-Fill Sculptra.

16 I have also passed out pictures prior to
17 diagnosis - actually, not prior to diagnosis, prior to
18 treatment. I am going to take you with me to the brink
19 of suicide.

20 At age 17, which was the early 80s, I was
21 diagnosed with Epstein Barr Syndrome. Unbeknownst to
22 me and my physician at that time, Epstein Barr

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1 Syndrome was secondary to what we later found out,
2 although I denied for some time was GRID, gay-related
3 immune disease, now known as HIV/AIDS. The year was
4 now 1987.

5 Eventually my denial reluctantly
6 retreated, and my involvement and awareness quickly
7 grew as I devoured whatever information I could find.

8 By 1990, I became a co-facilitator for a group called
9 Positive Teens & 20s. By '93, this being a live Los
10 Angeles support group had grown to over 100 members
11 that met on Sunday afternoons at the Los Angeles Gay
12 and Lesbian Community Center. I am approximately ?? I
13 think I'm one out of ten of us living. In fact, a
14 documentary was made about the group which centered on
15 how we coped independently, as well as in the group
16 when confronting fears, social stigmas associated with
17 HIV and AIDS.

18 Because people and friends dying of HIV
19 and AIDS couldn't wait for openings in the already
20 over-crowded hospices, I turned my home into a hospice
21 for my friends and peers who needed help. It was
22 during this time my ever-changing symptoms and

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1 emotions came face-to-face with wasting, or what is
2 now known as lipoatrophy. I've been calling it that
3 for years.

4 This was absolutely devastating. I
5 couldn't hide that drastic debilitating change in my
6 appearance. By 1998, I actually looked as if I was on
7 my deathbed. Isolation became my way of life. By
8 2000, I was not only contemplating, I was looking
9 forward to suicide.

10 Through this period of time, kindness
11 shown to me by compassionate strangers was emotionally
12 overwhelming. Psychologically, I felt I was too young
13 to have doors opened for me, or to have restaurants
14 give "a little discount" because they could physically
15 see I was very, very ill. My face was so concaved
16 that at my ten year high school reunion my friends
17 were pretty sure that they would be doing a memorial
18 for me at the 20-year, if I was to ever get there, or
19 my death.

20 By 2003 with depression again taking hold,
21 my psychologist warned me that lifetime drugs would be
22 needed to combat the depression. It was then that my

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1 HIV/AIDS physician offered a glimmer of hope. The
2 hope was a new drug trial called New-Fill.

3 I received six treatments for
4 approximately \$2,300, \$2,400 from June, 2003 through
5 October, 2003 from Dr. Humble at the Blue Pacific
6 Aesthetic Medical Group located in Los Angeles,
7 California. From the moment I started those
8 treatments, my friends and neighbors immediately
9 noticed a physical notice. I began to notice that
10 although people would look at me, they were doing so
11 without pity. I was being looked at as a normal
12 person. My appearance no longer silently screamed
13 AIDS when I entered a room. Now when acts of kindness
14 are shown to me, I think and feel that it is probably
15 because I'm a kind person.

16 Today as I offer testimony before you with
17 the face I shied away from myself, I can now tell you
18 I can look at my reflection more often than not, and
19 am very proud and thankful to have returned to the
20 human race.

21 At my 20-year high school reunion we
22 celebrated at Dodger Stadium. That was just last

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1 year, where I proudly stood and tearfully sang the
2 "National Anthem". I am a living, not dying, living
3 result of new treatments. Thanks to New-Fill, I have
4 a new lease on life, a new beginning and self-esteem
5 to match. I can hold my head up high and look people
6 in the eye and know that they aren't pitying me.

7 I am a proud American citizen living in
8 the best country in the world, and I am thankful and
9 grateful America has a Federal Drug Administration in
10 place that dutifully, mindfully, and aggressively
11 investigates and approves life-saving drug trials and
12 treatments, such as New-Fill Sculptra.

13 Today I can proudly look at all of you,
14 and let you know that yesterday was the a day I
15 thought I would never see. It was my 39th birthday,
16 and what a great place to be, in the nation's capital.

17 I now not only have hope for the future, I live with
18 hope for the future. Thank you.

19 I noted today that there were not a lot of
20 consumer speakers, and if you have questions, or if
21 the panel have questions throughout this morning, that
22 I'd be more than willing to answer them. Thank you.

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1 CHAIRMAN CHOTI: Thank you.

2 MS. DOE: Good morning, panel. Dermik
3 Laboratories has paid for my travel, my hotel and
4 expenses for this trip to this hearing. I have no
5 additional financial relationship with the company.
6 The statement I am providing today is my own opinion,
7 and Dermik has not advised me what to say.

8 I also want you to know that I took 30
9 hours of my personal vacation time, including time
10 away from my family, to be here today. Also, I will
11 not be using my real name in my statement.

12 I was diagnosed with HIV in 1996. From
13 the beginning, I didn't want to be treated any
14 different than I was before diagnosis. I had decided
15 to tell my immediate family and close friends, since I
16 am concerned about any stigmatism that might affect my
17 career, or that my child might receive if my diagnosis
18 was public.

19 I have been on combination therapy since
20 the end of my pregnancy in 1997. I have never had an
21 opportunistic infection and consider myself in good
22 health.

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1 In 2000, I first recognized the subtle
2 changes, the lipoatrophy, as I was putting on a formal
3 gown. I noticed that my arms were not as fat as I
4 remember them from the previous year.

5 Prior to that, I would hesitate to wear a
6 sleeveless gown due to my self-consciousness about my
7 fat arms. But little did I know that over the next
8 two years, the fat would continue to disappear,
9 leaving my arms, my face, and my legs.

10 By early 2002, my appearance had changed
11 dramatically in comparison to how I looked in 1999, so
12 I decided to look into cosmetic procedures. I asked
13 my HIV physician what he recommended, and he sent me
14 to a doctor that did Fascian injections in my cheeks
15 and temples. Twenty-four hundred dollars worth of
16 painful injections gave me lumps, and after they
17 subsided there was no improvement.

18 By late 2002, my atrophy had progressed to
19 the point that I'd already resolved to the fact that I
20 would never wear shorts or sleeveless shirts again in
21 public. I had decided to save money and continue to
22 research for something else to try. I had heard of

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1 New-Fill and had interviewed two patients in my city
2 who had it done by a nurse at a spa, but I wanted a
3 licensed, insured, trained, and experienced doctor
4 working on my face. This is my face, it is my calling
5 card, and it is who I am. I didn't want a nurse
6 without any legal ramification giving me injections,
7 but at this point I was getting worse by the month and
8 getting desperate.

9 At Thanksgiving dinner that year,
10 relatives that I had not seen in years were there.
11 During the day, I saw family members pulling my mother
12 over for private conversations, and my parents and I
13 had a family discussion about it later about how my
14 facial appearance had caused concern about my health.

15 My family was asking things such as is she okay?
16 What is wrong with her? She doesn't look well. Do
17 you think that she's anorexic? The interesting thing
18 about all this was that I was still wearing the same
19 size, but because of my thin arms and my face, they
20 felt that I was ill.

21 Another memorable incident that year, I
22 had attended a baby shower that my mother hosted, and

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1 some of my mother's dearest friends were there, people
2 who were unaware of my diagnosis, and afterward called
3 her to inquire about me with loving concern, saying
4 things such as what is going on with your daughter?
5 There is something terrible wrong with her? You have
6 to do something. And my mother uncomfortably tried to
7 dismiss their comments, but they were not persuaded,
8 saying can't you see your daughter's health is
9 deteriorating? What kind of mother are you? So my
10 mother naturally asked me well, what do I tell people?

11 And at the same time, my husband was also getting
12 approached from people that we knew with questions
13 about me.

14 At work, my profession entails that I'm on
15 the phone thankfully with customers, and I was
16 considered for a position that required face-to-face
17 customer interaction, but my atrophy was so bad that I
18 would never feel comfortable in that type of a job. I
19 felt an immediate need to do something about my face
20 or disclose the diagnosis, real or made-up, it might
21 offer some explanations.

22 I saw numerous plastic surgeons in the

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1 major metropolitan area in which I live, and none had
2 anything to offer me. For example, fat transfers
3 might not be the same from one cheek to the other, or
4 might get reabsorbed totally or unevenly. Cheek
5 implants might be seen through thin skin or might have
6 to be anchored with pins to prevent flipping due to
7 lack of tissue.

