

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,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 some were upset that they didn't feel them because
2 they thought that maybe the product wasn't working as
3 it should.

4 As far as touch-up treatments, now I have
5 my first patient was injected almost exactly three
6 years ago, and I would say that about half of the
7 patients so far are requiring at least a partial
8 treatment every year or so, probably my guess is
9 because of continued fat loss.

10 In the patients that are not requiring
11 touch-up treatments, they tend to be patients either
12 that have switched antiviral therapy, or have
13 otherwise maintained visibly their fat elsewhere in
14 their body, as well. So I think that is a dependent
15 process somewhat based on additional fat loss.

16 In the patients now that are at least a
17 couple of years out, I've had several that have
18 actually looked even better than they looked
19 initially, and maybe this is because of some slight
20 regain of fat because of switching their regimes. I
21 have not reported any additional nodules that have
22 occurred after the first noted ones. It seems that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 when these micro papules form, they're going to form
2 in the first couple of months as the tissue responds
3 to injection of product. I don't see them forming
4 anew later, so I don't find any new significant micro
5 nodules forming later.

6 I do not know if Dr. Mest and Humble have
7 reported any additional or have any different findings
8 that I've reported, and I'll let Dr. Mest answer that.

9 DR. CHANG: Thank you.

10 DR. MEST: Thank you, Peter. Dr. Doug
11 Mest, Clinical Director of Blue Pacific Aesthetic
12 Medical Group in Hermosa Beach, California. I am the
13 principal investigator of one of the IDEs and as such,
14 was asked to be here by Dermik and they, therefore,
15 paid for my travel and lodging. Due to my experience
16 with the product they've also asked me to be a
17 consultant. Otherwise, I have no financial interest
18 in Sculptra or have any ownership stock in Dermik or
19 its parent company, Aventis.

20 A couple of questions. I'm going to try to
21 get them all because so many things went through, so
22 if I forget to answer something, please remind me.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 CHAIRMAN CHOTI: Just try to be brief.

2 DR. MEST: We have not seen any redness,
3 irritation, erythema around any of the nodules that
4 have occurred in our IDE, these are all patient
5 reported events. That was one of the questions asked
6 and the answer we did not search for them. But
7 again, to reinforce it, they are not bothersome. Our
8 nodules tended to occur within the first six months.
9 We did not see any late occurrence of nodules, and we
10 now have patients out from ?? DAAIR patients all the
11 way out two years.

12 I believe Dr. Vleggaar may have
13 information on histology of what they actually look
14 like in answering. The assumption is that they're
15 excess product and a reaction to them.

16 CHAIRMAN CHOTI: Well, one question, Dr.
17 Mest. There seems to be quite a variability in these
18 micro nodules from 9 percent, even in the two pivotal
19 trials, 30 percent to 50 percent. Do you think there
20 is a technical aspect to the development of these
21 nodules? And if so, what's your opinion regarding
22 special training in the technique?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 DR. MEST: I think it's both. I think
2 it's one - if you look for them, you'll find them, and
3 that was probably evidenced in the VEGA study. If
4 they press the skin and are specifically looking for
5 micro nodules, you'll probably find them. The other
6 is, I think it's technique-dependent in terms of if
7 there's excess product put in. This product is a
8 little different than say collagen or something like
9 that where if you have this huge depression you're
10 going to put more product in that area. In this
11 product, you wanted to wait and act, and so therefore,
12 less may be more in terms of allowing it to work. And
13 so the amount of product placed needs to be non-
14 excessive. And so in terms of specialized training, I
15 think that's relatively easy to get across. It's just
16 different than what people who are used to using
17 other facial fillers may know to do, and so some
18 simple training to that effect, that this is
19 different. You need to treat, wait and assess is
20 probably all that's necessary.

21 CHAIRMAN CHOTI: Thank you. Let's go to
22 Dr. Munk, and then Dr. Leitch.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 DR. MUNK: Yes. I have a couple of
2 questions about your definition of success, and then
3 some on durability. One of the studies used a 10
4 millimeter thickness as a criterion for success, and
5 I'm curious what that's based on.

6 DR. LEVY: You're correct. That was
7 included in the plan for the VEGA study, and it was
8 really just an estimate at the beginning for the
9 purpose of sample size computation at the beginning.
10 And we can show a slide here that was used really
11 arbitrarily for the calculation of how many patients
12 they would need to have entered in the study. And
13 those patients were termed responders.

14 We can see here that the proportion of the
15 patients at each visit who were "responders" peaking
16 at the one year mark, 61 percent of the patients, went
17 tailing off a bit over the balance of the study after
18 two years.

19 DR. MUNK: Okay. Maybe we can keep this
20 slide for a minute.

21 DR. LEVY: Certainly.

22 DR. MUNK: In the VEGA study, the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 inclusion criterion was total cutaneous thickness,
2 less than 2, and yet the baseline slide indicated that
3 the average baseline was 3.

4 DR. LEVY: May I make a clarification
5 here?

6 DR. MUNK: Please.

7 DR. LEVY: I'm sorry. The inclusion
8 criterion was that their adipose layer be less than 2
9 millimeters, which it was. Actually, one patient was
10 2.1 at study start, but on average most of the
11 patients had no detectible fat. The remainder of the
12 skin layers that we were discussing earlier, that is
13 what averaged 3 millimeters at baseline.

14 DR. MUNK: Okay. In the Chelsea and
15 Westminster study, in the delayed group there was a
16 marginally significant increase in cheek thickness in
17 the delayed group. I think my question may have been
18 partially answered in that treatment changes were
19 allowed. And it appears that no data were collected
20 on total weight changes in the patients over the
21 course of the study, so these may have contributed to
22 facial fat thickness or skin thickness.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. LEVY: You are correct that in the
2 delayed treatment group prior to treatment, there was
3 one skin thickness measure in the left cheek that
4 reached statistical significance. And that measure -
5 and if we can go back to the main presentation when we
6 see the histogram of the untreated areas - the slide
7 before that. The visual helps.

8 Although there was statistical
9 significance at that point, the increase in skin
10 thickness was very small. It was .4 millimeters in
11 keeping with the rest of the changes. Additionally,
12 as our statistician explained to us, when one takes
13 what were done, 24 measures of untreated areas, it's
14 actually expected that one will be statistically
15 significant.

16 This is the statistically significant.
17 And with delayed treatment group, the second panel
18 there, the ?? yes, that's it, the left cheek. You can
19 see in the delayed treatment area that that yellow bar
20 is, indeed, a bit higher than baseline measure. But
21 in terms of absolute increases, we did not feel that
22 that was statistically, clinically relevant.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. MUNK: Okay. So going back ?? if you
2 can go back to that earlier slide, one of the things
3 that is difficult for me to understand is the
4 durability of the product, and the various studies.
5 There was either a fixed number of treatments, or
6 treatment to effect. In some cases there have been
7 touch-ups, and yet this clearly shows that there is
8 some reduction in total cutaneous thickness. And I
9 guess I would take some exception to the statements
10 that have been made about continuing fat loss because
11 the studies I'm familiar with typically show
12 lipoatrophy stabilizing after two to three years. So
13 I'm wondering about long-term durability of the
14 product.

15 DR. LEVY: If we could go back to the main
16 presentation slide, the data cloud that shows the data
17 points from all 50 patients. And let me just address
18 that from the reference that's correct, from the VEGA
19 study. We want to look at the data here again. So
20 these are the data.

21 In this case, as you mention, patients did
22 not receive a fixed regime. They received treatment

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 to effect. In fact, most patients, I think it was
2 about 85 percent, had either four or five treatment
3 sessions on average, completing it about week 14 of
4 the follow-up period. So these are the data from all
5 the patients. This is a bit different design than the
6 other studies, but this does give us a good time frame
7 for two years. The Chelsea and Westminster study was
8 not initially planned to go out two years, so efficacy
9 results can really not be looked at the two year mark.

10 We use that for safety.

11 The other comments from Drs. Engelhard and
12 Mest are coming from a more clinical situation in the
13 course of their trials. Is that helpful to you?

14 DR. MUNK: Yes. And finally, I guess a
15 comment which is as much for FDA staff as anybody
16 regarding the photos. There seems to be fairly low
17 interrater reliability on grading the photos, and I
18 would confess to some great difficulty in comparing
19 them. And I wonder if FDA doesn't have a guidance for
20 investigators on the lighting, the distance from the
21 camera, the positioning of the subject, and so on, so
22 that there would be greater comparability of pre and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 post treatment photos, because I think that would have
2 been very helpful in this case.

3 CHAIRMAN CHOTI: Dr. Leitch.

4 DR. LEITCH: I have a couple of
5 questions, and one again is sort of related to
6 durability issues. The Chelsea and Westminster study
7 photos that are in the booklet towards the back, and
8 they didn't have so many photos, and there were
9 comments that were written on the bottom regarding the
10 progress of those patients. And seeing that there
11 were several in which the comments were the patient
12 didn't feel like the product lasted in one case I
13 think passed three to four months, and another at six
14 months noted sinking-in at that interval, so that is
15 one question that I have.

16 And the other sort of a bit referable to
17 that is again this idea of mechanism of action. If
18 this is a filler, what I was sort of hearing is that
19 when you do the injection, you don't "fill-out" the
20 whole defect because there is something else that is
21 happening, so if it's not really the idea of filling,
22 I think for us in terms of making recommendations for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 labeling, or as you instruct physicians, there needs
2 to be some understanding of the mechanism for how it
3 acts to attain the thickness because people might be
4 inclined to fill the defect.

5 And I was wondering since there is a lot
6 of usage of this product in other countries, is there
7 not any investigational data on skin biopsies in the
8 patients who have received these not just the nodules,
9 but I mean actually of the skin that's being treated
10 to give a sense of what is the mechanism of action of
11 the filler.

12 DR. LEVY: It's a several part question,
13 and I think I'll be able to address some parts of the
14 first portion, and then we call a colleague with
15 experience in Europe, Dr. Danny Vleggaar, to answer
16 some of your questions at the end.

17 Regarding the Chelsea and Westminster
18 study, you're right. In that study, patients had a
19 fixed regime of treatment so if they needed more at
20 that point, as judged by the patient or the
21 investigator, by protocol they didn't get it as part
22 of the treatment beyond their three injections.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 In the photographs that we've presented to
2 you, those are all the photographic data that we've
3 gained consent for, was about 15 patients out of the
4 cohort in Chelsea and Westminster. And the comments
5 that you see at the bottom were collected at the one
6 and a half to two year mark after the study had been
7 completed. And that was included in the interest of
8 fullness of understanding the clinical situation.

9 In many instances as you remarked,
10 patients were not satisfied with three treatments, and
11 either asked for additional treatment with the
12 Sculptra product, which sometimes in cases they got,
13 or sought other treatments over that intervening
14 period of time. And looking at the photographs as
15 well, I think it harkens back to the earlier question
16 - yes, there are differences in photographic technique
17 between the two studies. And as we reviewed the
18 photographs in Chelsea-Westminster, they were taken
19 in a standardized fashion, but our sense is that they
20 may not have been taken with the optimal technique to
21 highlight the defects. They were taken at a 45 degree
22 angle, but without the type of overhead lighting that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 may have best shown the changes in facial appearance.

2 And we say that in looking in particular at the
3 baseline photographs in individuals who had very
4 little fat, but yet did not always have such a
5 demonstrated defect. You may actually be looking into
6 the defect from that angle.

