CHAIRMAN LoCICERO: Dr. Krause will read the voting instructions for the panel at this time.

DR. KRAUSE: The following are the panel recommendation options for a pre-market approval application. Medical device amendments to the Federal Food, Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990 allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market approval applications that are filed with the agency.

The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under the conditions of intended use outweigh any probable risks. Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended uses and conditions of use when labeled will provide

clinically significant results.

The recommendation options for the vote are as follows. You may recommend approval. Approval would be if there are no conditions attached. The second option is approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions. These conditions could be things such as physician or patient education or training, labeling changes, further analysis of the existing data. Prior to voting, all of the conditions should be discussed and voted on by the panel.

The third option is not approvable. The Panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the voting, the Chairman is asked to poll the panel members to give a brief statement outlining the reasons for their vote.

CHAIRMAN LoCICERO: The Chair will

entertain a motion at this time. Dr. Olding.

MEMBER OLDING: I would recommend that this be approved with conditions.

CHAIRMAN LoCICERO: Is there a second?

MEMBER NEWBERGER: Second.

CHAIRMAN LoCICERO: Since we are voting on approval with conditions, then we need to establish what those conditions are and discuss each one of those conditions and vote on those prior to voting on the main proposed approval with conditions. So the Chair will entertain a motion for the first condition.

MEMBER OLDING: I would recommend that we require a post-approval study of 18-month total, not an additional 18-month, 18-month total and that -- should I qualify the things that we should look at in those post-approval study or should that be something separate?

CHAIRMAN LoCICERO: They can be part of the discussions.

MEMBER OLDING: And that we take the opportunity to take a look at the histologic, give us some additional histologic verification of what

happens to the product.

CHAIRMAN LoCICERO: Is there a second?

MEMBER NEWBERGER: I have a question regarding post-approval studies. Does this mean that the product is approved with the understanding that while it's approved and being employed, these studies will be done or are these short-term studies that will be done prior to its being available on the market?

DR. KRAUSE: Well, that's up to you.

CHAIRMAN LoCICERO: I guess we can stipulate which it is.

MEMBER NEWBERGER: In that case, I would like to stipulate that prior to it being available for general use on the market, that these studies involving further delineation of the histologic character and mechanism of action be done.

CHAIRMAN LoCICERO: Okay, that's a qualification of Dr. Olding's -- excuse me, Mr. Melkerson.

DIRECTOR MELKERSON: That condition would actually then mean it's not approvable. In other words, you need to have that study prior to approving

the product so that would not be a post-approval study. That would actually be data required to approve.

CHAIRMAN LoCICERO: Okay, that qualifies it then. Would you like to modify your amended amendment?

MEMBER NEWBERGER: Well, I assume I can't make another motion while this one is being considered, okay.

CHAIRMAN LoCICERO: Correct, so we actually have a motion on the table and that is, post-approval study, a total of 18 months addressing histology. We need a second.

MEMBER MILLER: Second.

CHAIRMAN LoCICERO: Okay, that's seconded. Now we can open a discussion for that motion.

MEMBER LIETCH: How would we propose to do the histology, biopsying the sites that have been injected?

MEMBER OLDING: I purposely left that out because I think that's something that we, as a panel, should ultimately discuss, at least to some extent but

I believe that they need to have some histologic evidence of its presence presumably from the patients that they've already injected and they would have had to have injected previously. And yes, I would think it would have to be punch biopsies from the patient that had been treated.

MEMBER LIETCH: But would you get it with punch biopsies because that's sub-dermal?

MEMBER OLDING: Yes, you can with deep punch biopsies because it is -- in a punch biopsy you can get more than just dermis.

MEMBER LIETCH: So how big of a punch biopsy? I mean, you know, you've got to get the patients to agree to do this after, you know, they've already had the injections, they've already agreed to participate in the trial but they didn't agree to that, so you might have to re-consent them for the tissue biopsies. That has to go through IRB. I mean, I don't know how hard it is at the various sites where this was done, but you know, I know in most studies that's a major issue of, you know, reconsenting patients for -- particularly for tissue studies.

That's a big deal and then you've got to get the compliance of the patients to agree to do it.

It's one thing if up front you say, "Well, we're going to inject some in your forearm, we're going to inject in your face and, you know, we'll give it to you free if you'll do this forearm thing, too." You know, that's kind of a different sell than saying, "We're going to do this biopsy on your face now that you've had the injection, 18 months later". I mean, I just don't know how realistic it is that you'll get what you want.

MEMBER OLDING: Good point.

CHAIRMAN LoCICERO: Dr. Lewis.

MEMBER LEWIS: I support the recommendation for approval with conditions, but I disagree with the condition specified about a post-approval study. I don't understand the purpose of that and I don't see the practicality of it. I think the ones raised by Dr. Leitch are entirely correct but it seems to me any realistic histologic study in humans would require a fairly lengthy study because you'd have to start over. There's no group to be

followed, so you'd have to start over using a forearm or some other site.

I don't think biopsies on the face are reasonable. I think cosmetically that would be totally unacceptable. I can't imagine that all these patients would agree to that, so I don't think you'd get sufficient numbers. And it seems to me that the practicalities of doing that are pretty hard, so the only way to do that would be to start out with a new group and then run it for whatever period of time you thought was necessary to define the histology, but ultimately, I don't see the purpose of it. There's been nothing here calling in question the safety of the product and while I completely agree with the idea that the ultimate behavior of these granules in terms of how rapidly they disappear and how they're metabolized and all of the remains unknown.

It seems to me that's an issue more of, it's kind of scientific interest but it's not of much relevance to the marketing of a product which is focused on 12 months of effectiveness and is anticipated to have the need for additional treatments

in the future. So I guess I really don't understand the rationale for asking that and in particular, when that request strikes me as being exceedingly impractical. So I would -- the condition I would have envisioned was an explicit requirement for physician education relative to the process, but I would not agree with post-approval study.

CHAIRMAN LoCICERO: Okay, we need to continue with this. Is there any other discussion from anybody? Dr. Oldling, do you want to modify your proposal?

MEMBER OLDING: Yes, I would retract my recommendation for histologic study.

CHAIRMAN LoCICERO: Okay, the post-market study is retracted. We will now entertain a motion, another motion.

MEMBER LEWIS: Well, my motion would be for approval with conditions, the conditions being an explicit program of physician education addressing the issues we've already discussed about the technical details of doing this and it sounds as if from what's been stated parenthetically in the discussion that

such a thing may be already either in existence or partially in existence and something that would simply address the techniques of how to do this properly, how to place it at the proper depth, et cetera, would be, I think, appropriate.

CHAIRMAN LoCICERO: Okay, so to make it more succinct, that the we are -- you're proposing a physician education requirement.

MEMBER LEWIS: Yes.

CHAIRMAN LoCICERO: Okay, a second to that motion?

MEMBER LIETCH: Second.

CHAIRMAN LoCICERO: Okay, we have a second. Is there discussion? Yes.

MEMBER MILLER: How detailed of a recommendation must we provide as far as the education goes?

CHAIRMAN LoCICERO: I think we may be able to use what we -- how we answered the question. Mr. Melkerson, would you --

DIRECTOR MELKERSON: In terms of your suggestions, at least points of what you want the

education program to address is probably sufficient.

CHAIRMAN LoCICERO: Okay, now we had that discussion and made a summary to one of the FDA questions. Would that satisfy this? Dr. Lewis says yes. Okay, is there any further discussions? All right, let's go with a show of hands, please. All in favor. Okay, I understand we need to do this -- sorry. Dr. Olding, yes or no?

MEMBER OLDING: Yes.

CHAIRMAN LoCICERO: Dr. Lewis?

MEMBER LEWIS: Yes.

CHAIRMAN LoCICERO: Dr. Miller?

MEMBER MILLER: Yes.

CHAIRMAN LoCICERO: Dr. Li?

MEMBER LI: Excuse me, I just want to make sure I know what I'm agreeing to. Are we agreeing for the recommendation for physician education?

CHAIRMAN LoCICERO: Yes.

MEMBER LI: Yeah, then I agree.

CHAIRMAN LoCICERO: Dr. Leitch?

MEMBER LIETCH: Yes.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: Yes.

CHAIRMAN LoCICERO: Dr. Munk?

CONSUMER REP. MUNK: Yes.

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: Yes.

CHAIRMAN LoCICERO: Ms. Whittington?

PATIENT ADVOCATE WHITTINGTON: Yes.

CHAIRMAN LoCICERO: And Dr. Bartoo?

INDUSTRY REP. BARTOO: Actually, I don't think I'm allowed to vote, am I?

CHAIRMAN LoCICERO: I don't think so. Okay. Good for you.

(Laughter)

CHAIRMAN LoCICERO: Okay, the condition of physician education passed unanimously. Are there further conditions that the panel wishes to place on this approval with conditions? Dr. Leitch?

MEMBER LIETCH: Well, the motion was for the 18-month study as part of the condition or did you withdraw that totally, or just the type of thing first, that's one question I have.

CHAIRMAN LoCICERO: It's withdrawn.

MEMBER OLDING: Withdrawn.

MEMBER LIETCH: Okay, so one condition I would say is to have this 18-month follow-up, not have the -- not request the histology but some of these questions about a more detailed report of the texture of the tissue from the patient's perspective and the examiner's perspective and ease or difficulty of subsequent injections over time, what the observations are about that. Essentially, more clinical data about it and the question of do patients have events where there is confusion about the physical exam which prompts other radiographic evaluations or even biopsies for assumed problems? What's the frequency with which that occurs?

CHAIRMAN LoCICERO: Okay, we need to do this in the form of a motion. So you are -- your motion is --

MEMBER LIETCH: So my condition to add to the motion for approval is to complete the 18-month study with parameters that are a little more than what the -- you know, the study things have been done so far to essentially explicate those things I've

described.

CHAIRMAN LoCICERO: Is there a second?

