DR. DiZEREGA: Page 39?

DR. McCORMICK: On statistics, under the statistics section.

DR. DiZEREGA: And I think I can say this about that. It is 100-point score. It is calculated as was shown in the bottom of all of our LSOQ example slides. And, of course, we use these slides to give you a clinical meaning as to what these numbers mean because otherwise the numbers mean almost nothing. And if you look at the bottom of the slide, it gives you the formula that was used. It is interesting that the no pain is 1. It's not zero. So if you add all these up -- if a patient had no pain, the score would not be zero.

Actually, if you could just go back to that one. That's fine. And so it's simply a summation of the questions, in this instance, 9 through 14, minus the 6 because of the ones, and then going through this process to expand it to 100-point scales. And so the answer to your question is they're essentially all 0 to 100. That way we can compare one measure, leg pain, to another measure, back pain.

DR. McCORMICK: Yeah. They just didn't put the minus 6 in the hard copy. That's all.

DR. DiZEREGA: Well, that's --

DR. McCORMICK: So that's just a minor issue. Thanks.

DR. DiZEREGA: Yeah, we apologize for that. That's our mistake.

DR. BLUMENSTEIN: Yeah, I mean, I was very confused when I first read it, and I decided that you must have scored it 0 to 5, and what you described in your text was if you had done it 0 to 5. Well, if you look at that formula, that would be the same thing --

DR. DiZEREGA: Sure --

DR. BLUMENSTEIN: You just subtracted one from every score.

DR. DiZEREGA: I think that's a good point. Dr. Mabrey, were there any other questions other than the direct clinical questions about foraminal stenosis and preoperative treatment, et cetera that I could help the panel with at this time?

DR. MABREY: Dr. Horlocker?

DR. HORLOCKER: I'd just like some clarifications on the primate study. How many animals were included? When you did the injection, was this done directly so that you know that it went intrathecally? Were there any imaging studies done? Were there animals sacrificed? How do you know that

there wasn't any problem? It sounds like it was just a behavioral evaluation rather than doing some, you know, histologic evaluation or some imaging to see if there was any evidence of adhesions or arachnoiditis.

DR. DiZEREGA: I thought the most sensitive study, the most sensitive measure was increase in spinal fluid pressure, and there was no increase in pressure whatsoever. It remained constant throughout the measurement interval of time. Working with primates has its ethical limitations. As you know, these were not sacrificed. And so the measurements were made with peripheral bloods, with behavioral observations, including ambulation, but also with directly intrathecal pressures. There were no imaging studies performed.

DR. HORLOCKER: And then the other question I had or more a comment, also, about the anesthesiologist that injected the stuff as part of a spinal anesthetic. The fact that that block actually lasted longer is a bit worrisome because it would suggest that either there was some bonding with that as sort of being a, you know, prolonged -- versus local anesthetic toxicity that was potentiated by the device. So I'd like that reference. I'd like to take a look at that over the coffee break.

DR. DiZEREGA: We had the same question, and we actually went back and tried to look at the original case report forms, if you will. And I don't mean to be critical of any investigator that publishes information. We've all done that, and some is in better journals than others, and so forth. We were unable to recover in a reasonable way how much medication was actually used in an individual patient. It was very difficult to ferret that out. This is just an observation that I thought was worth bringing to your attention from a safety standpoint of view because there were no safety issues. I'm not at all convinced that there is a true prolongation of the pharmaceutical. My suspicions are, and these are just suspicions, that there were different amounts of opioids used in different patients based on other calculations that led to these observations.

DR. HORLOCKER: Do you have that reference, though, that we can look that up?

DR. DiZEREGA: I think we can produce that reference for you. It's been published in the last few weeks.

DR. HORLOCKER: All right. Thank you.

DR. MABREY: Dr. Sang, you had some questions earlier or have those all been addressed?

DR. SANG: No, I think that you mentioned that you were not going to present --

DR. MABREY: Use the microphone please.

DR. SANG: -- on some pre-clinical factors? You may not have access to those data --

DR. DiZEREGA: Right. The pre-clinical --

DR. SANG: In terms of from pharmacological management prior to -- I didn't mean pre-clinical. I'm sorry. Prior to enrollment?

DR. DiZEREGA: Right. Dr. Blumenthal will be presenting that momentarily.

DR. SANG: Okay.

DR. DiZEREGA: In fact, he's just waiting to get up here and talk to you.

(Laughter.)

DR. MABREY: Ms. Whittington, you had a question about the number of failed treatments prior to surgery?

MS. WHITTINGTON: Right, just to categorize the patient --

DR. DiZEREGA: Yes. For those of you that couldn't hear, the question was failed treatments prior to surgery and the categorization thereof. Dr. Blumenthal will also talk about that. He's a leading spine surgeon. He was involved with these

things directly. He can give you direct personal experience.

MS. WHITTINGTON: Okay.

DR. MABREY: Dr. Rao?

DR. RAO: Thank you. That was a very thoughtful presentation. Just a quick question. I wonder if you have the facts right now with you. You mentioned that 87 patients had more low back pain than leg pain. Do you have a breakdown as to how many of these patients were in the control group and how many were in the device group?

DR. DiZEREGA: Yes. It's equally distributed.

DR. RAO: Okay. The second question I have is you mentioned that there was two times, a 2x, increase in the osteoid activity using Oxiplex in a rat tibia model. A couple of thoughts on this. Number one, it seems partially conflicting. Substances that cause increase in osteoid activity also tend to increase local cytokine production and other inflammatory agents, whereas the presumptive mechanism is that this barrier device is reducing all local cytokine production. So it's just a thought I had. I don't know if you have any direct --

DR. DiZEREGA: We do, actually. And that's

why I mentioned sort of in passing the scaffolding aspect of it. What seems to be the case is that when you take these kinds of materials, these kinds of materials being materials that do not produce a cytokine reaction, that do not enhance inflammatory cell migration -- and keep in mind, this is a postoperative environment where there is a lot of opportunity for both of those things to occur. When you have a biomaterial that does not do that but that does support trafficking of cells, we think that's the mechanism of action in these tibia studies. But, as I say, those are early ongoing things. We've not seen any active biological markers. It just seems to be a mechanical scaffold support system.

DR. RAO: The second part of the same question is with this 2x increase in osteoid activity, do you have any concerns about the potential for long-term increase in post-laminectomy stenosis at the site of application from bony overgrowth?

DR. DiZEREGA: That's a very insightful question, and I'm happy to say that we followed up on that. This material has been available in Europe for many years, and so there is the opportunity to evaluate longer-term experiences from the standpoint

of view of a safety perspective. And DePuy and Medtronic have been involved with follow-up with these patients and with these physicians. And in going back and talking to the doctors, their view is no. Quite clearly, the patients do very well. There is absolutely no issue relating to bone overgrowth in any sense.

In some instances, there have been radiological studies, particularly in re-herniations, and there has been no issue at all about additional growth in additional places that they wouldn't have expected, which come back to us as been the surgical fields have been clear, and it's been easier to do the re-herniation operations.

DR. MABREY: Dr. Sang?

DR. SANG: You cited the Mannion paper, and you say in your slide that after decompression surgery outcomes should be measured within a maximum of 6 months after surgery based on their study. But that was a study that distributed questionnaires up to 6 months. So I'm not sure that this conclusion can be made from that particular study.

And I mention it because there is an animal study that I just looked up by Shamizzy (ph.), and you, in fact, cited a different study of his. What

he showed was that fibrosis can develop up to eight weeks of a rat's life, a rat who's gone through a laminectomy. Eight weeks in a rat's life span is pretty long, so that says to me that our suspicions in our failed back patients in pain clinics is probably pretty right in terms of the temporal patterns of pain that we see.

So immediately post-surgery, what we look for is, you know, is clearly reduction in pain, particularly in those patients who have a compression from a herniated disk and then in cases where there may have been significant inflammation from disc contents, and so on. That may take a little longer because of facilitation at the level of the central nervous system and sensitization, and so on. But then the development of the adhesions and fibrosis, and so on, that you are trying to -- that forms the basis for your hypothesis is -- just take a little bit longer.

And so I have to ask -- I know we've asked already -- what factors went into your decision to complete your follow-up assessments at 6 months other than the Mannion study?

DR. DiZEREGA: Two comments. One, because it's interesting what happens in the post-surgical

environment, whether it's a rat -- and I agree that we live longer than rats, and so you might think to extrapolate as a percentage of life. But from a post-surgical perspective, from the point of view of fibrosis, where there is a fair amount of data following peritoneal cavity surgery, following cardiovascular surgery, following surgery in the areas we're talking about today, the epidural space, the events that occur following surgery from the perspective of cellular infiltrates, cytokine production, reversal of the macrophages, movement of the nucleophiles, and production of fibrosis are very similar across species. There is not that much difference from a temporal point of view.

There are differences in terms of magnitudes of some of the factors. Some are more fibrogenic, prone to fibrogenesis. But in terms of the temporal aspect, it's always been interesting to me, someone that's been working on reduction of fibrosis following surgery for 20 years, how similar that aspect of the post-surgical time period is.

The second part related to how we picked 6 months. We were very driven, or very influenced -- excuse me. That's the wrong word. We were very influenced by the experience of people that

measure pain. And I mean we have some very accomplished pain specialists in this Panel. You know far more about pain than I ever know, and it is a very difficult, complex measurement with its limitations.

And as we talked to people that do spine surgery as we review the literature, 6 months made sense to us. It seemed like the appropriate period of time. We met with the FDA, and we discussed this with the FDA. We discussed longer time periods that might be appropriate for implantable devices, and things like that, and 6 months made sense to them, too.

So the 6-month time period was chosen based on interactions with clinicians. When this paper became available to us -- and it was a consensus paper. It was a consensus paper of the same type of information-gathering but from the European continent -- we felt very comfortable with the 6 months. And I think that's the basis of the decision.

DR. MABREY: Thank you.

DR. DiZEREGA: Thank you.

DR. MABREY: And as our next speaker comes up, I'll remind you that the Panel has ten questions from the FDA to address after this, so if we could

keep our comments concise, we're already running a little bit behind time.

DR. RHYNE: I'll be shorter.

DR. MABREY: Thank you.

DR. RHYNE: I'd like to answer the clinical questions of which there were a lot of overlapping. And they really fell into, as best I could tell, four categories: the back pain/leg pain interaction, the timing and pharmacology of the pre-operative care, exclusion criteria, and the re-ops.

First thing I'd like to do, however, is echo what I believe Dr. Hanley said at first, is that the discectomy operation is the most common and very satisfying operation that most spine surgeons do, and I really have to applaud the Sponsor for trying to raise the bar in a setting where the bar is almost very, very high, and it is quite high. And this is right in our bread and butter, which brings me back to lunch.

And the best analogy I could come up with is Dr. Rao and I -- I guess he likes lunch -- we're having lunch together, which, by the way, we didn't. And we both wanted a hamburger. Now, my enjoyment of the hamburger might be a little bit more if there was some lettuce on the hamburger. So we were able to

find some lettuce for the hamburger. Dr. Rao and I were both very happy with our hamburger, his without lettuce and mine with lettuce. I maybe enjoyed it just a little bit more. And I also had the advantage of after taking a bite, if I wanted to get to the meat, I could do it without the bun sticking to it and perhaps tearing the bun.