7 Regarding information of mechanism of
8 action, I would ask if Dr. Danny Vleggaar could
9 address this from his experience.

10 DR. VLEGGGAAR: Good morning. My name is
11 Danny Vleggaar. I'm working in Europe with various
12 injectable devices since four and a half year. I
13 gained quite extensive experience with the product
14 Sculptra. I am since one and a half year a clinical
15 consultant for Dermik. They paid for my travel and
16 lodging to come here, and I have no other financial
17 interest in the product.

18 To answer your question, indeed we see a
19 correction in patient after injection which goes
20 beyond the physical volume of product that has been
21 injected. There, to my knowledge, are no such studies
22 in Europe performed to demonstrate this mechanism of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 action, this delayed mechanism of action in patients.

2 There are animal studies, of course, one
3 described at Goglewski. What I can tell you from
4 personal experience and watching histological samples
5 from patient is that there is a foreign body reaction
6 and we see a fibroblastic response with formation of
7 in the beginning very young and early layers of
8 fibrous tissue which are developing in the later
9 states to more extensive layers of mature collagen.
10 And I think that this is another reason for the
11 clinical result, an increase in tissue which is
12 suggestive for formation of new collagen.

13 I'm only aware of some slides from the
14 very early days where the tissue has been marked with
15 a collage type one marker, and there was an increase
16 in collagen type one in the sample.

17 CHAIRMAN CHOTI: While we're on dermatic
18 pathology, Dr. Penneys, any questions for the sponsor?

19 DR. PENNEYS: Many of my questions have
20 been answered. As a dermatipathologist, there wasn't
21 much really for me to evaluate. I mean, there's a lot
22 of conjecture in these patients. I have a number of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 questions.

2 If the reaction to this material is a
3 foreign body-type reaction, then why are papules
4 local? Is it at the end of the syringe that there's
5 an accumulation of material? Is it site-specific, or
6 is not even related to the injection? For example,
7 when you put a needle through the skin, you could
8 perforate a hair follicle. I mean, there are many
9 different reasons why people get ?? actually people
10 get - I hate to use the word - papules, because as an
11 aside, as a dermatologist, language is important. And
12 the words I've heard this morning don't exist in our
13 dictionary. I mean a micro nodule is like jumbo
14 shrimp. Is that something you see under a microscope?
15 Is it a micro nodule? Same with a micro papule - I
16 mean, these terms have actual specific sizes.

17 For the company's benefit going forward,
18 please ask your investigators to estimate the size in
19 millimeters or something like that. Then there will
20 be no confusion about terminology.

21 And regarding the photographs, these
22 photographs - I realize you purchased them. They came

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 ?? you had no control. However, they're an example of
2 what you could teach what not to do. The backgrounds
3 are so distracting that it's hard to look at the
4 dramatic changes which are there. I mean, the
5 shadows. It's incredible. I've never seen anything
6 like it in a submission anywhere. If you look in a
7 journal, you won't see photographs like this.
8 However, that's irrelevant.

9 To get back to histology, it would be nice
10 to know what is there at the end of the period of
11 time. I mean, I recognize that this is a
12 reconstruction, and that there's an obvious clinical
13 benefit, but at some point, somebody's going to have
14 accumulate data because of what's going to happen to
15 this material once it's available outside of this
16 population. So I have no other comments because
17 again, a dermapathologist, there wasn't anything for
18 me to evaluate in terms of micrographs. It's people's
19 opinions about what might be there, what was there in
20 a rat, or what was there on one patient - none of
21 which represented accumulation of scientific data, to
22 me.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 CHAIRMAN CHOTI: Okay. Thank you. Dr.
2 Miller and then Dr. Fish.

3 DR. MILLER: Yes. I have a question about
4 the use worldwide. What percentage of patients
5 worldwide do you think are the HIV lipodystrophy
6 patients compared to the ones getting it for cosmetic
7 purposes?

8 DR. LEVY: We don't know specifically, but
9 in discussion with the commercial partners, our
10 estimate is that it's very low use for lipoatrophy
11 worldwide.

12 DR. MILLER: One percent, ten percent?

13 DR. LEVY: We have estimates somewhere in
14 the 5 percent, maybe 10 percent range. But the
15 experience that we've gathered worldwide is
16 predominantly in cosmetic usage.

17 DR. MILLER: So why is the PMA focusing on
18 use in lipoatrophy patients rather than just as a
19 general filler, tissue filler? Why the focus on the
20 lipoatrophy patients?

21 DR. LEVY: Well, I think as Dr. Forbes-
22 McKean mentioned, first of all most importantly,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 there's a real medical need. That's the first issue.

2 And then the data that we have available, the data
3 for presentation meeting scientific rigor for your
4 review are in this population.

5 DR. MILLER: Well, how does it compare - I
6 mean, it appears to me to be a filler, tissue filler
7 like ?? I mean, I haven't seen anything presented
8 which suggests to me, especially knowing now that it's
9 injected into the dermis. I was trying to envision
10 where this exactly is injected, and it sounds like
11 it's injected into the dermis like other fillers. And
12 it has some unknown mechanism of action which you have
13 to ?? I heard someone say you have to wait and let it
14 act which is something you don't have to do with other
15 fillers. So there's something going on here perhaps
16 that's different than another filler, but they compare
17 the effectiveness against other fillers. And since
18 that what it really is competing with, and I'm
19 concerned that this appears to be a product really
20 designed for aesthetic tissue filling like all other
21 tissue fillers basically are, but it's being pitched
22 as a unique product addressing a very difficult, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 no question, big problem of lipoatrophy. But I'm not
2 sure why this is uniquely suited to address that
3 problem.

4 DR. LEVY: Just as a point of
5 clarification, I hope this helps. I don't know if it
6 does for your question - this is just a schematic to
7 understand where the product would be implanted, as
8 many of the clinicians have mentioned, really at the
9 deep dermis, the dermal, hypodermal junction. And
10 it's typically implanted using a number of injections
11 with a condition like lipoatrophy that will involve a
12 large area. This could be delivered by a grid
13 pattern, so it's well distributed in the area right at
14 that junction.

15 Regarding the initial uses of the product,
16 you're correct - it was developed in Europe as a
17 product for the category, cosmetic category filling
18 and augmenting tissue for those type of defects,
19 wrinkles, folds, eyerings. But it was shown very
20 early on in its product history that it was
21 particularly useful in treating the larger volume
22 defects associated with lipoatrophy.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. MILLER: Just there's a number of
2 questions I have too. I can stop, I guess, but I'm
3 just curious about how long does the product stay? I
4 mean, the PLLA has a certain degradation and life, but
5 how do we ?? do you know how long it remains present
6 in the injection site after injection?

7 DR. FORBES-McKEAN: Just before we move
8 onto that next question, we would like to also ask Dr.
9 Peter Engelhard to come up and comment to your
10 previous question about why this particular product
11 has been used more successfully in the condition of
12 lipoatrophy versus other fillers that you brought up.
13 Would you like to have that addressed further?

14 DR. MILLER: Well, if he has data I would
15 like to see data on that comparison. What I'd be
16 curious about would be a direct comparison of this
17 product to other tissue fillers, which appears to me
18 to be a tissue filler. But yet, there's no comparison
19 of how this product performs compared to other tissue
20 fillers.

21 DR. FORBES-McKEAN: Initially, as Dr. Levy
22 said, the subject of this PMA is the data that we feel

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 is valid scientific evidence for the intended use of
2 the product as we've proposed with this application.
3 That other data is not currently available, so I was
4 ?? we were mentioning that Dr. Peter Engelhard has
5 some experience clinically with the other fillers for
6 lipoatrophy, if that's what you would like to have
7 addressed.

8 DR. MILLER: Sure, I'd like to hear that.

9 DR. ENGELHARD: First of all, I think
10 we're all aware that the general cosmetic use of this
11 product is the big deal in Europe, and will probably
12 eventually become the big deal here. But the present
13 application is for lipoatrophy, again because of this
14 expedited review for a need which is really poorly met
15 with most of the available filling agents or
16 procedures. And what I do with each of my patients as
17 they come in is review what options are open to them,
18 and what the pluses and minuses are of each of the
19 options. And that basically falls into really a few
20 broad categories.

21 You have surgical implants, which you've
22 heard from patients and from other physicians have

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 their drawbacks. The surgical implants, whether they
2 be solid teflon or silicone, are usually only designed
3 to fit one discreet area. And often, the lipoatrophy
4 loss is spread throughout the cheeks and the temples,
5 and cannot be fully addressed or adequately addressed
6 by a solid implant. Often we have to use the solid
7 and injectibles around it.

8 As far as injectibles go, the collagens,
9 whether they be bovine or human origin, seem to be
10 lacking in their durability. It's an extremely
11 expensive procedure to fill multiple dents as compared
12 to just wrinkles, and it really does go away within a
13 couple of months.

14 Also, perhaps lasting a little bit longer
15 are some of the particular fascia products. But
16 again, constant refills being necessary, and cost
17 being prohibitive in the long run of continuing these
18 injections.

19 There are permanent silicone products on
20 the market being used off-label, and I think there are
21 multiple concerns on the parts of the patients and the
22 physicians with silicone injections. Most notably,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 migration, and also as you know, residual effects,
2 even years later the formation of new granulomas, even
3 years down the line based on silicone. So of the
4 current available options, there aren't any that
5 really meet the need of long-lasting enough, and cost-
6 effective enough.

7 After a series of New-Fill injections or
8 Sculptra injections, you really have a respite of a
9 year or two before you need touch-up treatments.
10 However, there does seem to be some degradation, some
11 loss of product effect, so you're not talking about an
12 absolute permanent effect as you would with the
13 silicones. So it does sort of nicely fit this niche,
14 whereas other products don't fit this niche as well
15 presently.

16 CHAIRMAN CHOTI: Dr. Fish, quick question.

17 Dr. Lee, and then we'll take a break.

18 DR. FISH: My question is related to the
19 baseline CD4 and viral load strata. The first
20 question is, in the viral load criteria for the VEGA
21 Study, we have viral loads less than 5,000. I'm not
22 actually sure why that criteria was, but when we look

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 at the range of viral loads, it was up to 96,000
2 copies were allowed to enter the study. And it looked
3 like maybe 14 percent or so of patients actually
4 didn't meet that entry criteria. So that question.

5 And then the other question pertains to
6 the CD4 strata, in terms of did you look at those in
7 the Chelsea-Westminister trial. We do have the range
8 provided to CD4, so percent with CD4 is under 200 in
9 terms of severity of lipodystrophy presentation, the
10 response to treatment, and/or the adverse events of
11 the skin nodular formation.

12 DR. LEVY: You are correct. There were
13 some instances where the ?? in terms of CD4 count or
14 viral load that there were patients who enrolled,
15 sometimes outside the initial criteria. We did look
16 at treatment effect by CD4 count and viral load, I
17 believe, and I'm going to confirm this over the break
18 with our statistician.

19 My recollection on that is that we
20 stratified by the medium values, and then looked for
21 treatment effect and did not see any. But we'll be
22 able to get back with you on that probably after the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 break specifically.

2 DR. FISH: And one last question. In
3 terms of the reconstitution in the Chelsea-
4 Westminster trial, they had some lidocaine, one CC of
5 lidocaine. Can you comment, your recommendation it
6 looks like from your draft would be sterile water.
7 Was that an adverse thing? Did that help, did it
8 hinder with lidocaine?