PATIENT ADVOCATE WHITTINGTON: Second.

CHAIRMAN LoCICERO: You can't second either?

MEMBER BLUMENSTEIN: I'll second.

CHAIRMAN LoCICERO: Okay, Dr. Blumenstein seconds. Discussion?

DIRECTOR MELKERSON: Are you asking for new data to be analyzed or you are asking for a post-approval study that addresses that type of information? In other words, do you need to have this data for approval or you would like it --

MEMBER LIETCH: Not in my opinion, no.

DIRECTOR MELKERSON: So you may want to address that in your motion.

CHAIRMAN LoCICERO: Okay, so we're saying this is approved with the condition that we evaluate the patients up to 18 months who are currently in the study, is that what you're --

MEMBER LIETCH: Correct, no new patients and not requiring them to do anything else. There's

no requirement of the patient other than to show up in 18 months, to address those questions with them and maybe have a scale for the investigators to specifically address those questions.

CHAIRMAN LoCICERO: Okay, and expanded questionnaire at 18 months or -- at 18 months.

MEMBER LIETCH: And for people who are at 12 months, they could use that same questionnaire so they'd have consistency through -- for the people that need to get up to the 12 months, if they're not --

CHAIRMAN LoCICERO: Discussion about this?

MEMBER LEWIS: Could you define a little more clearly what issue you want to address? Do you want the patient's opinion or feedback or do you want an evaluator's measurement or something? What specifically would you like to see?

MEMBER LIETCH: Obviously, it would be nice to have patient feedback. I think, you know, the feedback that's been reported, I think is that the patients are happy with it probably regardless of how it feels because the appearance overcomes the how it feels. For, you know, physician evaluation, a primary

care doctor or whoever is following that patient in the long term, these texture issues may be a problem and it might prompt other -- I mean, that's what's being raised, that's the question that's been raised in our discussions here is that there might be a perception of a problem that would prompt other evaluations only to find out it's related to the injections.

And so the question -- and then the issue of since it's not a permanent product and you have to do sequential injections does that work out to be feasible over an 18-month period of time? So because I -- I mean, the other thing I predict is that this will be used for other indications and issues and those points, I think, become more important with expansion of use and if -- you know, if you have that data, you can address it one way or the other, the answer to those questions.

CHAIRMAN LoCICERO: Other discussion? Dr. Blumenstein?

MEMBER BLUMENSTEIN: Well, I mean, is it -- since I seconded this, I agree that what Marilyn's

characterization of what it was, I agree with that. To address the issue about what we could get out of this, I guess what's bothering me is that I don't feel that there's adequate data on the characterization of the longevity of the device. And it's kind of awkward because it's really part of labeling but yet, I don't think we're asking for it to be a condition of -- condition of approval. We're asking it be a condition of post-approval.

So, I guess I have a question about what happens to data like this. It won't take that long to get the additional data on to 18 months, but what happens if the labeling has already been created? Is there an opportunity to go back and include the additional data in the label, that sort of thing?

CHAIRMAN LoCICERO: Mr. Melkerson, yes.

DIRECTOR MELKERSON: Post-approval study data generally will require an update of the patient labeling as it exists. So results from post-approval studies will be augmented to the new labeling of the original approval.

CHAIRMAN LoCICERO: Dr. Bartoo?

INDUSTRY REP. BARTOO: Just sort of a minor point. It's sounded from the sponsor that they probably have already conducted their 18-month visit, so maybe a friendly amendment to the proposal is to just have 18-month or greater in terms of the follow-up?

CHAIRMAN LoCICERO: Would that be okay?

MEMBER LIETCH: That's okay.

CHAIRMAN LoCICERO: Further discussion?

MEMBER LEWIS: I just want to be clear exactly what we're proposing here. We are proposing that basically, the sponsor follow through on the data that they're already gathering and just complete that process and submit that. Is that basically what we're proposing here?

MEMBER LIETCH: I think that's basically what we're proposing, although I think the data set that we had to look at for the patients that have already been examined was -- by people who were reviewing it here, was felt to be insufficient to answer some of these questions about the texture and the ease of injection, these sorts of things. And if

some additional questions could be included, I think it would help to clarify that and make it clearer to physicians what the expectations are over time for managing this product in their patients.

CHAIRMAN LoCICERO: All right, we have texture, ease of injection, what else?

MEMBER LIETCH: And events that require further evaluation because someone examines the patients and thinks there's a problem or they have an x-ray done. I mean, this is what's been raised, it can interfere with x-rays. Well, you know, does that happen and what's the sequella of it? I suspect these patients haven't been questioned about that.

MEMBER BLUMENSTEIN: And the degeneration of effect.

CHAIRMAN LoCICERO: Qualify that.

MEMBER BLUMENSTEIN: Well, when do you need to retreat again? I mean, in my own way of thinking about it, I can see a Kaplan Meyer curve that would show time to failure where failure is defined as something appropriate, maybe a one point drop on the scale, something along those lines.

CHAIRMAN LoCICERO: Okay, let's see if we can get this stated clearly now. The condition that we're voting on is completion of the 18-month or greater study that is currently being conducted by the sponsor to include data on texture, ease of injection, events requiring further evaluation and time to reinjection. Dr. Blumenstein?

MEMBER BLUMENSTEIN: Yes.

CHAIRMAN LoCICERO: Dr. Munk?

CONSUMER REP. MUNK: Yes.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: Can you please use your mikes, thank you. Yes.

CHAIRMAN LoCICERO: Dr. Li.

MEMBER LI: Yes.

CHAIRMAN LoCICERO: Dr. Miller?

MEMBER MILLER: Yes.

CHAIRMAN LoCICERO: Dr. Lewis?

MEMBER LEWIS: Yes.

CHAIRMAN LoCICERO: Dr. Olding?

MEMBER OLDING: Yes.

CHAIRMAN LoCICERO: Okay, we have

unanimous approval of this condition. Is there a third condition? Dr. Miller?

MEMBER MILLER: Yes, I would like to add the condition that the labeling be very specific, that the indications for using this are for this specific set of patients with lipoatrophy, you know, the AIDS related deformity. I think the datas are completely inadequate for going beyond that group. They're barely adequate for that group, but I think the benefit is so great that all these open questions we can accept with a degree of uncertainty because the risk posed by those is overwhelmingly, I think, you know, counter-balanced by the benefit in these patients, but you move beyond these patients where you're doing other sites or other kinds of deformities, certainly cosmetic patients, I think that the unknowns become very significant at that point and I would -- I think we need to make it as strongly worded as possible that the approval is specifically for this PMA and this group of patients.

CHAIRMAN LoCICERO: Okay, maybe to state that a different way, you want the condition that the

labeling state that there is no data outside of this group of patients.

MEMBER MILLER: I guess I'll leave it to the experts in forming my words.

CHAIRMAN LoCICERO: We're approving the PMA specifically for this indication.

MEMBER MILLER: That's what I --

CHAIRMAN LoCICERO: So it's already narrow.

MEMBER MILLER: All right.

CHAIRMAN LoCICERO: Are you asking for something additional to that?

MEMBER MILLER: Well, I guess just something to emphasize that so it is crystal clear and in how the product is labeled that to used it in an off-label fashion is going beyond what this approval is regarding. Do you understand what I'm saying?

CHAIRMAN LoCICERO: Mr. Melkerson?

DIRECTOR MELKERSON: In general, you are approving the specific indication studied. If you are identifying, you would like warnings or precautions about the safety and effectiveness of other locations

not being known. Those tend to be warning statements, so if you're suggesting that, that is within their purview but issues related to off-label are not the purview of this vote.

MEMBER MILLER: Okay, then I would be in favor of a warning that says, "This device has not been studied adequately in patients other than these specific AIDS patients and that use in other indications can be hazardous to your health", I don't know, whatever.

CHAIRMAN LoCICERO: All you need to do is just stop there.

MEMBER MILLER: Okay.

CHAIRMAN LoCICERO: The label warning is that this has not been studied adequately in any other setting.

MEMBER BLUMENSTEIN: I'll second.

CHAIRMAN LoCICERO: Okay, that's been seconded. Dr. Bartoo.

INDUSTRY REP. BARTOO: I just have a question of Dr. Melkerson because this product has been cleared with 510Ks for three other indications,

so how does that play into this?

DIRECTOR MELKERSON: The product may be cleared but FDA defines a device by its indication for use and the product itself. So the labeling for this particular product will be reflective of its current approvals or clearances.

CHAIRMAN LoCICERO: Further discussion? All right, we're voting on a label -- a warning label that this product has not been studied adequately for injection in other sites.

MEMBER MILLER: Can I ask a question before we vote? I just want to understand for sure what the implications officially of a warning label are. I mean, I don't want to place -- I mean, I don't have a sense of, in practical terms, when you put a warning label on, what category of products does that suddenly put it into. I mean, is it like cigarettes? I mean, I don't know if it needs a warning label that, you know, we know for certain this causes you harm, but I would like to be sure of the connotations of putting a warning label on it are what I want to communicate.

CHAIRMAN LoCICERO: Okay, we can get a clarification.

DIRECTOR MELKERSON: I'll try to do the way I think of it. A precaution is something that you haven't studied it and you don't have an inclination one way or the other. A warning tends to be something that you have some information that says it's bad but you -- if you use it on-label, it's fine. And if you choose to use it off-label, buyer beware. In terms of contra-indication, there's actually data that says you should not be using this for that indication for use.

CHAIRMAN LoCICERO: So do you want to modify your --

MEMBER MILLER: I think it's -- if warning implies that there are data that suggests this harms you, I haven't seen that. But I think that a precaution that data is inadequate to justify or to support use in other areas. I think that is appropriate.

CHAIRMAN LoCICERO: Does the seconder agree to a precaution?

MEMBER BLUMENSTEIN: After I make a query.

CHAIRMAN LoCICERO: Yes.

MEMBER BLUMENSTEIN: What's the difference between data and information?

