high of almost 40 percent. So the 22 percent where we were, were -- it was right there in the middle of it. But the average, I guess, for the studies that they looked at were 12. But, again, I can't remember which studies we looked at.

MAJ KADRMAS: Okay. And my final question -- I apologize for all these questions -- is similar to Dr. Endres' study for a lateral meniscectomy. You say the periphery of the meniscus is being used to support those compressive and hoop stresses in the medial meniscus, so it's simply the tensile stresses that are being seen, similar to the shoulder and the Restore patch. If you extrapolate that to the lateral meniscus going back to the red/white zone or red/red zone at the popliteal hiatus and they will be experiencing those hoop stresses there. Do you have any comment on its function in the lateral meniscus as opposed to the medial meniscus?

MR. DICHIARA: Yes, I'll let Dr. DeHaven --

DR. DeHAVEN: Well, that's an important question, and it's a bit of a tossup right now because in Europe, where they are using it, they're using it in both cases that have a bridge, a popliteal bridge, and in cases that do not have a popliteal bridge. So I personally would be reluctant

to put one in if there was no popliteal bridge there to connect the anterior and posterior parts of the lateral meniscus. But some have been done. We'll see whether there is any difference in the outcomes as time goes on. But the experience is fairly early. Bill, when did they start that with the lateral side? About a year and a half ago? So it's still early. But that point is still in play.

MAJ KADRMAS: Thank you very much.

MR. DICHIARA: Just to let you know, we're collecting data in Europe on those lateral cases. And, you know, the preliminary data that we've looked at was to look at safety of using it in the lateral meniscus, one of the concerns, of course, being -- the major concern being the popliteal hiatus. And, you know, this safety data that we saw as far as failure rates on the lateral side, and we only have a year and half follow-up in that, were comparable to what we saw on the medial side. Adverse events were very similar also. But we don't have any long-term data on that.

MAJ KADRMAS: Thank you.

DR. MABREY: Dr. Shawen? Any other question?

(No response.)

DR. MABREY: Dr. Kelly, you had another question?

DR. KELLY: Yeah, I just want to say that I was very much impressed by the lack of inflammation. And I guess I'm going to back to original question which I -- I guess I'm not quite satisfied. There's been some reports, at least with the shoulder, of, like, the Restore patch evoking exuberant inflammation. Is there something about the -- and, actually, Dr. Arnoski's (ph.) lab I think has shown that the more foreign the tissue, the more processed the tissue, it may be the processing itself which may be the devil that may evoke inflammation. So there must be some sort of proprietary preparation of this substance to, I think, explain the lack of inflammation. Am I correct in assuming that?

MR. DICHIARA: Yes. The processing of the product certainly is -- has a major effect on that. As Dr. Badylak talked about, you know, the processing of these different materials is different. Ours is different than any of the others just as they are different. The immunology study that we did was for just that reason because you have to remember that this study was designed in 1995. And at that time, you had collagen, soluble collagen, and you had

reactions to the soluble collagen, so there was concern about immune response. That's why we did the blood testing and did the humoral response to the actual material itself.

That was done outside at the University of Arizona. It was a blinded study where they were sent the serum samples directly from the investigational sites. They analyzed the samples blindly and saw no difference in humoral immune response. And I think Dr. Vigorita can talk about the actual cellular response that he saw in the histology to the material compared to say other materials that he looks at.

DR. KELLY: I guess what I'm asking in a roundabout way, doctors, is that would our patients be better served with more of an allogeneic substrate or is there something that you say would outweigh those disadvantages, because, clearly, the shoulder literature is showing more of an exuberant inflammatory response for some of the more bovine or equine products.

DR. VIGORITA: Well, you're asking a very important question, which depends on a host of processing issues and a host of possibilities of carrier molecules along the way. And it's my understanding -- I wasn't involved in the manufacture

of this material, but as John alluded, that they took into question a lot of the previous history on even formalin causing a reaction in tissue.

But I can tell you based on what I was seeing -- and by the way, the material that I presented to you was presented by the histologists not in conjunction with ReGen Biologics but as our own interested study at the academy, where I went into much more detail on some of the occasional cellular responses that were seen. They were rarely observed, and I think they can clearly be broken down into two categories.

One, which I think nicely fits Dr. Badylak's discussion of mononuclear cell microenvironment remodeling, which would appear to be a helpful response, and then that rare occurrence, which I showed in my last slide of something reacting to the graft. But that was a very rare -- that could even be an infectious agent or an infection in the actual procedure.

So, again, I think manufacturing would be the clue to really understanding the lack of a lot of carrier molecules and processing steps that we learn from history to avoid.

DR. BADYLAK: I'll be brief, and I've got

two responses to it. One is that with all of these surgical meshes and all of the applications and surgical meshes that are used for hernia repairs as well have been criticized for having seroma formations and other things that could be equated to the types of responses that are seen in the shoulder to some of the surgical meshes that are there. But the issue is nobody understands whether that -- those reactions are a result of an immune response or part of the inflammatory system or part of the remodeling response, and that's work yet to be done. But that's questions that we are not going to answer here.

I think the second part of the question, though, is basically -- it's related but unrelated. And that is the consideration before you is does the collagen scaffold that we're talking about today cause -- is it as safe or better than the surgical meshes that have already been, you know, out there as predicate devices. And I think that's the way this needs to be considered. So I think from the information that you've seen both in the pre-clinical studies and the clinical studies, there's not a hint of those types of responses that you're speaking about, other devices that are already out here. So if you had to go to the equivalent or better, my

response would be that you're seeing a better outcome than you are to the predicate devices. So the immunology question we could sit here and debate all day and bore everybody in the audience with it, but it is an interesting and important question.

DR. MABREY: We can go to Dr. Endres and then Dr. Shawen.

DR. MONTGOMERY: I just wanted to reinforce that the -- obviously, every clinician that was involved in the IDE study was concerned about any type of immunological response. With the Restore patch, it was cleared with five patients with a three-month follow-up, and then the literature started coming out. And those were very small series. So we have one with a 20 percent reoperation rate, another with a 26 percent reoperation rate, and another with a 16 percent explant, meaning they had the severe reaction and they were pulled out.

We had 160-some odd patients. We had, you know, almost no response at all immunologically both looking at their blood tests and looking at the biopsies, which we did not have on any other mesh. And, clinically, the patients have done well. So we were concerned. We were worried. But it didn't seem to happen, and kind of the proof is in the pudding.

It doesn't seem like there is any ill effects from it.

DR. MABREY: Dr. Endres, go ahead and --

DR. ENDRES: I think you've shown histologically and clinically that this device promotes new tissue growth, but I think you would also agree that the new tissue does not function biomechanically like a normal meniscus. So I'm wondering -- your conclusion is that the patients at least in the chronic group were able to regain more of their activity level, so I'm wondering why you think that is. And do you think that this new tissue alters the low-transmission between the femur and the tibia, and, if so, how, if it's not -- if you're not restoring the circumferential fibers and restoring the ability to dissipate hoop stresses with compression?

MR. DICHIARA: I'll let the surgeons --

DR. DeHAVEN: Well, I think the answer to the question is that the extra tissue makes a difference, and how much of a biomechanical difference, we don't have any way to quantitate that. But, you know, an interesting individual patient of mine might at least reflect what happens.

This was a 43, 44-year-old Master's

competitive runner, distance runner, who had had a well-down partial medial meniscectomy in the community, and he came to see me. And, you know, it reflects the importance of the Tegner discussion we had because for ADL, activities of daily living, he had no symptoms, no problems, but if he tried to run, he couldn't go 200 yards without getting severe pain. So he entered the study, was an implant, had 70 percent regeneration at second look, and functionally by nine months, he was running 25 miles a day without any problems. And by a year he was up to 30 miles a day and a successful competitive runner again.

Two years later, he tore the medial meniscus in his other knee. He met the criteria, and he entered the study for the other knee. This time he is control. To this day, he has not been able to return to running because of pain in the opposite knee. I mean, that's one patient, but -- and you can't, you know, make a summer out of that, but at least as his own control, it's pretty interesting.

And if we were only looking at Lysholm data, his original partial meniscectomy would have been considered a great success because he was not having symptoms because he was limiting himself to activities of daily living.

But, you know, these are my thoughts about how to answer your question. It's an important question, and we're --

DR. ENDRES: I guess I'm --

DR. DeHAVEN: -- anticipating that there's a likelihood, say, at ten years, of showing radiographic evidence of biomechanical function at least.

DR. ENDRES: Um-hum.

DR. MABREY: Dr. Shawen, I want to get to your question, and then we're going to go to break.

DR. ENDRES: Can I --

DR. MABREY: I'm going to go to Dr. Shawen. Thanks.

LTC SHAWEN: This is a yes/no question. During the development of the product, was the sample ever implanted just in soft tissue to see the inflammatory response rather than intra-articular?

MR. DICHIARA: Yes, it was. Bill Radtke (ph.) --

LTC SHAWEN: Okay.

MR. DICHIARA: Do you want to comment on it?

LTC SHAWEN: And if yes, then what was the response?

MR. RADTKE: I'm Bill Radtke. I'm affiliated with the company and do have an interest in the company and the device. I've been one of the original developers of it. Early on, very early on, we implanted some of this material just subcutaneously for this very reason. What we saw was it was initially encapsulated with a fibrous type of tissue when we looked at it at three weeks. As we followed it out at six weeks, three months, and six months, by the end of six months, it was completely resorbed, and we found nothing except the permanent suture that we had left there for it. So we didn't see -- when we looked at it histologically, we did see early on some inflammatory cells and a few giant cells, but after that it was just a very benign fibrous response.

DR. MABREY: Any other questions from the Panel?

(No response.)

DR. MABREY: Then what I'd like to do is call a break at this point. It's almost 10:40. If we could be back here at ten minutes before 11, that would be very helpful, ten minutes before 11. If you have any personal items and want to use them, please take them with you. And Panel members, remember,

there should be no discussion --

(Off the record at 10:36 a.m.)

(On the record at 10:55 a.m.)

DR. MABREY: 10:55. I'm calling the meeting back to order. The FDA will now give their presentation on this issue. Dr. Kessler, one hour.

DR. KESSLER: Thank you. My name is Larry Kessler. I'm the Director of the Office of Science and Engineering Laboratories in the Center for Device and Radiological Health. I'd like to thank the Panel for the deliberations and coming here. I'd also like to thank the Sponsor especially for the impressive team of people they brought to have this important dialogue with us and with you as the Panel.

Some of the material I will present is very similar to things you've seen from the Sponsor. There are some subtle differences. We'll try and point those out.

The ReGen Collagen Scaffold is indicated for use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists. This, in particular, is the statement that we reviewed in 510(k) K082079. Okay. So it's important to note

this was for the chronic soft tissue injuries. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the collagen scaffold must extend at least into the red/white zone of the meniscus to provide sufficient vascularization. So that is very specifically the indication which we reviewed.

From the executive summary of ReGen, we note the modification by the Sponsor, and it's not included in the pending 510(k) although we have looked at it previously. So the difference here is that it includes both chronic and acute. It does not distinguish just the chronic patients, and that's the difference.

