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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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ORTHOPEDIC AND REHABILITATIVE DEVICES PANEL

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November 14, 2008
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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NATHAN ENDRES, M.D.	Consultant
MAJ WARREN KADRMAS, M.D.	Consultant
JOHN KELLY, IV, M.D.	Consultant
COL JOHN KRAGH, M.D.	Consultant
HOLLIS POTTER, M.D.	Consultant
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INDEX

M E E T I N G

(8:00 a.m.)

DR. MABREY: I would like to call this meeting of the Orthopedic and Rehabilitation Device Panel to order. I'm Dr. Jay Mabrey, the Chairperson of this Panel. I'm also Chief of Orthopedics at Baylor University Medical Center in Dallas. My training involves fellowship training in both total joints and in biomechanics at the Hospital for Special Surgery. My practice revolves around knee and hip replacement, knee and hip arthroscopy.

At this meeting, the Panel will be making a recommendation to the Food and Drug Administration on the 510(k) Application K082079 for the ReGen Collagen Scaffold. This device is intended for use in surgical procedures for the reinforcement and repair of chronic soft tissue entries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists.

In repairing and reinforcing meniscal defects, the patient must have intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient

vascularization.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address this Panel during one of the open sessions, please provide your name to Ms. AnnMarie Williams at the registration table. If you are presenting in any of the open public sessions today and have not previously provided any electronic copy of your presentation, please arrange to do so with Ms. Williams.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

I would now like to ask our distinguished Panel members, who are generously giving their time to help the FDA in the matter being discussed today, and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. And I'll begin with Mr. David Spindell.

DR. SPINDELL: David Spindell. I'm the vice president of Medical Affairs for Abbott, and I'm the industry representative.

DR. MABREY: Ms. Dalrymple?

MS. DALRYMPLE: Jeannette Dalrymple. My background is in clinical research and bench science. I'm the consumer rep.

DR. PROPERT: Kathleen Propert. I'm a professor of biostatics at the University of Pennsylvania specializing in clinical trials.

COL KRAGH: I'm John Kragh. I'm Army orthopedist from San Antonio and interest in combat casualty care.

DR. KELLY: John D. Kelly IV. I'm an associate professor for orthopedic surgery, University of Pennsylvania. My clinical research interests are in joint preservation and injuries to the shoulder.

DR. JEAN: Ronald Jean, the Executive Secretary of this Panel.

DR. ENDRES: Nathan Endres, assistant professor of orthopedic surgery at the University of Vermont, Division of Sports Medicine and Shoulder Surgery.

DR. POTTER: Hollis Potter, professor of radiology at Cornell Medical School and chief of MRI at the Hospital for Special Surgery, where I run the Research Department for Imaging.

MAJ KADRMAS: Warren Kadrmas, orthopedic surgeon in the United States Air Force at Wilford Hall Medical Center in San Antonio, specializing in sports medicine and shoulder surgery.

LTC SHAWEN: I'm Scott Shawen. I'm an assistant professor at Uniformed Services University and also at Walter Reed Army Medical Center, foot and ankle trained and primarily lower extremity reconstruction.

DR. SCHULTZ: I'm Dan Schultz, Director of CDRH and a general surgeon by background.

DR. MABREY: And a special welcome to our military representatives. Thank you all for being here. Now, Dr. Jean, the Executive Secretary of this Panel, will make some introductory remarks.

DR. JEAN: Good morning. I'll just make a few general announcements. Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is 410-974-0947. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Let me take the time to introduce our FDA press contact, Ms. Peper Long. Are you here? Ms. Peper Long will be our press contact when she arrives, and I'm sure she'll make an introduction.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area at any time during the meeting, including breaks. If you are a reporter and wish to speak to FDA officials, please wait until after the Panel meeting has ended.

Finally, as a courtesy to those around you, please silence your electronic devices if you have not already done so.

I will now read into the record the Conflict of Interest statement. The Food and Drug Administration is convening today's meeting of the Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with federal ethics and conflict of interest law is covered by but not limited to those found at 18 U.S.C., Section 208 and Section 712 of the federal Food, Drug and Cosmetic

Act, are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers for this purpose.

Related to the discussions of today's meeting, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C., Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of a

pre-market notification application for a collagen scaffold Sponsored by ReGen Biologics. This device is intended 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. 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.