So at any rate, one of the issues concerned itself with the leg pain/back pain interaction. And while the study really wasn't designed to study the relationship, we certainly did find that the patients with greater back pain tended to have greater leg pain, those that were in the more favorable treatment group. But, clearly, 95 percent of the patients in the study had both back and leg pain. To read the first line from the SPORTS study, "Lumbar discectomy is the most common surgical procedure performed in the U.S. for patients have back and leg pain." So, really, it's not surprising that there was that percentage of patients with both back and leg pain.

We also know that from our clinical practice, there is overlap in what the patients consider back and leg, and sometimes, you know, we have to be more specific and quite specific with those patients.

Onto the conservative care issue, and one of the issues that came up a couple of times was the two weeks of non-operative treatment prior to the patient being eligible in the study. The rationale for this was basically a floor and not the norm. Certainly, most of the investigators adhered to the standard four to six-week treatment, and, in fact, most of the investigators practice in referral settings where the patients had been seen for weeks if not months and had had conservative treatment, including, as was mentioned, perhaps selective nerve blocks or epidural steroid injections.

Certainly, what was allowed was the type of conservative treatment that would be normally done either in the community or your practice. It was recorded, although we didn't specifically stratify them and look for subtyping of responses depending on what type of conservative care they had.

The only exception was that the patients could not have had an epidural steroid injection, including selective nerve root blocks within the 30 days of the surgical intervention. And Dr. Sang came up with about six studies during her comments, and I think they're all very well taken, in terms of our evaluation of mechanisms of neuropathic pain.

In terms of the exclusion criteria, there were some questions regarding the use of fat graft, as well as there was a question on foraminal stenosis.

Intraoperatively, whether the patient was randomized to the control or Oxiplex, it was specifically indicated that we could not use any barrier. This was already alluded to. So if the surgeon mistakenly put in one of these, and it really would only occur in a control patient, the patient was excluded from the study. If the surgeon felt that either fat graft or hemostatic agent was needed to safely close the patient, then the patient was excluded from the study as well, and this was a very few and far between occurrence.

In terms of foraminal stenosis, foraminal stenosis was an exclusion if that was the patient's sole source of pain. So, in other words, many of our patients will have some degree of foraminal stenosis and a concomitant herniated disc if clinically you felt that the herniated disc was the source of the patient's pain either clinically, through selective nerve block, or however, then those patients could be included. If it was foraminal stenosis as the primary diagnosis, then they were excluded.

There was also a question of whether or not we would advise or I would advise or, clinically, could this be used in a surgery for decompression of foraminal stenosis? It was beyond the scope of the study, but, certainly, I wouldn't see any contraindication in a patient that had no other contraindications.

Finally, the last question, and this was a very good question, was on the re-ops. As mentioned, there were seven re-ops, one in Oxiplex, six in the control. We did not mean to imply a causal relationship between Oxiplex and the lower re-op rate.

The one thing that does need to be clarified, however, is that the question was, was that decision made by the surgeon. And the answer is yes. And, of course, we were the only ones unblind because we had to apply the Oxiplex or not if it was a control patient at the time of surgery. We were instructed, and, in fact, at least at the two highest enrolling sites, we did not record in the operative note whether the patient got the Oxiplex or not, and those of you with busy spine surgery practices know the chance of us remembering who got it was very small and I can attest personally that, you know, by

the time their two-week visit came, I just knew that they were a study patient. I didn't recall whether they got the Oxiplex or not.

Having said that, the seven re-ops were spread across seven different sites. So that's it on the questions that -- six?

UNIDENTIFIED MALE SPEAKER: Six different sites.

DR. RHYNE: Six different sites.

DR. MABREY: Any other questions from the Panel for the Sponsor?

(No response.)

DR. MABREY: Does the FDA have any responses to the questions posed to them --

MR. MELKERSON: Jack Zhou will address the one question with regards to the statistical analysis plan.

MR. ZHOU: The question earlier, I believe, was about since the statistical analysis plan was FDA-approved why there is such disagreement between the, you know, Sponsor and FDA. I think that was a very good question.

I have two comments on that. Number one, the FDA-preferred way of specifying statistical analysis -- is before -- is at the IDE stage, which

the Sponsor provided a preliminary statistical analysis plan, and the GEE model was very simple at that time. And a few months before the PMA submission, the Sponsor submitted a very -- a more comprehensive statistical analysis plan, which was not the ideal time to do that. The best time to do is -- was supposed to be at the IDE stage.

And my comment number two was even in the very comprehensive statistical analysis plan, the Sponsor came up before -- a few month before the PMA submission. I think the Sponsor specified all clinical irrelevant covariates will be screened. And as Dr. Chiacchierini pointed out earlier, they didn't specify how they would study interactions. And I quote, in their statistical analysis plan, they said they will study interactions.

So I think, you know, screening for variables is one thing, but screening for interactions is another thing. So it's kind of unusual to screen interactions. That's one of the reasons we are -- we didn't really expect this at that time.

DR. MABREY: Dr. Sang, you look like you have a question or a comment.

DR. SANG: I apologize if I missed it. Did

you look at concomitant opioid use post-op?

DR. DiZEREGA: Yes, we did look at concomitant opioid use post-op, and there essentially was no appreciable difference between the groups.

DR. MABREY: All right. Thank you. Any other final questions from the Panel before we start to address the ten FDA questions?

(No response.)

DR. MABREY: Not seeing any, at this time, we can focus our discussion on the FDA questions. Copies of those questions are in your meeting handout, and Ms. Jose, would you like to read the first question, please? And I would suggest that you look at the questions as they are in your three-ring binder. The ones that were handed out earlier seem to be in microfiche and a little bit difficult for some of us to read. I think they're under the second tab in the three-ring binder.

MS. JOSE: Okay. So we'll move on to the Panel questions. The first question we have is the Oxiplex/SP gel is a gel applied during lumbar spine surgery, designed to act as a physical barrier between tissues. The proposed indication for use states that it is intended to be used as a surgical adjuvant during posterior lumbar laminectomy,

laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain, and neurological symptoms. The primary endpoint was reduction in the composite leg pain score of the Lumbar Spine Outcomes Questionnaire, and the secondary endpoints were composite back pain, leg weakness, physical symptoms, subject satisfaction, disability score, and activities of daily living.

Please discuss the appropriateness of the primary and secondary effectiveness endpoint in the study conducted as supporting the proposed indications for use.

DR. MABREY: So the question has to do with the primary and secondary endpoints, and just to be fair, I'll start with Dr. Hanley on my left and go around the table.

DR. HANLEY: Well, I think in the proposal, the proposed study submitted at the beginning, the primary and secondary endpoints are appropriate. The whole issue here is those weren't really addressed in the analysis of the data.

So I think that, yes, as an appropriate thing to study, that's correct, but the analysis doesn't do what they proposed to study to the original proposal.

The proposed indications for use, the proposal was primarily for leg pain. Some of the data mining, or whatever you want to call that statistical stuff that was done, found some other soft things that might been included, such as the back pain and neurological symptoms. So leg pain as the primary effective thing is appropriate. The other two, back pain and neurological symptoms, while there may be some weak data supporting them, I have a little question about that. And that concludes my remarks.

DR. MABREY: Thank you. Dr. Horlocker?

DR. HORLOCKER: I agree with Dr. Hanley's comments and would add to them that we saw a lot of analysis of the group of patients with severe pain to begin with, and that was not one of the initial primary or secondary endpoints. We've got a subgroup analysis that much of the data was presented and revolved around. So I would add, again, that I think that that was probably a not appropriate way of presenting this since it was not in the initial description of what the pivotal study was going to evaluate.

DR. MABREY: Dr. Goodman?

DR. GOODMAN: I would concur with the two

comments already made. I think that the endpoints were very specific and very clear. And as expressed by the Sponsor, the overall group did not meet those endpoints. However, a subset that they identified did.

DR. MABREY: Dr. Rao?

DR. RAO: I agree. I believe the primary and secondary effectiveness endpoints in the study are appropriate for the evaluation of this device as they were stated in the study.

DR. MABREY: Dr. McCormick?

DR. McCORMICK: So I think the primary and secondary endpoints are completely appropriate. The problem I have is the proposed indications for use. This study was very specific in the patient population. These are patients with unilateral, one-level herniated lumbar disc with radiculopathy. That's it.

If you look at the proposed use, the proposed indication for use states is intended to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing. And so my point is, is that that is way too broad of a proposed usage of it, particularly since the primary unadjusted analysis

was completely negative for both primary and secondary endpoints, and the positive outcome that was noted was for a very selective subset in their series, which represented the majority of their series. But the high level of back pain makes me wonder about the generalizability of this group. So I have concerns with the proposed usage.

DR. MABREY: Dr. Evans?

DR. EVANS: Well, when you select endpoints for trials, there is a number of characteristics you like those endpoints to have. Certainly, you start out that you want the endpoints to be clinically relevant and something that addresses the scientific question. And you would like them to be easily attainable in that you can quantify and qualify them in an unbiased manner. And I think with the blinding involved here with the possible exception of -- I think it's still a question of whether the surgeons being unblended could potentially do something to affect pain be collected in a blinded manner later on.

But you want these endpoints to be sensitive to changes that are induced by treatment. They should be hopefully affordably obtained and result in a reasonable sample size. And I guess the

big issue is that you want endpoints that are, when the analysis comes around, that they're easily interpretable.

And so the point I made earlier today was about composite endpoints, and to think critically about the relative importance of the components of a composite because if they differ in importance, that could cause some confusion in interpretation. And I think the Sponsor addressed that issue, to my satisfaction, and others may want to think critically about it as well, but -- so I think the bottom line is I think, in terms of the endpoint selection and the way they were defined I think was acceptable.

DR. MABREY: Dr. Sang?

DR. SANG: Thank you. I agree with all the comments so far. I do want to add as a corollary about selection of subjects, I completely agree that if the potential indication is for radiculopathy, then it would be important to exclude those subjects with mechanical low back pain or any suggestion of mechanical low back pain, which is the basis for my -- was the basis for my question about selective nerve root blocks with local anesthetics, which you may -- you probably cannot answer.

Understanding that, obviously, this would

compromise the generalizability that you're looking for because there are a number of different -- radiculopathy alone is, in fact, not that common. We usually do see radiculopathy in the presence of other back problems like degenerative spine disease, and so on, but I think for something like this, it would work to your -- it would power up your studies, it would work to your favor to have homogenized your sample.

I think that you have really chosen your primary outcome to be quite ambitious. In the context of analgesic clinic trials, as I mentioned, this is not -- a composite score is not usually used. It is the patient's self-report of pain intensity that's usually used. I think, in fact, you might consider that. I agree that a composite score, particularly one that's not commonly used in analgesic trials and certainly at 6 months, you know, I think lessons can be learned from the area of analgesic trials. I think that still pain intensity is a very good primary endpoint.