As I understand it, the Panel -- I understand the Panel process, the FDA is allowed to receive the input on this. It's a prior indication, so we do look for you to help us with that. However, I want to make it very clear that that's not the indication that we reviewed, and so most of my presentation will focus where we can, on the chronic patients. There are certain data we took from the company's submission of the 510(k) as well as from

the literature that combined chronic and acute. They were not separated. I'll try and indicate those when I get to them.

Now, as the Sponsor mentioned, the excerpt from the *JBJS* article, the implant ReGen Collagen Scaffold was not found to have any benefit for patients with an acute injury. And the Sponsor has said that this is taken out of context. Well, in the context of 510(k) review and assessing effectiveness of this device relative to other surgical meshes, the FDA must consider evidence of effectiveness derived from clinical trials including the comparison of this device to the surgical control as originally identified in the IDE protocol approved by the FDA and conducted by the company.

There we go. Why have the Panel meeting. First of all, the ReGen Collagen Scaffold has in our interpretation a new indication for use. To establish substantial equivalence, FDA must consider effects of the new indication and what it might have on safety and effectiveness for legally marketed predicate devices. We consider why this new indication does not affect safety and effectiveness of the device when used as intended by the manufacturer -- predicate devices labeling. And this

is going to be critical later. I'm going to point out that we review certain indications of the manufacturer, who do not regulate the practice of medicine, and so how devices are used as indicated, as we review them, as what we expect to happen in clinical practice. FDA must determine if data reasonably suggests the new device is substantially equivalent devices, when the predicates are used, again, in accordance with their labeled indications. This will become a pivotal point when we later talk about the way we interpret the Restore DePuy as a surgical mesh and as a predicate or not.

We must rely on valid scientific evidence from which it can be fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of the device under its conditions of use. And there are specific questions FDA has for the Panel. They're in Tab A, and they'll be presented later by the Executive Secretary, Mr. Jean -- Dr. Jean. I'll talk about the device. I'll talk about the pre-clinical information, the clinical data, substantial equivalence to a predicate device, which is certainly what this meeting is about, talk about some predicate device information, and then later you'll have the

Panel questions.

As you've heard the ReGen Collagen Scaffold device is a resorbable matrix composed of Type 1 collagen. It is semi-lunar in shape with a triangular cross-section for use in a meniscus. The surgeon trims the device to size necessary repair of damaged or weakened soft tissue. It is sutured in place through a minimally invasive arthroscopic procedure. And we note the shape of the device is unlike the predicate surgical meshes. It is well-designed for this meniscal application.

As pointed out by the company, we asked them to do a number of pre-clinical tests, the tensile strength, biocompatibility, viral inactivation, sterilization, packaging and shelf life, done by the company. We have no disagreements. We agree all the information you have in your packet should be adequate. If you have further questions, we'll be sure to address them.

What we'd like to do is focus on the bench testing, the suture pull-out strength, the animal testing, the canine model, and talk very briefly about the biomechanics of the meniscus compared to forces in the shoulder. You've already heard a detailed presentation from the Sponsor about this,

and what we're going to do is talk about the biomechanics of the meniscus compared to the shoulder with respect to the indications for which we cleared the DePuy-Restore surgical mesh. So that's where this is going to come in later.

At the bench, the suture retention of strength of the ReGen CS is similar to predicate meshes. We note those predicate meshes are not cleared for meniscal repair. So they are comparing to the predicates and they are similar, but we note those are not for meniscal repair. Why is that important? We asked the company to do a suture pull-out study from canine native meniscus, and as you'll see, from these data that we got from the company, the suture pull-out strength needed for the canine native meniscus is three to six times higher than that from the ReGen Collagen Scaffold in the canine model anywhere from 0 to 24 weeks. So all along, suture pull-out was substantially less than was necessary in the canine meniscus. In the environment that this new indication is indicated for, that's a concern.

Clinical data. So the feasibility study has been presented. You've seen that and you've seen some data from Europe. Now, in fact, in the

submission in the 510(k), there were limited published results from Europe. We've seen much more extensive data that we had not seen in the 510(k) submission. That's what we were looking at. FDA's clinical data presentation will focus on the approved IDE protocol and the IDE data presented in the 510(k) as well as the article that's been discussed several times, the Radtke, et al. article that was in *JBJS*.

We note, again, that in the context of 510(k) review, we have to look for effectiveness or benefit, clinical benefit, and we're looking for that here in the study that we approved, and we think this is valid and reasonable even in the context of 510(k) review.

So we'll give an overview of this study. It was a well-designed, randomized control, clinical trial of the ReGen Collagen Scaffold. It's a multi-center clinical trial. It was approved in 1996. Enrollment completed April 2003, and, as you know, follow-up has continued. Sample size, 144 patients, 72 per group with a minimum of 64 evaluable necessary to power the study adequately for the effectiveness endpoints. I'm going to talk about those in a little bit.

The IDE study compared the clinical

outcomes of the partial meniscectomy group, that's the control group, to the partial meniscectomy followed by the ReGen Collagen Scaffold treatment group.

There were two -- the firm says two study arms. There's in fact two different protocols. There is an acute protocol with no previous meniscus treatment and the chronic group, with a meniscal injury (1 to 3 previous meniscus treatments). The only difference between the arms is the number of prior surgeries. In the 510(k) we reviewed, and I'll be discussing largely here, they requested clearance for only the chronic patient group. We've already pointed out that's a little bit different than what you've heard today, but as we've already pointed out, the acute group, the study that we looked at in *JBJS*, showed no difference.

Protocol study endpoints. Safety, assessment of serum markers and adverse events. We'll review those in detail. The clinical endpoints for effectiveness, pre-defined success, either two out of three, VAS pain score, Lysholm pain and function knee score, and patient self-assessment. I'd like to note that the effectiveness, in contrast to what the Sponsor said was powered for an

improvement in the treatment group not just to stay the same as the very successful partial meniscectomy group that Dr. DeHaven mentioned.

Surrogate endpoints. CS status assessment, arthroscopy, histopathology, and radiographs, and we'll talk about some of those data as well.

In addition, there were additional endpoints that were in the protocol. There were 14 of them, including what you'll see bolded in here, the Tegner Activity Level. This is not the Tegner Index. We'll talk about that later. But something called Tegner Activity Level was indeed one of the 14 additional endpoints, and each of those endpoints have a pre-defined success/failure criteria in the IDE protocol.

So three steps to the ReGen surgical technique. First, there's the assessment of the meniscal defect. And we note that the meniscal defect criteria includes irreparable injury. This is the same for the partial meniscectomy control group. So it is the same patient population that we use in partial meniscectomy. It's for traumatic or degenerative origin, both attachment sites for the anterior and posterior horns are intact, as you've heard already. The site preparation must result in a

full thickness defect, and a defect site must extend into the red/red/ zone or the red/white zone, and exclude unstable segmental defects in which the meniscal rim is not intact. And I think this is consistent with what you heard from the Sponsor. Then a partial meniscectomy is conducted, and, finally, there's the preparation of the defect site and the implantation of the ReGen Collagen Scaffold.

The rehabilitations protocol, as you expect, would be different between the collagen scaffold and the control group. In the collagen scaffold, you've got non-weight-bearing with passive motion of one week, followed by five weeks of partial weight-bearing with passive motion, and a slow progression for full activities by six months. In a successful partial meniscectomy, generally, you get returned to full activities in two to three weeks.

So the patient enrollment. In the chronic arm, 85 subjects have partial meniscectomy and 69 subjects had only partial meniscectomy. The complete accounting of the patient enrollment was provided in the FDA executive summary, and you can also find it in the *JBJS* article.

Primary endpoints were evaluated at the 12 or 24-month endpoint. We note that at the three to

seven-year annual follow-up of time points, there's approximately 50 percent of the data available and 50 percent missing, and it is not clear in our evaluation of the 510(k) how missing data at time points later than 24 months affects the presentation of safety and effectiveness endpoints. So while the analysis was done and did include data from past 24 months, which is a substantial amount of missing data, and it is unclear from our review of the 510(k) how the missing data were handled

I'm going to talk about clinical data now. And, again, this is comparing the ReGen Collagen Scaffold with the control group. The serum analysis, we told you it was one of the safety endpoints, no difference.

The serious adverse events, there are several things to note. First, we'll look at serious adverse events, and there are two lines in each of these four rows. Total events divided by total patients. So you can get multiple events per patient, and that's expressed more or less as a rate. Patients with events divided by total patients, so here in this case, multiple events per patient, the patient is only counted once, so that would be expressed properly as a percentage.

So, for example, here, in serious adverse events, there were 21 in the ReGen Collagen Scaffold patients who had one or more events divided by 87. That's a rate, a percentage of 24 percent and a 20 percent in the controls. Total events divided by total patients, 0.43 divided by 0.33.

As you would expect the serious device-related adverse events and non-serious device-related adverse events largely collect in the ReGen group. These are data from the firm. We're not exactly sure how you get device-related adverse events. We just want to point out that there are non-trivial numbers of both serious device-related and non-serious device-related events.

In the context of evaluating a 510(k) for this indication, we're particularly interested in are there any safety concerns. So are there serious device-related events that would generally not exist in this control group. And the answer is yes. You'll see 14 out of 87 total events and 8 patients out of 87, or 9 percent. And then non-serious, higher, .59 is total events for total patients. A third of patients with the ReGen Collagen Scaffold experienced at least one non-serious device-related events.

If you look at all adverse events, you do see this very slight difference in favor of ReGen Collagen Scaffold. Here 295 total events per total patients, 3.39 versus 3.48 in the control. But in terms of patients per events, 85 percent of the ReGen Collagen Scaffold had some event versus 78 in the controls.

What kind of adverse events are we talking about? So here, these are data derived from the Sponsor's submission by the FDA. And so let's take a look at the serious adverse events, and you'll see surgery operative index in the knee, tear medial meniscus, intra-articular swelling and effusion, four here versus two in the control. Down here, you get five pain experienced versus control, et cetera. So totals here are a little higher than in the control.

Serious device-related adverse events and non-serious device-related adverse events, you do see a couple here that we got from the firm. We want you to focus on the column about the serious device-related adverse events and the non-serious events. In the chronic study arm, these are the kinds of events we saw, saphenous nerve injuries, squeaking and creaking, stiffness, numbness of the lower extremity, patella-femoral complaints, locking or

catching, torn implants, plica, lateral meniscus tear, implant fraying, popping and clicking of the knee. Those are the additional non-serious device-related events.

And then there were some non-serious adverse events in general that did not appear to be device-related, including knee range of motion, worsening osteoarthritis of the operative knee, and a tear at implant meniscus interface.

Another issue of safety for us is explants. There were six ReGen Collagen Scaffold explants during the study, in five patients, one due to infection and five due to mechanical failure, and this is from our executive summary.

Now, I'm going to turn to the effectiveness results, and I'm going to draw these data from the *JBJS* article. And as you've already heard, there are no differences between the ReGen Collagen Scaffold and the control group in the three measures pre-defined in the agreed upon IDE protocol in 1996. Pain score, no difference, Lysholm score, no difference, and patient self-assessment, no difference. So there's no difference in effectiveness in any of the three pre-defined endpoints of the original IDE study. And I'll

repeat, in the context of looking at the 510(k) even comparing to predicates, when you're looking at this kind of indication, all evidence even from this randomized trial is appropriate.

