at the time the protocol was designed. I have not reviewed whether or not those have changed at all currently but I would expect that they likely have not but I'm not certain of that.

The instructions for use that existed at the time that this protocol was designed were silent as to which technique would be appropriate and both techniques were appropriate for use of the material. Whether or not Inamed has since created marketing materials that then direct people to use something different from what they had directed in 2003 when we designed the study, it's possible that they've created some new marketing literature in that process and I appreciate Dr. Newberger, your bringing that to our attention. But the way the study was designed was using the available information at the time, using best practices for this material based upon the knowledge that we had in 2003 when the protocol was written and reviewed with FDA.

Also importantly, this whole question gets to -- whether or not collagen was appropriately used really gets to the question of did the patients achieve

optimal correction. In fact, the key intent in being able to compare the Radiesse treatment group versus the collagen treatment group is about whether or not the patients achieved optimal correction. The study was designed to ensure the patients achieve optimal correction by virtue of allowing continued treatment until the patients got there.

And so the fact that each of the patients received multiple injections to achieve an optimal correction point on the collagen side creates the baseline for the comparison between the two groups and it's clear that each of the clinicians believe that the technique that they were using was appropriate for their patients and was successful at achieving optimal correction because they ceased providing treatments when that was reached. The other point that may be instructive on this, if we can pull up the slide, is that we have, in fact, on a site by site comparison given the data that we've just learned that three of the sites used a threading -- oh, actually, this slide is -- please take this slide off. That slide actually only has the Radiesse folds. We need to do the similar

analysis for the CosmoPlast folds to determine the site by site comparison. I apologize that that data would not be applicable to this point.

But we will do an assessment of the relevant data and the best indication, really would be to look at the photographs for optimal correction and determine that the patients, in fact have reached optimal correction. We have the photographs for every patient if you'd like to go through that. We also have the photographs for representative patients and Dr. Bass already presented to you the first four patients as a serial group from each of two clinical sites, and you can see for yourself that the patients did in fact, achieve optimal correction on the collagen side. Thank you.

CHAIRMAN LoCICERO: Just for completeness sake, since one site is serial injection, how many patients were entered from that site?

DR. BASTA: That site had 16 of the 117 patients.

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: Well, I mean, I'm

still curious about why you didn't have the photographs for the optimal correction score. That would have -- that would go a long ways towards providing some data, some assurance that there was an equal or approximately equal baseline.

MEMBER BLUMENSTEIN: I'm sorry, you said we should have provided the --

MEMBER BLUMENSTEIN: Having the photographs from the optimal -- from the judgment of an optimal achievement scored, that in other words, you said previously that you didn't score the photographs taken at the time that it was judged that the treatment was optimally achieved. Another thing is that you had a limit of three sessions and so what would happen if, for example, in the control arm that optimal -- optimality was not achieved, you had to stop there.

And the third thing is that I'm still bothered by the fact that there's an admitted whole site that violated the protocol because the protocol clearly states and goes on to state other things about it that this tracking method will be used for both products.

CHAIRMAN LoCICERO: Okay, there's still another question on the floor. Dr. Bass, there were two significant differences that you were going to talk to us about.

DR. BASS: Yes, this was a comparison of the lipoatrophy study patients and the nasolabial fold study patients. And at one interval, there was a higher incidence of pruritus that was of statistical significance in the nasolabial fold study group. This was one patient in the lipoatrophy group and five patients in the nasolabial group. It's a small number of -- in terms of the overall incidents and it's an adverse event that was of short duration.

The same applies to the erythema, the numbers of patients who experienced erythema was more significant. There was some difference between the two groups, again, with more erythema in the nasolabial group which is a more superficial injection in some circumstances and this was likewise a short duration injection, duration result or adverse event. So I don't have a mechanistic explanation for why that difference was observed but the time course and the

experience of these kind of events is something that's seen again pretty much with all injectable therapy use so it's not clear if that's a material-related phenomenon, an injection technique-related phenomenon or just a product of the small numbers of patients involved in those particular adverse events.

CHAIRMAN LoCICERO: Dr. Olding, do you have additional questions concerning the African American patients versus the Caucasian patients concerning erythema?

MEMBER OLDING: No, but I did think about that in the break we had. Were the patients blocked the same way, both the HIV lipodystrophy, if they were blocked with say Xylo with Epi then they might not have shown those things as much as the nasolabial folds if they were treated differently.

DR. BASTA: The clinical protocols were flexible as to anesthesia methodology that would be used by each investigator and so we would, again, have to review the complete patient records to determine what block was used for what number of patients and I don't believe we have that analysis immediately handy.

The other element on this point is the conversation we're having regarding persons of color reflects the fact that we had only two African American patients in the nasolabial fold clinical trial. It would certainly be a reasonable conclusion of the panel that that's inadequate to determine safety in that population. We felt that it was important in the context of having information from subdermal injection in another population that included African American patients to have that data also be available for consideration but it's -- but we don't presume to draw a conclusion that that, in fact, should be applicable. That would be your medical judgment as to whether or not that provides adequate comfort in that population or if an additional study might be needed in an African American population in order to determine safety.

We presented the data which we have available and unfortunately, the number of African American patients in our nasolabial fold study was small.

MEMBER OLDING: Thank you.

CHAIRMAN LoCICERO: Dr. Leitch?

MEMBER LIETCH: Back to the question of comparing those two populations, would it be safe to say that the lipodystrophy patients' injections would have been deeper than the nasolabial fold injections? I know both of them say subdermal but I think this morning in the presentation there was discussion about deeper injections.

DR. BASTA: It is possible that that was the case, but again, that would be specifically a conversation with each of the investigators as to whether or not in addition to subdermal, if they inject it at another level.

MEMBER LIETCH: I guess the reason I asked, I guess --

DR. BASTA: The guidance was for subdermal injections.

MEMBER LIETCH: -- the reason I was asking that is with the nasolabial fold it's kind of a line.

DR. BASTA: Right.

MEMBER LIETCH: And I'm not a plastic surgeon, so I don't know exactly how this is done, but, you know, the defect is a linear defect whereas with

the lipodystrophy it's more of a broad plane defect. So I can envision a person might try to run that line which could give a more superficial injection, which might be a bigger problem than a person with more skin pigmentation because there might be more reaction in the skin than if the injection was truly subdermal and more diffuse.

DR. BASTA: Your medical judgment here might be instructive in that regard. I don't know that we have that level of detail regarding each injection.