An alternative, if you want to choose a composite score, I mean your choice of the composite score seems perfectly fine, but I'm not familiar with other trials that have shown a treatment effect in

this context or in any low back pain trial context. So I would recommend choosing one that has shown some success in another pain condition, preferably low back pain.

In fact, BPI may be -- brief pain inventory, which was designed by Charles Cleeland, may be one to look at. It's a composite score. It incorporates pain intensity as well as function. It does look at certain things, and I think you hinted at this, that, in fact, you brought out words, descriptors, that may be more telling than actual means. And so the brief pain inventory looks at, you know, maximum pain, minimum pain, average pain, pain at the moment. That's a composite score that may help you.

The secondary measures I agree with. I would only have added concomitant opioid use to what you already are looking at.

DR. MABREY: Great. Thank you.

Dr. Blumenstein?

DR. BLUMENSTEIN: Yes, one has to assume that there was a great deal of discussion that went on in the choice of these endpoints, and so you have to assume that the Sponsor, in choosing leg pain as being the primary endpoint, is taking their best shot

based on the prior data that they had. And I think the Sponsor's specification, identification of primary and a hierarchical closed testing procedure for all the secondary endpoints, that's wonderful. That's just what should have been done in this case. So they get credit for that.

However, there is one aspect of it that bothers me. And, as I mentioned before, and I'll probably say it again and again, is I worship at the altar of randomization. And the choice of endpoints are, for lack of a better term, not ITT-able in the sense that there was loss of patients due to missing data. And so I would have preferred to see primary endpoint that could have had a definition despite a loss of data; that is, something like an assumed no response or a composite response where assumed no response was possible.

And so what we are left with here is a loss of a great number of patients because they failed to come in for their 6-month evaluation. And so that's one of the things that bothers me about this particular choice of endpoints.

DR. MABREY: Thank you. Ms. Whittington?

MS. WHITTINGTON: I think you selected an excellent tool for your endpoints. In so many of the

things that we do, we don't have an endpoint that's focused on what the patient's perception, which is reality to them and how they function. So I applaud you for selecting this.

While we may lose patients because they don't come back, pursuit of those is very important, as he indicated, to get as much rich data as you can. But I think that what you're looking at here is very important.

I agree, however, with Dr. Sang in the fact that you need to be able to correlate not only opioid but other anti-inflammatory meds or other treatments that the patient's in and ensure that that's included with your reports on both their pain and functionality because that does significantly affect that. And I think that that's also needed to be with this. So I think that the tool you've selected and the things that you're looking at are very appropriate because it's really -- the patient is who needs to benefit.

DR. MABREY: Ms. George?

MS. GEORGE: Being the non-clinical person up here, a lot of the stuff that you guys are all saying makes no sense to me, but that's okay. What I do look at is, is that I think that the study was a

difficult one for them to identify, but I think if you look at the indications for use and you take the sequence of what they've identified even in the indications for use, they do say leg pain, which is their primary.

And then the two secondary ones that they list are back pain and the symptoms, which if you look at the sequence of their secondary are the number one, two, and three in the secondary portion. The number two correlates somewhat, I would think, to leg pain, but, again, not being clinical, I just think about myself as a person.

And then the other three, just as Connie mentioned is, is I think that one of the things in all the other panels that I've participated in that come up frequently is we forget about the patient. We look at the data only and think about the clinical side of it solely and forget the patient. So I think that that was good.

DR. MABREY: Thank you. Mr. Melkerson, in regards to Question 1, the Panel generally believes that much of the data did not address the original endpoints, although certain subsets of that data did. The Panel also has some concerns about the proposed indications for use, as they differ from the study as

it was conducted. And also that their choice of endpoints were affected by significant loss of data. Is this adequate for the FDA?

MR. MELKERSON: Thank you very much.

DR. MABREY: Can we have the second question, please?

MS. JOSE: Second question --

UNIDENTIFIED MALE SPEAKER: You need to get a little closer.

MS. JOSE: The Sponsor provided biocompatibility -- and immunotoxicity under --

UNIDENTIFIED SPEAKER: Mike on?

DR. MABREY: Jismi? You need to get a little closer to the mic.

UNIDENTIFIED SPEAKER: Need a mike?

UNIDENTIFIED SPEAKER: I don't think the mike's working.

UNIDENTIFIED SPEAKER: Here you go.

MS. JOSE: The Sponsor provided biocompatibility, toxicity, and animal performance testing and based support for chronic toxicity, carcinogenicity, and immunotoxicity on a rationale and literature search. The Sponsor stated that due to the length of time Oxiplex remains in the body, based upon their pre-clinical animal studies and

literature search and the use of components contained in Oxiplex and other medical device applications, chronic toxicity, carcinogenicity, and immunotoxicity testing are not necessary.

Please comment on the adequacy of the non-clinical testing and pre-clinical animal studies conducted by the Sponsor. Please discuss whether the animal studies are expected to be predictive of the performance of the device for its proposed indications for use.

DR. MABREY: Thank you. I'll begin with Dr. Horlocker.

DR. HORLOCKER: Yes, I do not believe that the testing was adequate. The pre-clinical testing on the six rabbits only looked at histology. So saying that there is no problem with chronic toxicity on just six rabbits I do not believe is adequate. And, likewise, the primate study, looking at CSF pressure with injection of 1 milliliter of solution, you would not expect to see an increase in CSF pressure. So without additional toxicity studies, I do not believe that there has been an adequate evaluation.

DR. MABREY: Thank you. Dr. Goodman?

DR. GOODMAN: Well, I was trying to get the

Sponsor to give us more information individually on these materials and together. I think that they're individually known to be very safe. And I believe together they're probably safe, too. It would have been optimal had more studies been done in greater detail to support these facts. I think they relied more on the literature than doing, as Dr. Horlocker said, the real studies that were needed to be definitive.

I think that the studies in the literature and from what they did probably point to the safety issue being met. The efficacy issue is a total other issue that we'll discuss.

DR. MABREY: Dr. Rao?

DR. RAO: I think the animal testing, in terms of safety issues, appears adequate. I would be happier if we had more animal testing in terms of basis of efficacy, in terms of response of or the result or effects of the device on markers of inflammation, cytokines. And also, based on the Sponsor's response earlier, I would suggest increased animal testing in terms of increased osteoid production potentially at the local surgical site.

DR. MABREY: Thank you. Dr. McCormick?

DR. McCORMICK: Yeah, I would echo

Dr. Rao's view. I think for the safety standpoint, based on the history, empiric and clinical, I think their testing was adequate. They did raise some interesting hypotheses. I'm not sure whether they're biologically plausible or not. I'm still struggling with that. But it would be interesting to see some further work, but for the safety issues, I think it was adequate.

DR. MABREY: Thank you. Dr. Evans?

DR. EVANS: I don't really have any comments to this question.

DR. MABREY: Thank you. Dr. Sang?

DR. SANG: I agree with all the comments so far.

DR. MABREY: Dr. Blumenstein?

DR. BLUMENSTEIN: Since this has nothing to do with randomization, I have no comments.

(Laughter.)

DR. MABREY: Thank you.

MS. WHITTINGTON: I have nothing to add.

DR. MABREY: Ms. Whittington -- Ms. George?

MS. GEORGE: I think, as everyone stated, that the safety aspect has been tested, as they've identified using international standards that are well known. And I believe that they also identified

in the package as well as communicated in the presentation that there are other devices out there that are made up of the same material that have been used for many, many years, as well as the over 100,000 outside of the United States that they have no evidence of issues with. So I actually feel that they have proven the efficacy as well.

DR. MABREY: Dr. Hanley?

DR. HANLEY: It seems like the stuff's inert. That may be the problem.

DR. MABREY: Is that it?

(Laughter.)

DR. MABREY: Mr. Melkerson, the Panel generally believes that the device, as tested, is probably safe but that more studies would be useful. The Panel also has some concerns about needing more testing with respect to efficacy and perhaps mode of action and its effects on the surrounding tissues. Is this adequate for the FDA?

MR. MELKERSON: Yes, it is. Thank you very much.

DR. MABREY: Thank you.

MS. JOSE: On to Question 3. Before I continue, I'd like to note that our clinical and statistical questions that are following are based on

the PMA CC population because that is what our presentation focused on.

So some variability in patient outcomes among sites was shown in the unadjusted analysis on the 6-month leg pain change from baseline by site/pseudo-site on the completed cases population. In the generalized estimating equations model on leg pain improvement, the treatment-by-site interactions were shown to be statistically significant, with a P-value of .01 in the PMA CC population.

Please comment on the validity of pooling data from different sites, taking into consideration the demonstrated site variability. Please discuss what impact this may have on the interpretation of the clinical data.

DR. MABREY: On the topic of the impact of different sites on interpretation of clinical data, Dr. Goodman?

DR. GOODMAN: Who was it who said, "There are lies, damn lies, and statistics"?

(Laughter.)

DR. GOODMAN: I think I saw a lot of the same data being presented in two different ways, one by the Sponsor and one by the FDA. And the two presentations seemed a bit contradictory. There

seemed to be a great deal of site variability with regards to meeting the effectiveness bar when the FDA presented it, with a lot of site variability. And the opposite was true by the Sponsor.

As I said before, I think site variability is an issue here. And I'm not sure how that can be resolved, although I have taken several statistics courses and believe in randomization. I think our statisticians will probably more than I can to this situation, but it is of concern to me that there is so much variability when the FDA presented the data.

DR. MABREY: Dr. Rao?

DR. RAO: I think site variability to some extent may be anticipated and may be excused. I don't think I have any specific comments about site variability itself. My comments pertain specifically to what appears to be discrepancy between the FDA's analysis of site variability and the Sponsor's analysis of site variability. What I remember is a graph during Jack Zhou's presentation, Mr. Zhou's presentation, where there was negative correlation, I think he termed it, between control and Oxiplex at about half the sites, whereas the Sponsor's presentation suggested that at all sites, Oxiplex did better than control -- was my interpretation. So

that discrepancy is what bothers me. Outside of the discrepancy, I wouldn't have any objection to small degrees of site variability.

DR. MABREY: Thank you. Dr. McCormick?

DR. McCORMICK: Yeah, I think the discrepancy came from two sources. The first is that they used different CC subgroups. The FDA used a more complete version. There were an additional 66 patients that were not in-windows, who were apparently removed from that analysis, and that affected the outcome. The difference of 6, in terms of the leg pain, 6 points on the LSOQ scale, that was shown for the patient with severe back pain by the Sponsor. Was only 6 when it was shown by the FDA because of the two different groups.

And the other difference is what the FDA showed, in terms of the site variability, was an unadjusted analysis of all patients were -- I believe all we were shown on that slide was just patients with severe low back pain. So I think that's where the discrepancies came from.

I actually think based on the -- I don't think the site variability is a big issue here. I think there is going to be some variabilities from site to site in any clinical trial. The numbers are

small for most of the sites, and these are predominantly patient-generated outcomes. So I don't think that that's a big concern here.

DR. MABREY: Thank you. Dr. Evans?