9 DR. LEVY: You are correct that again
10 these were investigator designed, and the
11 investigators chose in the Chelsea and Westminster
12 study for the reconstitution volume of 3 mLs to use.
13 One of those mLs was lidocaine for patient preference
14 just as an anesthetic. And I think again, that was
15 used uniformly. We can look at the results of that
16 study and look at the results of VEGA.

17 In terms of skin thickness at the
18 referable time points, three months, six months,
19 results were very comparable.

20 CHAIRMAN CHOTI: Dr. Li.

21 DR. LI: I have kind of a follow-up
22 question to Dr. Newburger's and Dr. Leitch's about

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 mechanism. What is the role of the PLLA in this
2 formulation? You know, it's 40 percent PLLA and 60
3 percent other things, carboxymethyl cellulose and the
4 mannitol, so exactly what is the role of the PLLA in
5 this?

6 DR. LEVY: Well, we can tell you that the
7 other components, the excipients are reasonably
8 handled by the body, the carboxymethyl cellulose and
9 the mannitol.

10 DR. LI: I understand that.

11 DR. LEVY: And reconstitution volume is
12 very transient. The issue of mechanism of action has
13 been coming up this morning, and the durable component
14 of it is the PLLA, so our feeling is, of course, that
15 the tissue effects that we're seeing are in response
16 to that PLLA, which is implanted. When we've had
17 scant information typically from adverse events from
18 the worldwide database, one could see a foreign body
19 giant cell reaction, and that's consistent with what
20 was seen in the pre-clinical studies. Dr. Handler
21 could address that further if that's helpful to you.

22 DR. LI: Well, this is kind of a lead-up

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 question too. If the PLLA is important to the
2 mechanism of filling in the tissue, how did you
3 optimize the PLLA? In other words, why did you pick
4 the PLLA you picked? You know, why not some other
5 particle size, why not some molecular weight? Why not
6 some other resorbable polymer, or why even a
7 resorbable polymer?

8 DR. FORBES-McKEAN: Okay. Well, we chose
9 a resorbable polymer for the biocompatibility
10 advantages that it offers. And as far as the particle
11 size range, this particle size range was selected
12 because it was believed that the particles were big
13 enough to cause the effect that's clinically desired.

14 However, not so large that it would be impossible to
15 inject the product. And also, not small enough so
16 that you would get an immediate engulfing by the
17 macrophage, and get an inflammatory response that you
18 didn't want.

19 DR. LI: Was the empirically determined or
20 was this based on some studies, or just really good
21 luck for the first three guys that did it?

22 DR. FORBES-McKEAN: I think there's a lot

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 of available information out in the literature about
2 PLLA, and I'd ask Dr. Russell Parsons to come up to
3 specifically address the properties of the PLLA.

4 DR. LI: Well, at this point I'm just kind
5 of more interested in kind of the general how you
6 picked it. My concern is, you know, let's just say it
7 works well the way it is, how sensitive is it to
8 changes? In other words, if you put in a little more,
9 a little less of the particle size, you drift the
10 time, just how sensitive is the PLLA characteristics
11 to the performance of the product? Do you know?

12 DR. FORBES-McKEAN: Well, we actually have
13 looked historically at the lots that have been used
14 out in the ?? with the current use of the product in
15 Europe, and that's how we devised the specifications
16 that we have proposed for the PLLA, which will be
17 controlled after the PLLA is milled and then gamma
18 irradiated. And we'll have a desired range that we've
19 shown in the clinical use of the product that is
20 giving us the desired safety or the desired efficacy,
21 as well as the safety with the product in that range.

22 DR. LI: So, it's empirical basically,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 based on your experience essentially then.

2 DR. FORBES-McKEAN: Yes.

3 DR. LI: Okay. Then my final question for
4 the moment is for these - whatever - is papules the
5 correct - for these little lumps there. Is the
6 material involved in those nodules, in other words, in
7 the histology of those nodules, the center of those
8 nodules, is there material?

9 DR. LEVY: Those nodules that were
10 described in the pivotal studies, none of them were
11 biopsied. I mentioned in comments about the post
12 marketing experience, there have been individual
13 reports with commercial use of the product of cases
14 that have been biopsied. In general, those show
15 foreign body reactions. Sometimes there are particles
16 detectable through polarized light.

17 DR. LI: The reason I ask is in other
18 studies and other orthopedic devices specifically,
19 where you've injected a whole host of things into the
20 subcutaneous layers of many animals, that you often
21 get what we would call nodules or growths around
22 clumps or concentrations of material. So my question

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 is, is there ?? have you looked for any kind of
2 correlations between the presence and the size of
3 these nodules to perhaps the number of injections the
4 person's got. I understand that sometimes more than
5 one dose is applied, and there's also some difference
6 apparently in the amount of material in each vial.
7 You know, you focus around 400 milligrams, but it goes
8 from like 270 to 500 or something like that. Is there
9 any correlation between the amount of material and the
10 presence of these nodules?

11 DR. LEVY: The VEGA study was not designed
12 ?? I mean, the adverse events such that we could
13 analyze that versus the amount of treatment, but the
14 treatment sessions which should reflect amount of the
15 product because that was fixed on a per cheek per
16 session. The patients in the VEGA Study, virtually
17 all of them had four or five treatment sessions.
18 There were few people who fell to either side at three
19 or six, so that doesn't give us a great span to try to
20 examine that, the nodules in that population.

21 DR. LI: Thank you.

22 CHAIRMAN CHOTI: I think the best term I

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 thin are "Bbs", probably the most accurate. Why don't
2 we take a 15 minute break now, and then we may follow-
3 up with some additional questions with the sponsor,
4 and then proceed to the FDA presentation. Thank you.

5 Let's start promptly at 11:00.

6 (Whereupon, the proceedings in the above-
7 entitled matter went off the record at 10:41 a.m. and
8 went back on the record at 11:01 a.m.)

9 DR. KRAUSE: We are going to start again
10 in a minute. There were a few comments, a few points,
11 that I wanted to point out before we start again.
12 Some individuals who may have wished to speak, and who
13 got here a little bit late, or were not here at the
14 scheduled time, we would still like for you to be able
15 to speak.

16 So if you contact Ayana, you can either
17 give me your written statement, or give her your
18 written statement, and it will be read in the
19 afternoon open session by one of us if you would
20 prefer not to read it yourself.

21 And also I would just like to remind all
22 the speakers when you do get up to the podium, please

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 adjust the microphone so that it is in a position
2 where the things that you say will come out clearly.

3 It is important for the transcriptionist
4 and for us in the audience. Since you are facing this
5 way the audience has difficulty hearing you if you are
6 not speaking directly into the microphone. I
7 appreciate that. Dr. Choti.

8 CHAIRMAN CHOTI: Thank you, Dr. Krause. I
9 think most of the panel has asked their questions of
10 the sponsor, and so now we will move ahead to the FDA
11 presentation. Dr. Lerner.

12 DR. LERNER: Good morning, Dr. Choti, and
13 Dr. Krause, and Members of the Panel, and guests. I
14 am Dr. Herb Lerner, a reviewer for the Plastic and
15 Reconstructive Surgery Devices Branch at the ODE.
16 Today, I will be presenting the FDA's review of the
17 PMA for Sculptra.

18 Sculptra is intended to correct the shape
19 and contour deficiencies resulting from patient fat
20 loss from lipoatrophy in people with human
21 immunodeficiency virus.

22 Sculptra is a sterile solution consisting

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 of PLLA, sodium carboxy-methyl cellulose, mannitol,
2 and sterile water. Listed on the screen are the
3 members of the review team for this PMA.

4 Dr. David Berkowitz will be making a few
5 remarks regarding the toxicology of the device, and
6 then I will be presenting the PMA. Dr. Berkowitz.

7 DR. BERKOWITZ: Good morning. The
8 components of Sculptra have long histories of medical
9 use. The components are carboxmethyl cellulose,
10 aerolaytic acid, and mannitol. The components of
11 Sculptra have long histories of use in medicine, and
12 the carboxmethyl cellulose is used, for example, in
13 wound dressings and adhesion barriers.

14 Larger amounts are used orally as bulking
15 agents and laxatives. Polylactic acid is used in
16 orthopedic implants and sutures, and all of the
17 polylactides, or if all of the polylactides from three
18 vials of Sculptra were hydrolyzed at once, the lactic
19 acid produced would be less than the amount present in
20 500 mils of lactated Ringers Solution.

21 The use of microparticles for PLLA is new.
22 Mannitol has been used systemically at does of 2

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 grams per kilogram to reduce intracranial pressure.
2 The dose of Mannitol in three vials of Sculptra is
3 about 6.4 milligrams per kilogram for a 60 kilogram
4 patient.

5 So all of these have histories of safe
6 use. The purpose of the toxicology testing is to
7 assess the safety of this particular combination of
8 products. The slide summarizes the testing performed.

9 Cellular toxicity was done by placing Sculptra
10 directly on a lawn of L929 cells. There were no
11 significant cytotoxicities.

12 Sensitization was tested in a Magnusson-
13 Klingman test, and Sculptra was diluted one-to-one for
14 sensitization, but was used undiluted in the
15 challenge. There was no significant sensitization.

16 The acute systemic toxicity Sculptra was
17 tested by IP injections in mice at doses of 5 grams
18 per kilogram, and again there was no systemic
19 toxicity. Subchronic toxicity was tested by following
20 in cutaneous injection for 90 days in rats.

21 Extensive general health parameters were
22 monitored, and no significant toxicity was observed.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 At the implant site, there was a normal foreign body
2 reaction that we heard about.

3 Implant material was present at 90 days,
4 though only five implant sites were examined
5 physiologically. Genotoxicity was tested in a
6 bacterial reverse mutation assay, a chromosomal
7 aberration assay, and an in vivo micronucleus test.

8 Sculptra did not increase mutations,
9 chromosomal aberrations, or mouse micronuclei.
10 Complement activation was not affected by Sculptra.
11 Both the CH-50 test and the measurement of the amount
12 of SC5b-9, and that is the membrane attack unit, were
13 measured and both were normal in human serum.

14 So none of the testing raised significant
15 toxicological concerns. All of the essential
16 toxicological testing was completed. Sculptra
17 physical characteristics are described here.

18 The molecular weight is 40 to 50 thousand,
19 and the PLLA particles are of irregular shape, and the
20 sizes of the particles are 40 to 63 microns, with 10
21 percent of the particles allowed to be less than 40,
22 and 2 percent that exceed the 63.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Two hours are required for optimal
2 suspension of the material, and the two hours are
3 primarily for wetting. Sculptra is physically,
4 chemically, and microbiologically stable for 72 hours
5 after suspended as we discussed, or as was discussed
6 previously.

7 Sculptra resorption kinetics were looked
8 at, and there was no weight loss for 24 weeks in
9 phosphate buffer 7.4, at 37 degrees. There was a 19
10 percent weight loss at 50 degrees.

11 Foreign material was seen histologically
12 for 90 days after implant, subcutaneous implants in
13 rats. So it means that at least some of the material
14 was present after 90 days.

15 The resorption rate is a function of
16 molecular size, weight, crystallinity, and particle
17 size. Gogolewski did some studies on various types of
18 PLLA implanted, and in this particular study, he used
19 4-by-7 millimeter rods subcutaneously in rats.

20 And the material was 95,000 molecular
21 weight, and 19 percent was degraded by one month, and
22 by 3 months, 40 percent was degraded, and at 6 months,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 56 percent was degraded.