8 Some European approved injection materials
9 have a lumpy appearance that I would never consider,
10 and collagen doesn't last. Sculptra is the only
11 product that met my needs and addressed my concerns
12 about safety, natural appearance, longevity, and my
13 face would be in the hands of a licensed trained
14 physician.

15 Sculptra has changed my life. I now have
16 the confidence to pursue my professional goals. I
17 have also noticed that my family and colleagues are
18 not concerned about my health. If it wasn't for
19 Sculptra, I'd be retreating from professional
20 endeavors, as well as avoiding family and other social
21 situations. Thank you.

22 CHAIRMAN CHOTI: Thank you. Are there any

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1 other public statements? If not, I think we can move
2 ahead to the Applicant Presentation.

3 Let me remind the public observers that
4 while this portion of the meeting is open to public
5 observation, public attendees may not participate,
6 except if panel members ask specific questions. And
7 there will also be another opportunity this afternoon
8 for additional public comment. So we are now ready to
9 begin the applicant's presentation, representatives
10 from Dermik Laboratories.

11 DR. FORBES-McKEAN: Good morning, Dr.
12 Choti, Members of the Panel, and Members of FDA. My
13 name is Kim Forbes-McKean, and I'm the Senior Director
14 of Product Development and Commercialization at Dermik
15 Laboratories.

16 Thank you for giving us the opportunity
17 today to present our data on Sculptra. We hope that
18 you found the panel package informative, and that with
19 our presentation today, we may address any questions
20 that you may have.

21 I'd like to start with a brief overview of
22 our presentation. First, I will give a brief

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1 introduction to the product, and following that, Dr.
2 Marcus Conant will discuss the condition of
3 lipoatrophy in general. Following Dr. Conant, Dr.
4 Jeffrey Handler, who is the Director of Safety
5 Assessment and Evaluation at Dermik Laboratories, will
6 present a description of Sculptra, and also present
7 the pre-clinical studies in support of the safety of
8 this device. Following Dr. Handler, we will have Dr.
9 Sharon Levy, who is our Senior Director of Medical and
10 Scientific Affairs at Dermik Laboratories summarize
11 the rationale and the clinical data, and post
12 marketing data available that supports the efficacy of
13 this device in people with Human Immuno Deficiency
14 Virus. After that, Dr. Peter Engelhard will present
15 his experience obtained through the use of this device
16 in both sponsor investigator studies and through a
17 compassionate use study. At the request of FDA, the
18 results of these studies are also included as
19 supportive data in our PMA. Lastly, I will return to
20 present the final conclusions of the presentation
21 today.

22 We have with us a number of colleagues and

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1 invited experts that are available to assist us in
2 answering any questions that you may have. They are
3 listed here on this slide, and I would specifically
4 like to point out that we have Dr. Mest from the Blue
5 Pacific Aesthetic Medical Group in California, who has
6 gained clinical experience in the U.S. with this
7 product through a sponsor investigator IDE.

8 We also have Dr. Danny Vlegaar who has
9 acquired clinical experience with this product outside
10 of the U.S. in a large number of patients. We have
11 Dr. Dror Rom, our consulting statistician, available,
12 as well as Dr. Russell Parsons, a materials expert,
13 available as well.

14 Dermik Laboratories is a division of
15 Aventis Pharmaceuticals, and has been in the business
16 of developing and marketing prescription and OTC drug
17 products for dermatological applications for over 50
18 years. The subject of today's advisory panel is
19 Sculptra, and the proposed indication that Dermik is
20 seeking for this injectable poly-L-lactic acid device
21 is to correct shape and contour deficiencies resulting
22 from facial fat loss, lipoatrophy, in people with

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1 Human Immuno Deficiency Virus.

2 As we have just seen and heard in these
3 patient testimonies, the condition of facial
4 lipoatrophy is a debilitating condition, and one for
5 which there is currently no approved medical
6 treatment. Because of these reasons, and for the best
7 interest of the patients involved, this PMA was
8 granted expedited review by the FDA.

9 The product was originally developed by a
10 French dermatologist of Biotech Industries. The
11 device was originally approved in Europe in 1999 under
12 the name New-Fill. The original indication is shown
13 here on this slide, and that is New-Fill is suitable
14 for increasing the volume of depressed areas,
15 particularly to correct skin depression, such as in
16 skin creases, wrinkles, folds, scars and eyerings.

17 Recently, as recently as February in 2004,
18 the indication in Europe for New-Fill was expanded to
19 include the use for large volume corrections of the
20 signs of lipoatrophy. The product is intended to be
21 marketed by Dermik in the United States under the
22 trade name Sculptra. In this presentation, we will

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1 refer to the product as Sculptra.

2 To illustrate a brief history of the
3 product, on this slide, as I pointed out, the product
4 was originally approved in Europe under the trade name
5 New-Fill, and is currently marketed in 33 countries
6 outside of the United States.

7 The pivotal lipoatrophy studies which are
8 included in this PMA were initiated in 2000 in France
9 and the United Kingdom. Limited patient access in the
10 U.S. began in 2001 through the Direct Access
11 Alternative Information Resource buyers network, and
12 also under sponsor investigated U.S. IDE studies.

13 Dermik acquired the product in May, 2002,
14 and then gained access to the data after the pivotal
15 lipoatrophy studies were completed. For patients whom
16 reconsent was obtained, Dermik source verified all
17 primary efficacy data, and Dr. Sharon Levy will
18 present a summary of this data later this morning.

19 Dermik then prepared the necessary
20 documentation to submit the PMA in December, 2003.
21 And as I mentioned previously, because we are seeking
22 approval for a device for a condition for which there

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1 is an unmet medical need, the FDA granted expedited
2 review status for this PMA.

3 I would like to now introduce Dr. Marcus
4 Conant, who will speak about the condition of
5 lipoatrophy in general.

6 DR. CONANT: Thank you, Kim. Mr.
7 Chairman, ladies and gentlemen of the panel, thank you
8 for the opportunity of addressing you this morning.
9 I'm Mark Conant from San Francisco. I'm Clinical
10 Professor at the University of California in San
11 Francisco, where I have been since 1964. I am
12 currently Chairman of the Conant Foundation, which is
13 a patient advocacy education group, and I've been
14 caring for HIV/AIDS patients since 1981. I actually
15 described the first patients of Kaposi's sarcoma in
16 San Francisco.

17 My colleagues and I built the largest
18 private HIV practice in the world, which existed until
19 sometime about 1998. I have no financial investment
20 in Dermik. I'm not a Dermik employee. I recently
21 became a Dermik consultant. I don't own stock in
22 Aventis.

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1 I've been doing what's called protocol for
2 the last four months. This is not supported by
3 Dermik. It's a physician initiated protocol supported
4 by the Conant Foundation. Dermik did supply the New-
5 Fill for me to use in these patients. Dermik did pay
6 for my travel and lodging here. So I speak to you
7 this morning from an unusual position. I not only am
8 an AIDS doctor, and have cared for some five to six
9 thousand HIV positive patients. I've been caring for
10 those patients since 1981, but I'm also a board-
11 certified dermatologist who has used this product.

12 In the time period from 1981 until 1996
13 when we had highly activated antiretroviral therapy
14 available to us, the major problems that we faced
15 managing our patients were first, Kaposi's sarcoma and
16 the cosmetic and medical ravages of that disease,
17 obviously Pneumocystis pneumonia, which until 1987-88
18 was the major cause of death resulting in some 60 to
19 70 percent of the deaths in our HIV positive patients.

20 After we began prophylaxing against PCP,
21 Mycobacterium avium became the most common cause of
22 death in my practice in the time period 1989, '90, and

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1 '91. And so the opportunistic infections leading to
2 death were really the issue that confronted us until
3 we had ways of reducing the viral load below the level
4 of detection. Next slide, please.

5 From 1996 until today, from the
6 introduction of highly activated antiretroviral
7 therapy, our priorities have changed considerably. As
8 all of you know, our patients are now living much
9 longer. As a matter of fact, when I'm asked how long
10 will they live, I can't answer the question because
11 our patients are, in fact, doing extremely well. We
12 have some concerns, concerns perhaps about HAART
13 disease later on. But right now, managing HIV
14 patients has changed dramatically.

15 The biggest problem we have is compliance.
16 How to ensure that patients are taking their
17 medication, because as we know, if their viral load
18 rises, they will become resistant to the drugs they
19 are taking, and we will have to change their
20 medication. So compliance, resistance, drug side
21 effects are a major problem. Each drug has its own
22 particular set of side effects. And fortunately, now

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1 we have enough different drugs that we can usually
2 change the patient's drug treatment regime to address
3 these issues.