Per Dr. Blumenstein's question earlier as to the number of patients that had stopped after three injections to determine whether or not the patients, in fact, reached optimal, I believe only 7.7 percent of the collagen patients received three injections. The others were determined to be -- to be optimally corrected after two injections, so that that limit in the protocol did not have a material or should not have had a material impact on a significant number of patients in the study. The majority had reached optimal correction after only two corrections.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: Yes, I have a question for Dr. Bass. Is there a difference in technique for using the collagen and the -- you know, your new material and is there -- would somebody have to learn those differences or would they be -- if they know how to inject collagen, can that knowledge just translate directly into, you know, the new material or would you have to relearn some new techniques to inject the new material?

DR. BASS: I think all of the injectable materials have small differences in their handling properties, the characteristics of the syringes they're preloaded into, but these are relatively minor variations. Again, unlike the lipoatrophy corrections, which are sizeable in volume and in anatomic areas that are not routinely treated by aesthetic providers or by all aesthetic providers, the nasolabial fold application and these sort of commonplace aesthetic applications are fairly characteristic.

I think the technique relates much more closely to techniques used with Restylane because

threading is more common with Restylane than it is with collagen materials but all of these are minor variations that require a very short learning curve, not a complete transition to a new approach.

MEMBER MILLER: Thank you.

CHAIRMAN LoCICERO: Are there any further questions of the sponsor? If not, we're ready for the FDA presentation.

DR. LERNER: Well, this afternoon I'm going to be presenting T050052, Radiesse for nasolabial folds. I would just like to comment that your discussions over the last 45 minutes or so have basically encompassed everything that I was intending to say, so I'm going to go fairly quickly through these. And I'm going to be highlighting the safety issues and our statistician, Dr. Bonangelino will be discussing the effectiveness data.

I'm going to just really go quickly through these rather than just sit and read all of them. You've seen our review team. The objective of this presentation is to review the data of the PMA and present the panel with our concerns or issues for

further discussion. You know about the device. You've heard about the study design. Inclusion criteria, as noted, included a Lemperle Rating Scale of three or four. The protocol allowed for two repeat injections, no over-correction and follow-ups to six months with touch-up at that point.

Quickly, a study synopsis, you've been discussing that in the last half hour or so, just to note that the patients did have a diary for two weeks after each injection to collect some of the immediate adverse events which are seen in the injectable filler, with the injectable fillers. Photographs were taken at each visit and there was a patient guess at which device they were getting at three and six months. The highlights, loss to follow-up was minimal. Of the 117 patients receiving treatment, 115 were available for the primary effectiveness measurements at three months and 113 at six months. The safety analysis included all 117 patients of whom 113 were available at six months.

Adverse events were generally related to the injections and the protocol of deviations were few

and minor. We've discussed here a lot about the patient demographics. You've seen this slide about the amount of material injected at the two-week and four-week period. As discussed a few minutes ago, the safety profile included five major adverse events, ecchymosis, edema, erythema, pain and pruritus and there again, is that other characteristic of other. We did look through that data and there was no real reporting of what we discussed this morning about nodules. There was I think only one nodule reported.

We discussed earlier the radiographic evaluations that were performed and I won't go through that again. In summary, one of our main concerns was that there were few persons of color in this study and your discussions over the last half hour or so addressed this. Most adverse events were minor and the radiographic evaluation was adequate. Before the effectiveness data is given by Dr. Bonangelino, I just wanted to show you this one set of photographs. Radiesse is on the left and control in the right. This is before treatment. This is at optimal correction, three months and six months and you can see that the

patient has -- the control has gone back toward baseline. Dr. Bonangelino.

DR. BONANGELINO: Good afternoon. Today I will be presenting some aspects of the effectiveness results for this pre-market application. The basic outline of the study is as follows, and this may be a bit of repetition so please bear with me. This was a split-face, randomized design, comparing Radiesse to CosmoPlast, which is an approved human collagen product. The primary end point was a change in Lemperle Rating Scale scores at three months. The sample size was 117 patients and the primary effectiveness analysis was performed by three physician evaluators from photographs in a masked manner.

The first statistical issue I would like to address concerns the non-inferiority or superiority of the Radiesse treatment to the control. First, note that non-inferiority of Radiesse to CosmoPlast was demonstrated at three months. The problem is that the control was not at all effective at three months. Therefore, non-inferiority is not a appropriate to evaluate. However, note the superiority of Radiesse to

CosmoPlast was also demonstrated at three months.

As a prelude to what follows, note the following statistical comment regarding assessing both non-inferiority and superiority. This is that it is an accepted principle that with proper planning it is possible to use the same data to test first for non-inferiority and then for superiority without a statistical penalty provided the non-inferiority margin were pre-specified. This was the case for the Radiesse statistical plan.

The criteria which were used for clinical superiority were as follows. First, statistical superiority should be demonstrated. Second, at least 50 percent of evaluation should rate Radiesse superior to the control. Third, the point estimate of the difference in the mean change in Lemperle Rating Scale score should be an improvement of at least one point. Finally, there should be effective masking of the evaluators of the primary end point.

For the primary effectiveness results, the sponsor used the median rating of the three evaluators. Using this method approximately 85 percent of

evaluations rated Radiesse superior at three months. With the same data, McNemar's test was highly significant for statistical superiority of Radiesse at three months. The P value for this comparison was less than 0.0001. Thus, the first two criteria of statistical superiority and of greater than 50 percent of evaluations rated superior were met at three months.

To assess the mean difference between treatments, the sponsor used a model that included all three evaluator assessments. The sponsor found the following 95 percent confidence interval for the mean difference of Radiesse minus the control and you can see it there at the bottom of the screen. Note that negative values denote greater effectiveness and therefore, the mean improvement was greater than one point. This can be seen as the entire confidence interval as below negative one. FDA had concerns about the sponsor's statistical model and conducted our own analyses of the effectiveness data using a repeated measures model with an exchangeable correlation structure among the three evaluators.

It can be seen in the confidence interval at the bottom of the screen that a 95 percent confidence interval for the mean difference is slightly wider than the sponsor's but once again, the entire confidence interval is below negative one. Thus, the qualitative conclusion is the same. The difference in mean improvement is greater than one point and another criterion for clinical superiority has been met at three months.

The final criterion for clinical superiority was effective masking of the study. In this regard effectiveness of masking among the three evaluators does not appear to have been assessed. Thus there is a remaining question about the adequacy of the masking.

The second primary statistical issue which I have chosen to address concerns the degree of agreement among the three evaluators in the study. I have chosen to comment because at first glance the level of agreement appears somewhat low. One common way to measure agreement between more than one observer is the kappa statistic and the general idea can be seen

in the following slide. Note that the rating by Evaluator 1 is along the left side and the rating by Evaluator 3 is along the top. Those numbers along the diagonal are the observations where Investigator 1 and Investigator 3 agree.