DIRECTOR MELKERSON: In terms of -- again, I was trying to simplify the legal implications but in terms of precaution, you have a thought that there may be a problem but you may or may not -- maybe not published, it's just a concern you have. A warning, there's actually some information available to lead you to believe there may be a problem.

MEMBER BLUMENSTEIN: Okay, that's not quite what you said the first time it seems. Then I would go along with it being a -- what did you call it?

DIRECTOR MELKERSON: A precaution.

MEMBER BLUMENSTEIN: A precaution instead of a warning as long as the tilt can be towards that it's possibly a bad thing.

CHAIRMAN LoCICERO: We need to get a clear statement of this precaution.

MEMBER MILLER: Okay, I would move that we include a condition -- a precaution that it is unknown

how this device performs outside of the indications approved under this PMA.

MEMBER BLUMENSTEIN: See to me, that doesn't have a bad thing tilt.

MEMBER MILLER: And it can hurt you.

MEMBER BLUMENSTEIN: Yeah, okay.

(Laughter)

MEMBER BLUMENSTEIN: I mean, it's merely a hypothesis.

MEMBER MILLER: Yes.

MEMBER BLUMENSTEIN: But I think that, you know, that's what we're here for is to be experts and if people feel that it's -- like for example, keloid, if it's felt like that's a bad thing to use this off-label in a person who has a high keloid potential, then we should say that or make it definitely tilted against it.

MEMBER MILLER: This is my concern, we don't know. I mean we don't -- I can imagine ways that there could be problems in using this in other settings other than these patients where the benefits suddenly would be overwhelmed by the risk involved.

We don't have any information which documents that or proves the but I can envision settings where that may be the case. So I'm very comfortable with these patients doing this, even given some of the uncertainties, but beyond that, I'm not. So I guess I'm trying to come up with some way --

CHAIRMAN LoCICERO: Okay, Dr. Lewis wanted to say something here. Maybe he can help clarify.

MEMBER LEWIS: I guess I don't fully understand these concerns, because at least in what we've heard here, we haven't really heard of anything harmful coming out of this. We have heard about a lack of information about certain aspects of things but I haven't really heard anything that suggests that this is harmful. I mean, there have been no essentially real adverse requirements health-wise. And the experience that's reported is that this product has extensive and long-term and widespread use in multiple other applications without any evidence -- I mean, harmful to me means it might be carcinogenic, that it you know, improperly used would result in major skin sloughs and other things that would be --

we haven't heard any of that. So I don't quite understand the concern. I mean, I think what's being requested is kind of a limited use product that's not being guaranteed for 10 years and that's what the PMA says and I guess I don't quite understand the concern and caution over saying that this approval is for a limited product. And if a statement were put in to say this product has only been tested in the HIV positive population, period, I have no problem with that, but the warning aspect of implying that there's something hazardous in the background, it seems to me is not there.

This is not like cigarette smoking where, you now, it causes cancer. So I don't quite understand that concern.

MEMBER MILLER: Shall I try to explain that?

CHAIRMAN LoCICERO: Okay, go ahead.

MEMBER MILLER: Yeah, I mean, it's -- what you really need to do is give me a statement so that we can vote on it.

MEMBER MILLER: Okay.

CHAIRMAN LoCICERO: All right, so why don't you try writing something down for me and in the meantime, Dr. Blumenstein, you had talked about earlier the fact that there were exclusionary criteria and --

MEMBER BLUMENSTEIN: Exactly.

CHAIRMAN LoCICERO: -- that the point was that this product was not going to be used for those other situations because it hadn't been studied and that this would be acceptable in labeling.

MEMBER BLUMENSTEIN: Yeah, I mean, I think it's very clear that if you read the list of exclusions, there are certain elements there that can be interpreted as having been put there because of a fear that this would not work as well or maybe have some adverse events associated with it or whatever. But the exclusions that are in the protocol are a -- is an anchor to the concern that -- one of the concerns, at least, that we have here and those exclusions should possibly be part of this statement because they're in the protocol.

CHAIRMAN LoCICERO: Dr. Miller, do you

have something for us?

MEMBER MILLER: I'll just say a precautionary statement saying this device has been adequately studied only in HIV positive patients with lipoatrophy and its performance and other indications is uncertain.

CHAIRMAN LoCICERO: Okay.

MEMBER BLUMENSTEIN: That doesn't get it for me. The population of patients studied is what you said plus excluding patients with high keloid potential, patients with silicone injections, et cetera, et cetera.

CHAIRMAN LoCICERO: And actually, we could entertain some exclusions as a separate condition.

MEMBER MILLER: My concern is that this is a -- and maybe Dr. Olding would have some comments on this and maybe my concerns are skewed by the type of patients I see, but you know, this is a scar forming material. This material works by making a scar, okay. Now, that's okay in certain settings, if the scar fills a volume for you and does the job for you. The tissue that's made is a piece of scar. Now, I can

imagine scenarios where a large plaque of scar is not desirable. One is an keloid scar former or a hypertrophic scar former or one is somebody with Scleroderma, you know or some of these disorders that have tendencies toward abnormal scar formation. Now, this is just conjecture on my part.

I don't know that there's a concern here but I can envision there being a concern and the other thing I vision is that this will be used widely and because there's such a market for soft tissue fillers, and a good long-lasting soft tissue filler, and I envision it being used by everybody with a needle in their hand and a patient who wants it. And so I guess I would just like to avoid the possibility of discovering the downside of this material by -- just by accident because it's being used so widely.

You know, this is my concern and I -- again, my experience may be skewed because the patients I see have complications from this type of thing. I mean, they have sinuses and they have scarred areas, but my patients are unusual because they're cancer patients, they get radiation treatments

and all kinds of stuff. So maybe I'm not seeing things in a, you know, proper way.

CHAIRMAN LoCICERO: Dr. Lewis?

MEMBER LEWIS: Just in an effort to clarify, if you'll look at the list of exclusionary criteria, most of those things were in there, I would guess, simply because they would interfere with the cosmetic assessment of this product, not because they are problems in terms of reactions or whatever. The only one that's really in there that potentially is negative is keloid formers. And so would it be acceptable to say that in your precaution, that this product should either by used with caution or should not be used in those with a propensity for a proven history of keloid formation, since that's really the only one in there that would seem to be a negative?

CHAIRMAN LoCICERO: We need to get something different from Dr. Miller's three paragraph labeling.

MEMBER MILLER: And I don't mean to make it complicated but it's tough because of the situation that we're in. We just don't -- I would like to just

say a precaution that basically what I've already stated. I know Dr. Blumenstein would like something more strong but --

MEMBER BLUMENSTEIN: Excuse me for interrupting, but I mean, I'm not an expert and I'll take Dr. Lewis' word if he thinks that the keloid is the only one of the exclusions that represents the potential for harm. I mean, I don't know what -- I don't know why a prohibition, an exclusion with respect to silicone prior injections was in there, and you may be right. It may be just something that has to do in the context of the clinical trial to not interfere with the assessment of the outcome. And I don't know that, but you know, it seems to me and one that I focused on initially was the keloid one. It seemed to me that was a --

MEMBER LEWIS: Well, I certainly have no knowledge of the company's motives or putting one or not. It's just my assumption that if you're doing a study that involves cosmesis you would not allow other inter-current cosmetic interventions that would interfere with the assessment of that outcome. And it

was just my assumption that that's why they're in there. The company is here. They can address the issue. They, I would think, could comment on that but there's no -- no one has ever mentioned any interaction between silicone or any of these other agents and Radiesse and so I know of no reason to think that that's a problem. But again, I have no other knowledge.

CHAIRMAN LoCICERO: Okay, Dr. Newberger wants to comment.

MEMBER NEWBERGER: In terms of silicone and any other filler, I think those of us who do use this modality have found that people who have had silicone in the past and then will have an additional filler, are at an increased risk for getting a hypersensitivity reaction.

CHAIRMAN LoCICERO: Okay, Dr. Miller, we still need to get a clear statement that we can vote on. So I'll let Dr. Li make a comment while you formulate that.

MEMBER LI: I'll give you a few minutes to formulate your idea. As a follow-up to Dr. Lewis, I

can see in one particular case, for instance, sculpture, which is a bio-lactic acid, if that was there ahead of the Radiesse, the bio-lactic acid, local ph would certainly, I would expect, accelerate the degradation and dissolution of the HA, the hydroxy appetite. So I think, if I could just offer a comment, I think what you're -- perhaps at least from my -- I'll just say for myself, I think my own discomfort here is as Dr. Miller said, it appears as far as they've tested and I understand the clinical protocol was approved by both the company and the FDA, that it kind of just barely satisfies the safety and efficacy and that's only if you don't look real hard.

And I think that's -- and that's the discomfort. In other words, you know, we're kind of being asked to approve something where we actually don't know how long it stays there. We don't know what the -- we don't know what the reaction is to this material histologically and certainly we don't know what it does in a group of patients that isn't immuno-compromised as far as the cellular action goes. There's probably way more we don't know about this

than we do know about this and I think that's the discomfort, at least I'm feeling, Dr. Lewis. It's not so much that I have a specific thing I'm worried about but there is so much basic about this material I don't know, it just makes me worry on this and it would be to no one's surprise if you put this in a patient that had either another implant in them or some other kind of pathological thing, that the response is different.

I don't think any of us would be surprised at that. And I think that's the discomfort and the worry that Dr. Miller is struggling here to get around it. Maybe it's not but that's my sense of it.

MEMBER MILLER: No, I think it is.

CHAIRMAN LoCICERO: Okay, do you have a statement for us now?

MEMBER MILLER: Here's the statement. A precautionary word to say, this device has been studied adequately only in patients with HIV related lipoatrophy. It's use for other indications is unproven and may cause adverse results (example, keloid or hypertrophic scar formers).

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: It's going to take me awhile to parse that.

CHAIRMAN LoCICERO: All right, we'll get Dr. Bartoo's comment.