4 Most patients on these drugs, particularly
5 the protease inhibitors, suffer from diarrhea. That's
6 a constant complaint that I hear in my practice on a
7 daily basis. But the thing that was bothering our
8 patients the most is the facial lipoatrophy. And you
9 may ask well, what number of patients are we talking
10 about?

11 There have been various estimates. Carr
12 has the best data from Australia. It looks like
13 somewhere in the range of 50 percent of patients will
14 have perceptible facial lipoatrophy three years after
15 they've started highly activated antiretroviral
16 therapy. And so the lipodystrophy syndrome of which
17 facial lipoatrophy is a component, is the biggest
18 problem that we're facing in our day-to-day practice
19 of seeing people who are stable on their
20 antiretroviral therapy, who have viral loads below the
21 level of detection, who are compliant with their
22 treatment program, and whose CD4 counts are slowly

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1 rising. You heard in one of the letters that the
2 patient who was anonymous, CD4 count was over 1,000.
3 We would not have seen that prior to 1996.

4 The lipodystrophy syndrome consists of the
5 components that I've put on the board. It is
6 hypercholesterolemia, sometimes to considerable
7 heights, hypertriglyceridemia, sometimes over 1,000,
8 insulin-resistant diabetes, particularly in patients
9 who are on protease inhibitors. The facial
10 lipoatrophy, the loss of fat in the face, but it's a
11 strange syndrome because not only do you lose fat in
12 certain areas, you gain fat in other areas.

13 Patients develop abdominal obesity and
14 buffalo hump. And again, as you heard in the
15 testimony from the public, they then begin to lose fat
16 peripherally, so there's peripheral fat loss,
17 abdominal fat gain, buffalo hump. For the clinicians
18 in the audience, I'm describing Cushing's disease.
19 Right? That's what we all thought it was initially,
20 but it's not Cushing's disease.

21 We don't know if this syndrome is because
22 of HIV infection. Many patients showed facial atrophy

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1 before highly activated antiretroviral therapy. Rock
2 Hudson did. Was it due to the disease itself? Was it
3 due to certain of the antivirals we were using,
4 Crixivan and d4T were implicated, or was it because
5 the new drugs just kept people alive long enough to
6 see it, or is it a multi-factorial syndrome that we
7 don't fully understand?

8 The pharmaceutical industry is currently
9 investing considerable amounts of money looking for
10 drugs that don't cause this problem, because obviously
11 if you could develop an antiretroviral that didn't do
12 this, that is a tremendous market for you. But
13 unfortunately, we do not understand the true ideology
14 of this syndrome.

15 Now let me show you a couple of pictures.
16 This is severe facial atrophy in one of my patients.
17 And as I say, this or a lesser degree of this is now
18 being seen in about half of the patients that we are
19 managing in San Francisco.

20 This is a buffalo hump. The patient has
21 accentuated fat pad across the shoulders. I don't
22 need to suggest that this is abdominal obesity. This

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1 man has gained weight. He has increased omental fat
2 again as part of this syndrome. And the peripheral
3 wasting, patients call this "roping", becomes clearly
4 demonstrable. As the patient loses peripheral fat,
5 the vasculature is accentuated.

6 Facial lipoatrophy, the subject that we're
7 discussing this morning, has become the Scarlet Letter
8 of AIDS. Early on we could identify AIDS patients
9 when we would go out in public in San Francisco.
10 Remember we lost 36,000 men before we had high active
11 antiretroviral therapy in a city of 700,000 people.
12 You could identify AIDS patients because people had
13 Kaposi's sarcoma that you could see.

14 I could go to the opera and pick out
15 people who were HIV positive because they had
16 seborrheic dermatitis at the corner of their nose.
17 Today when you go to the opera, it's not seborrheic
18 dermatitis you see, it's facial lipoatrophy. You can
19 identify the patient when he walks into the room,
20 particularly in an area with lots of HIV positive
21 patients, where everyone recognizes this syndrome as
22 being HIV positive.

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1 I think that was clearly demonstrated with
2 the testimony you heard this morning, where the
3 individual speaking did not want to be identified.
4 And yet, they are identified simply by their
5 appearance. Because of this, patients refused
6 medication. They wait to start, even doctors wait to
7 start medication until the CT4 count falls down to
8 something like 300.

9 Why do we wait? Wouldn't it be better to
10 treat patients? Mighten we reduce transmission if we
11 treated patients? Yes, but we wait because of the
12 side effects of the medication and the fear of
13 developing resistance. So doctors delay treatment,
14 patients refuse treatment, patients fly to Mexico, or
15 Europe, or Brazil for treatment. And unfortunately,
16 some patients even discontinue their treatment because
17 of the facial lipoatrophy.

18 And so this morning, speaking as someone
19 who has managed thousands of these patients, and as
20 someone who has used this product, I feel that the
21 product is safe and effective, and that my patients
22 would be tremendously benefitted by the approval of

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1 Sculptra. Thank you very much.

2 DR. HANDLER: Good morning. My name is
3 Jeff Handler. I'm the Director of Drug Safety
4 Assessment and Evaluation for Dermik Laboratories.
5 And what I'll be doing over the next few minutes is
6 taking you through a description of Sculptra,
7 including the physical description of the product, a
8 bit about poly-L-lactic acid or PLLA, and a summary of
9 the biocompatibility studies that were conducted to
10 support the product.

11 Sculptra is provided in vial as a sterile
12 lyophilisate reconstituted in 3 mLs of sterile water
13 for injection, USP using a 26-gauge needle for
14 administration. Some of the critical design elements
15 and product characteristics, particle size, molecular
16 weight which is controlled after gamma-irradiation,
17 sterility, stability. Sculptra is stable for up to 72
18 hours after reconstitution, and up to two years as a
19 lyophilisate. Also, ease of use - the wetting and
20 syringeability of the product.

21 Poly-L-lactic acid is a synthetic polymer.
22 It's non-animal/non-human sources. The L-form was

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1 selected for slower degradation than either the
2 racemic mixture or the D-form. Sculptra consists of
3 microparticles of irregular shape with a particle size
4 distribution, the d50 is 28 to 60 microns. A variety
5 of devices contain PLLA. PLLA has been used for over
6 20 years with excellent safety profiles. Devices that
7 use PLLA include absorbable sealants, flow
8 restrictors, fixation systems, suture anchors and
9 absorbable sutures, fixation screws, and tissue
10 regeneration products.

11 A bit about how poly-L-lactic acid
12 degrades, starts as a polymer and through a non-
13 enzymatic hydrolysis goes to lactic acid monomers,
14 which are then either metabolized by the Kreb's cycle
15 to carbon dioxide, or incorporated into glucose via
16 the chore E cycle.

17 Other components of Sculptra include
18 carboxymethylcellulose as a suspending agent, and
19 mannitol as a lyophilization enhancer. Both of these
20 chemicals are safe and very widely used in a variety
21 of injectable products.

22 Just a bit about potential lactic acid

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1 burden. It's important to note that PLLA is
2 hydrolyzed slowly, not immediately. There is no
3 evidence of lactic acidosis in the preclinical or
4 clinical studies, as you'll hear a bit later.
5 Sculptra has a minimal impact on lactic acid burden.

6 Biocompatibility testing was based on the
7 ISO 10993 standards and the FDA G95-1 guidance for
8 tissue and bone devices with duration of greater than
9 30 days. A variety of tests were conducted, including
10 cytotoxicity, acute toxicity, the subchronic toxicity,
11 sensitization and irritation, genotoxicity,
12 implantation, and also hemocompatibility and
13 pyrogenicity. And I'd like to note that Sculptra
14 passed all of these tests.

15 The only findings of note in any of these
16 studies was in the rate subchronic 90-day study, the
17 finding of focal granulomatous inflammation with giant
18 cells surrounding foreign polarizing substances in
19 deep dermis in five out of 20 animals, and in a rabbit
20 implantation study where observations of macrophages
21 and giant cells organized around the PLLA crystals was
22 noted. These were very expected foreign body

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1 reactions that had been noted previously in the
2 literature for PLLA-containing devices.

3 Sculptra was well-tolerated in mice, rats
4 and rabbits. It was non-irritating after
5 intraperitoneal subcutaneous or intradermal
6 administration. Sculptra was non-sensitizing, devoid
7 of genotoxic potential. There were no indications of
8 systemic toxicity in any study. And as I noted on the
9 previous slide, there are minimal and expected local
10 tissue responses which are characterized by foreign
11 body reactions.