The kappa statistic measures the proportion of observations in the diagonal adjusted for the proportions that would have occurred by chance. Weighted kappa which is what was used by the sponsor, includes off diagonal observations, weighted by their closeness to the diagonal. Here you see one interpretation of possible kappa values. Note that this is only a rough guide, particularly since the sponsor used weighted, not unweighted kappa. As mentioned previously, the problem is that the kappa measures of inter-observer agreement appear to be somewhat low. Weighted kappa values range from approximately 0.3 to 0.5 indicating only fair to moderate agreement among the three reviewers.

However, note that it could be argued that noise in the assessment is precisely the reason for having more than one evaluator. In addition, kappa

values were computed on month 3 photographs individually rather than on the relative difference between Radiesse and the control. That is, two evaluators could have rated individual pictures differently but could have been consistent in the comparison of the Radiesse side to the control side. Furthermore, other measures show greater agreement. The following table shows that the percentages rating Radiesse superior, equivalent or inferior are highly similar among all three reviewers at three months.

In addition, in FDA's repeated measures model, the correlation among the three reviewers was estimated to be 0.76 at three months. After adding a term that adjusted for baseline differences, the estimated correlation among evaluators was almost 0.9 at the three-month time point.

Other statistical issues; one such issue could be missing data. However, for this PMA this is not an issue as only two of 117 patients were missing at three months. In addition, missing values were counted as no change for both treatments. Note that this is conservative in a superiority comparison.

Another possible issue is whether there were side effects for effectiveness or safety. With regard to effectiveness, there were no significant differences among the four study sites. With regard to safety, there do appear to be some differences among sites for ecchymosis and pain. These differences appear to be due to Sites 3 and 4 showing relatively more adverse events for the control than for the treatment.

My conclusions are first, that relatively low kappa values for inter-observer agreement may not be as problematic as might have appeared. Second, it was demonstrated that at three months statistical superiority was met, a majority of evaluations rated Radiesse superior and the difference in mean improvement was greater than one point. However, note that there was a question about assessing the effectiveness of the masking of the three evaluators and the resulting impact on the effectiveness claims. FDA has a panel question which includes this issue. Thank you very much.

CHAIRMAN LoCICERO: It's now time for the panel to discuss the presentation by the sponsor and

the FDA. Anybody have any comments at this point? Dr. Blumenstein, anything?

MEMBER BLUMENSTEIN: I'm still thinking about what I want to say.

CHAIRMAN LoCICERO: I'm catching people off guard today. Dr. Leitch?

MEMBER LIETCH: What does the FDA think about the issue of the blinding of the patients and the significance of that?

DR. BONANGELINO: The patients were blinded at the initial point of the study. At about three months, approximately three-fourths correctly guessed the treatment assignment and by six months nearly all of the patients had correctly guessed the treatment assignment, but there was really no patient-based measure of effectiveness.

MEMBER LIETCH: So what do you make of that, that data? What's the importance of it?

DR. BONANGELINO: Well, it's apparent that the blinding is compounded with the effectiveness. In other words, there was an anticipation that Radiesse would be the longer lasting treatment and, therefore,

the patient in seeing both sides of the face would have guessed that Radiesse was the better treatment.

CHAIRMAN LoCICERO: Thank you.

MEMBER LI: Excuse me, this is a follow-up question on that. Is that the known reason that they guessed the Radiesse treatment?

DR. BONANGELINO: I think the sponsor states something to the effect that there was known greater durability of the Radiesse treatment.

MEMBER LI: It wasn't the number of injections or anything that was stirring them.

DR. LERNER: I don't remember in reviewing this that that particular point was addressed, that there was a correlation table between number of injections and assessment of which side was which in any of these patients.

MEMBER LI: Okay, so you believe that the only way the patients would have guessed as correctly as they did was just the durability?

DR. LERNER: It appears that the expectation was that this -- yes, I think if they were -- the patients were made aware to the best of my

recollection that they were studying something that would be longer than something that's already on the market and by seeing one side go away as quickly as it did and the other side not making those clinical changes, they just had to look in the mirror and see what -- and make that correlation between the two sides.

CHAIRMAN LoCICERO: Dr. Blumenstein.

MEMBER BLUMENSTEIN: This is not my only question. While we have the FDA here, how does the FDA feel about the potential for there to be a difference with respect to the optimal level achieved?

DR. LERNER: Well, I think, as was pointed out by the sponsor, a lot of our studies have that end point, that it's up to the investigator who's doing the injection to determine what the quote "optimal" end point is. I mean, I don't know since we started with this device in 2003 and we've progressed over the last several years, we have not come up with that personally I know any other method of defining precisely what the end point would be in these wrinkle filler studies. It has to be a perceived optimal correction. So there's

no scoring system that you could reach. There's no -- it's sort of like beauty is in the eye of the beholder and what the investigator perceives to be the point to stop is where that assessment starts from. So --

DR. BONANGELINO: Can I just add that in a superiority comparison that is not so much of a statistical concern. I mean, it is an oversight of the sponsors and probably also ours in our reviewing that the optimal correction was not assessed, you know, rated from the photographs but in demonstrating that the product is actually superior, I mean, if it was non-inferiority then it would be a more critical issue, I believe.

MEMBER BLUMENSTEIN: Yeah, I mean, this is the feeling that I'm developing is that things are kind of working here because this is so superior --

DR. BONANGELINO: That's correct.

MEMBER BLUMENSTEIN: But if this were not so superior, we'd be sitting here really stewing about it, I think.

DR. BONANGELINO: Exactly, yes.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: What is the feeling of FDA about the fact that at three months the supposed active control has very little or no activity at all? The control, on the basis of FDA studies, was supposed to have certainly benefit at three months and at six months. That's for the control. What do you make of that?

DR. LERNER: Well, we've talked about that a lot internally, having seen the data and looked at some of the other studies that we've -- that are in progress or that we have come in front of the panel. And I think there are several points to consider. The first is that at the time that this study was initiated, there were very few comparators to use. So that we -- the sponsor, along with the Agency, chose what they thought would be a reasonable comparator at the time.

The second is the method of assessment. We noted in this trial that the assessments are made mostly on photographic evaluations and photographs are not live assessments. One of the things that the sponsor talked about in the types of design that could

be used and was not chosen is something that we've actually started to lean toward and that is evaluator's independent of the injectors, so that we don't have -- we have the assessments right after injection or at optimal treatment by a blinded assessor rather than the investigator who's doing it. We're learning over time.

This was an early study. When you see the others coming down, hopefully they'll be a little bit different, but we appreciate your concern. We just dealt with what we had.