DR. EVANS: I guess I premise this with a few comments. I'm perhaps a little bit less worried about the site variation as well. And the reason is that they are often small sample sizes at sites, which, therefore, there is large variation, you know, when you have small sample sizes. And so part of this site-to-site variation may just be reflected in the sample sizes within each site. So some analyses that you can look at is -- well, I guess my first comment is not to overreact to necessarily that although it's worth investigation.

The other thing is that because of small sample sizes at sites, at least the summary that I remember looking at in the analysis, was primarily about sort of summarizing means and things like that, And particularly with small sample sizes, you might go to something more robust like medians. And outliers and things like that, certainly, with small sample sizes can start to pull stuff around pretty quickly.

So the other comment I have -- I guess the

direct question is a comment on the validity of pooling data. Well, I also worship at the throne of randomization, and randomization, again, gives you valid inference when you pool over sites, as long as you're adhering to ITT principles. Now, that doesn't necessarily mean that effects are homogenous across sites, but it gives you valid inference.

So it's worth investigating why. So the natural question is why would there be site variation? And whether this could be related to the fact that different sites have different surgeons, and these particular surgeons, as we mentioned, are unblinded, and could that potentially affect something, I don't know.

But I think the bottom line is I think it's worth investigating. I'm not sure there is an easy answer to this question. But because of the small sample sizes at sites, there is going to be variation in sites. You still have valid inference. And I would, in my investigation, perhaps look at and realize that extreme values and things like calculating means and stuff, within site, particularly with small sample sizes, can really, you know, pool summary statistics, so you might want to look at medians, and things like that.

DR. MABREY: Thank you. And I would let the record show that Dr. Evans is sitting on the throne of randomization whereas Dr. Blumenstein worships at the altar of randomization.

(Laughter.)

DR. MABREY: Dr. Sang?

DR. SANG: So understanding that the data presented by the FDA were group means for each site, still, my understanding is that the sample site calculation has to -- sample size calculation has to take in account the number of sites, as well as the variability between sites, the differences in variability between sites and variability within each site. And so it suggests to me that perhaps the sample size that was initially calculated may not have been high enough. But I'll defer to the statisticians on that.

What it also suggests to me is that perhaps the mechanism of -- the pain mechanisms involved in the pain syndromes at each site on average could have varied sufficiently, and it would be useful to have a better understanding of that.

DR. MABREY: Thank you. Dr. Blumenstein. I agree with Scott Evans that I'm not getting too concerned about this. And I would add that if you

believe the non -- undisciplined searching for a significant covariate type of analysis, that is, the originally specified primary analysis, where there is no treatment effect, then what you're doing by looking at the site data is reading tea leaves. And so I wouldn't be -- I'm not too concerned about the site variability. It's just the variation in the stuff that is going on there.

But other avenues that might be interesting to look at: if one is focusing on subset analyses for exploratory purposes, one might want to look at the randomization, exactly how it was done, and how it fell out, and whether it might be contributing to differences in site within subsets, and also whether there is any kind of a relationship between missingness of data in the sites and the outcome. And these are very complicated issues, but, you know, must be looked at in the context of exploratory analyses.

DR. MABREY: Thank you. Ms. Whittington?

MS. WHITTINGTON: I think some of it is different surgeon's techniques and iatrogenic issues that can occur at the time of surgery, and maybe more importantly, the chronicity of disease of some of the patients that may have been included in the study.

Not all of them could be acute, and somebody with chronic back pain that had a procedure like this may not have as good an outcome quite as quickly as someone who's been having issues for a shorter period of time.

DR. MABREY: Ms. George?

MS. GEORGE: Just to re-echo a few things, I think Dr. McCormick said that it is a reality that you're going to have some variability, and I think that is something that has to be understood when a clinical study is put together because not everybody -- not all the patients are alike, not all the physicians are alike. I think Dr. Evans made the statement that we should try to understand why there is that variability.

And one of the things that came to mind, which is going to sound funny coming from me rather than Ms. Whittington is something that maybe should be considered is, is there a socioeconomic impact? Are they places where they're less compliant with the whole aspect of the clinical care. Are they the more overweight patients? Are they other issues that are inhibiting them from maybe feeling as good or maybe feeling better because it's the first time they're having any positive outcome. So that could be

swaying some of the results as well.

DR. MABREY: Thank you. Dr. Hanley?

DR. HANLEY: Yeah, I'm not concerned about the variability. I think that's expected in a study sample of this size. I think it may just reflect the small sample size.

DR. MABREY: Thank you. And Dr. Horlocker?

DR. HORLOCKER: I'm surprised nobody's blamed anesthesia. That's what usually happens at my institution.

(Laughter.)

DR. HORLOCKER: I agree. Actually, with a real negative outcome, as far as no major improvement, to see half the sites reported improvement and half not is really along the statistical mean. So --

DR. MABREY: Thank you. Mr. Melkerson, with regards to Question 3, the Panel generally believes that site variability is less of an issue and that it is probably due to the smaller sample size. We've also heard from the statisticians that randomization is important.

(Laughter.)

DR. MABREY: The Panel had some concerns about the discrepancy of data analysis between the

FDA and the Sponsor, and there has been some concern expressed about the effects of missing data.

Is this adequate for the FDA?

MR. MELKERSON: It is. Thank you very much.

DR. MABREY: Thank you.

MS. JOSE: Okay. Question 4. The Sponsor included 10 covariates and 5 treatment-by-covariate interactions in its multivariate analysis of the primary effectiveness endpoint, which was comprised of leg pain, using the generalized estimating equations on the completed cases population. The Sponsor's interpretation of this analysis is that it demonstrates the statistical significance of the primary endpoint based on the significance of treatment-by-baseline covariate interactions.

Please discuss whether the Sponsor's multivariate analysis is appropriate, and, to assist the FDA with the interpretation of whether the study met its primary endpoint, discuss this conclusion based upon the analyses conducted by the Sponsor to determine statistical significance of the primary endpoint.

DR. MABREY: Thank you. Dr. Rao, I'd like to begin with you.

DR. RAO: I think my concerns with the multivariate analysis have been expressed earlier today. I think the results of a multivariate analysis will depend essentially on what we put into it and the factor and the variables we choose to put into a multivariate analysis.

I think the FDA asked the Sponsors to look into all covariables that may affect outcome, and the Sponsors, to my understanding, have looked into the different statistical methodologies that may affect outcome, and therein lies some of the discrepancy.

I believe that in an attempt to become statistically sophisticated, we may be tripping over ourselves and losing sight of the main goal, which should still be that primary effectiveness endpoint. Thank you.

DR. MABREY: Thank you. Dr. McCormick?

DR. McCORMICK: Well, I think this is the hardest question to comment on. I think it was clearly appropriate that the analysis was done. I think that we need to have this information to try to do what's best for what truly is a very heterogeneous population. The idea that each patient is equally likely to achieve the same mean response to a treatment is really the underlying premise of most of

theses prospective clinical trials. And we know from treating these patients that they're very heterogeneous and they respond different to treatments. Whether or not back pain severity is a covariate, a meaningful, a causal covariate, that may predict a better outcome, I'm not sure we can conclude that based on the fact that it was generated from a post-hoc, multivariate analysis.

But I'll tell you what I'm still not clear about is whether or not the degree of pre-specification was clear to the FDA to approve it. If they played by the rules, in terms of this analysis, then we should accept it. If they didn't, then we should have concerns. As someone who does peer review, I have concerns over it, because I think it was a post-hoc multivariate analysis.

DR. MABREY: Dr. Evans?

DR. EVANS: Well, I have a concern for the inflation of a false positive error rate. And the reasons why are pre-specification protects you against data-driven analyses, but it does not protect you against multiplicity by itself. And I agree that there is sort of a vagueness into what was pre-specified and what was not. And there's some important details in that clarification because

there's a difference between pre-specifying a multivariable analysis, which is still exploratory by nature, versus clearly defining what subgroups will be analyzed and how they will be evaluated.

And even if you examine the subgroup that was identified, high versus low back pain, although the analysis may pre-specify that you're going to look for, potentially, these subgroups, there was no pre-specified necessarily definition of low versus high back pain. That definition was based on the median of the observed pain in the trial. So in a sense, it's been pre-specified at a vague level but hasn't been clearly defined, definitively, and is thus somewhat exploratory in nature.

And it's reasonable to do, but I think the bottom line is, the way I see it, is you've asked whether this analysis is appropriate. I think it's an appropriate analysis for hypothesis-generating, but not for confirmation. The Sponsor this afternoon mentioned that it is very complicated to quantify the false positive rate in this trial. And I completely agree. It is very complicate to try to quantify what the false positive rate is here. But it's because of this uncertainty that subgroup analyses are considered to be hypothesis-generating and require

validation and confirmation with new data.

And so, generally, I view this -- that's the way I view this. You know, I think if you are going to confirm subgroups, you predefine them with a biological explanation of why you're looking. You define how many subgroups you're looking at, exactly what those subgroups, how they're defined, and you set aside a statistical error spending approach that controls error rates. Otherwise, we've really lost certainty about where those error rates are. So I have concern about saying -- putting confidence in that this is not a false positive result.

DR. SANG: I completely agree. I think independent of a choice of a primary endpoint that I think is ambitious, still, not defining subgroups ad hoc, the stepwise data mining is very interesting, very interesting to people like myself. But for your purposes, I think it was not a valid analysis.

DR. MABREY: Dr. Blumenstein?

DR. BLUMENSTEIN: I'm not going to say anything different than Scott Evans just said, so what I'm going to say is redundant, and I'm sorry about that. But I'll say it a different way, and maybe it'll catch on.

To me, it's totally inappropriate to

attempt to assess the significance in this kind of a setting by doing these kinds of analyses that are basically modeling rather than clearly pre-defined hypothesis testing with a very strict alpha control. So I can't agree with that.

And number two on my list is I don't agree that what the Sponsor did was following what the FDA requested that they do by taking into account the covariates. In other words, the FDA had an intent there, and I think what the Sponsor did went way beyond the intent.

And, then, the third point I want to make is that the -- I don't agree with what the FDA asked the Sponsor to do by adding the covariates. Again, randomization should take care of these things, and I don't like the idea of loading up a model to assess the significance of an efficacy finding with a bunch of covariates. I'm not sure what you do with that. I'm not sure what the meaning of it is.

And the fourth point I wanted to make is that I believe that the exploratory analyses that the Sponsor did, that is, all of this modeling, was artfully done. And I'm using the term artfully purposely because there is an art to it. There is no one way to approach this kind of thing, and then that

reflects right back on to the first point, and that is that you can't really know the alpha because it is art, not a strictly identified pre-defined analysis.

And then I completely agree with what the Sponsor did in assessing the -- excuse me -- the interaction first in their exploratory analysis. I think that's the way I would have done it, and, therefore, I agree with them for an exploratory analyses.

DR. MABREY: Thank you. Ms. Whittington?

MS. WHITTINGTON: I have nothing to add.

DR. MABREY: Ms. George?