At the one-year relook, there were surrogate endpoints. There is the Outerbridge score, which is the evaluation of articular cartilage surface. And you'll see that in the collagen scaffold, pre-op was 1.5, went to 1.3, and there's 1.7 in the control group, and as you've heard from the Sponsor, no one-year relook was performed. The evaluation of the ReGen Collagen Scaffold attachment to meniscal rim, firmly attached, 84 percent, and not firmly attached, 16 percent. And change in knee compartment for the ReGen CS subjects -- and here, notice in both of these, acute and chronic arms are combined. We did not have them separately from the company. Improved, 23 percent, unchanged, 59, worsened, 18 percent. So, again, in effectiveness, some of the things we're looking at here, and we see a worsening in the change of knee compartment for 18 percent, or 25 of 141. The reason you see 141 is because we're talking about both the acute and chronic arms. We did not have those data separate.

Surrogate endpoints. Cellular in-growth.

Here, we're talking again about the acute and chronic arms marked with cells resembling fibrochondrocytes, 45 percent, marked 20 percent slight and none. Extracellular matrix organization, here, you see the proportions of fibrocartilaginous tissue, sections of continuous chondroid matrix, random organization, or no matrix organization. And I'll note here and maybe again later that we saw, the FDA saw, no evidence that true meniscal tissue oriented in the right way and collagen was being produced supplanting the collagen scaffold region. That's one of our concerns. The tests that were done histopathologically are not convincing to tell us that we have Type 1 or 2 collagen nor that it's oriented in the way the meniscus needs to, to perform the function necessary in that region.

Inflammatory response, acute and chronic arms, minimal to none, 94.7 percent, 0.8 mild, 0.8 moderate, severe, and 2 percent missing -- inflammatory response. Again, acute and chronic arm data are presented together.

Radiographic evaluation is here. Surrogate endpoint with a radiographic evaluation. Change from pre-op for combined acute and chronic study arms. Take a look here fairly directly at the P-values. No

difference between 12 months and 24 months between CS and control group, whether you're talking about osteophyte formation, Fairbank-Ridge, et cetera, et cetera, so all the measures and parameters evaluated, no statistical differences between collagen scaffold and the surgical controls.

Another effectiveness measure is the amount of tissue. And you'll see here collagen scaffold versus control group, percent meniscus remaining here and here. As you can imagine, percent defect filled not measured in the control group, only here in the CS group. Percent tissue surface area here, and this proportion here, this 40 percent, this mean, is drawn from here. It's assumed by the Sponsor, and it's reasonable that without intervention that there would not be more tissue surface area here. Again, I'd like to cite that the type of tissue here that's being grown, we don't have evidence from the Sponsor that we were able to evaluate to show that we're talking about Type 1 or 2 collagen.

The Sponsor places a lot of emphasis on the Tegner Index. And so we'd like to point out from the IDE protocol that, first of all, the Tegner Index was not a pre-specified endpoint. What's related is the Tegner Activity Level that was one of 14 additional

endpoints. And in the *JBJS* article, the chronic CS patients regained more lost activity level than did the controls, here. But information that's important to us to evaluate whether this Tegner Index is meaningful was the mean score at annual time points and follow-up rates. The data analyzed in the Tegner Index appears to us to have been after the two-year follow-up, and all data was used but with variable cut-off. And with an enormous amount of missing data, it's almost impossible to tell exactly what the meaning of the Tegner analysis is in this context. In addition, it was not done as a pre-specified endpoint, and since all of the primary endpoints failed, we are at a loss to understand the analysis plan for the secondary or tertiary analysis of the Tegner Index.

Some more information here on Tegner Activity Level, mean scores. Most recent report for both the CS and control chronic arm patients provided in IDE annual report. Follow-up was 70 percent at 12 and 50 percent at 24 months. No difference at 12 months and only a 0.6 point difference at 24 months. And, again, some questionable analysis technique to figure out what this will mean after 24 months. These data are provided in the IDE annual report,

2003.

The clinical significance of the Tegner Index has not been reported in the literature as we understand it. And, again, we and the firm can argue about this. That is, we think it's designed to complement other functional scores, for example, the Lysholm knee score for patients with ligamentous injuries. Lysholm was one of the primary endpoints, was not found statistically significant in the original design. If the firm had wanted to have Tegner Index as a primary endpoint and had specified it, we may be having a different analysis plan, but we don't. We have the plan that was given at the time of the protocol.

Reoperations is an issue that you can find in the *JBJS* article. And so you'll see eight reoperations in the control group and 15 reoperations -- I'm sorry -- in the CS group -- I apologize -- and 15 in the control group. However, the *JBJS* article did not include five reoperations in the control group and 17 reoperations in the CS device patients. The reasons provided for removing those reoperations, reoperation on the same patient, four in CS, five in the control, procedure during the one-year relook, n=10 for the collagen scaffold

group, and reoperation not related to meniscus, n=3, evaluation of saphenous nerve, excision of neuroma, and infection/device removal. And so the rationale given for these being removed is that they were incidental operations.

So we had our orthopedic surgeon, Dr. Barbara Bruch (ph.), look at it and develop our own subjective reoperation inclusion criteria. For the controls, we included anything that could be considered a failure of the meniscectomy, and if the procedure was due to trauma, excluded.

For ReGen Collagen Scaffold, we excluded if the procedure was solely due to the second-look arthroscopy. If during the second look additional procedures were performed and accompanying meniscal or medial symptoms and pain were noticed, then the patient/procedure was considered to have had an additional procedure or reoperation. So we counted those. All explants included as considered procedure or device-related, procedures to repair or revise, for example, smooth the edges or repair tears in the device, were also included. And similar to the controls, if the procedure was due to the new trauma, it was excluded.

So our analysis showed that you compare

whether it's number of procedures or number of patients between the CS and the control group, basically you get 18 or 17 procedures or patients in the CS group and 11 in the control group. So our analysis of the reoperations is not consistent with the company's analysis.

Now I'm going to turn to talking about substantial equivalence to a predicate device. And quite a bit has been made of this by the Sponsor, and I've already noted previously that in the context of looking at this indication in the knee environment, where there will be significant load-bearing, we believe that we should be looking for how this will work as indicated by the Sponsor.

So from Code of Federal Regulations, a surgical mesh is a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples of surgical mesh are metallic and polymeric mesh for hernia repair and acetabular and cement restrictor mesh used during orthopedic surgery.

As outlined in Table 1 of the FDA executive summary, current predicate surgical mesh devices are indicated for patients to reinforce soft tissue where weakness exists, including the following, rotator

cuff, hernia, anal, rectal and enterocutaneous fistulas, urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support, soft tissue of the lung. There are no legally marketed surgical mesh devices indicated for the reinforcement and repair of chronic soft tissue injuries of the meniscus. We note this is critical because you're talking the weight-bearing situation in the knee.

And we'll contrast that, as the firm has done, with DePuy Restore Surgical Mesh. This is one of the key points, although not the only point the firm is trying to make about its predicates, but we'd like to talk about this one in some detail because we and the Sponsor have a disagreement here. So this is a surgical mesh indication for use cleared by the FDA. It is for use in general surgical procedures fro reinforcement of soft tissue where weakness exists. In addition, the implant is intended for use in the specific application of reinforcement of the soft tissues which are repaired by suture or suture anchors during rotator cuff repair surgery. The Restore implant is not intended to replace normal body structure or provide the fully mechanical strength to repair the rotator cuff. Sutures to

repair the tear and suture or bone anchors to reattached the tissue to the bone provide the mechanical strength for the rotator cuff repair. The Restore implant reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue.

And so we've highlighted these issues of what it's for, repair by suture or suture anchors, and where the load is going to be born by the suture or bone anchors. This is the indication FDA cleared. That is not to say it that it is not used in other ways. This is what we cleared, and this is the indication that we reviewed for Restore.

So when you compare the surgical mesh, the rotator cuff does stabilize and support the shoulder joint. And our clearance of that device was for the use of this surgical mesh, the Restore mesh, in the rotator cuff, to create a smooth area over a suture repair. That was the intent of the clearance for the 510(k) that Restore gained.

So, here, this is pictures from the DePuy Restore surgical treatment, and we copied it with their permission to show where the overlay is and where the support is supposed to be gained by the sutures. And so this is a rotator cuff not

replacement but an overlay.

I'm sorry. I don't know why this is in there. Okay. Oh, I'm sorry. Now I know. I apologize. So we're going to contrast that with the surgical technique suggested by ReGen. Again, remember, we're talking about irreparable injury for the meniscus and how its prepared. Then there's the partial meniscectomy followed by preparation of defect site and implantation. And, clinically, if you look at this, it's going to be quite different than the way in which the technique for Restore is.

So you've got the tear. You saw the dotted outline from the Sponsor and how this mesh will be used. And we ask the Panel to inquire what will happen with the mesh in this place, with this collagen scaffold and what kind of forces it will bear, and we look for your dialogue about this.

When we're reviewing within 510(k) a review of surgical mesh with new indications, the type of data that we will ask for will depend on the new indication. For example, differences in clinical situations, the specific indication the Sponsor is requesting or specifics about the products will suggest more or less data in biocompatibility, sterility, bench or animal testing, and varying

degrees of clinical data. So a new indication with certain kinds of clinical situations that might be of concern would be a case where to establish effectiveness or safety, we might see, need to see a lot of clinical data. The Sponsor's executive summary and 510(k) include statements concerning how FDA determined substantial equivalence for legally marketed predicates, and we actually disagree with the characterization of their FDA determinations. And the firm is not privy to the information FDA reviews for all of its predicate products.

So in the case of Restore, for example, we saw from the firm their interpretation of how Restore is used or what they got from the literature. I'm showing you what we cleared and the data relevant to Restore. So there's a little difference here and may be worth discussion by the Panel.

I want to summarize now. The clinical environment for this indication is one where there are weight-bearing forces that will certainly apply to the ReGen Collagen Scaffold. While the ReGen Collagen Scaffold is designed to be replaced by meniscal tissue, we have seen no evidence that the tissue replacement for the collagen scaffold is meniscus-type. We don't know that it's Type 1 or 2

collagen, no evidence of that.

Safety issues. The treatment group of the ReGen Collagen Scaffold device has, as you would expect, some, and we think significant, device-related adverse events. The explants, the six explants you saw in five patients, suggest mechanical failures of the device are possible.

In the effectiveness side of this, the ReGen CS did not attain significance compared to the partial meniscectomy group in any primary endpoint. So we see no evidence of clinical effectiveness. And the analysis of the two -- I'd rather call them -- additional clinical endpoints, the Tegner Index is a post-op endpoint done with possibly many analyses. We do not know how many analyses were done of the 14 endpoints, and so the analysis for the FDA is questionable and in the presence of no primary endpoint further questionable. And, finally, the reoperations that the firm cites, the inclusion and exclusion criteria we believe were subjective. Our analysis of our own criteria suggest possibly a different outcome.

That's my summary. I want to thank the Panel again and the Sponsor. I'll try and take as many questions as I can. And I only note that I'm

the Director of the Office of Science and Engineering Lab, so my background is mostly statistical/mathematical.