INDUSTRY REP. BARTOO: I just have a suggestion. In the sponsor's precautions right now, in their labeling, proposed labeling, I should say, they have, for example, one of the exclusion criteria had to do with pregnancy and they have a statement in there, "Safety of Radiesse for use during pregnancy, in breast feeding females or in patients under 18 years has not been established." And I was wondering if that type of wording might get to both of your, you know, intents. It clearly states that safety in those situations hasn't been established.

MEMBER MILLER: I think a sentence like that would just be fine.

MEMBER BLUMENSTEIN: Yeah, and would these be normally part of labeling? Do you go down the exclusion list and do you put in a statement in the label for each exclusion or for the applicable exclusions?

CHAIRMAN LoCICERO: I think Mr. Melkerson can help us.

DIRECTOR MELKERSON: In terms of labeling, if you have suggestions along that line, in general we do have precautions that follow exclusion criteria or also suggestions from the manufacturer. And you may want to ask them what they think about their exclusions.

MEMBER BLUMENSTEIN: I mean, that's really all -- that would meet my concerns.

MEMBER MILLER: Are we ready to vote?

CHAIRMAN LoCICERO: We're getting close. Since Mr. Melkerson opened the door, we'll ask the sponsor concerning exclusions that we would list and precautions.

DR. BASTA: I'll answer that question without the benefit of having the entire exclusion list in front of me, but in general, it would be our intent to discuss with FDA the details of the populations at which the material was tested, any populations that were excluded from that that may have a safety impact for patients would clearly be

delineated. In the precautionary notes as to what has not been evaluated. And obviously, if the panel votes for an indication in a population, the implication is not beyond that in terms of the safety and effectiveness demonstrated based on the data that has been presented to date. But we will certainly take under due consideration the nature of the conversation the panel has had and even without a specific condition, we will work with our reviewers at FDA to make sure that the labeling is appropriate to address the concerns that have been voiced by the panel through this discussion.

CHAIRMAN LoCICERO: Thank you. All right, I think we're ready to vote on this condition. This condition is as stated, a precaution, that it has been tested only in individuals, HIV patients, with facial lipoatrophy and that it is unclear -- safety in other situations is unclear and the specific exclusions will be delineated later. Dr. Blumenstein, vote?

MEMBER BLUMENSTEIN: I'm happy with that. Yes.

CHAIRMAN LoCICERO: Yes. Dr. Munk?

CONSUMER REP. MUNK: Yes.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: Yes.

CHAIRMAN LoCICERO: Dr. Leitch?

MEMBER LIETCH: Yes.

CHAIRMAN LoCICERO: Dr. Li?

MEMBER LI: Yes.

CHAIRMAN LoCICERO: Dr. Miller?

MEMBER MILLER: Yes.

CHAIRMAN LoCICERO: Dr. Lewis?

MEMBER LEWIS: Yes.

CHAIRMAN LoCICERO: Dr. Olding?

MEMBER OLDING: Yes.

CHAIRMAN LoCICERO: We have a unanimous approval of that condition. Are there any additional conditions? Hearing none, we're ready to vote on approval with conditions as we have outlined. This has been -- we have a motion on the floor. It has been seconded. Is there any further discussion? Dr. Newberger?

MEMBER NEWBERGER: I just would like once again to underline my concern. This is a small study.

MAUDE data base has 45 adverse events reported. Sculptra, which has been available as well, for HIV lipoatrophy, which has been used off-label as well, only has 11 in essentially the same time period. I'd also like to underline the aggressive cosmetic off-label proposals for this product that have been -- these are from 2003, okay, and I think that any attempt to really try to keep this to an HIV only indication is not going to -- not going to work out in practical terms.

CHAIRMAN LoCICERO: Thank you. Dr. Olding, any comments? Anybody else have any comments concerning this motion for approval with conditions? Okay, let's vote? Dr. Olding?

MEMBER OLDING: Yes.

CHAIRMAN LoCICERO: Dr. Lewis?

MEMBER LEWIS: Yes.

CHAIRMAN LoCICERO: Dr. Miller?

MEMBER MILLER: Yes.

CHAIRMAN LoCICERO: Dr. Li?

MEMBER LI: No.

CHAIRMAN LoCICERO: Dr. Leitch?

MEMBER LIETCH: Yes, yes.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: No.

CHAIRMAN LoCICERO: Dr. Munk?

CONSUMER REP. MUNK: Yes.

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: Yes.

CHAIRMAN LoCICERO: Dr. Whittington, I think you're non-voting. You're non-voting, okay. So we have, okay, five yes and two no. That's a majority. Okay, so Mr. Melkerson, the recommendation of the panel is that the pre-market approval application for Radiesse for the treatment of HIV associated facial lipoatrophy from BioForm Medical, Incorporated be recommended for approval with conditions and the conditions have been outlined in our discussion.

Okay, I think it's time for a short break and we'll come back for the second half.

(A brief recess was taken at 2:19 p.m.)

(On the record at 2:27 p.m.)

CHAIRMAN LoCICERO: Okay, we're going to

start again as everybody filters back in. We have one piece of business before we move on. We need to ask each of the voting members why they voted the way they did on this PMA approval. So we'll begin with Dr. Blumenstein, who voted approval.

MEMBER BLUMENSTEIN: I felt the efficacy data showed efficacy in the population studied and again, balanced against whatever safety issues are there in this population, in the population studied is okay, and I have faith that the FDA will make sure that the right labeling is there.

CHAIRMAN LoCICERO: Dr. Munk?

CONSUMER REP. MUNK: Yeah, I agree that the application supports the efficacy and safety in the limited population studied for the limited time period of effect.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: I voted against approvable because I felt that this study was quite small, too small for me to feel comfortable about safety and efficacy. I felt it was flawed in that things that had been done for other fillers in the

past with one exception, including histology and more characterization of the basis of mechanism of action were clarified better for other fillers, I didn't have any information about this. I felt there wasn't enough rigor and although it wasn't part of this PMA, I felt because of the background of noise in the community because it is under such extensive off-label use, what I have seen on that FDA website and what I have heard in the community makes me feel quite uncomfortable about its use.

CHAIRMAN LoCICERO: Dr. Leitch, let's see if your mike works.

MEMBER LIETCH: There we go. I voted for approval because I do think that the product is efficacious and in this particular population with fairly dramatic results for the people who received it and I guess the -- you know, the patient satisfaction with it as reported was very convincing to me that from the patient perspective, the risk benefit ratio for them was favorable and there were no serious adverse events that were reported in this time period, so that accounted for my vote in this particular

circumstance of patients.

CHAIRMAN LoCICERO: Dr. Li.

MEMBER LI: I voted for not approvable because I just thought that there was -- the safety and efficacy was again, good to the point that they carried it out. However, it was really in that sense safety and efficacy because they didn't find anything but I don't think they looked hard enough, if you will. For instance, we don't know some very basic information. We don't know, for instance, does it migrate, yes or no. Do we know exactly how far and fast it dissipates and what the variation is between patients, we have no idea. We don't have any idea what the histology is. All we know about all those things is as far as we looked, there doesn't seem to be a particularly large problem, but that's one of those things where we have -- again, it's the absence of evidence, not the evidence of absence.

So we also don't know things -- we haven't exactly talked about, for instance, we touched on the use of this after you've used some other filler, there might be some interaction. We have no idea what that

is. We have no idea what the dose response is. The physicians are left to decide if they need a little touching up, to add some undisclosed amount or undetermined amount until the physician decides at that moment how to add. So we have no idea, for instance, what the dose response is of this.

And in general, I feel that if we offer approval, the barn door is kind of open at that point and any post-approval is almost, it's almost useless. So I think if you're going to do anything to try to answer any of these questions, in my view these have to do ahead of approval and there are other skin fillers out there, so it's not like we're depriving a community of any skin filler whatsoever. And that's why I voted no.

CHAIRMAN LoCICERO: Dr. Miller?

MEMBER MILLER: I voted yes because I feel like the sponsor demonstrated efficacy in this group of patients and a risk profile that was acceptable for this group of patients, so I voted yes.

CHAIRMAN LoCICERO: Dr. Lewis?

MEMBER LEWIS: Basically the same answer

as Dr. Miller. I thought in this group of patients they demonstrated safety and efficacy and while I agree with what the other panelists have said in terms of shortcomings, it seemed to me that they were not directly sufficient to preclude approving this based on what was shown.

CHAIRMAN LoCICERO: Dr. Olding.

MEMBER OLDING: I voted for approval although I do have some concerns about the lack of information regarding the histology, the length of durability but there have been no significant potential complications noted. And in this patient population, the quality of the photographs that we saw today, the quality of the improvement compared to other treatments that are available I think surpassed those, at least photographically they do. And therefore, I feel that it is certainly demonstrated its effectiveness safety ratio.

CHAIRMAN LoCICERO: Mr. Melkerson, would you care to make a statement?

DIRECTOR MELKERSON: First, I'd like to thank the panel for their in-depth discussions of the

issues, but I had a request from the audience to clarify the vote because they heard six yeses and two voting against. Please clarify the voting status of the different members for the audience and the final vote was five/two, I believe.

CHAIRMAN LoCICERO: It's -- the final vote is five to two. Dr. Munk, actually, technically can't vote. Before we move into the sponsor's presentation of the next PMA, we'd like to open for public comment. Is there anyone who wishes to publicly comment at this time? We'll dispense with the reading of the necessary public comment statements and go directly into the applicant presentation. This is BioForm Medical Radiesse for treatment of nasolabial folds.

DR. BASTA: Thank you. Excuse me for one second. Since this is a new PMA, I'll introduce myself again. Steve Basta, I'm the President and Chief Executive Officer of BioForm Medical. For the record, my presentation for this PMA in terms of background regarding Radiesse, regarding the company and the context of multiple clinical studies that we

have conducted with Radiesse would involve the same slides and rather than going through those slides, I would offer to the panel, we could either go through those slides so that they are on record for this PMA or Dr. LoCicero, I don't know if it would be appropriate for the panel to accept that those slides will be entered into the record rather than listening to them a second time. But we're certainly happy to do so as you would feel appropriate.