2 But the published material indicates that
3 PLLAs in several cases in fibrous tissue actually
4 outlived the material itself. That is, it took longer
5 for all of the fibrous tissue to disappear than it did
6 for the PLLA to disappear.

7 That's all I have, and I think that Dr.
8 Lerner will now present a summary of the clinical
9 testing.

10 DR. LERNER: New-Fill is the name of the
11 device that is commercially available outside of the
12 United States. Sculptra is the intended name of the
13 device as it will be marketed within the United
14 States.

15 For this review, the use of these names is
16 interchangeable. The safety and effectiveness of the
17 device is supported by five investigator sponsors'
18 clinical studies. As noted on the slide, two studies
19 were done in Europe, one in France, and the other in
20 England.

21 The U.S. studies were done in Florida and
22 in California. None of the trials were controlled,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 randomized, or blinded. All were open labels and were
2 single center studies. Note that the C&W study had a
3 delayed treatment group to serve as a, quote, control.

4 Additionally, photographs were taken
5 during all studies. Panel members were presented a
6 copy of these photos for their review. Patient
7 confidentiality does not allow us to project these
8 photos for public viewing.

9 All the studies used some measurement of
10 skin thickness to assess the effect of device
11 implementation. In the VEGA study performed in
12 France, total cutaneous thickness was measured by
13 summoning the ultrasound measurements of the buccal ft
14 pad and skin thickness.

15 In the C&W study from England, there was a
16 Doppler ultrasound measurement of the full thickness
17 of the area to assess the thickness. Common to all of
18 the studies that I will be presenting is the inclusion
19 criteria that the patients be HIV positive, and have
20 been on antiretroviral therapy prior to enrolling in
21 the study.

22 It is recognized that some patients

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 stopped these medications to prevent the sequelae of
2 lipoatrophy. This was taken into consideration when
3 the FDA terminated that this PMA should receive
4 expedited status.

5 For the VEGA study in France the inclusion
6 criteria included HIV positive, a plasma viral count
7 of less than 5,000 copies, current antiretroviral
8 therapy of greater than or equal to 3 months, with at
9 least a previous 3 years of a history of
10 antiretroviral therapy, and an buccal adipose tissue
11 of less than 2 sonometers.

12 As noted the sponsor used the measurement
13 of buccal adipose tissue as a criteria for inclusion
14 and for success. As I will discuss shortly the total
15 cutaneous thickness measurements were determined for
16 each of these patients and used for the effectiveness
17 evaluation.

18 Exclusion criteria included cutaneous
19 Kaposi's sarcoma of the face, infections, or
20 concurrent herpes labialis, previous facial fillers
21 within 6 months, and patients unwilling to meet the
22 study follow-up timetables.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 The study was an open label, non-
2 randomized, and uncontrolled study. Patients were
3 given biweekly injections to maximum correction, and
4 in this study the device was mixed with 3 cc's of
5 sterile water.

6 All patients had at least three
7 treatments; three patients had six. They were
8 followed for up to 96 weeks to gather data on adverse
9 events, and total cutaneous thickness measurements.

10 Measurements were again made by Doppler
11 ultrasound at several predetermined locations on the
12 face, including the zygomatic arch and the center of
13 the buccinator muscle.

14 Fifty patients were enrolled and 47
15 patients completed the trial. Two withdrew at 72
16 weeks, and one withdrew due to an unrelated event.
17 The average mean years of age was 44.9, and 98 percent
18 were male, and 84 percent were caucasian, and 6
19 percent hispanic.

20 Fifty percent of the patients had had an
21 AIDS defining event as was previously mentioned, and I
22 won't repeat them, but the CD4 HIV viral loads, TCT

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 measurements, and adipose tissue measurements are on
2 the screen.

3 Safety endpoints. The design to look for
4 changes in standard biological parameters. Several
5 events, such as injection site bruising, 3 percent of
6 the patients; hematoma, 30 percent; and nodule
7 formation in 52 were noted during this study.

8 Nodules appeared from 9 days to 2 years
9 post-treatment. Most nodules were of mild intensity,
10 as judged by the investigator. There was one patient
11 with injection-site hemorrhage, and another with
12 edema.

13 There were no clinically significant
14 changes in CD-4 salt count, and there were no
15 clinically significant changes for baseline in viral
16 load or lactic acid levels, during this study.

17 The mean increase above baseline ranged
18 from 5.2 to 7.2 millimeters throughout the study
19 period for the total cutaneous thickness measurements.

20 These were statistically significant at each time
21 point.

22 The number of responders, those defined as

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 a gross TCT greater than 10 millimeters, peaked at
2 Week 48. This was an arbitrary point. In addition to
3 the TCT, the sponsor performed a Visual Analogue Scale
4 for evaluating global well-being, and assessing
5 quality of life.

6 At baseline the median score was between
7 6.1 and 6.7, indicating a satisfactory physical or
8 emotional state. After treatment the scores increased
9 by .3 to .8, which was statistically significant at 6
10 and 12 months.

11 Remember that there are no controls for
12 evaluating these results and the data must be looked
13 at accordingly. This slide you have already seen.
14 The efficacy endpoint was established as a proofing on
15 the TCT over time, and as you can see on this slide
16 again, the increase is constant and reproducible.

17 The Chelsea and Westminster study in
18 England, inclusion criteria again were HIV positive,
19 with mild to severe lipoatrophy, and not pregnant or
20 lactating.

21 Exclusion criteria included active
22 opportunistic disease or wasting, current growth

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 hormone therapy, current chemotherapy for malignancy,
2 or non-hypersensitivity to PLLA. Thirty patients were
3 enrolled, and again an open label, non-randomized, and
4 uncontrolled study.

5 Patients in this study received three
6 treatments, spaced approximately 2 weeks apart. The
7 patients in the delayed group had treatments at Week
8 12, 14 and 16.

9 In this study the device was mixed with 2
10 cc's of sterile water, and one CC of lidocaine.
11 Ultrasound was used to determine facial thickness at
12 the nasolabialfold, the corner of the mouth, zygomatic
13 arch, and centrally in the buccal fat pad.

14 Visual analogue scores were between zero
15 and ten, with zero being as thin as it had ever been,
16 to 10, not thin at all. Antidepressant/anxiety scores
17 were scored between zero and 21, and with zero as
18 normal, 8 to 10 suggestive of a mood disorder, and 11
19 to 21 with the possible presence of a mood disorder.

20 The demographics are similar to that in
21 the previous VEGA study. The safety end-points
22 included a change in viral load, a change in CD4

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 count, a change in blood chemistries, or adverse
2 events, and there were no significant changes in the
3 CD4 count or viral load counts over time for either
4 treatment group.

5 As in the VEGA the most common adverse
6 events were treatment related, with 80 percent of the
7 patients experiencing at least one event. The most
8 common event was bruising, and 31 percent of the
9 patients developed an injection site nodule. Few of
10 the events were severe. One patient did develop a
11 skin infection.

12 For all measures there was significant
13 improvement from baseline. There was significant
14 changes in dermal thickness in each group. Generally
15 there was a 4 to 5.5 millimeter improvement in buccal
16 thickness at week 12 and 24 of the first group, and at
17 week 24 in the second.

18 The VAS scores showed improvements in body
19 perception, and HAD scores changed from suggestive of
20 a mood disorder to normal. For the face the VAS
21 scores improved from 2.3 mean at baseline, to 7.2 at
22 week 12.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 And from 2.3 to 6.1 at week 24. HAD
2 scores changed from 7.9 to 7.2, and anxieties from 5.1
3 to 4.8, indicating improvement in patient self-
4 assessment.

5 In this study the device was injected into
6 several areas of the face. The slide shows the
7 improvement of buccal thickness for the initial group
8 of patients, and the results are comparable to the
9 delay group. I know that it is hard to see, but if
10 you look at the cheek area, you will see that the
11 range of improvement over the period of time for the
12 study.

13 Common findings in both studies. There
14 was nodules at the injection site, 52 percent in the
15 VEGA study, and 31 percent in the C&W study. The
16 average on-set was up to 218 days, with a range from 9
17 to 748.

18 Most of the nodules were reported as mild
19 and not visible, and there is no histologic data
20 available. A review of Dr. Englehard's study, and is
21 a investigative sponsored compassionate use study.

22 This is the APEC-001, the inclusional

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 criteria include HIV positive and demonstrable
2 photographic lipoatrophy, and exclusion criteria
3 included active infection, Kaposi's sarcoma, or
4 Herpes.

5 They must not have had facial injections
6 within the last 3 months or be on interferon or
7 steroid treatment. This study and the two which
8 follow are primarily valuable for their safety
9 analysis.

10 In this study, treatment could be to the
11 cheeks and temple, but not to the temples alone.
12 Subjects could receive up to six treatments, and the
13 majority had up to three.

14 Patients were treated with 1 to 8 CC's of
15 New-Fill. Treatment was at 3 to 4 week intervals, and
16 two patients in the group have died, one due to ,
17 cryptosporidiosis, and the other to mycobacterium
18 infections.

19 Four patients did not return for their
20 first visit, and 38 of 96 have not completed the 24
21 month follow-up. Fifty-eight have reached the 1 year
22 point, but not the 2 year point.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Nodules were reported as the main device-
2 related adverse event. Subject satisfaction with the
3 correction at 6 to 12 months after treatment was high;
4 a rating from 8.1 to 10 on a 10 point scale.

5 At 24 months, it was 7.5. These are not
6 validated scores, but due reflect patient responses.
7 Investigative ratings showed continued improvement,
8 with almost complete facial satisfaction at 12 months.

9 Again, although not validated,
10 investigative ratings went from 3.2 at baseline on a
11 scale of five, with five being worse, to 1.36 at 12
12 months.

13 The APEC 002 study. A hundred subjects
14 were enrolled, and 37 of the 99 patients had completed
15 their 6 month follow-up, and 34 subjects have
16 completed their 12 months.

17 The remainder are still within the study
18 guidelines. The majority of the patients received 3
19 to 4 treatments at 4 to 6 week intervals. Subjects
20 received an average of 7.8 cc's of New-Fill at each
21 treatment session.

22 Please note the similar HIV and HAART data

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 compared to all the previous studies. As in the other
2 studies, treatment related events predominated, but
3 were generally mild. There have been six nodules
4 reported to close the data.

5 Subjects related their lipoatrophy on a
6 scale of 1 to 5, 5 being low scale, and most severe.
7 At baseline, the average score was 3.71, and at 6 and
8 12 months, it was under one.

9 The California study. This study is
10 ongoing, and 15 of 95 patients have completed their 6
11 month follow-up, and patients received 1 to 6 cc's at
12 each treatment, for up to 6 treatments.

13 Adverse events, again, mostly treatment
14 related, with 8 nodules in 87 patients. Again, note
15 the similar HIV and antiretroviral therapy. Inclusion
16 criteria was similar to the APEC study. HIV positive
17 for lipoatrophy, infections, treatment with interferon
18 or steroids, uncontrolled diabetes, or lactic
19 acidosis.

20 The endpoints were to evaluate the
21 quantifiable improvement in facial wasting after
22 serial intradermal injections. The safety endpoint

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 were determined for repeated treatments, and the
2 efficacy for durability of New-Fill, and the
3 psychological impact on patients.

4 For this study, caliper skin measurements
5 were taken at treatment sessions, and up to 12 months.

6 The results were that there were eight nodules in 87
7 patients, and the remaining treatment-related events
8 were reported as mild.