MS. GEORGE: From my perspective, it is difficult to analyze whether the study was -- for the endpoint because of the fact that the data that we saw from the FDA and from the Sponsor did make use of the same raw data but extrapolated and extracted information out differently. So I think they each had their own starting point, and as has been said multiple times by the statisticians, it's very easy to take a bunch of data and present it in a format and presentation that shows the results that you want. So I think that what has to be done is a determination of really what was meant by the FDA's perception, and the Sponsor obviously had a different

perception of the same requirement.

DR. MABREY: Dr. Hanley?

DR. HANLEY: Yeah, I see this as complex data manipulation that I don't understand, and that worries me.

DR. HORLOCKER: I agree.

DR. MABREY: That it's complex or that you're worried?

DR. HORLOCKER: It's very difficult. It's a numerical --

DR. MABREY: Dr. Goodman?

DR. GOODMAN: I would agree with the previous comments.

DR. MABREY: Thank you. Mr. Melkerson, the Panel generally believes that this was the most difficult question posed. In addition to that, they seem to get a feeling that the multivariate analysis, while appropriate -- while it may have been appropriate and artfully done, may have been affected by the choice of endpoints based upon data post-hoc. There is some concern over the addition of covariates as one of the requirements.

Is that good enough for the FDA or would you like more clarification?

MR. MELKERSON: I believe you've discussed

the point appropriately.

DR. MABREY: Okay. Thank you. Question 5?

MS. JOSE: The FDA requested that the Sponsor calculate the simple mean difference of the composite leg pain improvement, which was the primary effectiveness endpoint, at 6 months between the Oxiplex and control groups. This mean difference was 0.9 on the 100-point LSOQ scale for the completed cases population.

Please discuss whether this mean difference between the Oxiplex and the control groups is clinically meaningful.

DR. MABREY: Dr. McCormick?

DR. McCORMICK: No.

DR. MABREY: Okay. Dr. Evans?

DR. EVANS: I agree.

DR. MABREY: Sang? Dr. Sang?

DR. SANG: No, but I have something to add.

DR. MABREY: Okay.

DR. SANG: So, no, but in the absence of -- pharmacological management blocks, adjuvants, and so on, it's hard to interpret what it means. And so I think it would be to a great advantage to have an understanding of that.

The other thing is that this composite

score may mean something very different to a subject 6 months after surgery versus six hours after surgery. And so the relative weights of the different components can change over time.

You might consider a global scale like a PGI or CGI, you know, something where a subject can do his own, you know, integrate for himself what's important to him at 6 months or choose other secondary measures that may be more relevant to chronic pain.

DR. MABREY: Thank you. Dr. Blumenstein?

DR. BLUMENSTEIN: The simple answer is no. I sure wish I had seen an ITT with imputed missing data or a data done at the 3-month time point or some other variations on this just to get a better picture of what's going on and to reassure myself that the missing data isn't a contribution to what's going on.

DR. MABREY: Ms. Whittington?

MS. WHITTINGTON: I agree with my colleagues.

DR. MABREY: Thank you. Ms. George?

MS. GEORGE: Nothing to say.

DR. MABREY: Dr. Hanley?

DR. HANLEY: For the overall leg pain group, no.

DR. MABREY: Thank you.

DR. HORLOCKER: For the overall leg pain group, no. And I think that this shows what the effect of that multivariate analysis was probably over the top.

DR. MABREY: Dr. Rao?

DR. RAO: I think this tough to be certain about because the question is what degree of clinical improvement is relevant or clinically significant. And I think the best guess estimate has to be based on a statistical test, and if it's statistically insignificant, I think we have -- we're forced to use that lack of statistical significance as meaning that this is clinically irrelevant also.

DR. MABREY: Thank you. Mr. Melkerson, in regards to Question 5, the Panel generally believes that it is not clinically meaningful.

Is this adequate for the FDA?

MR. MELKERSON: It's an appropriate response. Thank you.

DR. MABREY: Thank you. I was just going to announce, for the rest of the Panel's sake, Dr. Goodman had only one chance at a flight to get back to California, so he had to leave us.

MS. JOSE: Okay. The Sponsor's primary

effectiveness endpoint analyses screened 48 different covariates and their interactions with the treatment variable to be included in the statistical models. Some of these treatment-by-covariate interactions had unadjusted P-values less than 0.044, which led to subgroup analyses. For example, for the subgroup of patients with baseline back pain scores greater than or equal to 63 in the completed cases population, Oxiplex patients had a 6-point advantage over the control patients in the leg pain improvement at 6 months.

Please discuss whether the observed treatment effect for some subgroup of patients is clinically meaningful and whether the Sponsor's subgroup analyses may affect the interpretation of the safety and effectiveness of the device.

DR. MABREY: Dr. Evans, we'll start with you.

DR. EVANS: Yeah, so this is a question about clinical relevance, so this is actually harder for me than the other ones.

Six percent on 100 percent scale, that might be relevant to some people. However, I find a little bit of difficultly in the way the questions are asked, both Question 5 and 6, about clinical

relevance. This is a question about whether a 6-point difference is clinically relevant. That 6 points is based on an estimate observed in this trial. That's an estimate, and the truth is could be a little bit higher, could be a little bit lower. And if I knew the exact correct answer was a 6-point difference, then I'd probably say I'd take it, but because 6 has uncertainty involved with it, you can' necessarily say that it's relevant because it could be a little bit higher or a little bit lower.

I would like to clarify some understanding because it relates to the last comment. Non-significance does not imply no effect or no relevance. And the way that has to be interpreted when you see non-significance, is, essentially, non-significance says, well, zero is sitting in my confidence interval somewhere. I can't exclude zero. But it may also mean you can't exclude 10, 20, 30, or 40, which could be very relevant.

So the way to interpret "non-significant trials" is not due to high P-values. High P-values do not imply lack of relevance. So the only way you can interpret that is get a confidence interval, and you can exclude things outside the confidence interval. And so be careful about the interpretation

of "negative studies." High P-values do not apply that you've ruled out very possible and plausible with the data that's been gathered effects.

So I went off on a tangent and didn't answer the question, but that's my comment.

DR. SANG: It'd be useful to understand what the actual responses were in the control group and the treated, the Oxiplex group, because, in fact, we know from responder analyses in analgesic trials that in the act of arm, a 30 percent or greater reduction in pain intensity means something clinically, we think, at least based on some studies.

Here, it's hard to make an assessment just based only on the difference at 6 months. I think I mentioned before that there are a number of potential confounders that we haven't really heard enough about and that at 6 months, an assessment of one's pain can change.

So I guess my answer is possibly. My answer to the question as to whether or not this could have been -- this could have occurred due to chance is possibly because I feel that I don't have sufficient data.

DR. MABREY: Thank you. Dr. Blumenstein?

DR. BLUMENSTEIN: Well, I have some

uncertainty about the estimate of effect size. And it doesn't seem fair to pick a subgroup and then find an effect size that's large enough and then focus on that. That's what we've been talking about.

Ideally, one would have some clean room validation of the modeling that was done, that is, some people who could apply the art of modeling to these data and see if they come up with the same thing by pursuing their own style of modeling.

But I think the bottom line here as to whether this is significant or not, clinically significant or not, is going to rest with the Sponsor's decision as to whether to undertake, for example, to undertake a new trial focused on just the patients with severe back pain at baseline. In other words, how much does the Sponsor believe these data and whether they move forward. That's going to be interesting to see.

DR. MABREY: Thank you. Ms. Whittington?

MS. WHITTINGTON: I have nothing to add.

DR. MABREY: Ms. George?

MS. GEORGE: Nothing.

DR. MABREY: Dr. Hanley?

DR. HANLEY: The affect may or may not be real. I can't determine that, but I really don't

think it affects the overall view of the data presented.

DR. MABREY: Dr. Horlocker?

DR. HORLOCKER: I don't believe that we know the clinical relevance of this difference. And assuming that the statistical analysis was correct in that, then I agree we have to actually focus on a group of patients with severe back pain to begin with or leg pain to begin with and see if this actually did make a difference to the patients relevantly afterwards.

DR. MABREY: Dr. Rao?

DR. RAO: In the absence of a clear, clinical rationale for greater improvement in leg pain in the subgroup of patients with increased low back pain, I wouldn't attribute any significance to the statistical value.

DR. MABREY: Thank you. And Dr. McCormick?

DR. McCORMICK: If we accept that the multivariate analysis is valid, based on appropriate pre-specification to the FDA, then I think that the 6-point improvement is clinically meaningful. And the reason I say that is because this is what I kind of refer to as the tyranny of the mean, where we assume that every patient is going to be equally

likely to have the same average response to a treatment. And that's not the case. Some of the patients had less than 6. A number of them had greater than 6, sometimes twice as many as that.

In the context of a treatment that, in my view, has very little in the way of downside or risk to it, the idea that in -- maybe not on average, but in a significant number of patients you're going to get a measurable increase in their pain improvement in their leg, to me, is clinically meaningful. And as a surgeon, I would be compelled by those data.

DR. MABREY: Mr. Melkerson, the Panel seems to have varying opinions as to the significance of the data. It seems that this difference in -- the significant difference in this treatment in the subset of patients could be due to chance. But, then again, it may also represent a clinically significant response as well. The Panel has also suggested that the Sponsor may wish to look at a specific subset of patients in a new trial, specifically those patients with increased back pain or severe back pain prior to treatment in order to get some clean data on this.

Is that appropriate, adequate?

MR. MELKERSON: Yes, it is. Thank you.

DR. MABREY: Thank you.

MS. JOSE: Under C.F.R. 860.7(d)(1), safety is defined as a reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of the intended use when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks.

Do the clinical data in the PMA provide reasonable assurance that the device is safe?

DR. MABREY: Dr. Sang, safe, unsafe?

DR. SANG: Well, without a clear demonstration of efficacy and a probable but not clear --

DR. MABREY: We'll be addressing the question of efficacy in the next question.

DR. SANG: Well, this is a question about --

UNIDENTIFIED SPEAKER: Safety --

DR. MABREY: Question 7 is --

DR. SANG: Benefits outweighing risks?

DR. MABREY: Yes.

DR. SANG: Can't answer it. So I suppose, gosh, I supposed then my answer is no, I can't answer the question.

DR. MABREY: Okay. Dr. Blumenstein?

DR. BLUMENSTEIN: I concur.

DR. MABREY: Concur that you can't answer one way or the other?

DR. BLUMENSTEIN: That's correct.

DR. MABREY: Ms. Whittington?

MS. WHITTINGTON: I have to agree with them. It's a slippery slope. I agree. I concur with them. Very slippery slope.

MS. GEORGE: Well, naturally, I have to disagree, and the reason I disagree is that the submission includes all of the additional information of that there are no adverse events that were directly related to it and the fact of the rest of the world and all of the published papers that are included in the safety and efficacy data section of the submission clearly states that there are no adverse events that are directly related, so the device is safe.

DR. MABREY: Thank you. Dr. Hanley?

DR. HANLEY: Yes, it is safe.

DR. MABREY: Dr. Horlocker?

DR. HORLOCKER: Yes, it is safe provided that it's used as intended. I'm still concerned about intrathecal injection.

DR. MABREY: Thank you. Dr. Rao?

DR. RAO: Given that the definition of safety here includes that the benefits of health outweigh the potential risks of the device, I have to say that I can't answer the question.