12 On the basis of these data, Sculptra is
13 safe from the non-clinical biocompatibility test. I'd
14 like to turn the presentation over to Dr. Levy, who
15 will discuss the clinical data.

16 DR. LEVY: Thank you, Jeff. My name is
17 Sharon Levy. I'm the Senior Medical Director of
18 Scientific and Medical Affairs at Dermik Laboratories,
19 and I'll be reviewing with you today post marketing
20 experience with Sculptra.

21 As stated earlier, Sculptra has been
22 available commercially since 1999. It is currently

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1 marketed in 33 countries worldwide, and over that time
2 frame it is estimated that more than 150,000 patients
3 have been treated with Sculptra through December of
4 last year.

5 Over that same time frame and with that
6 patient usage, there have been 251 adverse event terms
7 reported to the Pharmacovigilance Safety Database.
8 These reports are from 188 individuals.

9 The most common event reported to the
10 Safety Database was injection site nodules. That's
11 the top line here, reported in 124 instances, followed
12 by injection site induration, granuloma, inflammation.

13 Other adverse event terms were reported at a
14 frequency of six or fewer over this time frame.

15 In that same time frame, over the same
16 commercial use of the product for four years, which is
17 primarily cosmetic in the rest of the world, six
18 adverse events were termed serious by the reporters.
19 One of these involved an infection, two allergic
20 phenomena, and three nodules.

21 The first case, infection, involves a 54-
22 year old woman from Germany who experienced a facial

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1 abscess following Sculptra treatment. She was
2 hospitalized, treated with intravenous antibiotics and
3 surgical drainage.

4 The next two cases involved allergic
5 phenomena following Sculptra treatment. In both
6 instances, the patients developed facial edema. They
7 had no other systemic symptoms. Patients were
8 hospitalized, treated with steroids and symptoms
9 resolved.

10 The fourth case is listed here as an
11 injection site granuloma. And it's included as
12 serious because it was in the setting of a previous
13 hospitalization for colitis. That patient was treated
14 with parenteral anti-inflammatory therapies, and in
15 the course of that treatment developed swollen nodular
16 areas at sites of previous Sculptra treatment.

17 Biopsy of the nodules showed a foreign
18 body giant cell reaction with elements consistent with
19 Sculptra. The patient's symptoms at those sites
20 resolved over a period of time, with continued anti-
21 inflammatory treatments.

22 The last two cases, injection nodule and

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1 ectropion involved nodules in the peri-ocular area.
2 In those instances, the patient had been treated with
3 Sculptra and developed nodules around the eyes. In
4 the first case, the patient was treated with steroids
5 and there was incomplete resolution of the nodule.
6 The nodule was excised.

7 The final case, the nodule interfered with
8 proper closure of the eye. It was termed an
9 ectropion. It was also treated with steroids and
10 excised. The histology of that nodular example showed
11 foreign body giant cell reaction again with particles
12 consistent with Sculptra.

13 Now let's look at the clinical data
14 supporting the lipoatrophy indication. These data
15 which we'll review over the balance of the
16 presentation come from two pivotal studies in France
17 and the U.K. I will present those in a moment, and
18 they are also supported by experience in the U.S. Dr.
19 Peter Engelhard will review this data. He was an
20 investigator on two of the three studies that will be
21 discussed.

22 Now for the pivotal clinical studies - the

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1 two studies were termed VEGA Study in France, and
2 Chelsea and Westminster studies. These were
3 independently designed and conducted studies by
4 investigators at their own academic medical centers.
5 In both instances, the studies were ethics committee
6 approved. And Dermik, as mentioned previously,
7 acquired access to the data after the studies were
8 clinically complete.

9 At that time, Dermik sought authorization
10 from the individual patients for review and
11 verification of source documents for those cases.
12 That was granted in 82 percent and 93 percent of the
13 cases for the two studies. At that juncture, Dermik's
14 source verified 100 percent the efficacy and safety
15 data for the authorized cases.

16 Now the VEGA Study. This was conducted by
17 Professor Christine Katlama and colleagues at Hopital
18 Pitie-Salpetriere in Paris, France. This was a study
19 of the impact of Sculptra cheek implants on HIV
20 positive patients with severe facial lipoatrophy.
21 This was a prospective but open label study with a
22 planned two-year follow-up.

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1 Patients were treated with Sculptra to
2 effect, to clinical effect and, therefore, they
3 received three to six injection sessions depending on
4 that effect. The product was injected one vial per
5 cheek per session.

6 In terms of the efficacy and safety
7 parameters, the primary efficacy parameter was total
8 cutaneous thickness or TCT. This was measured by
9 ultrasound by a single ultrastenographer for the
10 study. Serial photographs were captured over the two
11 year study course, and there was an assessment of
12 quality of life by a visual analog scale. Safety
13 events were captured as adverse events and laboratory
14 measures over the two year study course.

15 Now let's look at a schematic of the study
16 protocol. We can see on the bottom the injections
17 which were performed every two weeks, three to six as
18 needed. The upper portion we have a recall of the
19 efficacy and safety parameters I just mentioned.
20 These were performed at baseline and over the two year
21 study period or out to week 96.

22 This is a picture of the ultrasound

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1 equipment that was used in the study. It was a Logic
2 7 machine using a multi-frequency 7.5 to 13 megahertz
3 transducer.

4 This is an individual from the study, and
5 I think as we've heard and seen today, you can see all
6 the hallmarks of this condition of lipoatrophy on this
7 individual's face. He has dramatically hollow cheeks,
8 and there you can see an outline of the skeletal and
9 facial musculature from this condition. And if we
10 were able to see the upper portion of this photo, we
11 would also see hollow eyes and sunken temples. This
12 individual had an ultrasound measurement of zero for
13 his adipose at baseline.

14 Because the facial landmarks are so
15 outlined, it is actually quite easy to localize and
16 control the placement of the ultrasound transducer.

17 The main inclusion/exclusion criteria for
18 the study. All patients were, of course, HIV positive
19 and greater than 18 years of age. They were on stable
20 high reactive antiretroviral therapies, and clinically
21 stable, as well, with viral loads of less than 5,000
22 copies. However, they had severe facial lipoatrophy

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1 as noted by cheek adipose tissue levels of less than 2
2 millimeters at baseline.

3 Confounding treatments were excluded in
4 the study, and there was a significant commitment on
5 the part of the patients for the study course because
6 they were committing to a two-year process including
7 multiple procedures.

8 The patient accountability for the VEGA
9 Study, 50 patients enrolled and were treated, 47
10 completed the two years of follow-up. Three
11 individuals discontinued, one because of an unrelated
12 serious adverse event, lymphoma. And two patients due
13 to choice after the week 72 visit.

14 Here are the demographics in the study, 49
15 males and one female were included with an average age
16 of 45 years. The patients were primarily Caucasian,
17 although 16 percent non-Caucasians were enrolled. The
18 patients had been on longstanding HAART therapy, CD4
19 counts of about 400 cells, and viral load on average
20 200 copies. At baseline, their adipose tissue
21 measured .5 millimeters on average, although most of
22 the people in the study had no detectible fat. The

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1 total cutaneous thickness or TCT was 3 millimeters at
2 baseline.

3 Now we'll look at some data from an
4 individual in the study, and he is actually quite
5 typical of the patients in the study. On the lower
6 portion of the graph, you will see his TCT
7 measurements over time. Time is on the X axis
8 starting at baseline zero weeks, extending out to end
9 of study of two years. On the X axis, we have the
10 total cutaneous thickness as measured in millimeters,
11 and we can see his response to treatment over the
12 study course.

13 Here is the gentleman with his correlating
14 photo at baseline. Again, you can see all the
15 hallmarks of testimony. His baseline TCT measure was
16 about 3.5 millimeters. This patient was treated with
17 five injection sessions and here is his TCT response
18 at midyear or 22 weeks, and the correlating photo. He
19 has a significant change in his facial appearance, and
20 his TCT measure increased, as well.

21 Over the course of the study, his TCT
22 measurement remained relatively stable in the

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1 neighborhood of 10 millimeters, and you can see his
2 accompanying photograph at end of treatment. And I
3 will mention to the panel members that additional to
4 these photographs in their panel pack in the second
5 volume behind the green tab in the second attachment
6 area are photographs for all 28 of the study patients
7 who authorized viewing of their photographs. And
8 they're presented with their photographs and their
9 graphical display of TCT measures for your review.