9 There was high patient satisfaction, and
10 the average change in the total cutaneous thickness
11 was 6 millimeters at 6 months, and the ranges are
12 projected on the slide.

13 The overall conclusion for safety in
14 general, the majority of treatment-related events were
15 mild, and one being mild pain, bruising and swelling
16 at the injection site. Device events were generally
17 palpable subcutaneous nodules up to 15 percent, and no
18 major events were reported.

19 Total cutaneous thickness analysis in the
20 VEGA study showed an increased thickness. Normal
21 thickness changes in the C&W study showed significant
22 enhancement of the overall fitness.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Photographic evidence indicates sustained
2 effectiveness, and quality of life assessments show
3 improvement from baseline. While the study did not
4 use a validated statistical method, my review of the
5 photos shows effectiveness. We await your opinion.

6 I will finish with a short statistical
7 summary. Our statistician is here if you have any
8 questions. A mass assessment using a validated
9 severity scale was not performed.

10 Changes in ultrasonic measurement of
11 subcutaneous skin thickness were taken to be a
12 surrogate endpoint for improvement in facial
13 appearance.

14 There was a statistically significant
15 increase from baseline in total cutaneous thickness at
16 every follow-up for two years for the VEGA study, an
17 through week 24 for the Chelsea and Westminster
18 study.

19 There was no evidence that the effect of
20 the treatment was related to the length of time on
21 antiretroviral therapy, baseline CD-4 count, or
22 baseline skin thickness. However, there was more

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 change in skin thickness compared among those patients
2 who skin was thinner to start.

3 Overall, the sponsor demonstrated that
4 increased skin thickness was pictorially correlated
5 with improved appearance. Thank you

6 CHAIRMAN CHOTI: If that is the end of the
7 FDA presentation, it's open for the panel to ask any
8 quick questions to the FDA if there are any. Yes, Dr.
9 Fisher.

10 DR. FISH: This may be a question for the
11 statistician. In the breakdown, there was a breakdown
12 in the information that we received regarding
13 stavudine use and non-stavudine use in the Chelsea-
14 Westminster study.

15 In the immediate treatment group, where we
16 would be expecting a treatment response at Week 12 in
17 the non-stavudine use, it looked like that there was
18 not a treatment response at Week 12, and yet it came
19 at Week 24. The end is certainly smaller.

20 Is that a statistical anomaly or is there
21 an explanation for that?

22 DR. SILVERMAN: Well, the statistical

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 significance is very highly correlated with sample
2 size, and if the study is not powered to detect a
3 certain difference, then things can come out either
4 statistically significant and clinically meaningful,
5 or not come out statistically significant when they
6 are clinically meaningful. So it is really just a
7 function of the sample size.

8 CHAIRMAN CHOTI: Dr. Miller.

9 DR. MILLER: Yes, in your review of the
10 VEGA study there was one event of a difficult
11 granulomas problem in a patient, and I think I recall
12 it being mentioned that this patient had a
13 granulomatous disease, like Crohn's, or something, or
14 Cushing's. Well, not Cushing's.

15 But could amplify that a little bit? Do
16 you recall that or is that an issue that we have to be
17 concerned about with this device, and in somebody who
18 has a granulomatous disorder, they will be prone to
19 forming unfavorable granulomas with ingestion of this
20 device.

21 DR. LERNER: There was no data of that
22 patient population in the PMA. I don't particularly

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 remember the one patient that you are referring to,
2 but we did not have any data to correlate a patient
3 population with some sort of granulomatous disease
4 with outcomes in the PMA.

5 DR. MILLER: Okay. I guess it was just
6 mentioned in the sponsor's material.

7 DR. LERNER: Right.

8 DR. PENNEYS: I have a related question
9 actually because there are also variables that exist.
10 For example, what happens with this material if it is
11 injected into someone who forms keloids?

12 There is no information. I mean, their
13 response to trauma is markedly different than other
14 folks, and it is very common. So if you inject this
15 into a lipoatrophy and somebody who gets keloids, what
16 are you going to get? Are you going to get too much
17 response, or a lumpy response, or a keloid? Does
18 anybody know?

19 DR. LERNER: I could think that they might
20 want to, but I might want to address that given the
21 fact that there has been a lot of experience, not with
22 this product, but with similar products.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 We use Vicryl, for example, all the time,
2 and as far as I know, there is no significant
3 difference in patients who have keloids. That is
4 something that is -- you really don't -- I would not
5 stop using Vicryl because of keloids.

6 In fact, I probably would use it so that I
7 would not have to have stitches that go through the
8 dermis.

9 CHAIRMAN CHOTI: Any other specific
10 questions for the FDA?

11 PARTICIPANT: In the IDE study it was an
12 uncontrolled study, and I was wondering from the FDA's
13 perspective if you discussed that with the sponsor,
14 the fact that it was uncontrolled?

15 DR. WITTEN: Well, can I just comment,
16 which is that all of these studies are sponsor
17 investigator studies. So they were not initially
18 designed to support a marketing application.

19 CHAIRMAN CHOTI: Yes, Dr. Leitch.

20 DR. LEITCH: I am still trying to get back
21 to our mechanism of action. For the evaluation of
22 long term reaction in tissues, the injections in the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 rates were subcutaneous, right; here you had the five
2 sites with -- and looking at degradation of the
3 product over time.

4 And so there was some histologic findings
5 there, but because the injections were subcutaneous
6 does that -- would there be a difference in
7 degradation or reaction, or product performance;
8 subcutaneous versus intradermal?

9 DR. BERKOWITZ: It is hard to know that,
10 but all the reactions that we saw were normal foreign
11 body reactions, and they are similar generally
12 wherever they are placed.

13 And it may change the kinetics of the
14 reaction; that is, there may be depending on where it
15 is, there could be a longer initial inflammatory
16 response and take longer for cells to go through those
17 kinds of changes. So I would assume that would make a
18 difference.

19 DR. PENNEYS: A follow-up question to that
20 point. Do you think that the responses are directly
21 proportional to the intensity of the foreign body
22 response?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. BERKOWITZ: I don't have any data to
2 have --

3 DR. PENNEYS: What I am really asking is
4 if this were used in people with normal immune
5 resistance or more vigorous inflammatory responses,
6 would there be a different clinical response?

7 DR. BERKOWITZ: It is really difficult to
8 judge that.

9 CHAIRMAN CHOTI: Dr. Leitch, a question?

10 DR. LI: Yes. You compared or you spoke
11 about the use of PLA in orthopedic devices, and the
12 fact that the amount of PLA was equivalent to what one
13 might find in a bottle of Ringers.

14 However, a comment on that is that you are
15 not putting all the lactic acid in a Ringer solution
16 into one very small area, and so I am not sure that
17 the analogy to Ringers is actually relevant in this
18 particular case.

19 And also you mentioned that it is used in
20 orthopedic devices, but I am not aware of any
21 orthopedic device actually that uses a PLA with such
22 low molecular weight and with such a high surface

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 area, and placed into a relatively small area.

2 Are there any analogues that you can think
3 of other than the genetic fact that there are PLA-
4 containing materials in orthopedic devices?

5 DR. BERKOWITZ: Well, because these
6 particles are so small the surface area is relatively
7 huge. So I think that is a new feature of the
8 material.

9 CHAIRMAN CHOTI: Could you please use the
10 microphone for your comments.

11 DR. BERKOWITZ: I'm sorry, yes. The
12 surface area of the small particles is huge, and so I
13 think that is one different feature of this material,
14 as opposed to just say a plate of material that is put
15 over a bone, for example, so that the surface area is
16 much greater. So there really are not direct
17 analogues to this particular thing.

18 DR. LI: How about molecular weight? The
19 molecular weight that you are using is 40-to-50,000 by
20 the time that they are done gamma sterilizing and
21 injecting into the patient. Are there any orthopedic
22 devices that use lactic acid in that low molecular

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 weight range?

2 DR. BERKOWITZ: That I don't know. Sorry,
3 I don't know.

4 DR. LI: And then a kind of follow-up
5 question about that. I think it was you that
6 presented the degradation rate of literature study
7 using rods of PLA. But those rods of PLA were double
8 the molecular weight of the material being used in the
9 Sculptra.

10 And there was a 19 percent degradation in
11 one month in those rods, which have a smaller surface
12 area and higher molecular weight. And yet -- I will
13 ask the same question to the applicant later on, but
14 in their studies of degradation at 24 weeks, they saw
15 no degradation.

16 So how do you rationalize the fact that
17 you have a literature study that has a smaller surface
18 area, high molecular weight material, that degrades 19
19 percent in one month, compared with a very high
20 surface area, low molecular material, that does not
21 dissolve at all in 24 weeks.

22 DR. BERKOWITZ: Well, it is very

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 difficult, and I can only guess at that, and I would
2 assume that the particles -- it would depend upon
3 whether the particles are coated, and if they are
4 coated with collagen, or how exactly the reaction
5 forms. I mean, it is purely speculative.

6 DR. LI: Well, this was even in the in
7 vitro test if I understand right. At 24 weeks, they
8 saw no degradation.

9 DR. BERKOWITZ: Pardon me?

10 DR. LI: That was also in the applicant's
11 -- is that correct, in their in vitro testing where
12 there was little or no collagen available, but they
13 were still showing no degradation at 24 weeks.

14 DR. BERKOWITZ: Right, but I think that is
15 just for -- that was at 7-4, and so that was normal
16 aqueous hydrolysis, whereas I think that tissue fluids
17 may have esterases that could speed up that
18 degradation process.

19 DR. LI: Okay. Thank you.

20 CHAIRMAN CHOTI: Final questions for the
21 FDA? Yes, Dr. Fish.

22 DR. FISH: In the conclusions line, if I

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 understood it correctly, you stated that the
2 effectiveness occurred across CD4s counts. Do you
3 have the data in terms of the percent of patients in
4 the various trials who had CD4s under 200?

5 DR. LERNER: I don't have the documents
6 with me. I mean, it is in there, but I don't have it
7 with me.

8 CHAIRMAN CHOTI: Dr. Leitch.

9 DR. LEITCH: I know that you were charged
10 with looking at these trials -- the clinical trials is
11 what I am talking about now -- that were related to
12 the HIV positive patients, but did the FDA look at
13 other clinical trials done for cosmetic uses in Europe
14 to get a sense of issues like longevity of response of
15 the product?

16 DR. LERNER: No, we just looked for this.
17 We went back and looked at the data that the sponsor
18 submitted.

19 CHAIRMAN CHOTI: Yes, Dr. Li.

20 DR. LI: Just a quick question. I think
21 that this would be kind of a yes or no question. I
22 was a little confused as you read through the material

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 descriptions, the difference between specifications of
2 the product and what they actually measured.

3 So I saw a lot of measurements that they
4 made on the products that they did a nice job on, but
5 I don't recall seeing like a little table that says
6 the characteristics of these products shall be, for
7 instance, must be between such and such a particle
8 size, or the molecular weight must be between a
9 certain area.

10 Are those specifications in this filing,
11 or are they not?

12 DR. BERKOWITZ: Yes. I did not review all
13 of that, but you might ask the sponsor for that table.

14 I presume --

15 DR. LI: I think especially in the absence
16 of any kind of mechanism. You know, if you are just,
17 you know, by gosh or by golly, you kind of have the
18 magic formulation. If you don't understand the
19 mechanism, I think the requirements of making that
20 product ought to be very tight.