This is a particular matters meeting during which specific matters related to the 510(k) will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 of the FD&C Act to Dr. Hollis Potter. Dr. Potter's waivers address a personal consulting arrangement with a competing firm to the 510(k) device Sponsor, and she receives an annual fee of less than $10,001 for this arrangement.

The waiver allows this individual to participate fully in today's deliberations. FDA's reason for issuing the waiver are described in the waiver documents which are posted on FDA's website at www.FDA.gov/OHRMS/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30, of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. David Spindell is serving as the industry representative, acting on behalf of all related industry, and is employed by Abbott Laboratories Medical Products Group.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which a FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

DR. MABREY: We will now proceed to the Open Public Hearing portion of the meeting. Prior to this meeting, only one person requested to speak in the Open Public Hearing. We ask that you speak clearly into the microphone to allow the transcriptionist to provide an accurate recording of this meeting. Please state your name and the nature of any financial interests you may have in this or another medical device company. Dr. Jean will now read the open public hearing statement.

DR. JEAN: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the open public hearing or industry speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the Sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the Sponsor's payment of your travel, lodging

or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. MABREY: Ms. Pam Adams, our former panel industry representative, has requested to speak on behalf of the Orthopedic Surgical Manufacturer's Association. Welcome back, Pam.

MS. ADAMS: Thank you, Dr. Mabrey. As he said, my name is Pamela Adams, and I am here today representing OSMA, the Orthopedic Surgical Manufacturer's Association, which is a trade association with over 30 members companies. OSMA has financed my attendance at this meeting. As he said, I am also a former member of this orthopedic advisory panel, serving as industry rep from 2004 to mid-2008. Therefore, I'm pleased to address so many of my former advisory Panel colleagues. Also happy to see Mr. Melkerson, Dr. Schultz, Mr. Chairman, Mr. Executive Secretary, and so many familiar faces from the FDA.

On behalf of OSMA, I welcome this

opportunity to provide comments at today's Panel meeting. OSMA's comments should not be taken as an endorsement of the product being discussed today. OSMA asks instead that the comments be considered during today's Panel deliberations. These comments represent the careful compilation of OSMA member companies' views.

As a brief introduction, the Orthopedic Surgical Manufacturer's Association, or OSMA, was formed over 45 years ago. OSMA has worked cooperatively with the FDA, with the American Academy of Orthopedic Surgeons or AAOS, the American Society for Testing and Materials, ASTM, and other professional medical societies and standards development bodies.

These collaborations are sought to ensure that orthopedic medical devices and products are of safe, uniform, high quality and supplied in quantities sufficient to meet national needs. OSMA membership currently includes over 30 companies who produce over 85 percent of all orthopedic implants intended for clinical use in the United States.

OSMA has a strong and vested interest in ensuring the ongoing availability of safe and effective medical devices. The Panel's discussions,

deliberations, and recommendations to FDA today will have a direct bearing on the availability of new products. We make these comments to remind the Panel of the regulatory burden that applies to the 510(k) application for the product that's the subject of the Panel's deliberations today. In other words, this is not a PMA regulatory application, which reflects a different requirement for approval.

We urge the Panel to focus your deliberations on the requirements of substantial equivalence. For the product to be legally marketed, it must be substantially equivalent to the predicate device or devices. Substantial equivalence means the product is as safe and effective as the predicate device or devices.

The FDA is responsible for protecting the American public from drugs, devices, food and cosmetics that are either adulterated or are unsafe or ineffective. In addition, FDA has another role, to ensure the timely availability of safe and effective new products that will benefit the public. The Orthopedic Devices Branch has a staff of qualified reviewers who evaluate the applications they receive.

The feedback of this Panel, when convened,

supplements the analysis of the information and data in the manufacturer's application and will impact the availability of new products in the United States marketplace. Those of you on the Panel have been selected based on your experience and training. You also bring the view of practicing clinicians, who treat patients with commercially available products. OSMA is aware you've received training from FDA on the law and the regulations. I do not intend to repeat that information today. I do however want to emphasize the regulatory standard applicable to today's 510(k) deliberations, which is substantial equivalence.

A finding of substantial equivalence does not require that the product and the predicate devices be identical. The product and the predicate typically have the same intended use but are not required to have the same technological characteristics. If the product has different technological characteristics than the predicate device or devices, the application -- the applicant must provide information in the 510(k) to show that (1) the differences do not raise new questions of safety and effectiveness and (2) the product is as safe and effective as the predicate device or

devices.