DR. MABREY: Thank you. Dr. McCormick?

DR. McCORMICK: Yeah, it's a ratio. I think the risks are negligible, and I think there may be some small benefit in some small group of patients suggested by the data, so I think the answer is yes.

DR. MABREY: And, Dr. Evans?

DR. EVANS: I agree that the risks are small, given the data that we've seen, but I don't have confidence in making a statement that the benefits are likely to outweigh risks. I'm not convinced of the benefits, I guess.

DR. MABREY: Thank you. Mr. Melkerson, the Panel seems to be evenly divided between suggesting that the device is safe as defined versus not being able to answer the question with relationship to benefits outweighing the risks.

MR. MELKERSON: That's fine. Thank you.

DR. MABREY: Thank you.

MS. JOSE: Under C.F.R. 860.7(e)(1), effectiveness is defined as a reasonable assurance that in a significant portion of the 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 provide clinically significant results.

Do the clinical data in the PMA provide reasonable assurance that the device is effective?

DR. MABREY: And we'll start with Dr. Blumenstein.

DR. BLUMENSTEIN: No.

DR. MABREY: Ms. Whittington?

MS. WHITTINGTON: No.

DR. MABREY: Ms. George?

MS. GEORGE: I'm not going to give a yes or no, but I am going to say that I don't think that the Sponsor would be here if they didn't think so. But I do think that since we have question on how the data was manipulated that I think they have the data in the raw form and it should be re-evaluated and re-looked-at to see if it does, in fact, meet the endpoint criteria as defined.

DR. MABREY: Thank you. Dr. Hanley?

DR. HANLEY: In the question that says in a significant portion of the population, as in the proposed study, is what I interpreted that to mean, and it is only proven to be potentially, possibly

effective in a small subset, so my answer is no.

DR. MABREY: Dr. Horlocker?

DR. HORLOCKER: My answer is no.

DR. MABREY: Dr. Rao?

DR. RAO: No.

DR. MABREY: Dr. McCormick?

DR. McCORMICK: As written I'd have to answer no.

DR. MABREY: Thank you. Dr. Evans?

DR. EVANS: No.

DR. MABREY: Mr. Melkerson, in regards to Question 8, the Panel generally believes that the device is not effective.

Is that adequate for the FDA?

MR. MELKERSON: Thank you very much.

DR. MABREY: Thank you. Okay. We still have two questions pending regarding the possibility of a post-approval study and labeling. Yes?

MR. MELKERSON: The post-approval study is only if it is a recommendation for approval with conditions. Issues with regard to labeling. It's your prerogative whether you want to ask that now or --

DR. MABREY: I think we'll go into the post-approval study later, but I think while we're

still in the voting mood, I would like to address the question of labeling. The Sponsor -- following protocol here.

MS. JOSE: So I just want to remind you, a question on labeling should not be interpreted to mean that the FDA has made a decision or is making a recommendation on the approvability of this PMA device.

The Sponsor provided physician labeling/instructions for use for the subject device. The Sponsor did not provide patient labeling because they consider the device an adjunct to surgical treatment and believe the patient is not involved in the choice of using the Oxiplex/SP gel.

Please discuss:

a) The need for patient labeling; and

b) The appropriateness and/or adequacy of the physician labeling/instructions for use.

DR. MABREY: I did not plan my Panel rotation based upon this, but it seems that we've come to Ms. Whittington regarding the question of patient labeling. For the rest of the panel, I would draw your attention to a handout that was given to you. It is from Medtronic, a brochure of the benefits of lumbar surgery with MediShield, three

pages, and then the second handout is a copy of a Web page from a neurosurgeon in Australia who is advertising the fact that he uses Medtronic MediShield. And I would let you draw your own conclusions from that.

Oh, okay. And this labeling is outside the U.S.

MS. WHITTINGTON: You ready for me to answer? You ready?

DR. MABREY: Or to give you a chance to look at the material.

MS. WHITTINGTON: Okay.

DR. MABREY: I guess my only comment -- and I'll take the chairman's prerogative to point to the last page, where it says in the patient pamphlet, "How may I request MediShield's application? Talk with your surgeon to find out whether you are eligible." This is in Australia.

Ms. Whittington?

MS. WHITTINGTON: Well, I find this quite interesting. When I think about this device, I think about methylmethacrylate and the utilization in joint replacement, and I don't think that there is a lot of discussion about the use of that, when a total joint is replaced, and I think it's considered by the

surgeon a part of the procedure. I think if a physician is going to be using this device as they're doing a laminectomy or laminotomy that it may or may not be discussed, quite frankly.

I find the information here interesting. It certainly is not written in terminology for patients. It's written at, I think, probably too high a level for many of the patients who might receive this. So do we need to provide patient labeling? I think we should be transparent about what we're using in procedures, but I think, quite frankly, in other orthopedic procedures that are performed, we're not as transparent as they're asking us to look at here.

This is out of the country labeling, but I would anticipate the same kind of websites would be included or the same kind of information would be included. I'm not giving you an answer one way or the other. It's a dilemma. I think the patient wants to be informed. I think there needs to be informed consent, and I have to step back from my example from the methylmethacrylate in total joints. I don't think that that's always discussed. I think it's -- is should be discussed and there should be education for the surgeon. Dr. Horlocker's concern

about injection of this in a place that it shouldn't be needs to be addressed in the physician education as well.

DR. MABREY: Is that a yes or a no? Or --

MS. WHITTINGTON: Maybe.

(Laughter.)

DR. MABREY: Ms. George?

MS. GEORGE: Just a couple comments. One, the labeling includes the instructions for use for the physicians, so I guess I'd ask the physicians if that's adequate because not being a physician, I don't know if that's sufficient instruction. But, secondly, since we heard during the discussions that usually this was a decision that a physician made while the patient was under and open, whether they were a viable candidate or not, I'm questioning how you can ask the patient if it's okay to use it. So I would say there isn't a need for patient labeling because we don't ask patients which medical device we're going to use on them when they're in surgery in general.

And then I guess my last question is, is that on their package insert, there is the word tracking, and I'm assuming this is not a tracked device. This is just a traceable device, lot

controlled, and I guess that's more of a comment to the FDA because there is a difference between trackable and traceable devices.

DR. MABREY: And, again, I'd just like to clarify -- I'm just bringing this up because it's showing up elsewhere around the world, and that some physicians are using it as part of their promotion of their practice.

Dr. Hanley?

DR. HANLEY: Yes. Do not confuse informed consent and labeling of the device. I think they are two completely different issues. Labeling of the device is mandatory and should reflect the scientific information provided with regard to the clinical outcomes of the device. And so if deemed approvable, any labeling should reflect the scientific information that we validate as a panel and for approvability and then the FDA goes forward with. So, yes, there's a need, and, yes, it needs to be done appropriately based on information.

DR. MABREY: Thank you.

DR. HORLOCKER: I agree with that also just so that patients can have a version of this that is more understandable and directed towards them.

DR. MABREY: Dr. Rao?

DR. RAO: I think patient labeling may not be necessary based on what Ms. Whittington said, but physician instructions for use should clearly specify the subgroups of patients that the device may or may not apply to or may or may not be validated by this Panel or the FDA.

DR. MABREY: Thank you. Dr. McCormick?

DR. McCORMICK: I would not think that patient labeling would be important for usage for this substance.

DR. MABREY: Dr. Evans?

DR. EVANS: I agree with the subgroup comment, clarifying what subgroups this is shown to be effective in or not effective so that patients, for example, with low back pain and their healthcare providers can decide whether it's a purchase they want to make.

DR. MABREY: Dr. Sang?

DR. SANG: Patient labeling, no. Physician labeling, yes. I would recommend that the data that is in this proposed label be replaced by the FDA analyses that's based on the GEE completed cases not on the Sponsor's definition of completed cases.

DR. MABREY: Dr. Blumenstein?

DR. BLUMENSTEIN: Nothing to add.

DR. MABREY: Thank you. Mr. Melkerson, with regards to Question 9, regarding labeling, it appears the Panel generally believes that this device falls within the same realm as devices such as polymethylmethacrylate and that patient labeling, per se, is not necessary. But, of course, physician labeling is. One suggestion that newer data be incorporated into the physician labeling for instructions for use.

Is that adequate for the FDA?

MR. MELKERSON: That is adequate. Also, with regards to Question 10, you might as well discuss that as well, with the same context of based on what your future recommendation may be.

DR. MABREY: Okay. Could we read Question 10? And, again, this is if the device is approved and if a post-approval study is requested.

MS. JOSE: Right. So the main points are that the FDA's inclusion of a question regarding a post-approval study should not be interpreted to mean that the FDA has made a decision or is making a recommendation on the approvability of this PMA device. Please remember that the pre-market data much reach the threshold for providing reasonable assurance of safety and effectiveness before the

device can be found approvable and any post-approval study could be considered.

In the post-approval study outline, the Sponsor proposes a non-inferiority design to compare the reduction in the number of disability days from baseline within 30 days of 6 months following surgery in subjects who will receive Oxiplex versus the Oxiplex-treated subjects in the pivotal study. The Sponsor also proposes tracking adverse events and re-operations over the 6-month follow-up period.

Please discuss the following topics:

a) What questions, if any, need to be addressed by a post-approval study?

b) Is the post-approval study design appropriate to address longer term device safety and effectiveness post-market?

c) What is the appropriate population to address device safety and effectiveness post-market?

d) What are the appropriate endpoints needed to address the questions, if any, identified for a post-approval study? Is "reduction in disability days from baseline at 6 months" an appropriate effectiveness endpoint to address the device effectiveness in real-world settings?

e) And what is the appropriate duration for

the post-approval study having identified the endpoints to be used for the questions, if any, to be addressed by a post-approval study? Is a 6-month follow-up after surgery sufficient to address the long-term safety of the device, and identify potential adverse events?

DR. MABREY: And, again, my choice of rotation had nothing to do with the arrangement of the Panel, but, Ms. George?

MS. GEORGE: Well, assuming that the device would be approved, obviously, I think that the things that would be evaluated here would be larger population, site variability aspects that we've talked about earlier. I think that the population that should be addressed is whatever would be identified as the approved, based on the indications for use and the intended use of the device.

And then, generically, with regards to the long-term aspects, as with any medical device, there is, for the lifetime of the device and the patient, there is the engagement of the medical device reporting aspects so that there would be the adverse event reporting. I think one of the questions that probably would come to mind is, is since the device does expel itself from the body in a short period of

time, that what, if any, long-term monitoring would the surgeon have of that patient after that time frame and if there needs to be any engagement with a clinician.

And I can tell you that if that would be the case, you'd have fewer patients wanting to have this because if they have to continue to be monitored and there is informed consent and all of those kind of things that there would be a significant challenge. So that's very generically because a lot of this is much more clinical, which I think the physicians can answer better.

DR. MABREY: All right. Dr. Hanley?