DR. MABREY: Thank you. Could we have the lights back up, please? I'll start with Colonel Shawen. Do you have questions for the FDA?

LTC SHAWEN: Just one quick question. You had mentioned the canine pull-out, and you said necessary strength, and I don't understand how you determined what's necessary strength. Do we have -- essentially, you showed that the canine meniscus had a certain strength and that the collagen scaffold was less than that. And then you made a statement saying it did not reach the necessary strength.

DR. KESSLER: Oh, I'm sorry if I said -- that's a misstatement. We just wanted to tell you that we were looking in the pre-clinical data for suture pull-outs to look at the strength of the tissue that would be there because you're talking about a weight-bearing situation. And we're trying to figure out whether it's going to have the kind of strength necessary for the forces bearing it. And it's just very much less than the native meniscus of the canine.

LTC SHAWEN: Because what I'm trying to

understand is what is that necessary strength. I don't think that that was established.

DR. KESSLER: Good point. Fair.

LTC SHAWEN: I don't have any other questions right now.

DR. MABREY: Okay. Dr. Kadrmas?

MAJ KADRMAS: Similar to that, when you said the strength being far less, as far as pull-out strength, I think suture pull-out strengths in the meniscus probably aren't as important as they are in the rotator cuff in the Restore -- being as pull-out -- primary failure mode. Most of the rotator cuff repairs and not for meniscal repair, it's usually not -- we don't see failure as being pulled through the meniscus. So that may be something that, in my mind, is less relevant for this particular surgical mesh.

The other thing that I was a little bit interested in was the discussion of Outerbridge classification, and you said there was a concern that 18 percent of those worsened after the implant. And I think most would agree that articular cartilage and Outerbridge classification is a progressive thing. I think the more surprising fact is that 30 plus percent improved, again, this being a subjective

thing. In a chronic study arm, chronic being, you know the definition one to three surgeries, you know, the question is, is that -- pathway already gone down that pathway and is surgery going to -- or meniscal -- increase of meniscal tissue going to change that? That's probably a pretty wide debate.

But I think that the main concern for me anyway is that I don't -- I wouldn't expect with any of these studies for there to be a huge improvement or difference in the control between -- versus the implant at two years in a chronic study group. I think the more important thing for me is that we don't see a large decrease in their function or a large worsening of the function at two years. Two years in a chronic treatment group after a particular treatment is not a very long time to see any improvement. So the fact there's no difference for me isn't concerning. The fact that there isn't a big decrease in function and drastic increase in complication rate I think is important. But I don't know if you want to comment on some of the Outerbridge classifications, or anything.

DR. KESSLER: Not particularly. I just want to comment on the follow-up, two years versus longer. The firm does have longer follow-up, but --

LTC SHAWEN: True.

DR. KESSLER: -- a lot of the analysis was to cut off at two years in the original design. We've received further analysis of follow-up data, but in terms of the FDA, it's hard to tell because it's an uneven random cut off. I mean, if you're saying that longer-term data would be necessary, I think that's an important point for the Panel to consider.

DR. MABREY: Other questions? Dr. Potter?

DR. POTTER: Some of my concerns is around the subjective nature of some of the outcome. For example, the operative surgeon doing the Outerbridge classification as opposed to an independent assessment of cartilage wear. We do have the radiographs. They are at best a very indirect assessment of arthritis. The assessment of tissue regeneration, as previously stated, again was somewhat subjective. And so the numbers generated from those data are somewhat drawn into question about the reproducibility.

But to that end, did you require in any similar predicate device more objective outcome assessment than was seen today?

DR. KESSLER: Well, in the middle of that

was your question similar predicate device, and what the FDA would like to argue is that we have cleared no devices for meniscal repair. In this clinical situation -- one that concerns us because of the force we believe that would be experienced by a product in this region. So, you know, I can say at one point, no. The answer is no we haven't asked for any, but we haven't been looking at any for this specific indication. Generally, though, I think what you're more asking about is, generally, surgical meshes, are we asking for this level of reproducibility? I think I'm going to say probably not. I got a shake of the head. Probably --

DR. POTTER: Okay.

DR. MABREY: Dr. Endres?

DR. ENDRES: Just a quick question. I'm not familiar with the literature regarding the use of surgical mesh in general surgery or any of those areas, but I think I'm fairly familiar with the literature regarding the use of mesh for shoulder surgery. And, in fact, there is a paucity of literature, at least my understanding is, that shows really any benefit of currently, clinically, the use of surgical mesh in the shoulder. Would you agree to that statement or is there some literature that I'm

not aware of?

DR. KESSLER: I would not know, and I would probably turn to the guys that we have who are experts in that area. I am unaware of any. I just want to point out that the Restore product specifically was cleared for the indication we talked about, the covering, not for repair.

DR. MABREY: Okay. Dr. Kelly?

DR. KELLY: Thank you for that very, very succinct presentation. Couple questions. Could you elaborate further on the second procedures, how your dissection of that cohort show that many of them had additional pathology. But did all of them also have symptoms? I wasn't clear about that.

DR. KESSLER: I'm not sure what you're referring to. I'll --

DR. KELLY: When you broke down the second procedures that were sort of incidentally performed at one year --

DR. KESSLER: Ah, the relook? Hang on. Let's go back to that --

UNIDENTIFIED SPEAKER: For reoperation or relook?

DR. KESSLER: You talking reoperation?

DR. KELLY: At the relook --

DR. KESSLER: At the relook?

DR. KELLY: You qualified second procedures as if an intervention was done at the second look if incidental pathology was found.

DR. KESSLER: Yeah --

DR. KELLY: But I also read in the text, though, it seems that -- did all those patients also have symptoms or that's not qualified?

DR. KESSLER: That was not qualified. So here -- I think this is the slide you're talking about. So we looked at reoperations and developed our own inclusion/exclusion criteria, which, admittedly, are subjective for the ReGen group. Okay. And what we did not exclude was as follows, but I think here's where your -- is this what you're asking here, if during the second look additional procedures were performed and accompanying meniscal and medial symptoms/pain were noted then the patient/procedure was considered to have an additional procedure? Is that what you're asking?

DR. KELLY: Yes, yes. That's sort of implying that -- well, not implying. It's stating they all had symptoms. So it must have been known to the surgeon --

DR. KESSLER: Right.

DR. KELLY: -- that they had a complaint.

DR. KESSLER: Yes, exactly. If they did at the relook -- if at the relook they said, "I'm having pain," and it was recorded, we would then include that as part of the reoperations. Those may have been excluded by the firm because they were done at the relook. They might have -- the firm said we consider some of these incidental. We said, look, if we think that you've got symptoms or pain during the relook, that seems to us to be worth including as a reoperation that would count "against" either the CS or the control group.

DR. KELLY: All right. And just as a distillation of the data, am I correct in saying that if you look at the presentation by this morning's doctors that there was significance in pre and post scores from the pre and post evaluations in the control -- or the chronic and acute. But what you're really saying is that the controls versus the intervention there was no significant difference?

DR. KESSLER: Correct. But the presentations are very different in that sense. In the firm -- and those are data we evaluate in the 510(k) so it's not as if we haven't seen it. The pre to post changes in the treatment group only were

statistically significant as presented by the firm.

DR. KELLY: Right.

DR. KESSLER: The design of the IDE was to compare changes between pre-imposed treatment versus control, no difference, no difference, and I'll say it again, no difference.

DR. KELLY: And one final question. Thank you for your kind responses, but if you look at these 50 percent follow-up, was there anything in that data that would at least imply maybe some sort of selection bias?

DR. KESSLER: None that we're aware of. I will say that after the two years, when you start getting fewer and fewer data points and the analysis of that has been very hard, we just don't have enough data to tell you, but we had no indications of bias.

DR. KELLY: Thank you.

DR. MABREY: Colonel?

COL KRAGH: I have no questions at this time.

DR. MABREY: Dr. Propert?

DR. PROPERT: I'm still struggling with these sample sizes that I now see bouncing around even more than I saw before. Part of that is because I misread the consort diagram when I first saw it,

which is presented in an unusual way. But I have a specific question about one of your slides regarding sample sizes. Most of the things refer -- excuse me -- to their being 85 patients in the ReGen group. Your AE slide said 87. Can you explain where those extra two came from? It's unusual to see sample sizes go up.

DR. KESSLER: Right, I know. Pardon? Okay. These are data from the Sponsor, and we're not exactly sure. And if you wouldn't mind, can we take that offline and we can ask them about it and come back with an answer? Those data, the 85 and the 87 was the data that we got from the Sponsor, not our data, and we understood -- we saw that discrepancy, too. I was sort of hoping you wouldn't notice it.

DR. MABREY: And we'll have time this afternoon for both groups to address that issue. Ms. Dalrymple?

MS. DALRYMPLE: Okay. I have a question. The first one is that --

DR. KESSLER: Could you speak in the mike a little?

MS. DALRYMPLE: Oh, I'm sorry. How do you get six out of five or, yeah, six out of five explants? So does that mean that --

DR. KESSLER: No, five patients with six explants. One patient had two.

MS. DALRYMPLE: Okay. So when they do the original explant, they don't actually remove all of the CS ReGen?

DR. KESSLER: Oh, they had two implants in?

UNIDENTIFIED SPEAKER: They removed the first one --

DR. KESSLER: Then they implanted the second?

MS. DALRYMPLE: Oh, okay.

DR. KESSLER: Sorry.

MS. DALRYMPLE: So then the second implant also then had to --

DR. KESSLER: Was -- came out.

MS. DALRYMPLE: Is there a time frame between the first removal and the second removal?

DR. KESSLER: In that one patient?

MS. DALRYMPLE: Was it immediate or --

DR. KESSLER: No, no, no. It was certainly not immediate --

MS. DALRYMPLE: Okay.

DR. KESSLER: And I'd have to look. We'll have to look at the data specifically.

MS. DALRYMPLE: Okay. And then the other

question I guess goes back to my first question to the Sponsor panel was, again, about the rehabilitation period because here it says that in your Slide 19 or -- 19 I guess -- it says that the difference was actually two to three weeks in the control group up to one, five, six months --

DR. KESSLER: Um-hum.

MS. DALRYMPLE: -- in the ReGen group?

DR. KESSLER: That's right.

MS. DALRYMPLE: Which is that something that there should be a direction to the rehabilitation and should there be a comment whether it was different in that group versus the --

DR. KESSLER: No, this is more -- this descriptive. So let me take a step back. What are we trying to evaluate? We're trying to find out whether the ReGen Collagen Scaffold when placed in the meniscus for a repair in this region is going to be safe, is going to be effective. That's what we're trying to figure out, and it is like other surgical meshes. I mean, that's what we're talking about. So in the context of like surgical meshes, we'll do pre-clinical testing, et cetera, et cetera, but we're looking in this region where we see significant low-bearing situations. We want to see is it safe and is

it effective. So we're trying to understand what we're looking at. And in this case, we're just trying to give you a clinical description that the rehabilitation protocol for the collagen scaffold patients will be significant. There will be up to roughly six months of down time before you get back to full activities, which contrasts with the control group.

MS. DALRYMPLE: Right.