MEMBER NEWBERGER: I appreciate that and I certainly agree and I'm encouraged by the direction that you're going and I think that will eliminate a lot of bias but still, I get back to the three-month data. I don't know if Dr. Olding has this experience but I know that when I use the control as a filler for nasolabial folds, both visually and photographically, I'm going to still have some persistent benefit. Is that your experience, Dr. Olding?

MEMBER OLDING: It's -- you know, it's a little unfair to answer that because that becomes in both of our cases just based on our own experience, but

I believe that -- personally that the control is not as good as we effectively expect it to be. So no, that's not quite my experience unfortunately.

CHAIRMAN LoCICERO: Mr. Melkerson?

DIRECTOR MELKERSON: I just wanted to go back to the point that this -- the idea of using a control, we have to base it on what the study and the data in the PMA, personal experience of our panel. That's why we have you on the panel. There is an expectation, but in terms of how it's used should be based on what's in the PMA itself in making that cut.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: I just have a question about the concern you raised about the masking. I mean, my understanding of the study was that all the photographs were sent to an offsite location at Canfield or something and they were evaluated by people completely unattached to the study, so what you're looking for is some kind of documentation that the photographs were handled properly and that the people doing the evaluations were not, you know, aware of which patients received -- or which side received the

test and the control?

DR. BONANGELINO: I think what we were thinking of is something like asking them to guess which treatment they were evaluating in each photograph, similarly to what was done for the patients.

MEMBER MILLER: Okay, so, okay, is that a critical enough of a problem with this study design to challenge the findings?

DR. BONANGELINO: Well, it's a remaining question. How critical it is depends on what you believe the likelihood that they would be bias introduced from -- it's kind of hard to think that someone looking at each side of the face individually would have really introduced much bias but we just -- we just put it out there as a question to the panel.

MEMBER BLUMENSTEIN: I think that from my comment on this, that it's the nature of a statistician to behave differently than our justice system behaves. That we assume that there's cheating and you're guilty until proven otherwise.

DR. BONANGELINO: I understand.

CHAIRMAN LoCICERO: Are there any additional discussion points? Then let's proceed to the FDA questions.

DR. LERNER: Only two African American patients were enrolled in the Radiesse clinical study. There were 11 Hispanic and two others. The sponsor has not indicated in the device labeling that there are any ethnic considerations for treatment. Do you feel that the sponsor has adequately addressed this issue by providing data on persons of color in the facial lipoatrophy study along with clinical evaluations such as CD4 counts, et cetera.

CHAIRMAN LoCICERO: Okay, we've discussed this sort of extensively at this point and maybe we can summarize our feelings directly. Dr. Olding?

MEMBER OLDING: No.

CHAIRMAN LoCICERO: Is there any additional comment? Does this satisfy the FDA on question 1?

DIRECTOR MELKERSON: That's fine with me.

DR. LERNER: I told you we'd get through the afternoon quicker. Question 2, Radiesse is

composed of calcium hydroxy apatite which is visible radiographically. The sponsor was asked to provide a better understanding of how this device will look in the skin of the face and to assist the pattern of migration of any particles of radius. Provided for your review are radiographs taken at several time points to assess the possibility of this device mimicking the tumor or hiding a soft tissue tumor as well as device migration. Please comment on the adequacy of the information to assess the risks associated with this device, mimicking a tumor or hiding a soft tissue tumor after injection.

CHAIRMAN LoCICERO: This is -- this indication is a little different from the information that we had earlier because of its site and length of injection. Do you -- let's start with Dr. Li.

MEMBER LI: I guess my comments would be similar if not the same to the ones I made this morning, that you know, the information provided is good as far as the information goes. I don't know what else to say other than that. There's really -- we still don't have any evidence of how fast it actually

dissipates. We still don't know actually if it migrates, if at all. I mean, these are kind of open-ended questions. I'm not really pointing a finger that there's something wrong with the material in any way, but it's just that there's virtually no evidence that actually would help us answer those questions.

And as far as mimicking the tumor, I guess the -- I guess that's also kind of an open-ended question and it depends, you know, it's silly. It seems like it depends to me on how much Radiesse you put in and the size and type of the tumor. So I don't know, given the information, how it covers the entire lay of the land.

CHAIRMAN LoCICERO: Does anyone want to add a comment to that? Yes, Ms. Whittington.

PATIENT ADVOCATE WHITTINGTON: I would just -- I concur with you about. That is an important piece, I think, when they talk about labeling this device, that that has to be a caution because we don't know that. It certainly is closer -- it appears to me to be closer to the skin even though it's sub-dermal, it appears to be closer to the level of the skin and we

don't know. So I think it has to be a required part of the labeling.

CHAIRMAN LoCICERO: Other comments? Yes, Dr. Leitch?

MEMBER LIETCH: I think the obscuring of other things is probably less in this application because it's a smaller volume and over a -- you know, sort of a defined, a very defined spot. So I think it will be less of a problem in obscuring other things than the larger injections. On the other hand, as a more focal injection, it might be more likely to mimic a tumor because it's more focal so confusing an examiner, again, I'm not sure as much how much it would confuse a radiologist, but it might confuse an examiner a little more because it's a more focal thing if they can feel it.

CHAIRMAN LoCICERO: Dr. Lewis.

MEMBER LEWIS: I would agree with Dr. Leitch. It seems to me the significantly smaller volumes as well as the injection along a linear track rather than injection of a mass of material in a more global situation would prevent this from being an issue

very much here. It's -- the situation this morning where you have a larger volume in a globular sort of distribution would be a much more likely confusing situation. I find it hard to see how anyone could be very confused about this when you have a linear configuration with a very small volume and I just don't really see how it could be an issue of significance.

CHAIRMAN LoCICERO: Other comments? So to summarize, this would be less of a concern because of volume and geography of injection but that we don't have the final answer. Is this sufficient to satisfy the FDA on this question?

DIRECTOR MELKERSON: Yes.

CHAIRMAN LoCICERO: Ready for the third question.

DR. LERNER: As noted in the panel memo, the mean change from baseline of the Lemperle Rating Severity Score, if a radius was greater than one point at both three and six months, thereby meeting that requirement for superiority, the mean improvement of 1.5 and 1.23 points on the LRS. The control had no improvement at three and six months. In essence, the

device was superior to a control that did not show any effectiveness. Please comment on the validity of the sponsor's superiority claim for the device based on the statistical outcome.

CHAIRMAN LoCICERO: So the sponsor has given us a problem that we haven't had to deal with in awhile. Dr. Newberger, any comments?

MEMBER NEWBERGER: I know better than to argue with a statistician. I'm still having trouble with the particular control, but no, I don't have any other comments.

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: Actually, I meant to ask this before, I'm sorry, but there was a slide shown that said that you could proceed without penalty for superiority testing provided, and I don't remember what it said. I think it said that even if you didn't pass the non-inferiority test, is that correct?