DR. HANLEY: Okay. These questions that are projected are a little bit different than our books. I'll address them from the projection area.

a) What questions, if any, need to be addressed by a PAS? And the same questions that were proposed in the initial study, that of a primary outcome of reduction of lower extremity pain and the secondary outcomes as listed. This changing horses in mid-streams about what we're studying is inappropriate. Any long-term study needs to study the things that were deemed to be appropriate and are appropriate at the beginning of the study.

So I will also address the non-inferiority design. I think that's inappropriate. And the number of disability days from baseline is inappropriate, and that's what we're talking about in (b) -- need to go back to the beginning.

c) What's the appropriate population? I think we have the appropriate population that has been enrolled in the study. I don't think that needs to be expanded upon -- those people with herniated discs and radiculopathy, with or without a component of back pain.

What are the appropriate endpoints? Same thing as before that was proposed in the initial PMA. Again, reduction disability days from baseline is inappropriate. It is relief of leg pain in all comers relative to a control group.

Duration, I don't know the answer to that. It is probably, in my estimation, not 6 months, but we need to study this long-term, I would say. Two years is probably the appropriate study. In some of the devices, of course, the follow-up is deemed to be longer than that, but would say at least two year follow-up.

DR. MABREY: Thank you. Dr. Horlocker?

DR. HORLOCKER: I agree with Dr. Hanley's

comments, and I'll just address some things that I have additional comments for. One question would be whether you'd want to focus on a subgroup of the population, those that start out with severe back pain or continue with the all comers that -- or I'm sorry -- leg pain -- with the scores of 63, for example are greater versus all those patients.

The other thing is I do not believe that we should use historical controls from the pivotal study as the controls. I'm starting to worship or sit at the throne of randomization during the last couple hours, and I think we really need to have a randomized project because there is a significant placebo effect in this. We've heard this repeatedly, and those other patients that would be in their controls did not know the randomization, where the ones that would be in this post-study all would know they were receiving the device, and so there is this, you know, supposal or predisposition towards bias, or the placebo effect. So I really think that this has to be a randomization rather than using historical controls.

And the other thing I would state is that there should be a control in what the patients get for post-operative analgesia. As Dr. Sang has

alluded to a number of times, if you don't control what they're getting, the pain itself could be masked or unmasked by what they actually get. So there should be a formal analgesic regiment that these patients receive. And then look at not only their pain scores but also their analgesic requirements.

And I would agree somewhere between 12 and 24 months would be the appropriate duration of a follow-up for these patients. Just spine patients in general seem to require that amount to really determine the efficacy.

DR. MABREY: Thank you. Dr. Rao?

DR. RAO: I think a post-approval study is predicated on an approval, which is predicated on clear clinical superiority of the device over the control group.

If we had a study where the Sponsor showed clear clinical superiority of the study, then I'm not sure that a control group would be necessary for a post-approval study. In the event that we had clear, clinical superiority of this study, then the endpoints needed for a post-approval study would be the same primary and secondary effectiveness variables that have currently been used. Additional questions would likely be the possibility of efficacy

on back pain versus leg pain, local effect analgesic, or anti-inflammatory effect of the device on local cytokines and other markers.

The PAS study design as presented may not be entirely appropriate. I'm not sure that reduction in disability days at 6 months would be an appropriate endpoint.

And as far as the duration of a PAS study, I would say we have to balance out the difficulty to the industry and Sponsor versus the benefits to the patient and finding a midpoint between what Dr. Hanley said and what Ms. George said. I think maybe a 12-month period would be appropriate.

DR. MABREY: Thank you. Dr. McCormick?

DR. McCORMICK: You know, I just don't see a need for a PAS here. I think, in my mind, the safety issue has been addressed adequately and a further PAS study would not be helpful. And unless we're willing to, you know, maintain randomization and blinding, we're just going to end up with more bias and placebo that I think are going to not provide us with any valid information regarding effectiveness of this substance.

DR. MABREY: Dr. Evans?

DR. EVANS: I'll make a couple of comments

about non-inferiority. And I know this study is in very early design stage and has a lot of ironing out to do.

I guess my biggest question is, what is the objective with this trial? Non-inferiority studies typically are done to compare a therapy with some active control, but the underlying goal in showing non-inferiority to an active control is that you show -- also retain some of the effect that the active control has -- placebo. In other words, you're still hoping that you're better than, say, placebo or standard of care.

And so I'm trying to figure out if that's really still the goal is to show that you're better than surgery alone, and if that's the case, then why not just compare to surgery alone rather than what the gel did in prior trials. I guess I don't understand that question.

But then, so, assuming there is reasoning behind that, a couple of comments, one about the selection of the non-inferiority margin. So the non-inferiority margin or selection of that non-inferiority margin and non-inferiority trials is the topic of the decade for non-inferiority trials. And it's really a difficult choice, and it's a

combination of both statistical reasoning and clinical judgment.

But a couple of guidelines is, first of all, the choice of the non-inferiority margin must be smaller than the effect size that your active controls showed over placebo or standard of care. So, in this case, that was estimated to be 2.1, or whatever it was. Now, that's an estimate from a trial, and so, theoretically, you have to be -- your margin has to be less than that because, otherwise, you wouldn't be able to necessarily claim you've got effect size better than surgery alone.

And inherent in just the estimate of 2.1, you have to realize 2.1 is an estimate and you observed it in one trial. Could be a little bit more. Could be a little bit less. And so your selection wants to take into account -- you should try to take into account the potential uncertainty and variation in that estimate.

So that's one thing to keep in mind. And the clinical relevance of it is you think about, well, what's the maximum difference between -- that you would consider to be clinical irrelevant or the largest difference that you would be willing to give up in order to gain whatever the advantages are. So

that's one issue.

The other issue is the assumption in non-inferiority or one of the assumptions in non-inferiority trials is something called constancy, which essentially means that the effect that you saw in the historical trials continues into today, and with standard of care developing, those estimates you saw in historical trials may or may not apply tomorrow.

And so you have to think hard about whether this assumption of constancy is really going to hold because future trials, if you run an uncontrolled trial, in other words, without concurrent controls, you could get better results just because standard of care is getting better. And therefore, you're going to claim non-inferiority not because it's non-inferior but because standard of care is getting better.

And so those are sort of my general comments.

DR. MABREY: Thank you. Dr. Sang?

DR. SANG: I think that in terms of safety, you know, I would agree that this is likely to be safe, and it's not clear to me whether or not we need to go out a year or two years. I think, if anything,

6 months should be adequate.

But in terms of efficacy, I have a similar concern about the design that's based on a non-inferiority comparison, and I'm not sure that I understand this proposal.

But, given that, I would recommend that measures of pain and function be incorporated, and I would take it to 24 -- I certainly would take it to 12 months, if not 24 months, as others have suggested.

But now we're talking about a different kind of study, and now we're talking about a study in which I think a non-inferiority comparison probably isn't going to do the company justice. I think that they might consider a study in which they may, in fact, be able to find a difference within subgroups that they may have already identified.

And so I think that this answer deserves a lot more attention than we're giving it right now.

DR. MABREY: Thank you. Dr. Blumenstein?

DR. BLUMENSTEIN: Well, I'm really puzzled by this, because I would think that if the Sponsor had come in here and shown us data that met the original criteria that is -- we didn't have any fuss about the alpha and all that sort of thing, then I

would see very little reason to do a post-approval study because of the safety and adequate demonstration of efficacy.

If there is the possibility that the FDA would approve this product despite not meeting the original primary criterion, then I would guess that the basis of that approval would be based -- would be on the kinds of --

DR. MABREY: Just to clarify, this is -- we're still, you know, hypothetical --

DR. BLUMENSTEIN: Yeah, I'm talking hypothetically, yes --

DR. MABREY: Okay.

DR. BLUMENSTEIN: And so if that were the case, then I would think that the post-approval study would focus on the subset of patients that fail to show efficacy if you accept the exploratory analyses that were done showing the subset in which they did find efficacy. In that case, it would be a superiority study in that subset.

So I can't answer the question under the supposition that the study has adequate efficacy based on the original primary analysis, and it doesn't make sense otherwise.

DR. MABREY: Ms. Whittington?

MS. WHITTINGTON: I'm going to jump in. I can't design the study, but I think if it's approved and they do move forward with another evaluation, they certainly need to look at some subgroups, and I would say acute versus chronic disease because it's just a different not only physiologic issue but the psych that goes with it.

The endpoints I think that they used in their initial study were good and were appropriate.

And the length of the study, if it's a chronic population, probably needs to be extended to 12 months rather than 6 months. I think 24 months to tax an organization is probably too much because of the relatively inertness, as one of my colleagues said earlier, of what they're using.

DR. MABREY: Mr. Melkerson, I'll take back what I said before about Question 5 being the most difficult.

With regards to Question 10, over the hypothetical post-approval study, the Panel seems to have varying opinions. Although those opinions have been expressed, and I would assume that the transcript will aid the FDA should they need to develop a post-approval study, it is -- I do get the sense that with regards to Question A, the same

questions that were initially proposed should be those that are being answered, perhaps looking at the correlation between back and leg pain.

With regards to Question B, the non-inferiority design of the Sponsor's proposal would be inappropriate for this type of study.

With regards to the patient population to be looked at, either those with herniated nucleus pulposus and radiculopathy or perhaps focusing on a subset of patients with severe back pain and radiculopathy.

With regards to Question D, the Panel seems to recommend not relying upon historical controls. As Dr. Evans has pointed out, standard of care continues to improve.

And with regards to Question E, somewhere between 12 months and 24 months; or I should say somewhere between 6 months and 24 months.

Does that provide you with enough guidance?

MR. MELKERSON: I believe so, and I actually deferred to our OSB friends, and she's nodding yes.

DR. MABREY: Thank you. Okay. At this point, we'll now proceed with the second open public hearing of this meeting. One person has requested to

speak this afternoon, Dr. Patrick Fransen. If you're in the room, please come to the podium. Please state your name, your affiliation, indicate any financial interest, if any, in the device being discussed today or any other device.

DR. FRANSEN: Good afternoon. I'm Dr. Patrick Fransen. I am a neurosurgeon at the Clinique du Parc Léopold in Brussels, Belgium. I'm a member of the Belgian Society of Neurosurgery. I'm a board member, a member of the Societe de Neurochirurgie de Francaise, de Societe Francophone de Neurochirurgie du Rachis, and of the American Association of Neurological Surgeons. Currently, I'm the president of the Belgian Neurosurgical Spine Society and the vice president of the -- Commission in Neurosurgery at the Belgian Ministry of Health.

I am here today because I would like to express some support for the U.S. FDA approval of Oxiplex gel as a surgical adjuvant for spine surgery. By way of disclosure, I have no financial interests in this product or the Sponsor company. Other than paying for my travel here today, I have received no compensation from the company nor for my study nor for this product.

Oxiplex has a good safety record in

widespread clinical use outside the United States. As an example of the positive results that surgeons have with Oxiplex, I wish to report on a retrospective study of 396 patients that I treated with this product between January 2003 and December 2006.

The study was recently published in the annals of surgical innovation and research in 2008. It was also presented at the -- annual meeting in Washington D.C. last year.