CHAIRMAN LoCICERO: If everyone is comfortable, we'll dispense with the introductory slides. Okay.

DR. BASTA: Then by way of an introductory statement, thank you very much to the panel members for the due deliberation in the morning session. This afternoon we will be presenting to you the results of a double-blind controlled clinical study and with the treatment of Radiesse for nasolabial folds. Dr. Larry Bass will make that presentation. He was one of the treating investigators. Radiesse is the first product to be presented to the panel for two facial aesthetics indications with two clinical studies conducted under

US IDEs.

The clinical study which is being presented this afternoon is a clinical study done under an IDE reviewed by FDA with a protocol that had been agreed to by FDA is consistent with the design of other clinical studies that have been performed for other dermal fillers and in fact, addressed some of the observations of this panel in past sessions regarding deficiency and some of those clinical trial designs so that we could optimize the study for this material.

We have integrated those comments into the protocol review of FDA and per that approved protocol, we conducted a clinical study in 117 patients, head to head. Dr. Larry Bass worked through that clinical presentation. This is the third pivotal study for PMA review and approval that is being done with this tissue augmentation material and reflects the breadth of clinical data now in 296 patients in neurology applications, 100 patients for HIV lipoatrophy and 117 patients for nasolabial folds. We believe this is a very well-studied tissue augmentation material with

extensive clinical history.

DR. BASS: Thank you. Good afternoon to members of the panel. As Mr. Basta mentioned, I was an investigator in this clinical trial and served as a consultant to the company in that regard and have also been compensated for my time at this meeting as well as my travel expenses. So we'll have a short interlude. There we go, okay.

As Mr. Basta mentioned, this is a little different study from the earlier presentation. This is a prospective randomized controlled split-face trial comparing Radiesse in one nasolabial fold and a control material CosmoPlast in the other nasolabial fold in each patient. Basically, the data that I'll present demonstrated Radiesse to be safe, a safety profile of Radiesse in this study which was a comparison study, was comparable to that seen for the collagen control material that's been widely available for a great period of time. And 87 percent of the folds were demonstrated to be improved at three months, meeting the primary effectiveness end point, 82 percent of folds improved at six months. So that

all the secondary end points as well, at six months, were met. And there were a number of assessment methods used which I'll delineate in more detail.

As you heard there were 117 patients at four sites. The effectiveness measures made at three and six months included photographic assessments by three blinded evaluators. They primarily evaluated Lemperle Rating Scale as the primary end point and then global aesthetic improvement scale as a secondary measure. There was also a confirmatory effectiveness measure by the treating investigators, a live GAIS assessment as well as patient/physician preference ratings. And again adverse events were assessed along the way.

This slide demonstrates the structure of the Lemperle Rating Scale. Patients receive a grade from zero to five based on wrinkle depth and investigators -- I'm sorry, blinded evaluators sitting by themselves in a room would get a stack of left folds or a stack of right folds. They never saw both sides of a given patient at any one point in time together and they would compare that picture against

the standardized scale to create a grade for how deep that nasolabial fold was. The global aesthetic improvement scale is a comparative scale looking at the degree of improvement compared to the patient's baseline, in this case, baseline photograph so Lemperle is a ordinal scale, it's validated and published based on standardized photographs.

The patient photographs were compared against those standard photographs and each evaluator made their rating separately and independent of any other time point in the study or the contralateral fold in any given patient. The GAIS is a relative assessment. This was done, again, at a distinct time point from when the Lemperle ratings were done and it was a comparison of the patient's baseline photograph on one side with some later time interval photograph on that same side. Again, there were no contralateral comparisons made.

This study - This slide provides an example of how patients entered the follow-up period. They basically received between one and three injections to whatever it took to achieve an optimal

improvement on each side and that could be a different number of injections on each side. So for example, on one side a patient might require two injections to reach optimal. That side would them be timed from the point where the optimal injection was performed and they would be seen three months after that second injection. On the other side, they might only require one injection to reach optimal correction and they would then be seen separately for their three month visit of that fold when three months from that injection had been performed, trying to keep the intervals exactly synchronized from optimal correction.

Photographs were taken at the baseline visit and at each effectiveness end point. This was performed at the investigational site and then sent off to Canfield Scientific Lab. It was at Canfield that the three blinded evaluators performed their ratings independent of the sponsor and independent of the investigator sites. And you see on the bottom part of the slide patients could have up to three corrections. They were then seen at three months for

primary end point, at six months for secondary end point.

At that point, they could receive a touch-up injection on one or both sides and were then followed out to 12 months for any adverse events. All local and systemic adverse events were recorded on both the Radiesse and control sides through the 12 months of the study and this was done in the following several ways. Each patient was called 72 hours after each injection and asked if they were experiencing any problems. These were recorded. Each patient completed a diary for two weeks after each injection and was seen one month after each injection for a physical examination by the physician, again, to assess for any adverse events.

At any other visit that the patient came in effectiveness visits or otherwise, the patient would likewise be evaluated by the physician for any adverse events and any observations that were reported by the patient at any point in time in the study were likewise recorded. This slides lists the four investigational sites. There were three plastic

surgeon -- I'm sorry, three dermatologists and one plastic surgeon involved in the study located in geographically diverse areas. A listing of the inclusion criteria, both folds had to have either a rating of three or four on the Lemperle Rating Scale. If there was a higher or lower rating on either side, the patient was not included.

Patients had to be over 18, willing to sign an informed consent, and able to become available for the required follow-up visits and not undergo any other treatments. There was a list of exclusion criteria similar to the earlier study that you saw, mostly relating to various medical conditions, medications or other treatments which might interfere with the assessment of the outcome. Fifty-five or 47 percent of the patients had a score of three on both folds and then approximately 17 to 18 percent of patients had the other permutations of three and four Lemperle rating scores between the two sides.

This shows some of the demographics of the patient group. Ninety percent of the patients were female in distinction to the earlier study and 13

percent of the patients were non-Caucasian. Ages ranged from 31 to 76 years. Basically looking at the two Radiesse facial clinical studies, in aggregate a large body of non-Caucasian were examined and in those two studies no clinically significant adverse events were observed in any of the non-Caucasian patients. There was no evidence of keloid formation or hyper-pigmentation for Radiesse in any of the non-Caucasian patients. There were significant differences in the number of injections required to achieve optimal correction between the Radiesse and control sides. So 52 percent of the patients achieved optimal correction with one injection only on the Radiesse side compared to 32-1/2 percent in the control group and that was a statistically significant difference.

Likewise, the difference between two injections and three injections was also significant and only a small percentage of patients required three injections in either side. Radiesse also required significantly less total volume injected to achieve optimal correction. The average was 1.2 milliliters on the Radiesse fold with an average of double that,

2.4, on the control side.

I wanted to take a moment and say a few things about how the evaluations were done, the Lemperle Rating Scores, because that's critical to determining the validity of effectiveness. The evaluators were blinded to the treatment assignment. They didn't know that this was an injectable filler. They didn't know how many treatment groups there were or really anything else about the study. They were just asked to provide scores on the two grading scales. Each of the evaluators worked independently and each fold was assessed compared to the standard scale in a large group of folds. For the Global Assessment Static Improvement Scale it was by comparison of the baseline photograph.

The photographic technique was standardized and supervised by Canfield at all the investigator sites and the blinded evaluators were chosen and managed by Canfield Scientific completely independent of the sponsor or the investigator sites. So I'll show a few representative examples of how these patients did over the six-month effectiveness

assessment range and the study. This patient you see at baseline and then at optimal correction and now at three months and six months there's a good persistence of correction and total volume used was 1.5 ml. On the control side, again, good correction at this optimal point but at the three and six-month intervals, pretty much a baseline appearance to the nasolabial fold. Notice also that more than twice as much material was used, so this was a very extensive injection of material in an attempt to obtain optimal correction.

The other examples are going to demonstrate substantially the same thing. Baseline, optimal correction, Radiesse side, still an excellent correction at three months, slightly less at six months. On the control side, again, good correction obtained but baseline at three and six months with twice as much material used. Yet another example, Radiesse correction at three and six months, not quite as good at six but not at baseline. Early correction and then baseline at three and six months, good correction with reasonable persistence and on the

control side, a return to baseline at three and six months.

So looking at this data tabulated in terms of efficacy; at three months, the blinded Lemperle Rating Scoring showed 87 percent of the patients, one Lemperle Score or more improved on the Radiesse side and that was compared to 27 percent of the control sides being one point or more improved. When we compare how much of a change on the Radiesse side compared to the control side, how much of a change in Lemperle Rating Score, it was a greater score on the Radiesse side in 85 percent of the patients. It was about the same improvement in Lemperle Rating Score in a little more than 10 percent and that was obviously a very significant result.

When we look at six months, the numbers are very much the same, 82 percent of Radiesse sides improved one point or more, 27 percent of control sides and 79 percent of the Radiesse sides had a greater Lemperle score improvement than the control side and again about 15 percent had the same amount of improvement as the control side. When we look at how

much improvement that was, of course, at optimal correction you're going to be very nicely improved but at three months Radiesse patients on average or the Radiesse side on average had a 1.5 point improvement in Lemperle rating score and that tailed off slightly at six months but was about one and a quarter.

Again, the control sides, as you saw from the patient photographs, was completed consistent with the tabulated results, was back at baseline at both integrals. Now, if we look at the blinded GAIS at three months, so this is the scoring done by the blinded independent evaluators, 96 percent of the patients were improved or better on the Radiesse side and only 25 percent were improved or better on the control side. The amount of upgrading on the GAIS, the amount of improvement was superior on the Radiesse side in 84 percent of the patients and equivalent in about 15 percent, so very consistent with the Lemperle rating results.