21 DR. DURFOR: Charles Durfor, the FDA
22 chemist who reviewed this application. I certainly

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 don't want to have the company come after me, but in
2 answer to your question with regards to
3 specifications.

4 This is a discussion that we have ongoing
5 with the sponsor. There are refining the
6 specifications at this time, and they have done a lot
7 of work to characterize the product, and we are
8 working with him to make sure that the specifications
9 reflect the product that was used in the clinic.

10 DR. LI: My only comment that in the
11 absence of a mechanism, that the specifications should
12 be relatively tight, because you don't know what the
13 response is to small changes in the material.

14 For instance, if you have a batch that for
15 some reason has a 30,000 molecular weight in the
16 absence of a mechanism, that might cause a very large
17 histological change. I mean, I am just kind of making
18 that up as an example.

19 In the absence of a mechanism, I think the
20 specifications should be very tight.

21 DR. DURFOR: I fully agree. I think that
22 Dr. Berkowitz in this presentation talked about some

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 of the factors that are involved in the kinetics of
2 resorption and obviously related to the foreign body
3 response.

4 And we are requesting that the sponsor
5 work with us to make sure that those specifications
6 with regard to particle size, molecular weight, and
7 the like, all those things that can impact the
8 resorption kinetics of the product are defined as
9 final product specifications.

10 CHAIRMAN CHOTI: May we hear from the
11 sponsor just to address this specific question, if you
12 would.

13 DR. FORBES-MCKEAN: I am Kim Forbes-McKean
14 from the Drmik, in the product development area and
15 commercialization, and as Dr. Durfor mentioned, we are
16 currently working with the FDA on what will be our
17 final product specs for the product, and also what we
18 plan to do as in-process control to ensure that we
19 have consistent quality in specifications of the PLA
20 after it is milled and sterilized, and then put into
21 the product.

22 We have done extensive work to understand

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 what happens to particle size and molecular weight,
2 and crystallinity, et cetera, after the product or
3 during the process of making the product to ensure
4 that either through our in-process control
5 specifications, or our finished product specs, that we
6 will deliver a consistent high quality product.

7 DR. LI: Just as a follow-up question.
8 How will you determine what is an acceptable
9 specification? In other words, pick a factor. It
10 does not matter what it is. You know, how do you know
11 if for instance the molecular weight is too low or too
12 high?

13 How do you set those limits for the
14 particle size of the crystallinity? How would you
15 actually establish a link between those limits and the
16 clinical performance?

17 DR. FORBES-MCKEAN: We have done a
18 significant amount of work to characterize historical
19 batches that we have obtained through our -- who have
20 worked with the prior manufacturer to characterize
21 what were the characteristics of particle size and
22 molecular weight, and inherent viscosity, and all the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 parameters that we have been discussing here on the
2 lots that were used in the clinical studies that are
3 the subject of this PMA, as well as commercial batches
4 that have been out in use that have collected the
5 safety data through our adverse event reporting system
6 to characterize the product that we consider was used
7 to be validated in a clinical program, as well as in
8 the use that has been available in the commercial
9 distribution of the product, to devise the
10 specifications that we have proposed, which we feel
11 are suitable to represent the lots that were used to
12 do the clinical work, as well as what has been out
13 there commercially available.

14 DR. LI: So in a nutshell, we did it
15 empirically, and basically go back and look at all of
16 the specifications in all the lots that were
17 successful, and stay within those specifications?

18 DR. FORBES-MCKEAN: Yes.

19 DR. LI: Okay.

20 CHAIRMAN CHOTI: Thank you, Dr. Forbes-
21 McKean. Dr. Newburger, questions for the FDA?

22 DR. NEWBURGER: In your studies with the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 rats, Dr. Berkowitz, did you by any chance
2 characterize what the pH in the tissue was once the
3 PLA started to degrade? Was there any alteration?
4 Did you ever do --

5 DR. BERKOWITZ: No, I don't think -- that
6 has not been studied as far as I know. There are --
7 when PLA degrades rapidly, it can increase the osmotic
8 pressure and there can be some swelling in tissue, and
9 that would have been one of the published reports from
10 other authors.

11 And in fact I think it was for an
12 orthopedic implant, and two years after it was
13 implanted and it sort of got to a critical stage of
14 degradation, where esterase could reach it, and very
15 quickly release monomer, which increased the osmotic
16 strands.

17 And there was a time when there was edema
18 surrounding the tissue and it eventually went away on
19 its own.

20 CHAIRMAN CHOTI: Thank you. So we have
21 heard information from the company, and from the FDA,
22 and now it is time to summarize the comments from the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 panel.

2 What I would like to do is get opinions
3 from all members of the panel if we could, and just
4 kind of general comments and overview. Why don't we
5 go ahead. We are not going to be showing anymore
6 presentations, and why don't we clear the table in
7 front.

8 Let me start if I could ask Dr. Olding to
9 start with some comments, please, and then we will
10 kind of work our way around.

11 DR. OLDING: I have a relatively limited
12 background in terms of serving on these panels before,
13 but I must admit that the characterization which we
14 have asked about here today anyhow.

15 The characterization and how the material
16 works, and how long it lasts, and why it lasts so
17 long, are for me -- and I would suspect many panel
18 members -- very murky. The details for that are.

19 We don't know what the ideal-sized
20 particle is really. We don't know what the ideal
21 concentration of PLLA is even, and what is the ideal
22 reconstitution.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 We also are unclear about the nodule
2 formation, although to be honest with you, having done
3 some research with related products, and looked at
4 that histologically, it causes a relatively intense
5 histologic foreign body reaction, which we have not
6 seen any slides of, but we presume exist, and I don't
7 think it is rocket science from my point of view.

8 I think that it is an inflammatory
9 reaction, and probably the reason if you look back at
10 the studies, the nodules were often noticed first I
11 think at 24 weeks, I believe.

12 But the injections were at 2, 4, 6, 8 and
13 then the first visit was at 12 weeks. Any experience
14 that I have had with injections of materials that
15 cause foreign bodies, you have a generalized sort of
16 swelling and edema for a while, and so they probably
17 weren't seen at that 12 week period simply because it
18 was generalized swelling in the area.

19 Then the next time they came back was 24
20 weeks, and that does not necessarily mean that they
21 first noticed the nodules as they first developed, but
22 in fact you might be able to palpate it at that point.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 So that does not really bother me, and the
2 comments about the surface area, I mean, none of those
3 things have really been characterized very well. So
4 for me it is a little bit of an uncomfortable feeling.

5 However, I have had a lot of experience with
6 injectables, and I have seen a number of patients who
7 are HIV positive patients, with wasting.

8 And I actually ended up sending them to
9 someone in town who did use New-Fill, and I did that
10 because I didn't feel that I had an acceptable
11 alternative. I had seen the other ways of treating
12 these patients, and they have not been good, and the
13 results have not been good.

14 And I calculated just in between how much
15 it would cost me to inject, or how much it would cost
16 the patient to inject similar volume with either
17 collagen or with a relatively new product, Restylane.

18 For me, a patient coming in averaging 7.8
19 cc's per treatment would be \$6,000 per session. So we
20 are talking about \$12,000 a year if you presume that
21 it lasts 12 months.

22 Collagen is purported to last 3 months and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 in my experience it lasts less than that. But again
2 we are talking around \$8,000 a year for those
3 treatments.

4 So this product, although it has not been
5 well-characterized from my point of view, certainly
6 does what it is intended to do, and it does it at a
7 relatively inexpensive price, and it seems to really
8 fill a gap that is much needed.

9 CHAIRMAN CHOTI: Dr. Li, comments?

10 DR. LI: Similar comments. Let me first
11 of all say that it appears to work first and foremost,
12 although I am a little puzzled as to why. Which
13 basically I think that it focuses my discomfort that
14 the mechanism is unknown, and although the applicant
15 has done a lot of material testing, it is not
16 particularly type testing, where every lot of material
17 was tested in the exact same way to give you one very
18 clear picture.

19 There is a lot of mixed lots, and
20 different tests, and there is actually anomalous data
21 about how much -- about the crystallinity and some x-
22 ray data that were -- there was some hypothesis of why

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 that was done, but there were some anomalies in the
2 data that is very common for PLA material.

3 And which is a very difficult material to
4 synthesize and it is kind of made a batch at a time,
5 and my own experience is that there is lot to lot
6 variations, and it just does not seem in the absence
7 of specifications, which I hear they are developing,
8 they are either very lucky about what they are using,
9 or in fact that they are very insensitive to all these
10 factors.

11 And at this point, I really don't know
12 which it is. So that is kind of my discomfort. I
13 have a lot of specific questions about the materials
14 testing that I will maybe ask later, but in a
15 nutshell, it seems to work and I don't know why.

16 And I don't think that the
17 characterization is as stringent as it should be given
18 that a lot more patients is going to get this, and
19 probably in the HIV population, and that the material
20 specs are not well worked out.

21 CHAIRMAN CHOTI: Thank you. Dr. Penneys.

22 DR. PENNEYS: Thank you. Well, I would

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 like to say that the presenter has made a very
2 effective presentation of the need for this, and even
3 though the photographs were lousy, there was dramatic
4 improvement, and it was obvious that it benefitted
5 these patients.

6 And as a dermatopathologist, I have
7 nothing to say because I have had nothing to review,
8 and as a dermatologist, I have a major concern. I
9 basically do a lot of CME and everyone in the -- and a
10 large percentage of the discussion is off-label use.

11 Twenty-four hours after this is available,
12 it is going to be used off-label, and I don't know if
13 it is appropriate for this panel to discuss, but my
14 major concern was in that area, and that is that it is
15 the other uses and the other possible shoe reactions,
16 and all the other unknowns that I am concerned about.

17 CHAIRMAN CHOTI: Dr. Fish.

18 DR. FISH: As an infectious disease
19 physician, the infection rate is certainly low and
20 negligible, and I am very pleased with that. Clearly
21 it seems safe. There was one abscess that I think was
22 reported and that was about it in the infection

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 category.

2 I think also that I agree with Dr. Li that
3 it appears to work. I am certainly convinced, and I
4 think there is urgency, and Dr. Miller brought this up
5 earlier. Patients really do need something. I really
6 appreciate the consumers that came today and gave up
7 their time to tell their stories.

8 These stories are very real, and I have
9 had patients travel to New York City and travel to
10 Montreal to get these treatments, and they are
11 effective.

12 Their appearance has improved and it
13 appears to last. How long it lasts I think we don't
14 know, and probably is very variable from person to
15 person.

16 So I appreciate that and I think I do also
17 worry about how they are used for a non-HIV infected
18 population, and a non-lipoatrophy patient.

19 CHAIRMAN CHOTI: Thank you. Dr. Miller,
20 any comments?

21 DR. MILLER: Well, I appreciate the
22 comments that have been made and I agree that there is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 a real need for something to address this problem like
2 with atrophy. I feel that there is a pressure being
3 placed to approve this particular device because it
4 appears to address the problem.

5 But I have a tremendous discomfort over
6 all the uncertainties about this device that have been
7 mentioned already, in terms of mechanism and in terms
8 of many aspects of it that are really not well
9 characterized and they are not really even addressed
10 in this study, which basically tells us that the skin
11 appears better after its use in this very select group
12 of patients.