10 Now we'll see another gentleman in the
11 study. This is a gentleman in his mid-30s. He had a
12 TCT measure of 3.3 millimeters at baseline. His
13 adipose layer was a little bit less than a millimeter,
14 and you see on the left again the signs of facial
15 lipoatrophy in profile. And here is the same
16 gentleman at about the one year mark, TCT measure of
17 10.2 millimeters. And again, you can see the change
18 in facial appearance. The same gentleman at end of
19 study, the stability of his facial appearance and a
20 TCT measure of 12 millimeters.

21 Now the next gentleman we'll see had a TCT
22 of 3 millimeters at baseline, no detectible fat, and

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1 again, very severe facial lipoatrophy just as
2 explained earlier in the presentations. This same
3 gentleman is shown at the one year mark, 48 weeks.
4 His TCT has improved, but only to 7 millimeters.
5 Again, you can look at the change in facial appearance
6 significantly improved, if not exact restoration of
7 his facial appearance.

8 Now let's look at the data for the entire
9 cohort. This is a graphical display. On the X axis
10 we see weeks out to two years, again TCT measure on
11 the vertical axis. There are a grouping of dots at
12 the zero timeline because those are the baseline
13 measures for the cohort which range from two to four
14 millimeters prior to treatment.

15 One can see from the data displayed that
16 all patients increased their TCT measures at all time
17 points and, in fact, this is the gentleman who we just
18 saw a moment ago with the increase to 7.4 millimeters,
19 so he was one of the less dramatic responders by TCT,
20 and you saw his visual appearance.

21 Now let's look at these same data from a
22 statistical standpoint. The data are grouped by visit

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1 from baseline to week 96, numbers of observations, the
2 treatment mean which we just saw, three millimeters at
3 baseline increasing to eight, nine, and ten over the
4 study course, and the accompanying increase in mean
5 change from 5 to 7 millimeters over the study course.

6 All of these increases in skin thickness
7 were highly statistically significant. At the P less
8 than 0.001 level. There were other assessments made
9 in the VEGA Study. This includes an assessment of
10 quality of life by visual analog scale. Improvements
11 from baseline were seen at all time points, but were
12 significant only at months six and twelve.

13 During the study course, there were no
14 clinically or statistically significant changes
15 observed in laboratory parameters including blood
16 lactate. No clinically relevant changes were detected
17 in CD4 counts or viral loads.

18 Over the two-year study period, six events
19 which were unrelated to treatment were reported as
20 serious, and these events were deemed so because they
21 involved hospitalizations. They're shown here.

22 Additionally, 35 patients had one or more

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1 treatment-related adverse events during the VEGA
2 Study. The most common of these were related to the
3 injection procedure itself, including bleeding,
4 bruising, and edema. Additionally, investigators
5 noted nodules in 26 patients.

6 These nodules were described by the
7 investigator as "palpable but non-visible subcutaneous
8 micro nodules." These were observed in 26 of the 50
9 treated patients. The majority of them occurred
10 within the first year, actually the first six to
11 twelve months. In five instances, they resolved
12 without treatment. The others remained stable. In no
13 instances were there any medications or treatments
14 involved. In fact, the nodules were primarily
15 identified by the investigator rather than the
16 patients.

17 This is a gentleman, patient number 30,
18 who you again can see in your panel pack at baseline.

19 The same gentleman at week 27 when he was noted by
20 the investigator to have bilateral nodules. And I'll
21 just give you a moment to examine the photo.

22 To my viewing of the photograph, I cannot

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1 see any nodules here. And in the next photograph, we
2 see the same gentleman at end of study, week 104, when
3 again he was noted by the investigator to have
4 bilateral nodules ongoing.

5 For ease of review for the panel in the
6 panel pack again in your second volume behind the
7 yellow tab, you will see photographs of all the
8 patients who were identified as having nodules and
9 allowed review of their pictures. Those are 12
10 individuals, and you may review the photos. There are
11 full-page photos from each of the photographic visits.

12 Overall from the VEGA Study we see that
13 Sculptra was effective out to two years as
14 demonstrated by significant increases in total
15 cutaneous thickness, along with confirmation of
16 improvements in facial photographs.

17 Additionally, there was improvement in
18 quality of life measured by visual analog scale. And
19 as studied in this protocol, the treatment was shown
20 to be safe and well-tolerated by the patients.

21 Now we move to the second pivotal study.
22 This was the Chelsea and Westminster Study conducted

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1 by Dr. Simon Barton and colleagues in London, England.

2 It was a randomized open-label study of Sculptra
3 injections for cheek fat pad wasting in persons with
4 HIV-related lipoatrophy.

5 The study employed an open label design
6 with a planned 24 weeks of follow-up. It also
7 included randomization to immediate or delayed
8 treatment. This allowed for an internal control, but
9 additionally, all patients still received treatment.
10 I'll review this in a moment.

11 Patients were treated with three injection
12 sessions, so this differed from the VEGA study in that
13 treatment was fixed. Outcome measures, however, were
14 similar. The primary efficacy was evaluated by skin
15 thickness, again measured by ultrasound.

16 Additionally, there were assessments of
17 anxiety and depression using a validated hospital
18 scale, and laboratory measures which followed over the
19 study course including blood lactic acid levels. Body
20 shape changes were evaluated by questionnaire, and
21 patients were photographed at their study visits.

22 Additional to this, for the purpose of

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1 acquisition to data, a post study visit was conducted
2 at approximately one and a half to two years after the
3 study start, at which time the patients were queried
4 for any additional safety events.

5 This is a schematic of the study design.
6 We have on the X axis time and study from baseline to
7 24 weeks. In the upper portion, we see the regime for
8 the immediate treatment group. These individuals
9 received treatment at weeks zero, two, and four. Then
10 they were reassessed at weeks 12 and 24. The delayed
11 treatment group were merely observed for the first 12
12 weeks. Then they received Sculptra treatment at the
13 12th week, 14 and 16 week visits, and were re-evaluated
14 at week 24. Again, all patients came back for the
15 post study visit for data access and capturing of any
16 additional adverse events.

17 The patients included in the study were
18 all HIV positive with signs of moderate to severe
19 facial lipoatrophy. Confounding treatments were
20 excluded. Thirty patients were treated, thirty
21 patients completed. One patient at the time of the
22 post study visit declined access to his data and,

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1 therefore, today for this presentation results from 29
2 individuals are presented.

3 Demographics of the cohort, 27 males, 2
4 females, with an average age of 41 years. Twenty-
5 eight percent of the patients were non-Caucasian, and
6 patients overall had been on HAART treatments for an
7 extended period. Their CD4 counts were in excess of
8 400 cells, and at baseline their skin thickness
9 measure was from 2.1 to 2.7 millimeters on average.

10 These are the results of skin thickness in
11 the treatment areas for the immediate and the delayed
12 treatment group. The areas that were treated in the
13 study were, of course, the right and left side of the
14 face. The patients were treated in the nasolabial
15 fold in the cheek. They were also assessed at non-
16 treated sites at the corner of the mouth and at the
17 upper cheek bone or the zygoma.

18 We see the results here for the immediate
19 and delayed treatment group for the left side of the
20 face in the treatment area. The bars indicate time in
21 study, with baseline in gray, 12 week mark in yellow,
22 and 24 weeks in white. One can see in the immediate

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1 treatment group that at both the 12 and 24 week time
2 point at both treatment areas, there are significant
3 increases in skin thickness. For the delayed
4 treatment group who received their treatment only
5 starting at 12 weeks, there is an increase in skin
6 thickness only observable at the 24 week mark.

7 These are the results for the non-treated
8 areas for both of the groups. These are at the corner
9 of the mouth and the upper cheek bone. And one can
10 see from this display that those measurements were
11 relatively stable over the course of the evaluation
12 period.

13 These are the results shown in a
14 statistical format. We'll look now at the immediate
15 treatment group at 12 and 24 weeks. The changes for
16 treatment areas of nasolabial fold and cheek left and
17 right side are displayed as changes from baseline.

18 One can see the increases in skin
19 thickness or these changes at the 12 and the 24 week
20 mark. All of these changes are statistically highly
21 significant in all instances.

22 Now the results for the delayed treatment

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1 group. At 12 weeks there are very minor changes in
2 skin thickness at the 12 week mark. However, 24 weeks
3 following treatment, we see a significant increase in
4 skin thickness. Again, highly statistically
5 significant at all the assessed areas.