DR. BONANGELINO: No, I think it said that with proper planning it was possible to do both comparisons provided that the non-inferiority margin were pre-specified. In other words --

MEMBER BLUMENSTEIN: So you're saying --

DR. BONANGELINO: -- it would not be acceptable to a post-hoc, non-inferiority when the margin hadn't been pre-specified.

MEMBER BLUMENSTEIN: I don't know, I guess I'm puzzling about this because I would have thought that the requirement would have also included having passed the non-inferiority test.

DR. BONANGELINO: That is correct, that is also a requirement.

MEMBER BLUMENSTEIN: All right, so you just didn't put that up there.

DR. BONANGELINO: Yeah, I didn't mention that.

MEMBER BLUMENSTEIN: Okay, all right.

CHAIRMAN LoCICERO: So any comment based on that?

MEMBER BLUMENSTEIN: No, it's good, it's all good.

CHAIRMAN LoCICERO: This is just quite amazing. Okay, so I think to summarize, unless somebody has an additional comment, that we agree that

this product has shown superiority. Does this answer the FDA's question?

DIRECTOR MELKERSON: It's adequate, thank you.

DR. LERNER: 21 CFR 860.71(d)(1) states that there is a reasonable assurance that the device is safe when it can be determined that the probable benefits to health from use of the device for its intended uses when accompanied by adequate instructions for use and warnings against unsafe use outweigh any possible risks. Considering the data in the PMA, please comment on whether there is a reasonable assurance that the device is safe.

CHAIRMAN LoCICERO: Does anyone wish to comment on the safety of this product? Dr. Newberger?

MEMBER NEWBERGER: If this device is approved for cosmetic use in nasolabial folds, it will be used in the perioral location for sure and I suggest that checking back to my favorite MAUDE website, many of those adverse events are related to its use in lips and I would just like to comment that the safety is only for this site and not for off-label use. Very

specifically. There are different physical forces in the perioral location.

CHAIRMAN LoCICERO: Additional comments? Yes, Dr. Bartoo?

INDUSTRY REP. BARTOO: This gets back to question 1 with the African American population. You know, currently the labeling doesn't say anything about precaution in that group, so you know, as part of the consideration for safety to consider, you know, making sure that's in the labeling.

CHAIRMAN LoCICERO: Okay, Dr. Li?

MEMBER LI: I just want to reiterate perhaps one too many times, that I think in this particular case because the amount of material is so much less than the first application, any issue I had with a concern, you know, is proportionately diminished because just of the amount being used. But I think the same unknowns are still there versus migration, interactions and all those other things that we've talked about earlier. So the concerns are still there but the actual concern is diminished simply because of the amount used.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: Yes, I would agree with that. I think all the unknowns still exist for this but for some reason I feel more comfortable with this and I think it's because of the volume and the amount and also I think it's a much more convincing demonstration of the effectiveness of the device as well and I think it's -- I would consider the benefits outweigh the risks from what I see here.

CHAIRMAN LoCICERO: Ms. Whittington?

PATIENT ADVOCATE WHITTINGTON: I have concern that there is only six months follow-up on these patients. I think that's an awfully short period of time. The results look very nice but I think the -- you know, the time period needs to be looked at, you know, followed up a little bit more closely. That can be done on a post-approval review but I think six months is an awfully short period of time. Maybe one of you who do this all the time can reassure me that that's okay.

CHAIRMAN LoCICERO: Dr. Olding?

MEMBER OLDING: I actually have a question

regarding that. One of the most important things for the company, any company that is now producing something to inject is how long does it last. How long can they say that this lasts and who controls -- they say it lasts 18 months, 6 months, 3 months. Is there any number that the FDA will require them to say or not say based on this in the material? You know, this product lasts from -- you know, we think of some others lasting you know, six to nine months, others lasting three months. We have those ideas in our mind. Where do those come from and are they regulated?

CHAIRMAN LoCICERO: Mr. Melkerson?

DIRECTOR MELKERSON: First of all, I wanted to clarify for myself, we're trying to answer the question on safety so are we talking about the long-term safety of the product in terms of if a product is labeled, they have to have data to support whatever indication and duration of time they are proposing in their labeling.

CHAIRMAN LoCICERO: Dr. Blumenstein.

MEMBER BLUMENSTEIN: So that means the label will say this product lasts only six months?

DIRECTOR MELKERSON: Your labeling will be based on what primary end point, when they looked at it, and what the data actually supports.

FEMALE PARTICIPANT: So they have to put a time period on the labeling?

DIRECTOR MELKERSON: Our summaries, they are going to indicate a duration of use and it will be described as the basis of our decision is in our summaries of safety and effectiveness. So it may not actually be in the labeling but it will say, "Here's the data for this period of time".

CHAIRMAN LoCICERO: So make a mental note of that when we talk about approval at a later time. To summarize then, we have similar concerns that were discussed this morning although diminished because of the amount and location of the material but that it appears safe within the limits of the information we have. Is this -- yes, Dr. Li.

MEMBER LI: I'm sorry to interrupt but could I ask just a question that just struck me when you were speaking? If for some reason a patient, say just for discussion's sake six months is how long it

lasts and you have to be reinjected if you want to keep the effect. Is there any limit then? Does this treatment just go on forever with this patient as long as they've got the time and money and don't mind being injected? I guess the issue here is, when we talk about effectiveness, I guess I presume you mean the clinical effectiveness. You know, does it continue to do what it's supposed to do.

In my material sense, how long it lasts also is how long it's actually there. It's my experience in most of these things that have some sort of resorption that the material is around a lot longer than its clinical effect is. So for instance, at three months, it may have diminished enough to where you have to give another injection but maybe 50 percent of the material is actually still there. So if you keep doing this every three months, the amount of material builds up much more rapidly than can possible dissipate until something is going to happen sooner or later.

So I guess my question is, is there any sense of how much a patient can tolerate under these conditions and basically what the dose response to this

is if it's known?

CHAIRMAN LoCICERO: I would say, based on what we have so far, we don't know and we can't say, but we can talk about the six-month time frame and right now we're talking about safety. Anything additional to what I summarized?

MEMBER LI: Okay, then in that case then, okay, but just if the question is safety to six months, then my original statement stands, but if we're supposed to consider a longer length of time, then I'll go with your answer is that we don't know.

CHAIRMAN LoCICERO: Since it hangs around I think we still have to have that comment that we're not -- we don't have data beyond that point.

DIRECTOR MELKERSON: You have an adequate response to those questions.

CHAIRMAN LoCICERO: Okay, let's go onto the next one.