Comparable safety and effectiveness can be demonstrated through submission of a variety of information and data in the application, including proper labeling, safety data generated in the laboratory, in animals, in humans, bench testing and/or clinical performance data. Data in a 510(k) are provided to show equivalence in performance unlike a PMA. A 510(k) application is not required to include data to demonstrate the product's absolute safety and effectiveness. Rather, the data must validate that the product is equivalent or better in terms of safety and effectiveness compared to the predicate device.

It's also important to understand the FDA is required to consider the least burdensome means of demonstrating substantial equivalence and request information accordingly. FDA should not require a 510(k) submitter to submit data that are not necessary in order to make a substantial equivalence determination. In addition, the nature and scope of data requested should be consistent with what FDA has previously requested from 510(k) applicants for similar products.

OSMA also wants to emphasize that this

Panel is participating in a vitally important part of FDA's framework for regulating medical devices, the 510(k) process. Since its incorporation into FDA's governing statute in 1976, the 510(k) process has proven to be a highly successful means of bringing to market safe and effective medical devices.

Indeed, in 2007, FDA cleared for marketing nearly 3,000 devices through the 510(k) pathway. Most importantly, under the 510(k) regulation, FDA has the authority to request virtually any information that it needs in order to reach the substantial equivalence determination. While very simple devices are sometimes cleared for marketing in 90 days or fewer, more complex devices typically undergo a considerably more lengthy review involving multiple requests for additional information in testing. Thus, far from being a shortcut to market, the 510(k) pathway is a rigorous, risk-based approach that ensures medical devices receive an appropriate level of pre-market review.

We also note that as medical technology has grown more complex and diverse, so too has the 510(k) process evolved. For example, when it was first incorporated into FDA's governing statute in 1976, substantial equivalent meant showing that the device

was as safe and effective as a device that had been on the market prior to 1976. The substantial equivalence standard was amended to require a comparison of safety and effectiveness with a legally marketed device. As a result, today, manufacturers typically demonstrate equivalence to state-of-the art technologies. Thus, there's no merit to the criticism that devices are being cleared for marketing through a process that allows comparisons with antiquated, irrelevant technology.

No pre-market review system can provide an absolute guarantee of safety and effectiveness. Indeed, pre-market review is only one of the many requirements that FDA imposes on device manufacturers. Other controls, for example, good manufacturing practice regulations, adverse event reporting laws, are extremely important in ensuring safety and effectiveness of medical devices. However the 510(k) process continues to play a critical role in assuring the timely availability of safe and effective new devices.

In conclusion, the Panel has an important job today. You must listen to the information and data presented by the Sponsor, evaluate FDA's presentations, and respond to their questions

regarding the application. We speak for many applicants when we ask for your careful consideration.

Please keep in mind that the standard is substantial equivalence, comparing safety and effectiveness of the product with that of the predicate devices. The regulatory standard is equivalence in performance in terms of safety and effectiveness, not absolute proof of safety and effectiveness. Finally, when making recommendations for further analyses or studies, remember that the FDA takes Panel recommendations seriously. For example, FDA may interpret your comments as a need to delay the introduction of a useful product or require burdensome and expensive additional data collection.

Therefore, you play an important role in the process of bringing new products to market, products with you -- that many of you and your colleagues use in treating patients. Please be thoughtful in weighing the evidence. Remember the standard for a 510(k) application. While the regulations allow a broad range of data to be requested by FDA, a level playing field for any Sponsor of a new device, one which requires the same level of supporting data as has been relied upon to

make previous decisions on devices of the same type is desirable.

On behalf of OSMA, I thank the FDA and the Panel for the opportunity to speak today. I trust these comments are taken in the spirit offered to help the FDA obtain objective feedback from the Panel and to help the FDA decide whether to make a new product available for use in the U.S. marketplace. I'll be present in the audience and available to answer questions any time during the deliberations today. Thank you very much.

DR. MABREY: Thank you, Pam. It is nice to see you again. Is there anyone else who would like to speak at this time?

(No response.)

DR. MABREY: Since no one else has come forward, we will proceed with today's agenda. Please note that there will be a second Open Public Session in the afternoon.

We will now proceed to the Sponsor presentation for the ReGen Collagen Scaffold. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel. The

Sponsor will introduce the speakers. You have 90 minutes.