6 Other efficacy assessments in the
7 Chelsea/Westminister Study included measures of
8 anxiety, depression, and face shape change. For the
9 immediate treatment group, these were improved at both
10 12 and 24 weeks. In the delayed treatment group,
11 improvements were only seen at the 24 week mark.

12 Laboratory parameters. There were no
13 statistically significant or clinically meaningful
14 differences seen in laboratory measures, including CD4
15 counts, viral load, and lactate levels.

16 Treatment-related adverse events. There
17 were no serious adverse events reported in the study.

18 There were 45 treatment-related events reported in 17
19 patients. The most common of these were similar to
20 what we saw from the VEGA Study, and related to the
21 injection itself, including bruising, discomfort,
22 redness, inflammation.

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1 Additionally, one patient was reported to
2 have a "infected lesion". The investigator described
3 this as a reddened area similar to a pimple, but
4 without any pustular component. It was observed and
5 resolved without any specific treatment.

6 Additionally, at the post study visit,
7 nine patients were noted by the investigators to have
8 nodules. These were similar in character to those
9 described in the VEGA Study. So what we see from the
10 Chelsea and Westminster study is reviewed here.

11 In this study, with Sculptra treatments,
12 there were significant improvements from baseline as
13 noted in skin thickness measures, via ultrasound,
14 patient rated assessments of facial change, anxiety
15 and depression. Additionally, the product was shown
16 in this study protocol to be safe and well-tolerated
17 by these patients.

18 When we look across the two pivotal
19 studies, we see that Sculptra was effective out to two
20 years as measured by increases in skin thickness, and
21 associated improvements in facial appearance. Adverse
22 events with the product were generally limited to

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1 reactions at the site of injection.

2 Sculptra was shown to be effective and
3 safe in these studies for treating the shape and
4 contour deficiencies resulting from facial fat loss or
5 lipoatrophy in people with Human Immuno Deficiency
6 Virus. Thank you. And now Dr. Peter Engelhard will
7 review the clinical data from the U.S. experience.
8 Dr. Engelhard.

9 DR. ENGELHARD: Thank you, Sharon. As
10 Sharon stated, I'm Dr. Peter Engelhard. I'm in
11 private practice in Miami, Florida. I've been
12 treating HIV positive patients for 11 years, and have
13 had particular interest in the lipoatrophy syndrome
14 for the last 5 years. Next slide, please.

15 I am not a Dermik employee. I have been
16 recently made a Dermik consultant. I do not own
17 Aventis stock. I have two protocols involving New-
18 Fill or Sculptra for which I was the sponsor and
19 investigator, and no product or financial support was
20 provided by Dermik. Dermik did pay for my travel and
21 lodging here today. Next slide.

22 The U.S. data that we have on Sculptra and

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1 lipoatrophy falls into three categories. The first
2 category involves patient acquisition of product
3 mainly through buyers clubs. The second was a
4 compassionate use study that I initiated in 2001. And
5 the third are two sponsor investigator IDE protocols
6 begun in 2002, one by myself and one by Drs. Mest and
7 Humble in Los Angeles. Next slide.

8 Patient acquisition of product has been
9 going on since 2001. Most of this product has been
10 made available through DAAIR as was previously
11 described. We do have statements from six physicians
12 administering this product through this acquisition
13 method, which encompassed 1,200 treated patients. In
14 these statements it has been said that all the
15 patients are quite satisfied and that no serious
16 adverse events have been reported, and that the
17 injection procedures have been well tolerated. Next
18 slide.

19 I was actually made aware of the Sculptra
20 product by a patient in 2000 who was treated in Paris.

21 I was very interested, so I went to Paris and met
22 with Dr. Laglenne, the developer of the product, and

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1 went through a couple of her training sessions which
2 she did on weekends for European dermatologists. I
3 was so impressed with her results and her interest in
4 this product for lipoatrophy that I actually decided
5 there needed to be some sort of controlled method of
6 following this product to the United States, so I
7 initiated an IDE ?? an IRB approved protocol in 2001
8 which I will call APEX 001. I enrolled 100 HIV
9 positive males with lipoatrophy, 82 percent were
10 Caucasian and 18 percent were non-Caucasian. The
11 average age was 44 years and they had been greater
12 than 10 years with HIV. Next slide.

13 In this study, the patients received an
14 average of three treatment sessions. However, the
15 range was one to six, depending on the severity of
16 their disease. And the follow-up period was two years
17 after the initial treatment series.

18 On a scale of one to ten with ten
19 representing the greatest satisfaction rating,
20 patients gave a satisfaction rating 12 months after
21 the initial treatment series as 8.0, and 24 months
22 after the initial injection series as 7.5, so patients

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1 were very satisfied which is really our best outcome
2 measure from the study.

3 Adverse events that I reported during this
4 time period were three that were completely unrelated
5 to product, two were deaths due to progression of HIV
6 disease itself, and one was a stroke that was judged
7 to be unrelated to New-Fill by the attending
8 neurologist. The injection-related events fell very
9 much in line with what has already been presented,
10 some pain with injection, transient bruising, tingling
11 and swelling.

12 I reported nodules in this case in the 52
13 percent range. I grouped together both my reports and
14 the patients' reports of palpable but non-visible
15 nodules all into one number. Next slide.

16 The IDE study which I began in 2002 was
17 very similar in its structure, involved a series of
18 treatments. There were both my ratings and patient
19 ratings, as well as photographs done over the course
20 of time. In this case, serial laboratory testing was
21 also performed.

22 The demographics of the patient population

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1 was almost exactly the same, 85 percent Caucasian and
2 15 percent non-Caucasian, all HIV positive males, all
3 in their mid-40s, and mostly with long-time HIV
4 exposure. Next slide.

5 The results of the study at this point, 95
6 patients have completed treatments. An average of 3.5
7 initial treatments were performed, touch-up treatments
8 are ongoing as necessary, and there is again a very
9 high patient satisfaction in this group. This time I
10 used a scale of one to five, with five being the most
11 satisfied. And the average rating at month six was
12 4.7, and now we have 61 percent of patients at month
13 12, again reporting numbers in the same range. Next
14 slide.

15 The adverse events reported in this case
16 were two unrelated serious adverse events, one for
17 melanoma of the abdominal wall in a non-treated area,
18 and one for an MI which underwent coronary artery
19 bypass grafting afterwards. The same effects of mild
20 swelling and soreness at the injection sites
21 initially, and in this case I only reported the
22 nodules which the patients reported on their

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1 questionnaires, which at this point was 6 percent.
2 There were no effects on laboratory values over the
3 course of the treatments. Next slide.

4 This is an example of a patient that I
5 consider to be a better than average responder. This
6 patient had six treatments and ten months after his
7 final treatment you can see that he has excellent
8 results in correcting his lipoatrophy. Of note, this
9 patient's body weight is the same at both of these
10 photo visits. Next slide.

11 Here is a patient that I consider to have
12 below average but still good results. This patient
13 had four treatments, and you can see his physical
14 appearance six months after the four treatments. Also
15 of note, this patient has lost 10 pounds of body
16 weight between these two visits.

17 Also of note, I included treatment of
18 temples in most of my patients, and none of these
19 photographs actually reflect how good the appearance
20 of people is after the treatment of temples, as well.
21 Next slide.

22 And to show you a demographic that's a

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1 little bit different, this is a 66 year old black lady
2 that self-acquired product, and she had excellent
3 results. Two months after her third treatment, she
4 has almost full correction of her facial features.
5 Next slide.

6 Also in 2002, Dr. Mest and Humble started
7 an IDE study with very similar structure to my IDE
8 study. In addition, they added evaluation of skin
9 thickness throughout the injection series, as well as
10 digital photography. And again, a patient
11 questionnaire and well-being scale. They also took
12 laboratory values throughout their studies. Their
13 demographics included two females, but otherwise
14 mostly males. And again, mostly Caucasian with 15 or
15 14 percent non-Caucasian. Next slide.

16 At this point, 86 of their patients have
17 been treated. At month six, using that same scale of
18 one to five they get almost the exact same ratings
19 that I get, so opposite coasts, different
20 investigators, still same results.

21 They have had most of their patients now
22 reach the 12 month point and still have the same

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1 satisfaction rating, and they have shown with their
2 skin caliper ratings that there is a definite increase
3 in the skin thickness. Next slide.

4 There have been no serious adverse events
5 reports from Dr. Mest and Dr. Humble. They have had
6 the same incidents of mild transient bruising and pain
7 on injection, and about the same incidence of nodules
8 as reported by patients, again small, non-visible and
9 palpable. They have shown no clinically significant
10 changes in laboratory measurements. Next slide.