DR. LERNER: 21 CFR 860.7(e)(1) states that there is a reasonable assurance that a device is effective with it can be determined based on valid scientific evidence that in a significant portion of

the target population the use of the device for its intended uses and conditions of use when accompanied by adequate directions for use and warnings against unsafe use, will produce clinically significant results. Considering the data in the PMA, is there a reasonable assurance that the device is effective?

CHAIRMAN LoCICERO: Dr. Newberger is going to start.

MEMBER NEWBERGER: Yes.

CHAIRMAN LoCICERO: Any modifications?

MEMBER OLDING: Yes, within the time frame of the study of six months.

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: Well, I think we have to keep in mind that this -- had the margin of superiority been less or non-existent that we'd be in a difficult situation. That what we have here is we have data that are more or less overwhelming. In fact, you could almost answer this question by just looking at the one side of the face treated with the investigational maneuver. That there would be some evidence of efficacy, but there are enough, you know,

flaws in this study with respect to the things that we've already discussed that we have to recognize that this isn't the perfect study. And I think it's important to put that in the record.

CHAIRMAN LoCICERO: Okay, to summarize then for the indications sought, this is effective. Does this answer the FDA's question?

DIRECTOR MELKERSON: Yes, it did.

DR. LERNER: The sponsor has provided 12-month data to support the safety and effectiveness of their device adverse events were few and generally minor. The device itself, calcium hydroxyl apatite, is intended as a long-term implant. Based on the data provided and the length of follow-up in the clinical trial, please discuss whether a post-approval study is indicated to assess further long-term safety or effectiveness issues.

CHAIRMAN LoCICERO: Let's begin with Ms. Whittington.

PATIENT ADVOCATE WHITTINGTON: You know, I was going to comment. I agree, this is exactly what I think needs to be in a post-follow-up study. And as

far as length of time, I'm not sure what cap to put on it. I would hope that those of you who do these procedures could maybe help define what that length study should be but I think safety and effectiveness should both be looked at, not just one or the other exclusively.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: I'm looking at the 12-month data on the radiographic studies but I don't see it on the effectiveness. I don't see the 12 months.

CHAIRMAN LoCICERO: Yes, Dr. Lerner, was there 12-month data that was presented to you for clinical?

DR. BASTA: The 12-month data -- and I apologize, Dr. Lerner could easily address this. The 12-month data is regarding safety. The effectiveness data is only through six months since the control side was allowed to cross over to Radiesse treatment in the second six months of the study. So there was no effective comparison beyond six months.

CHAIRMAN LoCICERO: Dr. Bartoo?

INDUSTRY REP. BARTOO: On the post-

approval studies, I'd like to ask them to consider the effect or the tolerance of multiple treatments since this will be a repetitive treatment, so perhaps longer in the sense that you could follow like, you know, three to five courses of treatment and see what happens in that case.

CHAIRMAN LoCICERO: Additional comments? So in terms of this, the panel feels that there will need to be additional data obtained in the post-market situation, looking specifically at safety, efficacy and the effect of multiple injections. Yes, Dr. Lewis?

MEMBER LEWIS: Excuse me, didn't we just hear that would be impossible because there was a cross-over study and the control side has been injected?

CHAIRMAN LoCICERO: There are other ways, I guess, to look at efficacy. I'm not sure that they're going to continue the --

MEMBER LEWIS: But the statistical comparison of the two sides will no longer be possible, which is the basis on which most of the data was provided, so other than a comparison with baseline, I'm

not sure what the long-term measure would be.

CHAIRMAN LoCICERO: I think with that qualification that we -- the recommendation would still stand. Mr. Melkerson?

DIRECTOR MELKERSON: I was just going to say that in terms of post-approval studies, I think that -- the feedback from the discussions could be filtered into that.

CHAIRMAN LoCICERO: Okay, this concludes the questions of the FDA. We're ready to move on to any open public comment at this point. Are there any individuals here in the audience who wish to make public comment at this time? Since there are no individuals wishing to make public comment, we will dispense with the open public comment requirement section.

We are now ready for the FDA to summarize -- does the FDA have any additional comments to make at this time?

DIRECTOR MELKERSON: The FDA has none.

CHAIRMAN LoCICERO: Does the sponsor have any additional comments to make at this time? Dr.

Krause?

DR. KRAUSE: Okay, just for the record, I'll read the voting instructions again. "Medical device amendments as amended allow Food and Drug Administration to obtain a recommendation on designated medical device premarket approval applications. Remember the PMA must stand on its own merits and the recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. Remember that 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 the probable risks. Effectiveness, again, is defined as reasonable assurance that in a significant portion of the target population the use of the device for its intended uses and conditions of use when labeled, will provide clinically significant results."

The choices for your recommendation are first of all, approval if you have no conditions. The second choice is approvable with conditions and as I stated earlier, these could be patient or physician

education or training, labeling, further analysis of existing data. Again, prior to voting all of the conditions should be discussed and voted on by the panel.

The third choice you have is for not approvable. You may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or a reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling. Following the voting, the chairman will ask each member to present a brief statement outlining the reasons for their vote.

CHAIRMAN LoCICERO: Thank you, Dr. Krause. We're now ready to entertain a motion concerning this product. Dr. Miller.

MEMBER MILLER: I recommend approval with conditions.

CHAIRMAN LoCICERO: Is there a second?

MEMBER LIETCH: Second.

CHAIRMAN LoCICERO: Okay, we have a motion for approval with conditions. It has been seconded and

we must now go through the conditions and vote on each of those prior to voting on the approval with conditions. So the Chair will entertain motions for conditions. Dr. Miller?

MEMBER MILLER: I think it would be good to have the post-approval study that looks at the effective repeat injections which certainly will happen in these patients and get some idea about the duration of the effect beyond six months. It certainly looks like it's still effective at six months, and see when another injection is required and this sort of thing. I don't think it has to be compared to the control which it clearly is superior to control but I think that a better idea of what the sort of natural history of this material is and its use would be good.

So my specific recommendation is that the condition be a continuation of the -- or a post-approval study looking at the effective repeated injections.

CHAIRMAN LoCICERO: Is there a second?

MEMBER NEWBERGER: I second it.

CHAIRMAN LoCICERO: Okay, discussion. Dr.

Blumenstein?

MEMBER BLUMENSTEIN: I think we either need to be completely ambiguous about whether we are talking about a new sample of patients or to be explicit and one of the things that weighs on me is the under-representation of African Americans and that issue should also be studied and that would require another sample of patients. And so my inclination is to take what you said and to specify that this has to be a new study that will also focus on African Americans.

CHAIRMAN LoCICERO: Another way we can approach this is to have a separate condition looking at African Americans. Dr. Miller, do you want to leave that as a different condition from yours?