DR. KESSLER: No, there's no advantage. So we're trying to figure out what are all the potential safety issues versus all the effectiveness. So we -- quite descriptive here. And this is something that I think the surgeons will tell you for ReGen you would expect this kind of rehabilitation protocol. We're not -- this is not a criticism. This is descriptive of what's going on with the more significant surgery and needing a collagen scaffold area to repair, this is what you're going to experience. And --

MS. DALRYMPLE: Would that --

DR. KESSLER: -- evidence of no effectiveness, this may be concerning.

MS. DALRYMPLE: Would that in any way minimize the type of patient that should be available for this type of product?

DR. KESSLER: Not that I'm aware of.

MS. DALRYMPLE: Okay. Thank you.

DR. KESSLER: Thank you.

DR. MABREY: Dr. Spindell?

DR. SPINDELL: Hi, thanks. Could we have Slide 19, please?

DR. KESSLER: I can.

DR. MABREY: And could we get closer to the microphone?

DR. SPINDELL: Oh, I'm sorry, sorry --

DR. KESSLER: Not at all.

DR. SPINDELL: Sorry. So this slide we talked about. I mean, obviously, in this comparison group, there's -- this -- I mean, obviously, because device-related events, it's obviously significantly -- because in one group there is no device.

DR. KESSLER: Yes, correct.

DR. SPINDELL: Okay. So and I know you've commented on using all the information available, but my understanding is that in the evaluation of 510(k), it's substantial equivalence to a predicate device. So in the control arm, what is the predicate device?

DR. KESSLER: There is none in the -- the control arm is just the partial meniscectomy group.

So we're not comparing -- good point. We're not comparing a surgical mesh to another surgical mesh. We're trying to figure out how does this surgical mesh work in this indication?

DR. SPINDELL: Okay. I understand that. And in that vein, did you look at this data and compare it to other published literature data and other surgical meshes which are -- predicate devices for rates of adverse events with devices?

DR. KESSLER: No.

DR. SPINDELL: And was there a reason for that?

DR. KESSLER: Well, when you look at -- there is one chart from the firm about adverse events, and you take a look at adverse -- other surgical meshes, and you see that theirs is relatively low and relatively similar to other predicate meshes. There's one very tall bar from another product. That tall bar happens to be -- 90 percent to recalls not related to the device. So it's in the same range, that is, what we would expect to see from other surgical meshes globally.

DR. SPINDELL: Okay. So as far as substantial equivalence in forms of device-related events, even though I know there's not tons of data,

but the data to other surgical meshes does not seem to be unusually large?

DR. KESSLER: In other indications, not that we're aware of.

DR. SPINDELL: Okay. Great.

DR. KESSLER: But remember, we're talking about other surgical meshes not cleared for this indication.

DR. SPINDELL: I understand that.

DR. KESSLER: Okay. Good.

DR. SPINDELL: Could you go to 31?

DR. KESSLER: I can.

DR. SPINDELL: Hope I got my numbers right here.

DR. KESSLER: Yeah, and, if not, I can move around. Is this it?

DR. SPINDELL: Yeah, okay, so this is -- and this gets back to Dr. Kelly's point about the relook and the reoperation. I understand the difficulties in separating them out. I guess I'm having a hard time with the relooks at one year since the control group didn't get relooks at one year. Did we look at how many patients at one year had similar symptoms of pain to the people who got the relook and the surgery? Because my guess is a lot of

these patients, and of course, I'll leave it to my surgical colleagues, a lot of these patients in a year would have some pain, right?

So the control group doesn't necessarily get operated for the pain, depending on the level of the pain, because I don't know if we have quantitation [sic] of level of the pain. So they would not get relooked and who knows what they would find as opposed to the group that had the relook and they may happen to have pain at the time and surgeon that's in there, of course he's going to do whatever he can about the patient. So I understand your struggle with that as well, but I just wanted to bring that out that I think that's a really tough call either way.

DR. KESSLER: So, first of all, I want to agree. It is a tough call.

DR. SPINDELL: Right.

DR. KESSLER: I mean, there are certainly ways you could rationalize this. I'll tell you that it was not pre-specified in the protocol, so a little bit tricky when you're trying to do science and figure out what was and was not. These inclusion/exclusion criteria were not pre-specified. So they had to be created. Now, I'm not saying that

they're wrong or right but there are other ways of doing it.

Your point about the controls is excellent. I do not know the answer. When we take the break, I'll try and come back after lunch to find out what do we know about the controls at about one year and are we trying to compare in the reoperations apples to apples.

DR. SPINDELL: Right.

DR. KESSLER: Or in terms of the relook, did that introduce an orange in the mix?

DR. SPINDELL: Right.

DR. KESSLER: And, essentially, I think we were asked earlier about radiographic evaluation, and other things, when you're doing different things with the controls at one year, you know, then it makes some of the scientific comparisons difficult. And I'm sympathetic to you guys to try and struggle with us and to the Sponsor as well.

DR. SPINDELL: Right. Okay.

DR. KESSLER: I'll try and get you an answer as to what was going with the controls.

DR. SPINDELL: That's okay, and I just -- again -- I think there's a lot of, as you pointed out, there's a lot of difficulties interpreting some

of this data, and there is some subjectivity here. Could we go to Slide 36, because the Sponsor -- this is just the other indication information. I know that the Sponsor also this morning mentioned -- I think I wrote this down -- there's been mesh approved for Achilles tendon and patella tendon as well.

So that's a wide variety of clinical applications and a wide variety of different stresses and tensile strengths, and you guys know more about the hoop stress, stuff like that. Yet, those were approved. You know, very different indications were approved with almost no clinical data. So what did the FDA look at when they approved, say, the patella tendon, the Achilles tendon. There was one for a spine, which seemed like a very, you know, different application than a hernia, but no clinical data.

DR. KESSLER: I'm going to take that question after lunch.

DR. SPINDELL: Okay.

DR. KESSLER: Okay? Please?

DR. SPINDELL: Okay.

DR. KESSLER: Thank you.

DR. SPINDELL: Thanks.

DR. MABREY: Great. It's about a quarter to 12. I'd like to give everyone an hour for lunch.

I'd like to come back at 12:45. And I would remind you that this room will be closed down during the lunch period. If you need any of your materials, please take them with you, and we'll reconvene the Panel meeting at 12:45 in this room.

(Whereupon, at 11:47 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:50 p.m.)

DR. MABREY: And Panel members, remember, shut the door. We'll now begin the Panel deliberations portion of the meeting. And although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel.

At this time, I would like to recognize Dr. Kessler, who has to leave earlier this afternoon, and he is responding to specific questions from the Panel right before lunch.

DR. KESSLER: Thanks, Dr. Mabrey. There were a number of questions the Panel asked, and I couldn't give complete answers, and during lunch, I had a little bit of help, so I'm going to try and go back to some of them. The first thing I want to mention has to do with, again, just to rephrase and repeat the comment we made about 510(k) review and our precedents. So in the context of 510(k) review and assessing the effectiveness of this device relative to other surgical meshes, which is one of the issues the Sponsor has raised repeatedly, the FDA must consider the evidence of effectiveness derived from clinical trials including comparisons of this

device to the surgical control.

Specifically, Dr. Shindell [sic] asked about what about other surgical meshes --

DR. SPINDELL: Spindell. Shindell --

DR. KESSLER: Oh, sorry.

DR. SPINDELL: I'm Spindell.

DR. KESSLER: I thought I said Spindell --

DR. SPINDELL: You said Shindell.

DR. KESSLER: Oh, did I? I'm sorry. So the responsibility for conforming to precedent is FDA. So what we have to do is we have to make sure we are conforming to precedent. We take that very seriously. There have statements made by the Sponsor we slightly disagree with. However, we are not really in the position to disclose some of the details about the base on which some of those 510(k)'s were cleared.

But, as an example, you mentioned a number of indications, for example, a surgical mesh in the spine. So as an example of that specifically, that mesh was cleared after a bone graft operation, and it's a bag or a covering, so it's not a supporting kind of surgical mesh. So, again, we return to looking at this surgical mesh. We're trying to figure out what surgical mesh is equivalent for this

indication, meniscus repair. Since we have cleared none for this specific indication, we're trying to figure out what are the appropriate data that we need in terms of effectiveness and safety, is a challenge. It's one of the reasons we're turning to this Panel very specifically what are the right data? What are the right questions to ask?

So I want to go back briefly to the time frame that you asked about, about that one patient. So the one patient was explanted because of pain at four months, and, apparently, the clinical records suggest that the individual was actually on -- was working out on a treadmill perhaps causing the mechanical failure of the device. He was then reimplanted, pain repeated, this time after stationary bike work, and that was explanted at six months. The explants of the six range anywhere from 17 days soonest to six months or beyond. So that's your explant answer.

Somebody asked a really interesting question about the control group and the reoperations. What did we know about the reoperations at one year? What was the control group doing, and could they have actually had the same kind of symptomatology, maybe they should have been

reoperated on. So we don't have complete information, but here's what I can tell you.

So pain was evaluated at one year for both the treatment and the control group in the original IDE study. As we pointed out, there were no differences in the VAS pain score, as pre-specified by the firm. We counted those reoperations you asked about where there was pain only if the reoperation was intervention to fix something in the knee, not only for pain, not only for ameliorating pain.

And, finally, if you want some of the clinical details about this, they're in Appendix J of the 510(k). They're narratives for each reoperation, so you can judge yourself. And I want to add from a statistical standpoint, the measure of statistical significance of the reoperations being positive for effectiveness as the company claims, it's a very unstable measure. A change in one of those patients would change the statistical significance from the conventional under 0.05 to above. So a very unstable measure. And it's very subjective. It's one of the things that FDA has questioned, the validity of that particular measure.

Finally, last one, suture pull-out. You asked over there -- both of you asked about suture

pull-out, and why do we care, what's necessary? And so I talked to my mechanical engineers in the Office of Science and Engineering Labs, and it's a great point. We don't know what is enough force that's needed in this region.

Our comment about this was that we're trying to figure out whether the collagen scaffold and the tissue that is being replaced in that region by design is strong and how strong is it? Clearly, it does not appear to be as strong as the native canine meniscus. Now, is it sufficient or not? We don't have the answer. That's a great question. But what we do see is that it is dramatically less.

And if you look over the 24-week period in that animal study, you see no increase. So from zero to six months, no increase in strength. So you're talking about an implant now in a region of soft tissue where this does not have the same strength as the surrounding tissue. And that may be of surgical or clinical concern. So -- but necessary? Absolutely, you're right. We don't know what's enough. Thank you.

DR. MABREY: Thank you. At this point, I'd like to open up the discussion to the Panel members, and I would caution you that this is a general

discussion and that we will not be discussing the exact questions from the FDA until later on this afternoon. But if you have any specific questions for either the Sponsor or the FDA, this would be the time to bring up those points.

Oh, and before we do that, I should give the Sponsor an opportunity to address any outstanding issues as well.

MR. DICHIARA: Thank you. Yeah, regarding some of the issues that were brought up, you know, there was one issue that was brought up that they asked the Sponsor to respond to. That was the number of patients that you asked, 85 versus 87. The difference was that two patients were excluded by the authors of the *JBJS* publication due to that they didn't meet the inclusion criteria. They had greater than three prior surgeries to the involved meniscus and were excluded from that analysis since they looked at, you know, acute being no prior surgeries and chronic, one to three prior surgeries. Okay.