At six months, again, a similar story, this is again, the blinded GAIS done by the independent evaluators. Eighty percent of patients

improved or better on the Radiesse side, 23 percent improved or better on the control side and 75 percent of the Radiesse sides had a greater degree of improvement, more upgrading on GAIS. If we compare that with the live investigator assessments, again, there's a consistent result. The investigators graded 94 and a half or 94.6 percent of the Radiesse sides as improved or better and only 2.7 percent of the control sides as improved or better at the six-month interval.

If we compare the photo Lemperle rating with the photo GAIS rating, again, the numbers, as I mentioned before, line up to be very similar, very consistent result at six months. If we compare the live GAIS and photo GAIS, again, similar, the live assessments seem to demonstrate a little more improvement but basically a consistent pattern of result.

Patient and physician satisfaction at six months was virtually identical and the patients were blinded to which treatment took place on which side when they made this preference assessment. Ninety-seven percent of physicians and 97 percent of patients

preferred the Radiesse side to the control side. Here are a few more representative examples of a good early optimal correction with good persistence at three and six months and again, very deep fold but a good correction early on with return to baseline on the control side. Early correction and excellent persistence at three months, slight tail-off at six months but nowhere near baseline on the Radiesse side, and the control side, back to baseline. Again, good early correction compared to baseline, well-maintained over the six-month period on the Radiesse side and tailing off here and back to baseline at six months on the control side.

Good early correction, some drop-back but not to baseline and early correction and return to baseline on the control side, again in all cases, with significantly more material used on the control side. And a final example, good early correction and really with a very modest volume, very good maintenance of the correction and very good correction early on the control side with a return to baseline. And we showed all these examples to show that it's not just an odd

patient or a few selected patients that really look best but you can show this again and again and again and again. It was very consistent across the study. And finally, again, good maintenance at six months, good early correction but return to baseline.

When we compare the results evaluator to evaluator, the evaluators were fairly consistent. This is Lemperle Rating Scale superiority evaluation, very consistent between the three evaluators. And again, the blinded evaluators comparing intra-evaluator very consistent at this time interval and when we compare one investigational site to another, all the sites varied no more than .2 of a point from the mean Lemperle Rating Score improvement so there was very good consistency in the correction obtained at each investigator site.

Overall, I feel this data has demonstrated Radiesse to be effective with 87 percent of Radiesse patients improved at three months, 82 percent improved at six months; therefore, the primary end point which was the three-month end point with Lemperle Rating Scale was met and the secondary end points at six

months were met by each of the assessment methods, the Lemperle Rating Score and the blinded GAIS, the blind GAIS and patient and physician preference. There was more than one point of mean improvement in Lemperle Rating Score compared to the control at both three and six months and this was consistent across all the evaluators, all the investigator sites and all of the evaluation measures.

Now, it was one of the panel questions regarding the performance of the collagen control in this study, so I wanted to take a moment and provide a little bit of context for that because basically the collagen control showed no improvement, again, back to baseline three and six months on the Lemperle Rating Score. You know, in some ways that correlates with my clinical expectations of collagen durability and it correlates with some of the results seen in other injectable filler trials that have probably been presented before this panel but again, to provide a little perspective on it, first, the collagen was administered according to the labeled instructions of use and the treatment volumes were not restricted, in

fact, quite substantial treatment volumes were administered in an effort to obtain optimal correction.

And so the collagen did work in the sense that it did create a good early correction. It's just that the durability of that correction was shorter than the assessment time points in the structure of this study. So what I'm going to do is show you the baseline and optimal correction time points, not for a selected group of patients but for the first four patients from the first two sites so that you can see that collagen did, in fact, work. It did produce a result. It's just by three months that result was largely gone. So, again, you see the Radiesse side on top but the control side, which is the side that we're looking at this point is on the bottom and an excellent optimal correction early in Site 1 Patient. Site 1, Patient 2, again, a comparable degree of correction to what was obtained on the Radiesse side, Patient 3, comparable optimal correction, Patient 4, and going to Site 2, Patient 1 with a comparable degree of correction from baseline, Patient 2, 3, and

4.

So the collagen produced the end point we were looking for. It just didn't last as long as, perhaps the study construct expected it might. And then when you follow those patients over time, this is Patient 1 from Site 1, again, well corrected initially but at three and six months, baseline with more than twice as much material used, while the Radiesse side maintains a good correction. And Site 1, Patient 2, same things, well corrected initially, returning to baseline and back at baseline with a good persistent correction on the contra-lateral Radiesse treated side.

In terms of safety results in this study, Radiesse demonstrated a comparable safety profile to collagen. There were no unanticipated adverse device events. The adverse events that were seen were transient and they were typical injection related kinds of adverse events that are seen with all dermal fillers. No granulomas were seen and there were no serious adverse events. This table summarizes the percentage of folds experiencing each adverse events

category at some point in the study. And you can see, there's quite a significant amount of edema, erythema and ecchymosis and, in fact, that was significantly more in terms of edema and ecchymosis on the Radiesse side than the control side. All of the others were not dissimilar. They were comparable. And these were all short-lived, typical kinds of things. The other category was a category that included things like soreness, when the patient said soreness instead of pain, it wasn't listed as pain, it was listed under other as soreness. Headache, numbness and this category lumpiness, which was distinct from the physician determined presence of nodules, which you see was quite small in both sides and in fact, was only one patient on the Radiesse side and four patients on the CosmoPlast side, but not significantly different.

So in conclusion, this study to my mind, demonstrated a safety profile for Radiesse that was comparable to that seen with collagen. The primary effectiveness at three months was demonstrated and all of the secondary effectiveness end points at both

three and six months were demonstrated with more than 80 percent of the folds improved or better at both of those time intervals. Radiesse demonstrated clear superiority to the collagen control material at both three and six months both by the Lemperle Rating Scale and the Global Aesthetic Improvement Scale and patient preference and physician preference was overwhelmingly in favor of the Radiesse side compared to the collagen side.

So in summary these two pivotal studies of Radiesse demonstrated the use of Radiesse to restore soft tissue facial contours in a total of 217 patients between the two studies and we saw more than 80 percent of patients improved at both three and six months and 100 percent of the facial lipoatrophy patients were improved at three, six and 12 months. Thank you.

DR. BASTA: At this point in the presentation, we would, per the request of FDA in terms of preparing for this panel presentation, also present again, radiology study, the findings -- the clinical observations of the patients that were in the

radiology study and we have more patients for -- with nasolabial fold treatment in that study as well that we could show you images from, but it is substantially the presentation that you have already seen and so, Dr. LoCicero, I would ask for your guidance as to whether we should just submit that for the record and consider that presentation to have been made at this meeting or if you would like to have us go through that again.

CHAIRMAN LoCICERO: Does the panel agree that we don't have to do that again? Okay, so we'd like you to just put that with the presentation to the FDA.

DR. BASTA: We will do so, thank you very much. With that, albeit a brief presentation, this is the data from the pivotal clinical trial which supports the nasolabial fold indication. Again, this study was conducted under and IDE that was reviewed with the FDA, is consistent with the study design of other materials that have been tested and reviewed by this panel for nasolabial fold indications and the results of this study, I think, are quite self-evident

in terms of safety and effectiveness but obviously, we will wait for the panel discussion on that topic, thank you.

CHAIRMAN LoCICERO: Okay, it's time for the panel to ask questions of the sponsor concerning the presentation on this indication. Dr. Newberger?

MEMBER NEWBERGER: I have a question about the control used. Under your mode of administration, you write that tracking method is used with both the control and Radiesse. Those of us who do a lot of injection don't use the tracking method for CosmoPlast and if you go to the package insert and the CosmoPlast instructions from Allergan (phonetic) you see that the serial puncture technique is used. So I don't know that your control is being used in an optimal method that's comparable because certainly, when we do CosmoPlast injections for nasolabial fold correction in our office, we have far better results than you show here. So would you comment on the adequacy of the control and why you used a technique that is different than the manufacturer of the control recommends?

DR. BASS: I'm a little at a loss. I can't really speak to the comment in the package material you received. At my site and to the best of my knowledge at the other sites, the serial puncture technique was employed when placing the CosmoPlast control and this is in line with the -- again, the package insert instructions for use and the customary way that we clinically use this material.

By the same token, as you saw in the multiple control side optimal correction pictures that I presented, whatever technique may have been used, it certainly accomplished a good optimal consistent correction with the CosmoPlast material. So we did not have trouble in any patients that I'm aware of achieving the optimal correction end point on the CosmoPlast side.

MEMBER NEWBERGER: So you are saying then that the packet that we received which says under Section 2.4 Mode of Administration, the method of injection was tracking for both products is not correct?

DR. BASS: I am not familiar with the

terminology tracking at all and I can tell you that --

MEMBER NEWBERGER: Threading.

DR. BASS: Okay, the technique according to the protocol, as I understood it, was that each material be injected according to the customary practice of the physician which was threading for Radiesse in all cases and was left to the discretion of the investigator on the CosmoPlast side. It's my understanding that it was serial puncture in all cases and I know for certain it was at my site.

CHAIRMAN LoCICERO: Does this study have a medical monitor?

DR. BASS: Yes.

CHAIRMAN LoCICERO: Can we maybe get some comments concerning this?

DR. BASTA: The study was monitored. I've asked our clinical group to review the history regarding the instructions provided to the investigators and we will get you a response to that but certainly the use of CosmoPlast consistent with its instructions for use was the intent of the protocol and we will determine exactly what was

communicated and what procedures were used. I will have that data for you in a few moments.

CHAIRMAN LoCICERO: Other additional -- Dr. Miller?

MEMBER MILLER: First of all, I congratulate you on a really nicely done study. And I want to ask about the condition of the tissue at six months and if you would go back and reinject which often these patients, they want to have their correction restored, what's it like to go back and reinject at six months or longer? I mean, earlier it was mentioned that there was -- it's difficult to reinject where the previous material was placed. It is similar in the application you're using it in?