11 In conclusion, looking at these 286
12 patients, we can say that Sculptra treatments are safe
13 and well tolerated, and seem to have a durability at
14 least out to two years. They are effective and have
15 very high patient satisfaction. Next slide.

16 Also, there are many HIV positive patients
17 still out there that would benefit from treatment, as
18 you've heard today. And because lipoatrophy appears
19 to be strongly related to the number of years with
20 HIV, number of years on antivirals, there's going to
21 be increasing numbers of HIV positive patients with
22 significant lipoatrophy, so this is an increasing

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1 problem. I'm going to turn things back over to Kim.

2 DR. FORBES-McKEAN: Thank you, Dr.
3 Engelhard. I would just like to conclude our
4 presentation today by going over some of the key
5 points that you heard this morning.

6 Under the trade name New-Fill, this device
7 has been available outside the United States since
8 1999, and has been used in an estimated over 150,000
9 patients. Poly-L-lactic acid is a synthetic
10 biodegradable polymer that has been used in surgical
11 products safely for decades. Additionally, the pre-
12 clinical testing, as well as the clinical results,
13 demonstrate that Sculptra is biocompatible and safe
14 for use as a device.

15 You've heard and seen today that facial
16 lipoatrophy is an emotionally devastating problem for
17 people with Human Immuno Deficiency Virus. People who
18 suffer from this condition may feel well but look the
19 opposite, and are stigmatized by their appearance.
20 The psychological impact may be severe enough that it
21 may affect one's desire to continue their much needed
22 antiretroviral therapy.

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1 For these reasons, a safe and effective
2 treatment to correct the shape and contour
3 deficiencies resulting from facial lipoatrophy in
4 people with Human Immuno Deficiency Virus is needed.

5 Dermik believes that the data presented in
6 this PMA meet FDA regulatory requirements for valid
7 scientific evidence and for demonstration of safety
8 and effectiveness. Based on this data, Dermik
9 believes that Sculptra has demonstrated a favorable
10 risk to benefit ratio in people with Human Immuno
11 Deficiency Virus who are suffering from the
12 stigmatizing effects of facial lipoatrophy, a
13 condition for which there is currently no approved
14 medical treatment available to them in the United
15 States. Therefore, Sculptra would provide a much
16 needed treatment option to meet this unmet medical
17 need.

18 This concludes our presentation today, and
19 on behalf of Dermik, I would like to thank all of the
20 panel members for their time in preparing for this
21 advisory meeting, and for your attention today. Thank
22 you.

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1 CHAIRMAN CHOTI: Thank you, Dr. Forbes.
2 That concludes the presentation from the sponsor. Are
3 there questions from the panel that can be directed to
4 the sponsor? Dr. Olding, go ahead.

5 DR. OLDING: I just have a couple of
6 questions. During your presentation, you spoke about
7 total cutaneous thickness. You talked about the
8 thickness of the adipose tissue, and you talked about
9 the skin thickness. I'm not sure after hearing your
10 presentation that I'm sure what's thickened. Is it
11 really the dermis? I don't think the skin has
12 thickened to a millimeter or in some cases 1 point
13 something millimeters. I think that would create a
14 very mask-like effect, and particularly since it's
15 meant to be injected in the deep dermis. Where is the
16 thickness?

17 DR. FORBES-McKEAN: I'd like to address
18 this question to Dr. Sharon Levy.

19 DR. LEVY: If I may clarify, the increase
20 in total cutaneous thickness is indeed in the dermis.
21 The initial measurements from the VEGA Study included
22 the epidermis, dermis, and the adipose layer.

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1 Subsequent to that, the area that was measured for
2 follow-up was the epidermis and dermis, so those
3 changes reflect actual changes to the dermal
4 thickness.

5 DR. OLDING: And there's no subsequent
6 change in how the skin looks with skin that's suddenly
7 become a millimeter or more, a centimeter or more in
8 thickness because that's thicker than any skin that
9 I've seen.

10 DR. LEVY: Right. Well, let me address
11 that in two ways. One, we were able to see, I think,
12 as a group here the photographs that accompanied those
13 transcutaneous thickness changes. But I would also
14 ask the clinical investigators who have seen the
15 performance of the product in their clinic to comment
16 on the feel of the product for their patients, if that
17 would be useful to you. Dr. Engelhard.

18 DR. ENGELHARD: Again, I'm Dr. Engelhard.
19 What patients report and what we can feel in
20 patient's faces is simply a firmness in their face.
21 The skin itself does not feel hard or rock-hard.
22 Basically, you can tell the difference between treated

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1 areas and non-treated areas by simply a firmer
2 palpation. There doesn't seem to be any gross
3 abnormality when the patient is in their usual daily
4 activities of washing their face. Nor does anybody
5 associated with the patient notice anything different
6 about the appearance of their skin.

7 DR. OLDING: Perhaps while you're up there
8 you could answer another question. The nodules that
9 were discussed, is there a preponderance of location
10 for those nodules? Injecting other facial fillers, if
11 I have a problem it's usually around the periorbital
12 area where the skin is very thick. Are the nodules
13 then located in those areas which perhaps are ?? you
14 know, have a more cautionary note any time you inject
15 fat or other fillers.

16 DR. ENGELHARD: Absolutely. A lot of the
17 nodules that have occurred have been in patients
18 treated outside the usual clinical settings, and the
19 most common place for people to have complaints would
20 be in the thin periorbital area, or in areas where
21 there is underlying bone and the skin is stretched
22 over bone. For example, stretched across the forehead

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1 or stretched over the zygomatic arch, and that way you
2 may be able to actually see one of these nodules, as
3 you said, particularly around the eye.

4 How I describe these to patients when I'm
5 having initial consultation is that you may feel very
6 soft small little B-Bs in your skin. Some patients
7 are actually disappointed when they don't. Why don't
8 I feel these little B-Bs, but in general, patients do
9 not complain of them, nor do they say that they have
10 any problems with them. And again, as you had said,
11 when they do become obvious often in patients treated
12 outside the usual clinical setting, it's usually right
13 around the eye in patients that are a problem with any
14 injectable product.

15 DR. OLDING: But in the clinical study
16 from the presentation from your experience, there has
17 never been a nodule that's been visualized? It's only
18 been palpable. You've never seen a nodule.

19 DR. ENGELHARD: These have only been
20 palpable in the studies that we've done.

21 DR. OLDING: But none visible.

22 DR. ENGELHARD: Non-visible. The visible

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1 ones that we had seen have been done outside the
2 setting.

3 DR. OLDING: Okay. And do you have any
4 patients or experience of patients, the study went to
5 two years. That doesn't really answer how long you
6 think it lasts. Can you comment on that?

7 DR. ENGELHARD: I think our use in HIV
8 patients is somewhat different than the general
9 cosmetic use which has been in Europe for several
10 years. Besides the actual presence of product itself,
11 the presence of the collagen accumulation because of
12 product itself, but also in HIV patients you're going
13 to have continued fat loss, so response and time to
14 touch up treatments is dependent on, I think, three
15 factors - how long the product actually stays within
16 the skin, how long the collagen stimulation or
17 response to the product is apparent, and whether or
18 not there's continued fat loss.

19 In our touch-ups that we've seen in our
20 patients, the average patient that requires touch-up
21 usually gets a single partial treatment about once a
22 year. Now whether that is because of, again,

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1 continued product breakdown or because of continued
2 fat loss we are not sure. However, in general
3 cosmetic patients in Europe, the average touch-up
4 treatment seems to be two to three years, so there
5 must be confounding factors involved in our HIV
6 patients.

7 DR. OLDING: Thank you.

8 CHAIRMAN CHOTI: Dr. Newburger.

9 DR. NEWBURGER: Thank you. I have quite a
10 few questions. Number one, I'm a little bit
11 confounded by the use of the term nodule in these
12 studies. In dermatology, a nodule is generally
13 considered by definition to be a lesion that is one
14 centimeter or greater. Okay. And this doesn't follow
15 what the French study has, where they're talking about
16 one to two millimeter nodules, or indeed what Dr.
17 Engelhard is talking about in terms of the little B-
18 Bs, so what exactly do you mean by nodules?