DR. MABREY: Great. Thank you.
Dr. Spindell, any other points you'd like to bring up for clarification?

DR. SPINDELL: Well, actually, I'd like to ask the orthopedic surgeons, because one of the

things that seems to be a struggle here is that this procedure, this device, the benefits seem most likely long term and not short term, but we have short-term data, which shows no change, no change from controls, and I just want to hear some talk about what would they have expected at two years. When would -- you know, is this unexpected -- expected data, and their feelings on that.

DR. KELLY: That's a very insightful question. I would speak for myself only that I think that it is not something we usually see within that two-year window. In fact, there's a rash of studies now looking at medial meniscectomy alone doing actually better than many people realize. This is a sort of -- now, the literature is all over the place, is my understanding, but there actually has been some recent data looking at -- for isolated medial meniscus tears, the patients did better than many people initially realized.

I do think it's a short time period. I would also add that the fact that the tissue is not totally normal still may be somewhat protect, analogous to, say, microfracture versus hyaline cartilage. But I think in the answer to your question, it's still -- if you look at the joint

space narrowing, actually, Dr. DeHaven's been very, very helpful with all these studies, that some studies indicate for meniscus repair, repair alone, that what may look good at seven years becomes not so good at 15.

LTC SHAWEN: I think the time issue is fairly well understood as a number of empiric studies that look at meniscus injury will eventually cause a high rate of knee arthritis, and that is a major time issue. And the two years, it's small. At 35 years, it's high. And I think that's something that we know from recent European studies, and I think the very first study, Dr. Fairbank looked at that.

I think that what the patient experiences on an x-ray is -- those two things are separable. They're not the same. I think that there's a lot of fuzziness. I am personally comfortable with a lot of that fuzziness in the science, but I think that there is a substantial time factor. I think that the *JBJS* article obviously looked at short-term things, and that's the least likely to show benefit from this type of device.

DR. MABREY: Anyone else?

MAJ KADRMAS: I think one of the problems, and correct me if I'm wrong, one of the problems is

we don't know how much meniscus is enough, how much can we live with, how much can we not live with. We do know with Fairbanks, we take it all out, it's bad. So the trend is leave as much as we can. As much as we can? What does that mean? I don't think anybody knows.

There's some radial tear models that render a meniscus basically absent, but as far as I know no one's looked at if you remove 30 percent of the meniscus is the remaining meniscus enough? If you remove 50 percent, is the remaining meniscus enough? If you have the peripheral five millimeters to the red/white zone, is that enough? So I don't think we know that number. Surely the attempt is to leave as much meniscus as you can, as gray as that is, but I don't think we have a definitive answer as far as, you know, how low can you go or how much is enough.

DR. POTTER: You know, to some extent any discussion of the efficacy is based to a large extent on how well that device will function as a meniscus down in long-term follow-up. Right now you're faced with irreparable meniscus. It is either just live with it or meniscal transplant. That's what's available. Meniscal transplantation data is very mixed, depending on the time when the implant is

placed or the allograft is placed.

So I think the only way to really assess that is to get long-term, very good data on the rate of progression of osteoarthritis in a blinded fashion, independent analysis, to get a sense of how much meniscus is necessary and how well a device would function as a meniscus if the primary role is to delay the progression of osteoarthritis.

DR. MABREY: Does that answer your question?

DR. SPINDELL: Sort of, because I guess one of my concerns here is the FDA cited that they didn't see any difference in the effectively [sic] and that, you know, we'll discuss later about safety as well. I guess just -- because we're not going to have seven, ten, fifteen-year data here, and, to be honest with you, a seven-year study is probably an unreasonable burden upon a manufacture to -- for a product -- is what can we infer from the data we have here as to, you know, the fact that, you know, the potential that at two years, it was -- there was no difference. Is it likely, more likely going further down the road that having this extra tissue there will be helpful or not?

DR. MABREY: Ms. Dalrymple, questions?

MS. DALRYMPLE: Okay. Well, my question pertains to the extra tissue as well, because there was a mention that it's not oriented in necessarily the correct position as it grows, regenerates. And so I don't know anything about orthopedics necessarily as a surgeon, so my question would be can it develop into what would be kind of like scar tissue and then that would actually limit the motion of the knee in any way or -- because that, too, would go into, like, a long-term study. I'm just interested in, like, the benefits to the patient.

COL KRAGH: I don't think stiffness was an issue. That's not been my experience using similar surgeries, and I don't think that arthroscopic pictures show that, being adhesions between the implant and anything was a problem. If that's -- that's the type of scar tissue that we colloquially talk about. When you actually look at the device and the histology, that's what was shown. Does that answer that question?

MS. DALRYMPLE: Well, yeah. Again, just it not being in the proper orientation I was thinking in terms of flexibility and --

COL KRAGH: I think that's a separate issue in my mind, and I'll talk about that. Tissues like

muscle respond very quickly, relatively speaking, red meat, muscle, to reorganization, healing, et cetera. Bone, cancellous bone, tends to do it a little slower. Some tissues, like tendon, do it extremely slow, and fibrocartilage is much closer to that very slow thing.

So having something that looks like histology like on something of a muscle, essentially, in our science, which I do a fair amount of muscle work, there are very strong scientific arguments that the histology means nothing. Essentially, you can look at histology and see tea leaves. I'm just saying this is what some expert opinion is in this field, and that it's very difficult to tell whether treatment A and B are really different just based on histology.

So it's the general pattern of the results, not just the histology. Jeez, that looks like a scar on the slide. That's just one piece of data. And I think that the time issue is a major difference between some of the science for some of the other tissues. So fibrocartilage, I think, is a longer term plasticity of the tissue than other things. So I'm not all that surprised that it looks like such and such at five years. I don't think that's what

it's going to look at, at 15 years. I don't think we will know that for a certainty, but I think that the expectation is that these things change.

MS. DALRYMPLE: Thank you.

DR. POTTER: But that being said, matrix orientation we know is very tied to material properties. We know that it's very true for articular cartilage and probably it's true for fibrocartilage as well. A secondary sign that there was not increased stiffness would be that there was a lack of progressive cartilage loss by second look or a significant change in progressive cartilage loss. Most of the effect of a stiff implant in the knee will be progressive wear of articular cartilage and we didn't see that.

MS. DALRYMPLE: Okay.

DR. KELLY: I just want to add, I thought it was interesting, following what Dr. Potter said earlier, meniscus allograft transplantation has been not conclusively shown to be a disease modifier, but it has been shown in several series to increase -- to decrease pain. So it's a little -- and some of those studies do look as early as two years. So I thought it was a little surprising that there was no difference in pain. That would be a nice barometer

that's at least serving as some sort of spacer effect. So I will say that even though we don't have conclusive data for disease modification, some of these new technologies do give decrease in pain at least short term.

COL KRAGH: I think this gets to your question to what is effectiveness, and pain relief is something people talk about to us in the clinic. We can measure effectiveness on slides, on histology. We can use pull-out strength of sutures from tissue, and we've done these things. We're looking at what -- all the data that's available to us and assessing the quality of these data, and we have to have a certain level of comfort with the fuzziness of some of these essential surrogates of indicators of effectiveness. And they're not all that direct.

And so when do we do a visual analogue scale? Do we do that at two years or do we do that 35 years? These are, you know, pertinent questions. And there's a degree of lack of data that we talk about. So what exactly is effectiveness is a reasonable question.

And I think that histology is a limited factor in that. And I think that Tegner Scale is, you know, an attempt at trying to see how the

patient's doing, how you're doing activity-wise. Is it, you know, T2 gradient echo -- technology gathered at 48.5 months post-op on 92 percent of your patients? No. But it's still an attempt at seeing how people are doing. And this is the best that we got, apparently.

DR. MABREY: Dr. Propert?

DR. PROPERT: Another question to help my understanding from the rest of the panel, and it's -- you asked the first half of my question. My second half actually has to do with short-term improvements. Do you expect when -- and I realize this is somewhat hypothetical, but when you put some of this matrix into whatever joint that the improvement is going to be linear and just happen over time or is there going to be a point at which something has happened and then suddenly people improve, because I'm looking at some of the data here and setting aside the issue of missing. It does look like there's some things that sort of have an elbow in them. Does that make any scientific sense that that would be happening? This is of anyone but me.

MAJ KADRMAS: I guess I didn't understand that question. Can you repeat that?

COL KRAGH: I think is there a cusp? And

when one looks at the data from Fairbanks, there is no discussion of a cusp. When you look at the European data, there is no clear indicator. I think that the general history of the disease is wax and wane symptoms with a general progression usually measured on imagine. That's the most obvious data sets that we have, and that's the natural history of a tear. That's the natural history of a partial meniscectomy. I think that the time factor we've already cleared. I think that there is generally some data that says that the more tissue you remove the faster the progression, but that's very soft.

DR. MABREY: What's the experience of the rest of our Panel, those of you who routinely remove the meniscus or get to watch the meniscus removed at HHS?

DR. POTTER: You know, the rate of progression of osteoarthritis is so unpredictable because there are so many confounding variables, BMI, loads put on the knee, activity. And then there's this genetically mediated group of people that clearly have express inflammatory mediators and have a more rapid rate of progression of osteoarthritis, and it's almost impossible to screen for those individuals.

So I think you just do the best you can. You find a suitable BMI, in a study try to match for activity level, similar rehabilitation regiments. But people do well for two years. If you just look at cartilage repair data, two years, everything is great, and then everything drops off from two to five year follow-up, and that's where things spread out and the data points are not linear anymore. Just because we have all these confounding variables that it's very hard to control for. But it's generally related to the magnitude of osteoarthritis and how that patient responds in terms of pain and function to their disease.

DR. MABREY: Dr. Kragh, any other points, other questions?

COL KRAGH: I have none at this time.

DR. MABREY: Okay. Dr. Kelly?

DR. KELLY: It's just putting all this together in my aging brain here, I'm just trying to reconcile, you know, the meaning of all this in that I had the blessing before I came here of preparing a talk on meniscus repair, and I looked at all these data.

And, you know, Dr. DeHaven, who I hold is a very honest man, did some great working looking at, I

think, amount of meniscus resection did correlate with arthritic changes. But there's been some recent studies looking at the efficacy of repairs. Dr. Potter just alluded to long-term, even in the best of hands, repairs don't hold up in terms of disease modification. So I'm just still trying to reconcile the exact meaning. Even if repaired native tissue doesn't confer significant chondro protection, how can we expect the same of a substitute?

DR. MABREY: Dr. Endres?

DR. ENDRES: I have a couple direct questions for the Sponsor. One is I believe in the literature that has been provided it states that an absolute contraindication to the product is a bovine allergy. Is that correct?

MR. DICHIARA: Yes.

DR. ENDRES: How would I distinguish that when I'm talking to a patient? What do I specifically ask them?