DR. BASS: That's actually a very interesting issue. In most of these patients, at the six-month touch-up injection, the tissues felt similar to their baseline feel. Of course, much smaller volumes of material are being used here compared to the study we saw this morning. Some patients did have a slightly firmer feel on injection and I want to draw a distinction between the feel to the injector

advancing a needle through subcutaneous tissues and the feel to the physician examining a patient by palpation and the patient feeling their tissues. And so firmness at that interval was not observed and on physical exam, but in some patients, a slightly firmer feel was perceived on needle injection during the touch-up injection. This did not hamper injection or returning that side to optimal correction.

MEMBER MILLER: And I'm curious if you would have any -- I mean, you can take a large part of the discussion this morning about some of the uncertainties about this material and just cut and paste it into this afternoon in some ways. Having listened to some of the discussion this morning, do you have any comment about some of the issues raised that bear upon this application that come to your mind without reviewing them all?

DR. BASS: Well, overall, I feel this study is fundamentally different because it does have the virtue of a control material injected in the same patients, in the same site albeit on the contra-lateral side, a material that's been around for

decades and is widely used and has a very well-defined safety profile, and the profile of the Radiesse product, its performance at least till the end point of this study, 12 months, was in every way comparable except for a little more edema and a little more ecchymosis.

In addition, personally, as a plastic surgeon, having trained at a place where we used a fair amount of hydroxyl appetite in reconstructive facial applications, including granules, I just recall always seeing granules in the soft tissue at the conclusion of the procedure, after we tamped it into a bone defect and the decades of that use without a late untoward sequella is an added reassurance for me personally as a physician.

MEMBER MILLER: Thank you.

CHAIRMAN LoCICERO: Dr. Li?

MEMBER LI: Can you -- you've described comparing the control against Radiesse by the number of injections. Is the amount of material the same in the two groups? In other words, is one injection the same amount of the active material in both the control

group and the Radiesse?

DR. BASS: I mean, overall, the -- we're looking to see if we have the data spread out per injection, how much was placed per injection, but the total volume injected to achieve optimal correction, whether it was done in one injection or three, was on average, half as much on the Radiesse side as it was on the CosmoPlast side, an average of 1.2 on the Radiesse side, an average of 2.4 milliliters on the CosmoPlast see and we're trying to see if we can show how that was distributed by injection. And again, on an average fewer injections to get to the optimal end point on the Radiesse side.

MEMBER LI: Can you describe compare and control again?

DR. BASS: Right, so you can see here that as Injection 1, the mean volume on the Radiesse side was 1.0 ml and 1.7 ml on the CosmoPlast control side. At Injection 2, the mean injection on the Radiesse side, should a patient require a second injection was .4 ml and .9 on the control side. And at four weeks, the small number of patients that landed up there was

.5 and .7 ml.

MEMBER LI: Thank you. Let me rephrase my question. Per milliliter of each material, is there the same amount of say collagen versus hydroxy appetite, in other words, milliliter per milliliter for each one, am I injecting the same amount of collagen as hydroxy appetite?

DR. BASS: Well, probably not. I don't recall the exact amount of collagen in the material. Maybe Dr. Carruthers will help me with that. Thirty percent of the Radiesse material is hydroxy appetite and the remainder is the gel carrier.

MEMBER LI: That's 30 percent by weight or by volume?

DR. BASS: By volume, 30 percent by volume.

MEMBER LI: Okay, the density is so large, though that the amount can be quite different.

DR. BASS: I mean, again, it's --

MEMBER LI: I'm just trying to get a feel for if -- how comparable your control is to the Radiesse versus the active ingredient. In other

words, to tell me twice its volume is not very descriptive if there's half as much material and it's the same amount then, right?

DR. BASS: Well, it's descriptive in the following way. I mean, it's -- there are two -- well, I understand what you're saying. That's a very interesting point. I think there are two aspects to it. One aspect is th clinician/patient aspect. The distinction is important because if you are paying for the material or you're receiving the material, in multiple injections potentially, that has an effect on you in dollars and in time and inconvenience. From the point of view of the study, it's significant because even if -- even that being true, what you're saying, a lot of these patients came in and had one Radiesse injection and they got injected again and again and again with CosmoPlast to get them to an optimal correction and so even if the materials are not comparable by weight or amount, they had the opportunity to get enough amount to reach an optimal end point and that series of eight sequential patients all of whom got a comparable correction on their

control side and Radiesse side supports that.

MEMBER LI: No, I understand why you did it. I'm just trying -- I'm struggling with trying to get essentially a dose response indicator of some sort. So I understand -- how you did it is completely logical. I'm just trying to get a -- I'm struggling again for kind of mechanistic information.

DR. BASS: The dose issue is funny because the clinical condition being treated varies in severity widely from patient to patient. As you saw, on the Lemperle Rating Scale, you could be a one or a five. Now in the study they were all three and four but in the real world, patients walking in are anywhere from two, because a one really wouldn't need treatment, anywhere from two to five. And so the amount that people need varies, depending on the severity of their pathology and that's a customary -- this is now something that many clinicians are doing, that many clinicians have experience with by virtue of their residency training, and making the aesthetic judgments about how much is enough is part and parcel of that training that we received for years and years

and years when were developing our skills.

MEMBER LI: And just a quick question; you described initially this was a double blinded study. Which were the parties that were double blinded, because certainly the physician doing the injection knows what he's doing because they're different procedures, so when you say it's double blinded what exactly are you referring to?

DR. BASTA: I'm sorry, I may have misspoken. That comes from my old pharmaceutical days. In this context the evaluators were blinded so the study was done in a manner in which all of the primary end point evaluations were conducted by blinded evaluators, but the double blind nomenclature is an unfortunate slip that comes from having done pharmaceutical studies for many years.

MEMBER LI: Thank you.

CHAIRMAN LoCICERO: Dr. Blumenstein.

MEMBER BLUMENSTEIN: So I want to make an assertion and then hear a defense from you folks. I claim that this study is fundamentally flawed because optimal for each side could be biased because the

clinician delivering the intervention is not biased. In other words, the -- what's defined as optimal may not be the same on both sides of the face and it could be that clinician being biased would have left the patient in the control arm little less optimal than the patient in the investigation. Control side would have left the patient in less than -- a slightly less optimal condition than the patient in the investigational side.

DR. BASS: Let me comment from an operational point of view again as a clinician and then I'll let the company people respond from more of a structural view. It is true that the investigator is determining the end point of optimum and there is a little leeway there because optimum correction is not total correction. It's not you look 20 years old. It's the best we think injectable filler can reasonably correct the fold. And so there is a judgment there. That being said, again, in the multiple examples we showed, I think the degree of correction obtained was arguably to an approximation equivalent on the two sides not in many of the

examples we showed but essentially in all of them. And the response at three and six months was so divergent for the very, very close correction that I think that factors out. That's my clinical perspective. Let me let the company offer theirs.

DR. BASTA: Several insights may be helpful in regard to that question. One is that the phenomenon that you're describing is common to multiple studies in the nasolabial fold indication. That treatment to optimal correction as determined by the investigator is a common standard of practice in study designs in this area. There are, in fact, three ways that we considered designing this study that would have addressed that potential point as well but we believe that the way that we designed it is the most rigorous of the paths that is available and practically reasonable.

The three alternatives that we considered would have been a live evaluator assessment, but that has inherent in it all of the limitations of the fact that the live evaluator will see a patient and see a nasolabial fold that's responsive on one side and that

has not improved on the other side and so you have unblinding risk over the course of the study. So when we considered the feedback from this panel on prior clinical study designs, one of the criticisms that was offered was if you use a live evaluator, though they may be blinded as to treatment side there's a significant risk of unblinding if there's a symmetry that gets created and one of the products is longer lasting. So we dismiss that as a likely path for creating the best potential study design.

There is a second study design where you could have a blinded live evaluator do ratings for enrollment and for optimal determination and then have blinded evaluators but then you end up with potential discrepancies between the scores of the live evaluators and the blinded evaluators. We considered that option and chose to go with the pure blinded evaluator option. That creates a logistics just physically, in terms of taking the pictures, sending them to the blinded evaluators that would have made it difficult for them to rate optimal and determine whether or not injection would need to be performed

because the patients would have had to come in repeatedly, come in for a picture and then come in for injection, then come in for a picture, then come in for injection and so it becomes unacceptable to patients to implement that kind of a study design.

The best, most appropriate study design that we considered after careful and thorough work to evaluate each of these options and evaluate each of these options with our reviewers at FDA to look at what the best practices were in the industry, was one where the treating investigators would make the clinical assessment as to when they had achieved optimal injection for these patients with the observation of the inherent limitation, Dr. Blumenstein, that you've observed that they are, in fact, knowledgeable about which treatment is provided but as clinicians, we expect that they are providing the best possible care for the patients and therefore, really are treating the patients to optimal.

The other evidence that would point to the fact that the bias that you might be concerned about is not evident in this study is that the collagen

folds actually receive more injections and more material. So there was clearly a diligent effort to try to bring those folds up to optimal correction and if anything, bias to more treatment on that side rather than on the Radiesse side but I don't believe there was a bias. I believe that these clinicians are treating these patients with the intent of achieving the best possible outcome for the patients and that was the most responsible clinical approach with a rigorous independent blinding structure that we could create, but your point is well-taken.

MEMBER BLUMENSTEIN: Do you -- I gather from looking at the schema and so forth, that you did not take photographs of the optimal correction when it was judged that the correction was optimal, the two week after last injection visit.

DR. BASTA: Yes, we did take photographs. Those were the photographs that Dr. Bass presented. They were not rated by the blinded evaluators because it was not an effectiveness time point but they were, in fact, taken and as we showed in the presentation -- we'd be happy to bring some of those up. As we showed

in the presentation, we actually showed you the baseline photograph, the photograph at the optimal time point which is two weeks after the last injection when the investigator deemed that the patient had reached optimal correction and no further treatment was required and then at the three-month and six-month time points. We can go back through some of those as well but that is what Dr. Bass was describing for you was showing you those pictures.