MEMBER MILLER: I think it would seem to me perhaps these patients could be studied out longer and satisfy the requirement to look at that issue and then a separate study which maybe could be smaller and target African Americans and other ethnicities may by a good idea.

CHAIRMAN LoCICERO: Yes, Dr. Newberger.

MEMBER NEWBERGER: I believe that that should be two separate studies and the reason is that if you are finding adverse events developing in the African American population, you're going to stop, you're going to have them drop out of the repeated injection study. So I think they are two separate factors that have to be looked at.

CHAIRMAN LoCICERO: Okay, so we're -- I'm getting the sense that we want to make that as a separate condition. So with this particular condition, any additional comments? Ms. Whittington?

PATIENT ADVOCATE WHITTINGTON: What's the length? How long are you going to follow them? Is there an end point to what you're asking?

MEMBER MILLER: It would be a guess because at six months this looks like it's still having a good effect. So at least a year, maybe two years, I don't know. It would depend on what the projected longevity of the injection would be, I guess.

CHAIRMAN LoCICERO: Maybe we could leave the exact time to the FDA and their statisticians and the sponsor to determine if it should be 18 months or

longer.

MEMBER BLUMENSTEIN: And in fact, I mean, I would imagine that such a study would have value to the sponsor in terms of marketing. So it probably should be something worked out, in other words, less specificity from us and let them work it out.

CHAIRMAN LoCICERO: Additional comments? Okay, then we're going to vote on a post-market study that examines directly the effective repeated injections, the duration beyond six months and the safety of the product. 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: Yes.

CHAIRMAN LoCICERO: Dr. Leitch?

MEMBER LIETCH: Yes.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: Yes.

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: Yes.

CHAIRMAN LoCICERO: Okay, we have unanimous approval of the condition that there be a post-market study that looks specifically at safety, the effect of repeat injections and the duration beyond six months. Any additional conditions?

MEMBER BLUMENSTEIN: I move that African Americans be studied.

CHAIRMAN LoCICERO: Is there --

MEMBER NEWBERGER: I second.

CHAIRMAN LoCICERO: Okay, we have a motion and a second. Dr. Melkerson (sic)?

DIRECTOR MELKERSON: Just a quick question. Are you limiting it just to one ethnic group or other ethnic groups?

MEMBER BLUMENSTEIN: Good point. Maybe -- I hope I'm not going to be politically --

CHAIRMAN LoCICERO: I have a very good friend who is Egyptian. I would consider him African American. I also have a very good friend who is South African from the Netherlands, and I guess you would

consider him South -- to be an African American. So maybe we should be a little more clear.

MEMBER BLUMENSTEIN: Yeah, a point well-taken. I don't know what the politically correct way to state other than Whities or something like that. But the point -- I think the point is there.

CHAIRMAN LoCICERO: Dr. Newberger.

MEMBER NEWBERGER: I think that we want to look at the safety in people of color who are likely to develop hypertrophic scarring and/or keloid formation and that would certainly include many ethnicities, not limited to African Americans, other people of color.

CHAIRMAN LoCICERO: Dr. Bartoo?

INDUSTRY REP. BARTOO: I don't know if this should be a separate condition or part of this one, but until that study has been completed, to add in there precautions that the safety and effectiveness in these populations is unstudied.

CHAIRMAN LoCICERO: Okay, we can make that as a separate condition. That will be easy for us to do after we vote on this one. Is there further discussion on this proposal? Okay, let's vote. We'll

start with Dr. Blumenstein.

MEMBER BLUMENSTEIN: 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: And we have unanimous agreement that there should be a study conducted of persons of color and those who have a tendency toward keloid and hypertrophic scar formation.

DR. KRAUSE: Did we get a second?

CHAIRMAN LoCICERO: We did, yes.

DR. KRAUSE: Okay.

CHAIRMAN LoCICERO: Okay, we're ready to

entertain another condition or we can just say Dr. Bartoo here, it is a condition but a statement that until such studies are conducted, that it is not indicated.

INDUSTRY REP. BARTOO: Well, it is just added to the precautions in the labeling that it has not -- the safety and effectiveness hasn't been established.

CHAIRMAN LoCICERO: Okay, so it would be a statement added to the precautions. Any discussion about that? I would assume this is unanimous. Do we have any objectors? Okay, it passes unanimously. Are there additional conditions that the panel wishes to bring forth? Dr. Newberger?

MEMBER NEWBERGER: I'd like to get labeling not in microfiche that this is specifically for injection in nasolabial folds and not studied in the perioral or lips locations.

CHAIRMAN LoCICERO: Second?

MEMBER LIETCH: Yes.

CHAIRMAN LoCICERO: Seconded by Dr. Leitch. Question; do you want to add any comment about

its safety in those locations or is that comment sufficient?

MEMBER LIETCH: I don't know that it's necessary to put into the labeling that adverse reactions have been found with its use in the perioral location and it is not -- the safety is not studied at this time.

MEMBER OLDING: I just have a question. If we approve -- if -- well, we already have approved the other study with conditions and that is theoretically a perioral area, the cheek area is, it's around the mouth, I mean, if you mean lips, I think, then we should say lips because perioral is something in my mind different.

MEMBER NEWBERGER: Okay, let's say lips.

CHAIRMAN LoCICERO: Okay, so we're going to change it to lips. Okay, so the statement will be that the -- this product has not been studied for injection around the lips -- into the lips.

MEMBER NEWBERGER: And adverse events have been reported in that location; thus, its use is not recommended.

CHAIRMAN LoCICERO: Okay. Dr. Bartoo?

INDUSTRY REP. BARTOO: In the labeling that's been submitted there is a warning that the safety and efficacy of Radiesse for use of the lips has not been established. Does that satisfy your concern? It's already in the labeling that's been submitted.

MEMBER NEWBERGER: Okay, if it's in big print.

INDUSTRY REP. BARTOO: Well, it's right up front under warnings.

CHAIRMAN LoCICERO: Okay, all right, so it's already stated and so would you like to withdraw your motion?

MEMBER NEWBERGER: Yes.

CHAIRMAN LoCICERO: Okay. Are there additional motions? Dr. Newberger?

MEMBER NEWBERGER: Perhaps training in some format would be a good recommendation for labeling.

CHAIRMAN LoCICERO: Is there a second?

MEMBER OLDING: Second.

CHAIRMAN LoCICERO: Dr. Olding seconds.

Any comments? Dr. Miller?

MEMBER MILLER: I wonder if the training needs to be just to be able to demonstrate having been trained in using injectable fillers. My sense is that there's enough similarity in the use of this for this application that special training may not be required other than just having been trained in using injectable fillers.

CHAIRMAN LoCICERO: Dr. Olding?

MEMBER OLDING: I actually don't agree with that.