MR. DICHIARA: That certainly was a concern in the clinical trial. In doing a clinical study, you don't want to get patients who could potentially confound it. As a result, some of the testing, the immune testing that we did and the blood samples were to try to address that issue so that when it goes out

into the population that there isn't an issue. European -- the surgeons talked about European experience with the product. This product has been on the market in Europe since 2001. There have been between 2,500 and 3,000 patients. We haven't seen any indication from the complaint systems or any of the literature that would indicate that that has been an issue.

DR. ENDRES: What if one of my patients, and I could see this happening, potentially, what if they ask me if they're at risk for mad cow disease? What do I tell them?

MR. DICHIARA: Well, you tell them that the testing -- we did viral inactivation testing, and, you know, we presented to FDA. We also had to do in Europe very extensive testing for BSE, and the product met the standards to be able to -- to meet all of the current standards as well as the most updated standards. So from the BSE standpoint we feel pretty confident that the product doesn't have issues in that respect.

DR. ENDRES: Last question is I believe the age range of the patients was 18 to 60, with an average age of 40, if I'm not mistaken. Do you think there could potentially be any difference in the

clinical results based on age? And what I mean by that is, theoretically, there is less intrinsic healing capacity of the meniscus much like the rotator cuff the older you are. So, arguably, older patients might now have as robust a healing response. Is there any role for a subgroup analysis based on age or stratification --

MR. DICHIARA: Certainly in the trial we looked at correlation with age. There was no correlation with age, but I'll let the -- Dr. DeHaven talk about, you know, that as clinical --

DR. DeHAVEN: You know, I can't really add to that. I was thinking that might be an interesting stratification in terms of percent regrowth and quality of tissue, but it turned out that some of the low percentage ones were older, but some of the older ones had a lot of regrowth, and it looked pretty good. So it really didn't -- maybe it's an end problem, but we couldn't see any trend there, which is encouraging for the older group.

(Laughter.)

DR. MABREY: Dr. Potter?

DR. POTTER: No more questions.

DR. MABREY: Dr. Kadrmas?

MAJ KADRMAS: Yeah, I struggle with a few

of these issues. One of my concerns is -- one of the things that was brought up by the FDA is, you know, we can't compare this to a predicate device because nothing else has been approved as a mesh for meniscal repair, intra-articular -- I guess my question with that is, as far as I know, there's only one implant indicated for the spine, bone, holding, you know, bone graft in. So what standard was that held to as far as comparing to anything else?

And so it's hard to -- I kind of take that with a grain of salt that there hasn't been another device. I think that's the whole principle of predicate devices is, you know, there's not going to be the exact device that we're going to compare these to. And so what level of -- or what standard do you hold that to?

One of the things we all live by is, you know, first do no harm. So in a lot of these studies, what I can see, there hasn't been a whole lot of harm. While there may not be benefit, did the -- was it necessary for the Restore patch to show benefit as opposed to just standard rotator cuff repair, because we've seen in the literature, it hasn't been any benefit, and it may have done a little bit of harm. So I think, you know, there

hasn't been any harm shown.

The standards going through a lot of the predicate devices, which I've tried to review as much as I could, it's -- you know, what's standard or the new 510(k) is held to? It seems like the more data they present and the more studies you do, you open yourself to a lot more criticisms as far as comparison to controls or the standards as opposed to comparing to other predicate devices. I don't know those standards. I know this isn't a question. It's just a concern that I think for my edification needs to be brought up.

DR. MABREY: Well, I think we could ask the FDA to expound on their definition of the standards for 510(k). Is the FDA ready to respond to that, because as you point out that's a crux to the argument, and I think we really need to get our hands around this --

DR. KESSLER: I'm going to ask Heather ROSECRANS from the Office of Device Evaluation to come up, and she's really the expert on this. She lives this day in and day out. So Heather will give you the right answer. And I'm thanking Heather for me.

MS. ROSECRANS: So you're asking about the

standards for safety and effectiveness on a 510(k)?

MAJ KADRMAS: My question --

MS. ROSECRANS: I want to make sure I understand the question.

MAJ KADRMAS: My question is I guess because the FDA brought up, you know, this is a new indication, there's no other device that is used as a mesh for repairing the knee. My question is, then, what were the other ones compared to? What was the spine mesh compared to because there wasn't another spine mesh, so that was a new application? What was the, you know, the first rotator cuff for soft tissue in the shoulder compared to and what standards were those held against or based on going towards approval with only, you know, limited data?

MS. ROSECRANS: Okay. For a 510(k) in all pre-market applications, we have to look at the probable benefit compared to the probable risk, and we use valid scientific evidence in the review of pre-market notification submissions, as well as pre-market approval applications. So, again, being a risk/benefit, you look at the indication for use, how it's used, and what kind of data we need to support that and support that risk. So different indications obviously have different risks, and then we have

different amounts of data. And as far as a clinical response, I wouldn't -- I would have to refer to Dr. Schultz. Does that help?

MAJ KADRMAS: Yeah.

DR. SPINDELL: I have a question. Some of these devices which Achilles tendon, et cetera, were approved with actually no clinicals, so how did you do the risk/benefit on something with no clinical data?

DR. KESSLER: So the way you'll do that is to take a look at the indication, to try and look at any predicates that exist anywhere else, other anatomical structures, and you're going to make conjectures whether in fact the strength of the material, the appearance of the pores, how it's manufactured, whether all of that will look like and function in the same way so that, you know, we will be able to tell in many cases without requiring clinical data. We can do bench testing. And I'll give you a good example. In a very different world, suppose you're looking at something in ultrasound and the way it will ablate soft tissue in one part of the body. If you start ablating in another part of the body, I don't need to see an entirely new data system if it's working exactly the same way, if the energy

is going to ablate a tissue that's very similar, different part of the body. I just need to know that the bench testing is going to be the same, the power is the same. So, in meshes, you're looking for poor strength, et cetera, et cetera, depending on the application.

When all of the sudden, now talking ultrasound, I'm going from ablated soft tissue in one place to a very different clinical application. Now I'm going to ratchet it up, and I'm going to need to see different kinds of data. If the energy source is different, if the power is different, if the tissue I'm doing is different, and then I'm going to have to make the requirements whether it's biocompatibility, bench testing, or even clinical data, to fit the need to evaluate the effectiveness versus that predicate. And it's really, it's a little bit tricky. It really is. But it is different and a lower standard than PMA, absolute demonstration of safety and effectiveness.

So you're trying to sort of wend your way through, what more do you need to make sure that this is working as same as the predicate? When you wind up with a new indication, such as the meniscus, in our interpretation, now we're starting to ask, what

do we need to see here. Okay. Do we need biocompatibility? Yes, we think we need so. Do you need strength testing like the suture pull-out? Yes, we think so because of the forces -- going to bear. Why do we need clinical? Because we believe that this situation has clinical implications. There may be the next one around the corner that doesn't. Certainly, if we were to go to the spine, that's an area where we'd be very concerned, okay? Now, you asked about the spine mesh. What did you compare it to? It was a bag covering a bone graft, so we're talking about the indication was so relatively straightforward as to not require much more than equivalence at the functional or bench level. Does that help?

DR. SPINDELL: Yeah, it does help. So in the clinical study, you would look at safety and effectiveness being the same as the predicate?

DR. KESSLER: Yes.

DR. SPINDELL: You don't require it to be safer nor more efficacious?

DR. KESSLER: Absolutely not in a 510(k) regardless.

DR. SPINDELL: If I'm not mistaken, in the clinical study, you said before that the -- it was no

clinically significant difference in the effectiveness or the safety?

DR. KESSLER: No.

DR. SPINDELL: So doesn't that essentially meet the standards?

DR. KESSLER: No difference in effectiveness, none at all. You saw the safety concerns, the potential and what we think are real safety concerns, explants, reoperations, which we think is an arguable issue, but explants, serious device adverse events. In the face of no demonstrated clinical effectiveness, then if you have any safety concerns that gives us pause. That's why we're here, and that's why we're looking to you to debate: Do you see any evidence of clinical effectiveness? Do you see any evidence of safety? And the question is: Do you put a product on the market that has neither?

DR. SPINDELL: Okay.

DR. MABREY: In the interest of fairness, I'll point out that FDA is only allowed one person at the podium as well.

DR. KESSLER: My fault. I apologize.

MR. DICHIARA: May I make a comment?

DR. MABREY: Yes.

MR. DICHIARA: As far as, you know, the -- I think that was a very good question, and the regulations and the way that the regulations are applied -- 510(k) substantial equivalence is in some ways a lesser standard than PMA but in other ways a more difficult standard because it implies that you're comparing, as you said, the surgical mesh in the spine to a hernia mesh or a mesh in the abdomen to shoulder mesh. And in going from any one of those locations from -- to the shoulder, you have very high forces in the shoulder. To go into the anal/rectal fistula, you have other concerns about infection, the type of biochemical environment. So each one of these raises new questions.

And in our mind, we had the same question that you did. You know, you're making these jumps on all of these others, and now all of the sudden this jump seems to be much greater. And we pointed out that, yes, in the knee, the force, the major force, is still a tensile force, and the tensile force is very similar to tensile force in the shoulder. So you do have concerns in each of these areas, and they're addressed by varying amounts of data. But, certainly, the amount of data has been very limited on all of these -- there were 17 new indications

since 2002. None of them -- all of them combined probably had less clinical data than we're presenting on this product. Thank you.

DR. MABREY: Thank you. Dr. Shawen, I think we were --

LTC SHAWEN: I have no more questions.

DR. MABREY: -- at you. Members of the Panel, again, has this discussion brought up other issues that you'd like to have answered?

(No response.)

DR. MABREY: Okay. At this point, we'll proceed to the second open public hearing of the meeting. Only one person requested to speak this afternoon before this meeting, Mr. Jonas Hines. Mr. Hines are you in the room? Please come forward to the podium, state your name, your affiliation, and indicate your financial interest, if any, in the device being discussed today or any other device.

MR. HINES: My name is Jonas Hines. I am a staff research at the Public Citizen Health Research Group. I have no financial conflicts of interests at all.

So I would like to thank you guys for the opportunity to present today, or to speak about this issue today. I want to start out by addressing the

proposed regulatory pathway for this device. As you guys are aware, a device, medical device can reach the market either through a PMA application or through a 510(k). The FDA makes it clear that in order to proceed through a 510 -- or in order to qualify for a 510(k), you have to establish it is for the same intended use. So any device that has a different intended use cannot be considered substantially equivalent. However, different indications are permitted as long as modifications do not raise any new questions about the effectiveness or the safety or any new questions about effectiveness or safety.

Today, ReGen Biologics is seeking clearance of their collagen scaffold device, comparing it to 23 other predicate surgical meshes. The FDA has made -- the Agency has stated "has not previously cleared a surgical mesh for this specific indication."

The Sponsors in making their comparison provide only laboratory data. They do not provide any clinical data comparing the collagen scaffold to the predicate devices, and the data that they do provide is at best unconvincing. The FDA has already pointed to numerous fallacies in the comparisons between the collagen scaffold and the predicate

devices. In particular, one of them was in regards to the fact that the FDA requested a comparison of the collagen scaffold to human meniscus in order to assess whether or not the device could withstand the function of demands placed upon it over the many years it would take for it to be resorbed. The Sponsor chose to compare it to a dog meniscus instead. When they did do that, the suture pull-out strength was notably weaker than a dog meniscus.