13 It is very difficult to say that this
14 shouldn't go ahead because of the dire need of this
15 specific patient population, but all the uncertainties
16 about it make me very concerned about the issues, and
17 the off-label use, and the possibility of this being
18 used by many thousands of people who don't fall into
19 the specific category that we looked at in these very
20 limited and incomplete studies. And it puts us in a
21 very difficult situation.

22 CHAIRMAN CHOTI: Dr. Leitch.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. LEITCH: Well, I certainly have
2 concern about the lack of understanding of the
3 mechanism, and I think there are some questions about
4 duration of response from the Chelsea and Westminster
5 study as was mentioned, and in some of the other
6 studies injections were allowed to continue based on
7 response, and over time as people were dissatisfied,
8 which was not allowed in the other studies.

9 So perhaps that duration of response is
10 somehow related to getting more and more treatment.
11 And the failure to have an understanding of the
12 mechanisms and the impacts on how this influences the
13 injection technique, and discriminating it from
14 different fillers, where people might be accustomed to
15 using other fillers in some way.

16 But if this mechanism is different as is
17 being suggested based on the duration of the response,
18 then that has to be addressed in the education of
19 physicians.

20 And then I was also surprised that we
21 really did not get any data about its use and the
22 usual cosmetic use in Europe, and outcomes there in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 duration of response.

2 Or if there is data from both studies
3 about the mechanisms of actions with having skin
4 biopsies that would reflect that. And, of course,
5 none of these studies were controlled, and comparing
6 them to other known agents, although I think we heard
7 from people on this panel that perhaps those other
8 agents have not been as effective for these patients.

9 Clearly I think, you know, that we have a
10 great sympathy for the patients experiencing problems
11 that greatly impact their quality of life, and their
12 ability to go about in public.

13 So I think that when we are faced with
14 that type of a problem, then you may compromise on
15 what you think you would like to have in the
16 circumstances of approving this for cosmetic uses and
17 general use.

18 And I think what others have expressed is
19 that once it is approved that it could be used in
20 other contexts which have not been appropriately
21 tested based on the data that we have had presented
22 here.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 And the other thing to emphasize is that
2 the HIV population does have other -- you know, a
3 baseline medical condition and other medical issues
4 that impact their overall well-being.

5 And I think the idea of could there be
6 unusual reactions that occur in the long term, either
7 due to repeated injections, or a change in their
8 disease status that could be problems in the long
9 term.

10 CHAIRMAN CHOTI: Thank you. Let me make a
11 few comments. I really do agree, and my comments
12 reflect what has been said as well. I think the
13 problem in this specific indication I agree was well
14 defined, and I think it is important regarding the
15 efficacy in spite of the concerns.

16 And my concern as well about the mechanism
17 and the design of the trial. I think really based on
18 the photographs, and on the satisfaction, and as best
19 as can be perhaps designed in the trial design, and it
20 appears to work, and it appears to be effective in my
21 opinion.

22 So that is part of the concern. As far as

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the safety, I think the other issue is that the
2 numbers are relatively small, and it is a relatively
3 defined group of young caucasian males. So we really
4 don't have good evidence in the female gender, or in
5 other races, especially if it is going to be applied
6 in other patient populations.

7 But also in the HIV population, and so can
8 it be extrapolated to a larger population and these
9 are still unknown questions. But I do think that as
10 well that it appears to be based on the product and
11 based on at least the numbers that we have seen at
12 least relatively safe and effective. Dr. Chang.

13 DR. CHANG: I believe that from the data
14 presented here that two major questions that will be
15 asked of the panel is whether this product is
16 effective for the use that is proposed, yes, and is it
17 safe, and the data reflects that it is relatively
18 safe.

19 In the back of our minds, yes, there is
20 concern about off-label use, but a particularly off-
21 label use by persons of color. There is that issue of
22 how does one or how is one to predict who will be a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 keloid-former, and that would be potentially
2 disastrous with injection and such reaction in the
3 face.

4 My question is about potential long term
5 consequences and the data presented speak to a two
6 year follow-up. But if indeed a product is absorbed
7 and if indeed the thickness changes and touch-ups for
8 the treatment are required, then the question that I
9 would raise would these small palpable nodules
10 potentially coalesce.

11 Would they then become visible in the
12 future, and we don't have data for long term studies.

13 CHAIRMAN CHOTI: Dr. Blumenstein.

14 DR. BLUMENSTEIN: Well, despite being a
15 statistician, I am also a human, and I even have kids
16 and everything. I don't just work with numbers, but
17 anyway, I think certainly there is an unmet medical
18 need here, and I am quite sympathetic to that.

19 However, I feel like I have to comment as
20 a statistician here. First of all, I think that there
21 is a really cunning regulatory strategy going on here,
22 and at least that is one way to characterize it.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 That there will be off-label use, and I
2 can't bring myself to ignore the inadequacies of this
3 study relative to the potential for the off-label use.

4 For example, I just don't think that the safety
5 database is large enough given the data that we have
6 been presented.

7 And furthermore even the efficacy may not
8 be applicable to a wider use. We have very limited
9 data on gender, and racial issues are quite limited.
10 And keloids, which I am not even sure what they are,
11 but I hear that is a problem.

12 And then another thing that I would add to
13 that is the possibilities of technique in a wider use
14 leading to other kinds of problems. So from a pure
15 statistical point of view, that the end-points are
16 invalidated, and they are highly subjective.

17 The photographs that we were given, one
18 thing is when you have an unvalidated end-point, one
19 of the things that is going to be used to talk about
20 the need of that end-point is whether it has face
21 validity.

22 Well, it is a mixture of what we were

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 shown here, and it is so obvious that you really don't
2 have to do the validation testing. But in this case,
3 I am still disappointed with the photographs because
4 first of all there was no quantification of it.

5 The quality of them is poor and there
6 seems to be systematic writing changes across time and
7 some sets of these photographs, I found them to be
8 completely difficult with respect to helping me
9 understand that.

10 And then the study designs were just
11 completely inadequate, and the lack of a control
12 group, and the lack of randomization, and the one
13 study where randomization could have really helped out
14 there was none.

15 You don't know what kinds of patients were
16 in those two groups. And in short, yes, there are
17 significant P-values, but that does not validate the
18 study designs or the end-points.

19 As I already mentioned about the safety
20 database, there has been some word here about nodules
21 and what is the other term, papules, and so forth, I
22 mean, these are anomalies.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 And I don't know whether there is enough
2 experience here, especially given in a wider use that
3 there would be skill issues and other things like
4 that, and whether there is enough data to know what
5 these anomalies would -- how frequent these anomalies
6 would be in wider use.

7 And therefore I am coming back to the
8 statistician at the end of this, and I have to state
9 that I find this data leaving me in a state of
10 inclusiveness.

11 CHAIRMAN CHOTI: Dr. Newburger.

12 DR. NEWBURGER: I can't recall ever being
13 in such a peculiar position. I think we do have a
14 tremendous amount of pressure on us to give approval
15 for this very well established need on an expedient
16 basis because we are compassionate individuals.

17 But the information that we are given
18 right now is really empiric. There is no other
19 material that we have ever seen presented that has had
20 such a paucity of data, true data, and this makes me
21 very uncomfortable.

22 CHAIRMAN CHOTI: Thank you. Dr. Munk.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. MUNK: I don't want to repeat what
2 others have said, but I would stress that there is
3 risk to patients and clinicians in any off-label use
4 of any FDA approved product, and I think that the
5 particular application, whether it is a cunning market
6 strategy or not, this is a very serious leap for HIV
7 patients with facial fat loss and I think that we do
8 need to respond to that need, which has been stated in
9 the application.

10 I mean, it leads to discontinuation of
11 antiviral treatment, and in some cases it leads to
12 avoidance of anti-viral treatment in the first place.

13 It is a very critical need.

14 CHAIRMAN CHOTI: Dr. Bartoo.

15 DR. BARTOO: Since we are getting to the
16 end of the table, there is not a whole lot of new
17 comments that I can make, but clearly we keep saying
18 that it appears to be work, as opposed to having valid
19 scientific evidence potentially that it does work, and
20 that it is effective, and safe, and so that is
21 something to consider.

22 However, especially in terms of long term

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 effects. However, there is this pressing need, and I
2 would like the panel to consider the possibility of
3 potentially post-approval studies to address some of
4 these concerns, as opposed to recommending not
5 approvable.

6 CHAIRMAN CHOTI: Dr. Doyle.

7 DR. DOYLE: Yes, I think I have decided
8 that everyone who has spoken on this is a scientist so
9 far, and so I put on my consumer hat, and I was very
10 moved by the people who spoke this morning, and I
11 think that there is definitely a need -- and poor pun
12 -- needs to be filled.

13 But I am somewhat disturbed by the lack of
14 women in the data, because we do know that this is for
15 wasting, and women's fast deposition and metabolism
16 does differ from males. Any woman who has gone on a
17 diet at the same time as her husband can tell you
18 that.

19 And while I think that this is important,
20 and I think that in many of the things that are
21 brought up here, I would like to know the answers to
22 some of the questions.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 On the other hand, speaking strictly from
2 the consumer point of view, I appreciate the panel's
3 need and want to protect me down the line, but if this
4 were me, and I had wasting disease, I would be less
5 concerned that you were worried about what would
6 happen 5 years out when there are no indications from
7 the data so far that I could tell even of any hint of
8 serious long term reactions from the data that we have
9 been presented, that I would be concerned rather than
10 what was going to happen to me 5 years out, if whether
11 I would go off my medication and whether I would
12 commit suicide because I was so unhappy with my
13 current existence.

14 And to me it is not a question from a
15 consumer point of view, but at this point certainly
16 what we know from my point of view, the benefits would
17 certainly outweigh the risks for me.

18 CHAIRMAN CHOTI: Are there any other
19 general comments from the panel? So that concludes
20 sort of our general discussion. Now, I would like to
21 move to the specific FDA questions.

22 What we will do is go to about 12:30, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 then we will resume with the questions. So the plan
2 is not to complete the entire discussion before lunch.

3 DR. LERNER: Question 1: 11 CFR
4 860.7(d)(1) states that there is a reasonable
5 assurance that the device is safe when it can be
6 determined that the probable benefits thereof from use
7 of the device for its intended uses when accompanied
8 by adequate instructions for use and warnings against
9 unsafe use, outweigh any probable risks. Considering
10 the data in the PMA, please comment on whether there
11 is a reasonable assurance that the device is safe.

12 CHAIRMAN CHOTI: So for each question, I
13 would like to go through the panel and get the
14 comments and opinions. Let's start on the other end
15 of the table with Dr. Doyle. Response or comments to
16 question number one?

17 DR. DOYLE: I don't think we can
18 ultimately know if it is safe without long term data.
19 However, the data or lack of data of unsafe and
20 serious adverse consequences from Europe, where it has
21 apparently been widely used in uncontrolled
22 conditions, and in the data here, I don't see any

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 indications from the data here of any dangers at this
2 point.

3 CHAIRMAN CHOTI: Dr. Bartoo.

4 DR. BARTOO: I would have to agree with
5 LeeLee, in terms that we don't know the long term
6 safety at this point, but there is good evidence I
7 feel for short term at least to your safety data, both
8 for the intended use, as well as potentially cosmetic
9 use from the European data.

10 CHAIRMAN CHOTI: Dr. Munk.

11 DR. MUNK: I think we have all kind of
12 underscored the lack of data that would give us
13 comfort about this question globally. However, for
14 the proposed indication, I think the answer has to be
15 yes.