Epidural fibrosis and inflammation can cause compression, pain, and discomfort. A product that can safely protect against excessive fibrosis and nerve irritation without interfering with normal healing could therefore increase the success rate of spinal surgery and decrease the need for re-operations. Given the burden of the clinical problem and unfavorable experience with other types of agents, we decided to evaluate the safety of Oxiplex in the large population of patients undergoing spinal microdiscectomy for disc herniation.

The subjects underwent spinal surgery for one-level disc herniation. They had radicular pain resistant to conservative treatment and associated or not with motor or sensory loss. Some patients had

single-level spinal stenosis, neurogenic claudication, radicular pain resistant to conservative treatment. Their surgeries consisted of decompression followed by covering the nerve root with Oxiplex gel.

The patients' charts were reviewed six weeks after surgery. There were no measurable side effects during surgery, at the time of the application of the gel. The mean length of stay after surgery was five days, which is Belgium's normal country standard. The mean length of stay after surgery -- one patient -- sorry -- required re-operation after 13 days for infection, but we encountered no other abnormalities on wound healing among the 396 patients.

There were a total of five re-operations for recurrent herniation, two patients after less than one week, one patient after one month, and two patients within the first year. Although there was no scar tissue observed in the two patients with early re-operation, as expected, it was remarkable that there was a significant, clinically significant reduction in adhesions of fibrosis in patients re-operated at one month and within the first year. Specifically, in one patient having re-operation at

one year, the surgeon could easily see clear limits of the L5 nerve root, which facilitate dissection and separation of the nerve root from the surrounding tissue.

There appears to be no risks related to the use of Oxiplex gel. Oxiplex is a safe choice to achieve improved outcome in lumbar disc surgery and does not present any noticeable side effect in the way we use it.

We are currently using Oxiplex on a routine basis for all microdiscectomy procedures.

In conclusion, we have found that the use of Oxiplex has resulted in increased success rate of surgery, decreased need for re-operations, and it has facilitated re-operations by less adhesions and less scar tissue.

Thank you for allowing me to address this advisory Panel today. I hope that my experience with Oxiplex will support your decision to recommend that this product would be made available to American surgeons and spine patients. Thank you.

DR. MABREY: Thank you very much for your comments. Does anyone else have a statement to make to the Panel?

(No response.)

DR. MABREY: If not, it's 3:55, and in an effort to keep things moving along, I'd like to take just a 5-minute break and have everyone back here at 4:00. Bathrooms are down the hall that way.

(Off the record at 3:55 p.m.)

(On the record at 4:00 p.m.)

DR. MABREY: If we could close the outer doors? Is there any further comment or clarification from FDA? Ms. Jose? Mr. Melkerson?

MR. MELKERSON: FDA has no further comments.

DR. MABREY: Thank you. Is there any further comment or clarification from the Sponsor? And I would ask you to restrict your comments to about 15 minutes or less.

MR. KRELLE: Yes, there will be. Thank you. I'd like to ask Dr. diZerega to close. Thank you.

DR. DiZEREGA: Thank you, Dr. Mabrey and distinguished Panelists. We have very much enjoyed your comments and deliberations this afternoon and appreciate your consideration of our PMA for approval.

We would like to make some summation, staying within the time frame, and the summation will

bring some information we think is useful, given the conversations that you've had in reviewing the questions of the FDA, and some perspectives that we think are important from the standpoint of view of reasonable assurance of safety and efficacy.

If I could have the first slide, please? We certainly believe Oxiplex should be approved. We believe this PMA should be approved for many of the reasons that all of you have individually said at different times throughout the day.

The issue of safety has been discussed in a number of ways. I'll have a couple comments to say about that, but I'll draw your attention to a different aspect of safety that may have gotten lost through some of the deliberations.

We'll also talk about effectiveness. Some of the comments were made earlier today about the size of the subgroup, and, obviously, it's a subgroup that we're principally focusing on. Safety, of course, includes all patients, but from an efficacy point of view, clearly, we're focusing on this important subgroup, and I'd like to stress the size of the subgroup between 54 percent and 61 percent. And I'll clarify that for you as we go through the data.

But this is not a small subgroup. We're not talking about 10 or 15 percent of the study population. We're talking about the majority, and up to, in some instances, two-thirds of the study population. And we apologize if we didn't make that clear in our previous presentation. And as has been discussed by everyone, this is an unmet need. It's an important unmet need that we'd like to provide to our patients. Next slide, please.

Now, before I go into that part of my presentation, there was a lot of discussion about the Sponsor's presentation and the FDA's presentation, and, as we can all imagine, the FDA and the Sponsor have had a lot of discussions about this. But one thing I'm certain that we can all agree on, that is, the FDA and the Sponsor, that the preparation of the statistical analysis plan was performed prior to unblinding and was not post-hoc. The statistical analysis plan, which drove the analysis was performed prior to unblinding and was not post-hoc.

The second point is that the primary and secondary endpoints in this study never changed, and I think since 2002, they simply haven't changed. We agree with you. These are important endpoints.

Now, we talked about the LSOQ and other

ways of measuring pain, global scores, the issues of composite endpoints. Why did we choose the LSOQ? We chose the LSOQ because it had sensitivity to identify differences in a very heterogeneous population of patients, measuring an endpoint that had a high background, that is, pain. We believe very strongly that the important, the most important part of the pain measurement is the patient's perception of pain. And as was said, using the terms that are the patient's terms, we are trying to translate into numbers that can undergo rigorous analysis what is the patient's perception of pain. And that is at the end of all of this what we're trying to do.

So the clinical threshold of efficacy, whatever that might be numerically, the clinical threshold of efficacy is the patient's perception of pain or the change in the patient's perception of pain, to say that he or she is more satisfied, that he/she is better.

Now, the FDA showed you a number of 6 points, and there was discussion about whether that number was clinically significant. And I would just like to bring to your attention that that 6-point change did not occur out of 100 points. That 6-point change was a reduction of 21 points in the control

patient. This is the 21 points that were left over from the surgery that is typically very successful. All we had to work with in terms of showing an additional benefit to the patients was the 21 points. And when you look at it from the standpoint of view of additional reduction of pain to the patient, you get a very different percentage, and that's 29 percent. I think 29 percent, in my view, it would certainly cross a patient's threshold when he or she is talking about her pain or his pain is less. Next slide, please?

And to just finish up with this, just so the record is clear, that the FDA-approved statistical analysis plan did pre-specify all interactions. This wasn't something that came up later. They were all pre-specified. Secondly, the FDA required that all clinically relevant covariates be included in the multivariate analysis. In some of our correspondence with the FDA, we picked the ones that were obvious, and the FDA suggested that actually we expand that to all clinically relevant, and the quotations are there obviously to support that purpose.

The manner of screening was also pre-specified. This is not post-hoc. The manner of

screening was not pre-specified. The screening of items was performed all at once. The screening of terms was performed all at once. Once again, it may be artful, but it was intended to reduce any kind of bias as we move forward. The method of model selection was also pre-specified. This term pre-specified we believe is very important in considering the utility of this data and the validity of our conclusions. The Sponsor did the analysis exactly as agreed to with the FDA. Next slide, please?

Well, what did we find in the analysis that we would like for you to consider before we move to the next portion of this meeting? Oxiplex is safe. Oxiplex is very safe. Over 100,000 procedures since 2002, plenty of time to pick up problems with DePuy and Medtronic, as well as FzioMed, evaluating responses from a safety perspective. And through all those years, there were no AEs attributable to the device. There were reports. There were compliance issues in one thing or another, but out of all those patients that have received this device, there were no AEs attributable to device, and we think that is a very important point, in terms of real-world going forward.

Now, there's been a discussion about

safety, and some of you thought this might not be as safe as you would like it to be. Well, this is an aspect of safety that kind of gets buried when you do these balance tables and you have lots of numbers. Where there were differences that were important between Oxiplex and control with the safety screens, look at how those differences turned out.

We talked about reduced operation rates, a 0.6 percent versus a 3.4 percent, fewer in Oxiplex; reduced incidence of neurological symptoms, pain and hypoesthesias, fewer in Oxiplex; reduced incidence of musculoskeletal anomalies, fewer in Oxiplex. Patient satisfaction, disability days, I'll talk more about in just a moment. And then, of course, CSF leaks. But this is in all patients. This is a true ITT population. Everybody was followed, and where there were differences in these types of clinical measures, they all favored Oxiplex. Next slide, please?

Just a couple data slides that we haven't spent much time on, and this began to talk about getting away a little bit from the subgroup that we've been spending most of the day talking about. This is the entire CC population. This is irrespective of baseline back pain. This is disability days. How much more disability did these

patients experience; obviously, an important endpoint for lots of reasons. It wasn't the primary, but it's an important one.

And I just want to draw your attention to the fact that, in fact, there was a true disability, difference in disability days, over two days, in favor of the Oxiplex patients. That's a 27 percent reduction in disability. And that number is statistically significant. It's 0.0497. This is a real contribution, we believe, to healthcare on a going forward basis that is independent of any subgroup analysis. Next slide, please?

Now, we haven't talked much about the patient's perspective of how all this turned out, and we believe that patient satisfaction is, in fact, the most important clinical measure of outcome. Indeed, if you go through the literature, you will find that one thing that all the authors that generate scores and tests and schemes and reports, they come down at the end of the day to patient satisfaction. Are you satisfied with your treatment?

Well, we measured patient satisfaction. In the LSOQ, it is, in fact, the clinical measure of effectiveness. Patient satisfaction is the LSOQ clinical measure of effectiveness. And as you can

see, there was greater satisfaction in the patients that received Oxiplex compared to the control patients. And this measure of satisfaction we think is extremely important and addresses very much what I meant about the patient's perception of pain. The patient's threshold in pain is the way they think about what it is we're trying to do today. Next slide, please?

Now, I want to go back to the whole issue of general effectiveness. And we focused a lot on the primary endpoint, the primary endpoint, and I think we all understand the limitations of the primary endpoint in the study. But I think from an overall point of view, if you look at all seven measures of the LSOQ, all seven measures of the LSOQ, you'll find that they're all to the right of baseline. And, as we've said before, that's a very important observation. This is not a random event.

I don't know enough about statistics to talk about trying to reduce potential interpretation of error in confidence intervals. The way we did this mathematically is we did the O'Brien analysis, and what the O'Brien analysis does is it asks the question that you've been grappling with: are the positive results of Oxiplex a freak occurrence? Are

they simply a chance of throwing the dice? The O'Brien analysis says they're not. It clearly says they're not. For all seven of these things to be positive, obviously, is not a chance event. Next slide, please?

Now, let's take that subgroup again that we think the most important observations of efficacy really rely, and that is the patients with severe back pain. And what happens to this type of analysis in patients with severe back pain? Next, please, and next?

As you can see by these circles, there are now a number of endpoints, which, in fact, have reached statistical significance. This is not a chance occurrence. This is a very important observation. It isn't a matter of one thing or the other. It's the entire population showing the benefit, five endpoints of which are now statistically significant. Next slide, please?

What about the issue of the P-values that you spent so much time talking about and considering? Well, the P-values are what they are. They're expression of the statistical analysis, and I think you've done a good job characterizing that. What I'd just like to draw your attention to is the size of