The inappropriateness of considering clearance through the 510(k) devices can be demonstrated through a simple thought experiment. Imagine a clinical trial trying to compare the collagen scaffold to one of -- any of the predicate devices. For example, comparing the mesh implant in the knee to the mesh implant surrounding the shoulder joint. These sites are so different, no reasonable conclusions could be drawn from such a study.

I mean, this brings us back to the fundamental problem, and that problem is that the collagen scaffold is for a different intended use than any of the predicate devices and is thus not suitable for the 510(k) process.

A more appropriate path would be -- for this device would be through the PMA process, and,

indeed, the Sponsors have conducted a trial that would be ideally suited for a PMA. The problem is, is that this study fails to demonstrate either effectiveness or safety in this trial.

This trial, as was already discussed, is a randomized control trial comparing partial meniscectomy plus a collagen scaffold to just partial meniscectomy alone. I just think it's important to reiterate the fact that the apparently positive clinical endpoints that were reported by the Sponsor are only when the Sponsor considers those who -- patients who receive the collagen scaffold even though they did have data comparing them to a control. When that data of the control is included, the apparently positive endpoints all become negative, all three primary clinical endpoints are negative. Furthermore, there's three primary surrogate outcomes. The problem is that these surrogate outcomes all suffer from major methodological errors including unblinding and lack of control.

The two outcomes that the Sponsors claim demonstrate superiority of the collagen scaffold to standard partial meniscectomy, which are the Tegner Index and then also the reoperation rate have been

refuted by the FDA's analysis. The Tegner Index, as it's been pointed out, is a post hoc analysis based on a validated pre-specified and related secondary outcome, which was the Tegner Activity Score. However, an analysis of that -- of those values has not been provided either in the journal article or from the FDA materials.

Talking about reoperations, the FDA did, you know, did an analysis of the reoperations with a more conservative definition and found that what the Sponsor's claim, which was statistically significant lower level of reoperations in the collagen scaffold-treated groups disappeared with their new definition.

So, essentially, what we end up -- what we're left with here is a randomized control trial that demonstrates that this device is no better than the standard of care. The trial failed on its primary clinical outcome and it appears to have failed on the secondary -- or on the primary surrogate outcome.

Furthermore, when we're talking about adverse events, I think it bears to point out that initially the Sponsors argue that because this is a 510(k) application it is not appropriate to compare the device to the standard of care as far as

effectiveness goes. But then when establishing the safety, they use the adverse events from this randomized control trial as proof that this device is safe. They mention that the fact that there was no significant difference between adverse events between the control group, the people who received the partial meniscectomy, versus the people who received collagen scaffold is proof that this is indeed a safe device. And I also would like to just reiterate Dr. Kessler's point that the difference in the device-related adverse events is not trivial.

So at Public Citizen we reject the use of the 510(k) clearance process in this instance, and we believe that the device fails to meet device approval standards regardless of whether or not you consider 510(k) or the PMA. The bottom line is that when a device has been shown to add nothing to conventional therapy, it is hard to see how the public health is served by this. We understand that the pre-market review process raises a series of complicated legal questions, but I think that the saying, "you can only ring a bell once" -- or sorry -- I take that back. "You can't unring a bell" has a lot of relevance here. The fact is, is that any effort to push this device through the 510(k) process ignoring the fact

that a randomized control trial has been conducted that shows that this device does not offer any benefit over the standard of care needs to be recognized because, I mean, after all, the reason we're here is to improve patient outcomes. That's all I have to say, and I thank you guys, and I will take any questions if you have them.

DR. MABREY: Thank you, Mr. Hines. Questions from the Panel for Mr. Hines?

(No response.)

MR. HINES: Thank you.

DR. MABREY: Thank you for your testimony, and I'll remind the audience that copies of Mr. Hines' testimony are available on one of the tables outside.

Things seem to be moving along well. We have a scheduled break at the end of the open public hearing, and I'd like -- oh, anybody else that wants to speak? Seeing no one --

(Laughter.)

DR. MABREY: Sorry about that. But at this point we'll take a ten-minute break. It's 1:35. If we can come back at 1:45, we will start with the FDA and Sponsor summations at that point.

(Off the record at 1:35 p.m.)

(On the record at 1:50 p.m.)

DR. MABREY: Resume the meeting. Is there any further comment or clarification from FDA? And that shaking of the head indicates a no, I would take it?

Okay. Is there any further comment or clarification from the Sponsor?

MR. DICHIARA: Yes, I'd like to address several issues. I think one of them that -- a question that was asked that I don't think was answered adequately was Dr. Kadrmas'. Hopefully, I am not mispronouncing your name, but you had a very good question. You asked exactly, you know, what kind of effectiveness data was relied upon to move from one new indication to another. And, you know, we presented that information in one of our slides, where we looked at, for instance, anal/rectal fistula plugs, where you had 26 patients, you know, who were followed to discharge.

You know, the amount of effectiveness data is related to the fact that the device -- the effectiveness of these devices has to go back to what is the intended use. And the intended use of the device is to reinforce soft tissue or bone. And clinical outcomes are not typically looked at so that

when you looked at the shoulder, you weren't looking at a statistically significant in range of motion because you certainly couldn't have gotten that from a five-patient, a three-month study.

The same with any of these new indications. And to characterize the new indication and the meniscus as that different from any other indication is very difficult to understand, where you're going from, you know, something like a hernia mesh to the spine. And the spine is actually a polyester permanent implant that's a bag that's put into the vertebral body so the vertebral body is under compressive load with the bone graft material in it. So that is a very different indication, and, you know, there was no clinical data in those submissions.

So we're not saying that FDA had too little or too much. What we're saying is that the playing field and the way that these decisions are made was based on a certain amount of data. We've presented an extensive amount of clinical data. And I think that the clinical data that we showed shows that, you know, compared to these other meshes we have considerably more data to show the safety and the effectiveness of the device for its intended use,

which is to reinforce soft tissue.

Now, I'd like to also address the issue that was brought up about reoperation rate because I know that there was some confusion. We presented our analysis that was in our submission, which was part of the publication in the *JBJS* by the authors of that paper. And, you know, the FDA presented theirs. And I think that that needs to be put in context, and I'd like to have Dr. DeHaven address that issue.

DR. DeHAVEN: Yes, we have had some time to -- short period of time to try to compare the two ways of counting the secondary surgeries. And to the best of our ability in this short period of time here, we have identified ten of the second-look patients who had additional procedures that we feel should be excluded because those additional procedures were not done for anything that was relevant to the meniscus implant. They were done for partial lateral meniscectomy, exploring the pes anserinus for pes strain chronic symptoms, loose body, things of that nature.

And so our approach to what should be included and what should be excluded was clinical relevance to the implant that had been done. So we were criticized for having a rather subjective way of

going about this. Dr. Kessler agreed that their way is also subjective and that we could argue about this. But like the swing states in the election, you know, how those ten patients are counted or not counted make a big difference. And since it's been said repeatedly that the safety data is bad, if you agree with our approach of being clinically relevant, then it's -- it is safe. If you agree with the FDA that all of them need to be counted no matter what, whether it's clinically relevant or not or whether they even had symptoms, then it looks different.

So that's just I wanted to explain a little more about how we went about deciding whether to include or exclude those cases. And our approach was at least accepted by the reviewers and the editor of *JBJS*.

MR. DICHIARA: Again, you know, that reoperation rate, you know, I'm not sure that everybody understands, one of the problems with calculating that is that in looking at the two groups, the control group did not have a relook surgery and biopsy at one year. That relook surgery and biopsy provided the surgeons an opportunity to go into the joint, look around, see if there's a loose body, if the, you know, if there's loose fibers on

the meniscus to shave it, you know, if they notice that there is a small lateral tear to go and repair it. So, you know, it provided the opportunity for these minor surgical procedures to be reintroduced into this. And, you know, 141 of those patients had relook surgeries. None of the controls. So if you had done the same thing on the control, what would you have seen?

I'd like to also address, you know, one other issue about, you know, the meniscus and the uniqueness of the meniscus. The FDA has actually cleared a device recently also for use in the meniscus. Again, with a certain amount of data, they used animal study data, to clear a device which is a hollow tube that's made of resorbable PLA-type material. And it's placed into the meniscus in the area of the defect to guide cells from one area of the defect to another.

Although it's not a surgical mesh, you know, it's an absorbable implant being placed into the meniscus of the knee and the data that's relied upon to be able to make the decisions whether, you know, that sort of device is going to cause problems in the knee, in that case, you know, was based on animal study data. And, certainly, one would worry

about, knowing what we know about the resorbable meniscus arrows that are made of similar materials and the rigid plastics, you would certainly have a concern about the clinical effectiveness of some of those devices.

I'd also like to have Dr. Montgomery talk a little bit about overall impressions of the clinical data.

DR. MONTGOMERY: I'll be brief. I saw you look at your watch right there. We've all been sort of picking away at a lot of data, and the good news is there is a lot of data when many of these products coming in for 510(k) do not have that. But I wanted to kind of bring us all back home to why we're here. The medical literature has overwhelmingly shown that loss of the meniscal tissue can lead to arthritis. And in the U.S., if you think about it, every year, there's about 850,000 meniscectomies of which I've done thousands, unhappily, 150,000 meniscal repairs, but, unfortunately, another 400,000 total knee replacements. And that's really what we're here -- we're trying to slow down arthritis. And as the baby boomers are getting older, the arthritis rates are increasing.

And at this time, the only available

biologic treatment for pain secondary to meniscal insufficiency is a meniscal allograft. And very big procedure and still questionable with regards to the results. So the collagen scaffold gives the surgeon another treatment option to treat meniscal tears and insufficiency, which would be the only other option out there than just trimming it.

Unlike other surgical meshes, the collagen scaffold has a vast amount of clinical data as you've been seeing it all day today. And it's from an FDA -- most of it from and FDA-approved multi-center study. But unlike many of the other meshes, the real endpoint is arthritis, and, unfortunately, the prevention of arthritis, we may not see that for ten years, and there's not going to be a study that's going to just be a 510(k). Hopefully, we will get that data out there in the future, but, hopefully, the device is available before that occurs.

Now, if we look at the results, the two to five-year results show that the collagen scaffold is effective in treating meniscal defects. We have second look surgeries, and we show a significant regrowth of the meniscus. We're not sure exactly what type of tissue. It is meniscal-like, but there is an increase in tissue there, and, hopefully,

that's going to be working.

And, also, the clinical results show a significant improvement in pain and function. People have been showing differences between a meniscectomies and the patients with the implants, but the bottom line is, if you look at the patients that had the implant, there is an increase in -- there's an improvement in pain and function in those patients.

The results also show that the collagen scaffold is safe. There is no host immune response. There's no negative histological response. And it's comparable to the safety of a partial meniscectomy, which is remarkable because that's a smaller operation. And it's as safe, if not safer, than what we refer to as predicate surgical meshes, including the Restore shoulder implant.

So there are over 400 surgical meshes that are cleared by the FDA with vastly different indications in a variety of different body regions. But the majority of these surgical meshes were all cleared by the FDA with significantly less clinical information than is available for the collagen scaffold. And you've seen all that information today.