16 CHAIRMAN CHOTI: Dr. Newburger.

17 DR. NEWBURGER: I agree with Dr. Munk's
18 response and also I just want to reiterate that it is
19 only approved this last February for HIV lipotrophy
20 in Europe. So there isn't a long term experience with
21 it for that use.

22 CHAIRMAN CHOTI: All right. Dr.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Blumenstein.

2 DR. BLUMENSTEIN: I agree within the
3 context of the proposed use. There is enough data to
4 support short term safety.

5 CHAIRMAN CHOTI: Dr. Chang.

6 DR. CHANG: I believe that it has been
7 show in the population of white male patients who are
8 HIV positive that it is safe.

9 CHAIRMAN CHOTI: Thank you. Dr. Leitch.

10 DR. LEITCH: I would agree that it is safe
11 in the proposed population for this PMA.

12 CHAIRMAN CHOTI: Dr. Miller.

13 DR. MILLER: Considering safety, the
14 balance of benefit and risk, the benefit appears
15 tremendous for this, and because of that, we are put
16 in the position of accepting a tremendous amount of
17 unknown about the risk, and I am a little bit
18 irritated by the day that it is presented that it puts
19 us in a position to have to accept that because the
20 benefit is truly enormous.

21 And I would certainly would like to have
22 had more of an understanding of this material and how

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 it works. But I think it is difficult to argue that
2 the benefits are so enormous that we just have to
3 accept the situation.

4 My concern is that 10 years from now we
5 are going to have another hearing with a different
6 group of patients, who purport to be damaged by this
7 material, and questioning why did we let this go
8 through without understanding more about it. I mean,
9 I look forward to or I will be off the panel by then
10 probably.

11 CHAIRMAN CHOTI: Dr. Fish.

12 DR. FISH I am concerned about the lack of
13 data for women, and it is predominantly males as we
14 saw here, and then also certainly the other racial and
15 ethnic groups.

16 However, I like the way that Dr. Doyle put
17 it, there is nothing that has been seen thus far that
18 I think would preclude the approval, with the caveats
19 that Dr. Miller just stated.

20 CHAIRMAN CHOTI: Dr. Penneys.

21 DR. PENNEYS: I agree that for this
22 specific indication in this PMA that this is safe.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 CHAIRMAN CHOTI: Dr. Olding.

2 DR. OLDING: I have a question of Dr.
3 Witten. Dr. Witten, shall we totally disregard in
4 making our decision about this product for its
5 intended use the possible off-label use of this
6 product in making our decision?

7 DR. WITTEN: Well, when you make your
8 recommendation about the approvability of the product,
9 yes, you should focus on the intended use proposed by
10 the sponsor, but certainly in the discussion we are
11 interested in hearing what you have to say.

12 But when it gets to -- when we are asking
13 about safety and effectiveness, we are asking
14 specifically for the intended use proposed by the
15 sponsor, and the same would be true of the vote when
16 we get to the vote.

17 DR. OLDING: Thank you for the
18 clarification. I believe that the product is
19 certainly safe for its intended use.

20 CHAIRMAN CHOTI: Dr. Li.

21 DR. LI: The product appears to be safe
22 from what they presented, although I don't really

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 understand why. My own experience with these
2 materials is that this molecular weight, this
3 particle-sized distribution, there should be some
4 inflammatory response that we don't seem to be
5 getting.

6 So I don't really quite understand why
7 that is, but I have no evidence that it isn't safe,
8 and so I will go along with it being safe, but I would
9 like to keep pointing out that I don't really know
10 why.

11 And when I say it is safe, I mean under
12 the conditions that the material can be characterized
13 and say that future batches of this material are
14 exactly the same as possible to what has been tested.
15 And if they can't do that, then I think you have to
16 remove the safety feature.

17 CHAIRMAN CHOTI: So I think I can
18 summarize by saying in response to Question Number 1,
19 if this is all right with you, Dr. Witten, that I
20 think the consensus is that for the proposed indicated
21 use, I think the consensus of the panel feels that
22 there is reasonable assurance that this device is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 safe.

2 DR. WITTEN: Thank you.

3 CHAIRMAN CHOTI: The next question.

4 DR. LERNER: 21 CFR 860.7(e)(1) states
5 that there is a reasonable assurance that a device is
6 effective when it can be determined, based on valid
7 scientific evidence, that in a significant portion of
8 the target population, the use of the device for its
9 intended uses and conditions of use, when accompanied
10 by adequate directions for use and warnings against
11 unsafe use, will produce clinically significant
12 results. Considering the data in the PMA, is there
13 reasonable assurance that the device is effective?

14 CHAIRMAN CHOTI: Regarding question number
15 2, can I ask Dr. Miller to start the specific
16 comments.

17 DR. MILLER: I think that based upon the
18 material that we have that it appears effective.

19 CHAIRMAN CHOTI: Dr. Leitch.

20 DR. LEITCH: I think the material appears
21 effective. The duration of that effect though does
22 remain a question in my mind.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 CHAIRMAN CHOTI: Dr. Chang.

2 DR. CHANG: The product appears to be
3 effective.

4 CHAIRMAN CHOTI: Dr. Blumenstein.

5 DR. BLUMENSTEIN: For the patients study
6 and for the face validity issues, I think it appears
7 to be effective.

8 CHAIRMAN CHOTI: Dr. Newburger.

9 DR. NEWBURGER: I agree that it appears to
10 be effective in this use.

11 CHAIRMAN CHOTI: Dr. Munk.

12 DR. MUNK: I agree. I have some questions
13 about what are adequate directions for use.

14 CHAIRMAN CHOTI: Dr. Bartoo.

15 DR. BARTOO: I agree that it is effective
16 for its intended use.

17 CHAIRMAN CHOTI: Dr. Doyle.

18 DR. DOYLE: I also agree.

19 CHAIRMAN CHOTI: Dr. Li.

20 DR. LI: It appears effective.

21 CHAIRMAN CHOTI: Dr. Olding.

22 DR. OLDING: I agree.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 CHAIRMAN CHOTI: And Dr. Penneys.

2 DR. PENNEYS: I agree.

3 CHAIRMAN CHOTI: And Dr. Fish.

4 DR. FISH: I agree based on its face
5 validity.

6 CHAIRMAN CHOTI: Dr. Witten, based on the
7 comments that you have heard from the panel do we
8 think that we adequately addressed question number 2
9 specifically considering the data that there is a
10 reasonable assurance that the device is effective, and
11 I think there is a consensus that most felt that it
12 is.

13 DR. WITTEN: Thank you.

14 DR. LERNER: Question Number 3. Patients
15 in the European studies were followed-up for periods
16 ranging from 24 weeks to 2 years, and those in the
17 United States were followed for up to 2 years. If you
18 agree that there is enough evidence in the PMA to
19 support the safety and effectiveness of the device, do
20 you feel that a post-approval study to assess the long
21 term use of the device should be initiated, and if so,
22 please advise FDA as to the type of data that you feel

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 should be collected, and the appropriate duration of
2 the follow-up.

3 CHAIRMAN CHOTI: Dr. Newburger, I would
4 ask you to start the discussion in Question Number 3.

5 DR. NEWBURGER: Since I consider this
6 application to really be a work in progress, sure, I
7 think that there should be a post-marketing study.
8 Some of the things that I would like to see are
9 standardized photographs.

10 And attempt more to characterize the
11 reaction of the material in tissue by getting study
12 subjects to agree to give small biopsy samples. I
13 work for a cosmetically important or known as
14 cosmetically significant area.

15 I would also be interested in having the
16 rate of formation of these papules/nodules correlated
17 with the total number of CD4 cells since apparently
18 there is some type of non-inflammatory foreign body
19 reaction, and that seems like a paradoxical, and so I
20 am wondering if the relative reduction in CD4 cells
21 have something to do with this powerability in this
22 particular population.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 And so those are some of the things that I
2 would like to see looked for.

3 CHAIRMAN CHOTI: Dr. Munk.

4 DR. MUNK: I feel strongly that there
5 needs to be a longer term follow study, and in terms
6 of how long it should run, and I would say by at least
7 5 years.

8 I think that the study should collect
9 information on adverse events, and it should collect
10 patient weight and satisfaction over time, and the
11 number of touch-up treatments and whether those are at
12 patient request or on some other basis.

13 Any changes in antiviral treatments, and
14 the prior duration of treatment before the application
15 of the device.

16 CHAIRMAN CHOTI: Dr. Bartoo, comments?

17 DR. BARTOO: I agree that there should be
18 a long term study, a post-approval study, and I would
19 like to see in this long term study multiple
20 treatments applied and followed up afterwards so we
21 can see the effect of having multiple treatments.

22 I would like to suggest that these would

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 become well designed controlled studies, as opposed to
2 what we have been able to see so far.

3 CHAIRMAN CHOTI: Let me just ask you.
4 Give me a clue on how you would design your control
5 trial?

6 DR. BARTOO: Well, I mean, potentially you
7 can compare it to other fillers, for example, with
8 randomization of the peer group, and to have
9 characterization of the two randomized groups, for
10 example. Or to stratify between different factors,
11 such as viral load and other things like that.

12 CHAIRMAN CHOTI: Dr. Doyle.

13 DR. DOYLE: I think that there should be a
14 long term follow-up and it should be particularly
15 directed to looking at the increasing number of women
16 and minorities in this. Also, some follow-up of some
17 of what the -- on whatever you decided to call them,
18 the histologic follow-up on some of those in actual
19 analysis of what is constituting, and at least is
20 there AIDS left there.

21 CHAIRMAN CHOTI: Dr. Li.

22 DR. LI: I would like to -- I think there

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 should be additional studies, and I would like to see
2 some correlations if you will, or associations, of the
3 amount of material, and perhaps in key material
4 characteristics of the presence of nodules, and this
5 actually might also fit into different gender issues
6 then as well.

7 And actually I have not seen any
8 information about any kind of scaling of nodules. You
9 know, like there is one reported as a nodule, or is it
10 hundreds, and if it is location related, and is it
11 more applicable, and did it happen more often in the
12 temple, or some other location.

13 So some of this information I think is
14 needed. They actually might already have it if they
15 went back and kind of mined their own data, but if
16 they don't have it, I think these would be critical in
17 the absence of any longer term data.

18 CHAIRMAN CHOTI: Dr. Olding, comments?

19 DR. OLDING: I, too, would like to see a
20 histological and chemical characterization of the
21 mechanism of action of this product, as well as the
22 characterization of the adverse effects.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 I think that there is really a
2 surprisingly small amount of concern about
3 characterizing those adverse effects.

4 CHAIRMAN CHOTI: Thank you. Dr. Penneys.

5 DR. PENNEYS: Well, I think it would be
6 great fun to look at the reactions in a microscope,
7 and using markers, determine if it varies, depending
8 on the set-up of the individual, but I would urge the
9 company to anticipate the wide range of off-label use,
10 including use in children.

11 And the obvious immune status, and stating
12 the obvious, cosmetic uses, and every time that a
13 person gets an intralesional shot of corticosteroid
14 there is going to be atrophy and depression, and in
15 children who get it for alopecia areata.

16 People will be using this for these
17 entities, whether you like it or not, and so the
18 company should anticipate all these, and meet with the
19 panel and dermatology consultants, and think about
20 looking at all these various applications.

21 CHAIRMAN CHOTI: Thank you. Dr. Fish.

22 DR. FISH: I also have a question of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701