19 DR. FORBES-McKEAN: Again, I'll ask Dr.
20 Sharon Levy to come up to address this question.

21 DR. NEWBURGER: And then I have many other
22 questions.

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1 DR. LEVY: Regarding nodules,
2 concentrating first on the presented studies. From
3 the VEGA studies, as you mentioned France, the events
4 were termed nodules, or more specifically micro
5 nodules, so this did not fit the one centimeter
6 definition. In fact, from the investigator they're
7 actually quite indistinct, and were felt as more like
8 an irregularity in the deep dermis on direct
9 palpation, so they would not have met the one
10 centimeter criterion in that respect.

11 DR. NEWBURGER: So we really don't have a
12 consistent sense of what these are.

13 DR. LEVY: Yes. You are correct that
14 there is some variability there, because of course,
15 the two pivotal studies were conducted and designed
16 independently, so investigators used their own concept
17 for describing these events.

18 DR. NEWBURGER: Thank you. My next
19 question is for Dr. Conant. Do you have a sense, sir,
20 of the total number of patients in the United States
21 who are currently on HAART treatments?

22 DR. CONANT: Yes. We think that there are

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1 probably somewhere between 900,000 and a million cases
2 of HIV positive people in the United States. Probably
3 a third of them do not know that they are HIV
4 positive, and probably somewhere in the range of 20 to
5 30 percent are on HAART therapy.

6 As I said in my remarks, if it were my
7 choice, I would start everyone who is HIV positive on
8 HAART the minute they were diagnosed. To date, there
9 has been no direct demonstration that progressive
10 therapy reduces transmission. It's hard to believe
11 that if you're reducing the amount of virus the
12 patient is shedding, you're not reducing transmission,
13 but that study has not been shown.

14 However, as I mentioned earlier, remember
15 that people apparently progress to facial
16 lipodystrophy, lipoatrophy even in the absence of
17 HAART therapy. I have pictures of Rock Hudson before
18 and after his diagnosis. That was in 1985. AZT was
19 not introduced until 1987, and he clearly had what we
20 today call lipoatrophy. It was being called wasting.

21 Everyone was worried about keeping him alive, and no
22 one was concerned about the cosmetic appearance of his

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1 face.

2 May I also return to the question of
3 nodule? You're absolutely correct, they are papules,
4 they are not nodules. They're deep papules. I've
5 seen one that was located up near the periorbital area
6 in a physician who had gone to Europe to be injected.

7 I have not seen those.

8 And following up on the question about the
9 thickness of the dermis, in my informed consent I tell
10 a patient do you understand that we're replacing fat
11 with scar tissue, and all of the patients say yes, I
12 understand that. And yet, in the patients that I've
13 seen who have been injected elsewhere and in the
14 patients that I have done over the last four months,
15 the consistency feels pretty normal. So while we are
16 injecting a preparation that is primarily water, which
17 then stimulates collagen formation at the dermal fat
18 junction, the feel, the consistency of the skin feels
19 essentially normal, and their facial expressions are
20 essentially normal. Of course, you have some people
21 here who have been injected. They could probably
22 comment on that, as well.

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1 DR. NEWBURGER: Thank you. So then if I
2 can extrapolate from your statement that perhaps 50
3 percent of individuals have ?? will develop
4 lipodystrophy, then you're looking potentially at this
5 time somewhere between 150,000 and 300,000 individuals
6 in the U.S. who would benefit from a filler such as
7 this.

8 DR. CONANT: That would be my guess. The
9 Dermik people probably have even a better guess,
10 because they've probably looked at the market.

11 DR. NEWBURGER: Thank you. My next
12 question is, I'm not clear from the submission what
13 you feel the mechanism of action of this product is,
14 since the product itself seems to be resolving in a
15 relatively short period of time, and yet the cosmetic
16 benefit persists. And I'm wondering ?? I'm sure you
17 have studies which will show this. Could you share
18 some of them with us?

19 Additionally, the mechanism of action of
20 these papules or nodules since they can develop as
21 late as two years after initial therapy, what is the
22 mechanism of action there? I'd like to get a little

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1 greater sense of what's going on here.

2 DR. LEVY: I'll provide as much insight
3 into this as I can, and maybe supported by some of the
4 colleagues in other disciplines.

5 Regarding mode of action, in the data that
6 we presented that was not specifically addressed, as
7 you saw. Really what we saw, just as you pointed out,
8 were increases in skin thickness over time, and the
9 time course suggested activity actually some number of
10 weeks and months following last treatment that
11 suggests that there's an active process in the skin.

12 We know from animal data with this product
13 and in the data with other lactide products that when
14 implanted into the skin, there's typically a tissue
15 response. There may be foreign body reactions. There
16 is dissolution of product over time, and then there's
17 gradual stimulation of fibroblastin collagen, and that
18 has been seen in animals. It's possible that that's
19 the mechanism that we're observing overtly by the
20 increases in skin thickness measurements.

21 Now if I could ask you to repeat the
22 second question regarding nodules and time course?

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1 DR. NEWBURGER: In the packet from the
2 European studies, there's data that shows that some
3 individuals developed or noted the onset of these
4 nodule/papules at a great interval after their initial
5 treatment up to two years later. And I'm asking, do
6 you have any insight as to what this mechanism of
7 action is? Something clearly is going on.

8 DR. LEVY: Yes. Again, it's speculation,
9 and I'm thinking back to the case you're referring to
10 here from the VEGA Study. Again, the nodules that
11 were identified in that study were really micro
12 nodules, didn't meet your definition of nodule, and
13 were identified by the investigator, so the patient
14 did not identify them.

15 In the case I believe in VEGA that was
16 noted at the last visit out at two years, patient 35,
17 again when one looks at the photograph, we looked at
18 this to understand, we couldn't see any of the micro
19 nodules that were defined. In speaking with the
20 investigator to understand in more detail what this
21 was, understanding that they were identifying these
22 irregularities deep in the skin as nodules. It's

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1 possible that there may not even have been a change in
2 physical exam. They may have been picked up one visit
3 or another, but we cannot know for certain.

4 CHAIRMAN CHOTI: Final question, Dr.
5 Newburger.

6 DR. NEWBURGER: Thank you. I'm wondering
7 about the stability of the product once it's
8 solubilized in the vehicle; that is to say, how much
9 settling occurs of the product? How fast does it have
10 to be used, or does it just remain in an equal
11 homogeneous suspension?

12 DR. FORBES-McKEAN: Actually, we have a
13 draft in the PMA to recommend that the product be
14 reconstituted and allowed to sit for two hours before
15 it is injected. And we've actually done laboratory
16 studies to demonstrate that the product is stable for
17 a period of three days once it is reconstituted.

18 CHAIRMAN CHOTI: Dr. Chang, question?

19 DR. CHANG: I have two questions I'd like
20 to address to Dr. Engelhard. And in the APEX studies
21 2002, the report reported palpable nodules went down
22 drastically from 50 or 30 percent if you reported

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1 those that were perceived or picked up by the patient,
2 so they've dropped to 6 percent, and then the Mest and
3 Humble study down to 9 percent.

4 Do you have data of what percentage of
5 papules or nodules were still picked up by clinician
6 by your exam, and do you know of the Mest-Humble study
7 reported papules or nodules picked up by physician
8 examination?

9 And then my second question is, were any
10 of these patients post two year study requiring a
11 touch-up or additional treatment? My final question
12 can be answered by anyone, because this was a patient
13 on the VEGA Study, patient number 30 that was shown.
14 When I did look at the pictures at the completion of
15 the study where the nodule was present but not
16 visualized, to my eye, on a right lateral, right
17 oblique picture at the very last session, there seemed
18 to be some pinkness or redness over the cheek. So my
19 last question for anyone is were these nodules that
20 were not visible associated with any pink or red
21 color, just a faint pink color over this area?

22 DR. ENGELHARD: I'll actually answer your

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1 last question first. There does not seem to be any
2 erythema, or pinkness or redness associated with any
3 of these micro nodules in my experience. As to your
4 first question, I'm responding to number of patients
5 reporting nodules, let's call them micro papules to
6 make it more clear, patients reporting micro papules
7 as compared to myself, in the first APEX 001, again I
8 had presented this data with my findings and the
9 patient's findings lumped together.

10 In that case, the patient's findings were
11 about the same as what was seen in other studies. And
12 6 to 9 percent reported feeling these soft micro
13 nodules within their face. However, I can feel, if I
14 feel carefully in most of my patients, some
15 irregularities deep in their skin. And I simply
16 reported this.

17 There were no patients in either one of
18 these studies that recorded these as bothersome,
19 probably because they were pre-warned and pre-told
20 that this might be something that they feel. None of
21 the patients reported them as painful or otherwise
22 bothersome to them. And as I previously mentioned,

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