MEMBER MILLER: Okay.

MEMBER OLDING: Because I think this is a different filler than, you know, Zyderm, Zyplast, Restylane, all of them. It is different. I think you have to be a bit more careful about where you inject it and how you inject it. So I think it would be very appropriate and not too much of a burden to have to do some sort of a CD-ROM format or some sort of thing you would sign off on.

CHAIRMAN LoCICERO: We had a very similar stipulation on the first PMA. Would everyone be

comfortable if we use that same language? Okay, are there any objectors? Okay, that carries unanimously. Are there additional conditions? Hearing none, I think we're ready to vote on the approval with conditions. Is there any further discussion at this point? Dr. Newberger.

MEMBER NEWBERGER: Actually, I think my comment would be better after the vote.

CHAIRMAN LoCICERO: All right, I think we're ready to take a vote. We'll begin with Dr. Leitch.

MEMBER LIETCH: Yes.

CHAIRMAN LoCICERO: Dr. Li?

MEMBER LI: No.

CHAIRMAN LoCICERO: Dr. Miller?

MEMBER MILLER: Yes.

CHAIRMAN LoCICERO: Dr. Lewis?

MEMBER LEWIS: Yes.

CHAIRMAN LoCICERO: Dr. Olding?

MEMBER OLDING: Yes.

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: Yes.

CHAIRMAN LoCICERO: Dr. Newberger?

MEMBER NEWBERGER: No.

CHAIRMAN LoCICERO: For the record, that's five to two. So Mr. Melkerson, the recommendation of the panel is the pre-market approval application of Radiesse for the treatment of nasolabial folds from BioForm Medical Incorporated be recommended for approval with conditions as we have outlined.

DIRECTOR MELKERSON: I'd like to thank the panel for their deliberations and their time.

CHAIRMAN LoCICERO: Thank you. Now, we need to go through and ask each member of the panel their reason for voting. Dr. Leitch.

MEMBER LIETCH: I think the product has been shown to be effective in the time interval in which it's being studied and in the population of Caucasian patients and if the requirements that we've put on the sponsor are met, then I think it is safe and effective and it's reasonable to do. I think some of the concerns about the radiology obscuration is less of an issue because of the smaller volume of injection.

CHAIRMAN LoCICERO: Dr. Li.

MEMBER LI: I understand there's a fine line between being principled and stubborn and pig-headed, so as I toy with that line here, basically, I can't quite make myself vote for approval for a material that I really don't know the resorption rate, I don't know if it migrates, I don't know how much of it I can put in. We have questions over whether or not there's a race issue. We don't know what the maximum dosage is. We don't know how many injections we can put over a certain period of time. Now, in this particular case, it's a much tougher thing to consider because you're using a relatively small amount of material, yet, that seems to me to be as the materials and developer of these things an awkward line to say that if you don't use a lot of it, then you don't have to know any of these things.

So that, and I do believe that once approval is granted, then the barn door is open and all these things we're worried about, we have little or no control over assessing and I'm actually hoping that none of those things come true in our adverse effects, but I just don't feel we know.

CHAIRMAN LoCICERO: Dr. Miller.

MEMBER MILLER: Yes, I felt comfortable with this. I thought the -- it was much more forthcoming PMA because it dealt with a cosmetic application which I think is foremost in most people's minds and it was a very -- I thought given the limitations of this study, I thought it was a very convincing study, a nicely done study to show that this material is very effective and the level of risk involved. There's a lot of unknowns with it but I think that the material has a long history of use in a variety of indications and I think that, you know, the benefits of it outweigh the risks.

CHAIRMAN LoCICERO: Dr. Lewis?

MEMBER LEWIS: My opinions were essentially the same as Dr. Miller's.

CHAIRMAN LoCICERO: Dr. Olding.

MEMBER OLDING: And mine the same. I guess, if we get a chance to harp now is my time. I really think that it's important for the FDA when they're working with groups who bring fillers to market to be certain of that end point and understanding that

end point when they're presented. In addition to the limitations of this study based on the available material to compare it to, but by and large I think it's -- particularly in the smaller amounts this is one case where less is better.

CHAIRMAN LoCICERO: Dr. Blumenstein?

MEMBER BLUMENSTEIN: My yes vote has a big asterisk. I don't really consider this to be a true randomized study because of the inherent difficulties in bringing a patient to so-called optimal status. The randomization took place before that was actually done, so you're not really starting off with something that you can be assured is comparable. I'm not sure -- and also the fact that there was a truncation of three treatments which could further lead to a difference in comparability.

I'm also concerned that the photographs taken at the optimal -- at the assessment of the optimal status were not scored and were not compared. My inclination is to believe that just a -- that a two-group study would have had fewer of these problems though I'm not convinced that that's the complete

answer either. I recognize that this is a very difficult area to study as many things in the CDRH realm are. And so -- but I think the overwhelming evidence of some kind of efficacy sort of takes me out of a condition of doubt.

CHAIRMAN LoCICERO: Dr. Newberger.

MEMBER NEWBERGER: This was a better study than the lipoatrophy study. Too many unknowns remain for me to feel comfortable in voting for approval. Again, we don't have enough information about the science of this product. We have histology in Restylane and other hyaluronic acid fillers which last much -- which probably last for shorter periods of time. This is going to hang around a lot longer. I'm not comfortable with my understanding of what it does. It's already out there in the marketplace and I felt that more rigorous studies were really needed for me to feel any level of comfort with its overall safety.

CHAIRMAN LoCICERO: Thank you. I want to thank the panel personally for their time and of course, we have another session tomorrow morning. I'd also like to thank the FDA for all of the effort that

they've put into this and helping us have a venue that has been relatively comfortable. And I'd like to thank the sponsor for their ability to respond when our questions and demands were pretty significant. So this concludes today's deliberations -- Dr. Krause wishes to make an announcement at this point.

DR. KRAUSE: Just a little clarification on tomorrow. Tomorrow morning at 8:00 o'clock the panel members will meet in the Potomac Room. Margie Schulman will give us a brief presentation on classification, reclassification, just to make that clear. At 9:00 o'clock we'll meet here. There will be a brief closed session. Now, nothing clandestine is going to go on at that brief closed session. Basically, that closed session is for the FDA to let the panel members know the types of products that are in development and that may soon come before the panel.

We're not going to, you know, divulge any deep dark secrets of, you know, the stuff we're hiding from the public. It's just we're required every so often to do that and that's exactly what we're going to do. So the actual panel meeting for the

reclassification of the cyanoacrylate tissue adhesives for skin approximation will take place starting at about 9:30. Okay, thank you.

(Whereupon, at 5:32 p.m. the above-entitled matter concluded.)

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