MEMBER BLUMENSTEIN: Okay, but those weren't included in this book.

DR. BASTA: I believe that's right. They were not included in that book. They were introduced into the presentation. They were included in the presentation previously submitted to FDA. We had thought that that would be circulated to the panel but they were included in response to the FDA's question that we know the panel will be asked to address about the collagen effectiveness issue. We believe that it was an important question to answer, did the collagen side actually get treated effectively and did it get treated to optimal correction and the best evidence

for that was to go through a series of patients in sequential order, not selected for which ones had the best correction, but simply go through a sequence of patients and we would be happy to go through that again.

MEMBER BLUMENSTEIN: Are they on the CD?

DR. BASTA: My colleagues are nodding in the affirmative, that all of the photographs are on the CD.

MEMBER BLUMENSTEIN: Thank you.

CHAIRMAN LoCICERO: Are there other questions? Yes, Dr. Olding.

MEMBER OLDING: I just have a question about the demographics and the use of the patients from the previous study and your conclusions regarding the use of this product in the nasolabial fold in persons of color.

DR. BASTA: Could we have the question repeated? I'm sorry.

CHAIRMAN LoCICERO: Yes, we'd like a comment about the patients of color and the response.

DR. BASTA: And I'm sorry, what is the

question regarding persons of color?

MEMBER OLDING: Well, you presented or Dr. Bass presented in his list of demographics both in material from the last study and this one regarding African Americans. Is it your supposition in presenting that data that you can utilize the patients from the first study to make a conclusion or draw a conclusion that this is also safe in persons of color?

DR. BASTA: Well, I think that's actually a clinical question. Dr. Bass, do you wish to take that question? I'll allow him as a clinician to assist with a clinical judgment on that.

DR. BASS: I don't have the detail of the question again, I apologize.

CHAIRMAN LoCICERO: Okay, would you recommend this in a Black person is what we've boiled it down to?

MEMBER OLDING: That's not quite it. The -- you -- can you draw conclusions about the population of patients of color regarding the use of the material in that population correcting nasolabial folds? Are you drawing upon the previous study's

results to make any conclusions?

DR. BASS: I think the numbers in the nasolabial fold study by itself were small. So effectiveness judgments really can only be mated to the nasolabial study. I think safety judgments spread across really the body of patients of non-Caucasian patients in both studies and is quite a sizeable number of patients and was very consistent in its outcome, that there were no adverse effects and in particular the adverse effects we'd be most concerned with keloid formation and hyperpigmentation were just not present in any of the patients in either of the studies --

MEMBER OLDING: What about the fact --

DR. BASS: -- in any of the patients of color.

MEMBER OLDING: What about the fact that in the -- that the population of African Americans for example, that were involved in the first study were immuno suppressed? Do you think that makes a difference as far as the response to the injectable?

DR. BASS: Do you have the CD4 counts?

They were patients who have an immune disorder. The question is were they immuno suppressed in fact or not at the time of the study. Now, there is some CD4 count data --

MEMBER OLDING: Greater than 250, I think, is that right?

DR. BASS: Well, that was the study-wide criteria but I think they're trying to bring up some additional data that in that cohort of patients there was something approximating a normal count which would allow us to conclude that there was no special reason to think they would under-respond based on that additional laboratory data.

So here these are patients now with more than 500 on the CD4 count, so only patients with really a higher count level and they are in the lipoatrophy side of the study in terms of complications and adverse events both at 0-6 months and 6 to 12 months. Basically there was no incidents. It's not on the slide because there wasn't any of scarring, keloid formation, or hyper-pigmentation.

And so drawing on that experience in

conjunction with the 13 odd, approximately 10 percent non-Caucasian patients in the focus nasolabial study, I think that's a significant body of safety data to consider.

MEMBER OLDING: Didn't your study -- I'm not sure why you chose for this slide the CD4 count greater than 500 if you could get into your study with CD4 count greater than 250. I don't understand the validity of this slide if you allow people in it who are 250.

DR. BASTA: We actually have looked at the data segment at patients between 250 and 500 and patients greater than 500. The reason for presenting the data in the span is to address precisely the question that you're asking which is, is there sufficient data -- if I can paraphrase, is there sufficient data from the lipoatrophy study to indicate whether or not the product is safe in persons of color without HIV infection and any associated immune dysfunction that might occur, if that's a fair paraphrasing of your question.

One of the markers in HIV infection that

is used as a surrogate for immune health is CD4 count and, in fact, there's a significant body of literature associating CD4 counts greater than 500 with virtually normal immune function. And so if someone has a CD4 count range above 500 that is in the normal range, they have a competent immune system, we believe that therefore, that population represents a population that would be instructive for assessment of whether or not safety in normal individuals that are not HIV infected would be appropriate.

We did attempt in the nasolabial fold clinical trial to specifically recruit persons of color at each of the clinical sites. We placed advertising for persons of color in response to some of the questions that were raised by this panel in prior reviews. We simply had a low -- we actually had a moderate number of individuals present but then a low success rate through the screening for those patients to qualify with Lemperle Rating Scale three or four folds and qualify for the study.

And so we only ended up with a very small number of patients in the nasolabial fold study

despite specific recruiting for persons of color in advertising locations which would recruit that population and with ads targeted to that population.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: I have one other question about the slide that's up, please. It seems to me that those people with HIV associated lipoatrophy have a significant difference in terms of erythema as a side effect compared to those with nasolabial fold treatment. So could you comment on perhaps the impact that immune status might have on that?

DR. BASS: Well, the numbers in absolute terms look somewhat different but if you look at the P value, you can see that there's not statistical significance to that difference. Recall also that these are patients having on average almost -- having on average almost eight times as much material injected. So the fact that someone getting eight times as many needle sticks has somewhat more ecchymosis erythema, and they have less erythema.

CHAIRMAN LoCICERO: There are two cells we need to look at. The first is erythema in the 0 to 6

month group. That's significant for more problems in the nasolabial fold group. In the 6 to 12 month period pruritus is also a significant difference between the two groups, how do you explain that?

DR. BASS: Right, the pruritus difference is sort of a wash because if you look -- if you look in -- well --

CHAIRMAN LoCICERO: Why don't you take some time to analyze that and answer us later. Do you have the answer to the first question you didn't have an answer to?

DR. BASTA: If we could take that off the screen and Dr. Bass could review it. We will need to confirm with each of the investigators, the device technique which they used. The collagen instructions for use which we've reviewed are silent as to injection technique. So the instructions for use for collagen to our knowledge did not dictate what the precise mechanism -- what the precise technique for placement would be and we do know that there -- we simply don't have the opportunity today to speak with each of the investigators to determine what their precise technique

was for collagen in order to --

MEMBER NEWBERGER: Excuse me, do you mean that the collagen material doesn't give instructions for injection?

DR. BASTA: As to whether it should be a serial puncture or a linear threading, I believe that the -- yeah, if --

MEMBER NEWBERGER: I have it right here on my computer, the technique.

DR. BASTA: Dr. Newberger, I don't know what it is that you're looking at currently.

MEMBER BLUMENSTEIN: Let me just read a sentence here. It says, "The method of injection will be tracking for both products".

MEMBER NEWBERGER: It looks like it's on a protocol.

MEMBER BLUMENSTEIN: No, that's correct, that's in our protocol but as to what is in the collagen instructions for use, Dr. Newberger, you indicated that you believe that that is not a correct instruction for the injection of collagen. We had worked with the FDA to determine that the product would

be used in a manner consistent with the instructions for use for collagen.

MEMBER NEWBERGER: This is from the corporation that makes CosmoPlast and it says, Serial puncture technique recommended for nasolabial lines or furrows." This is their material.

DR. BASTA: Is that in the package instructions for use?

MEMBER NEWBERGER: I can't tell you if it's in the current package now but it's one of their publications for approved -- their recommended techniques for different areas from Inamed Corporation.

MEMBER BLUMENSTEIN: Well, but I think this is relevant. It says in the protocol it's tracking for both.

CHAIRMAN LoCICERO: I think it would be very important if this panel had the information concerning those investigators and the technique that was used. Is there some way that you can get that today?

DR. BASTA: I will ask someone to see if

they can contact each of the clinical investigators to find out if there was anything different from what has been described in the material that has been provided. The methodology was, in fact, reviewed with the agency and is consistent with the instructions for use but I do appreciate the fact that something different might be on their website.

CHAIRMAN LoCICERO: It might be appropriate to take our break now. We'll come back at five to 4:00.

(A brief recess was taken.)

CHAIRMAN LoCICERO: We're ready to begin again. We have two questions on the floor that the sponsors need to answer. Before that, Dr. Newberger has a comment.

MEMBER NEWBERGER: I have the source for the information on the recommended serial puncture technique for nasolabial lines or furrows and that is a document that comes from the Inamed representative who goes to each office to provide Zyplast, Zyderm, CosmoPlast and CosmoDerm, so that's the source. It's not, per se, in the package insert. It's additional

information that's given by the representative, the sales rep to the purchasers.

DR. BASTA: Thank you, Dr. Newberger, that's helpful context. We have, during the break, addressed the question which you had asked. We have contacted each of the investigators in the study. Three of the investigators -- and all of the investigators performed these treatments consistent with the instructions for use for the material which was -- and the material, in fact, comes packaged with two needles. The CosmoPlast material comes with both a short needle and a longer needle; the short needle appropriate for the serial puncture techniques, the longer needle for the tracking or the threading techniques.

Three of the investigators indicated to us that they used a threading technique. One of the investigators indicated that he used a serial puncture technique, both of which are techniques that are appropriate for the material. They used the needles which were provided in the material. We have also reviewed the Inamed instructions for use that existed