MR. DICHIARA: Good morning. My name is John Dichiara. I'm senior vice president of Regulatory Quality and Clinical for ReGen Biologics. I would like to pass around the sample of the collagen scaffold device so that you can see what it's like.

I'd like to thank all of the Panel members for devoting their time to this deliberation and providing their expertise and going through the questions that FDA has regarding this product. On the agenda today, I will provide a brief introduction regarding the regulatory status and regulatory precedents for the surgical mesh devices. And I will then introduce several outside experts who will provide their expertise in specific areas regarding the product.

First of all, I'd like to say that the subject of this meeting is the collagen scaffold. It's a surgical mesh, which is designed and engineered for implementation in meniscus injuries for -- following partial meniscectomy and designed to reinforce the defects in those meniscus injuries. Data demonstrate the device preserves and reinforces

the meniscus and provides a scaffold for tissue growth.

The CS functions as any surgical mesh does by reinforcing soft tissue and is as safe as any of the cleared surgical meshes that FDA has provided as predicates. The ReGen situation is that the device has the same intended use, materials, and technology as FDA-cleared surgical mesh devices, and we'll demonstrate that through the data presented today.

Use of the CS in the meniscus represents a new indication. As it does present these new indications, FDA has cleared numerous surgical meshes that were defined with new indications. Each of these new indications represents a first use of a surgical mesh in a specific anatomic location or in a specific indication. For example, anal/rectal fistula plugs or meshes for reinforcement of rotator cuff injuries were new indications for those devices outside of the indications that were previously cleared by FDA through the 510(k) process.

Any new indication raises the same issue of suitability for use. For a resorbable surgical mesh, these issues are centered on whether the mesh device provides reinforcement and serves as a scaffold for tissue growth. What each of these new indications

had in common with its predicates was not an anatomical location but the mesh function and its relative safety. And that function is, again, to reinforce soft tissue or bone.

ReGen has provided valid scientific evidence which establishes that the CS is as safe as its predicate meshes and functions as a surgical mesh in both acute and chronic patients. There may be some confusion in the documentation that was provided. The documentation that was provided by FDA was centered on chronic patients. I just wanted to let you know that while we are presenting data on the chronic patients, we are also presenting data on the combined patient population because as a surgical for use in reinforcement of soft tissue injuries, the device, we believe, provides that function in both chronic and acute patients equally. And we would like your consideration of both those populations. This has been discussed with FDA prior to this meeting, and we will present the data based along those lines.

The collagen scaffold is a resorbable collagen-based surgical mesh. It's bovine type 1 collagen. It's a semi-lunar shape, as you can see, and it's designed specifically to be placed within

the meniscal defect, to reinforce the remaining tissue in the same way that other meshes reinforce tissue in their indicated uses. Meshes have different shapes dependent on the specific anatomic location and the specific intention for those devices.

This device is intended to reinforce the residual meniscal tissue and provide a scaffold for tissue growth. It's sutured in place for immediate reinforcement and for the preservation of native tissue. The resorbable scaffold is then filled with the patient's own tissue, and that tissue provides the long-term reinforcement of the device.

The FDA defined the intended use of a surgical mesh very specifically in the regulations. Surgical mesh is intended to be implanted to reinforce soft tissue or bone where weakness exists. And that's the intended use of all surgical meshes. And the thing that makes the comparison between any number of these -- anatomic locations and indications possible.

The scope of regulation has expanded by FDA, FDA's 510(k) decisions. Resorbable surgical meshes provide a scaffold to be replaced by the patient's own tissue. Over 400 surgical meshes have

been cleared by the Agency. Seventeen new indications for surgical mesh have been cleared since 2002.

The scope of these surgical mesh indications for use is very varied. When viewed in the abstract, one can say that all of these devices, whether it's for an Achilles tendon or for bladder support or for a fistula plug or for a vertebral body to maintain the position of bone graft material, the one thing that they have in common is to reinforce or soft tissue or bone. They're all intended for that use. And if you look at them from an anatomic location, you would be hard-pressed to be able to compare an Achilles tendon to an anal fistula or to the vertebral body of the spine.

The indication that we would set forth and it has been set forth in previous 510(k) submissions, which are referenced in the materials that you were provided for the collagen scaffold is a bit different than the chronic indication that was read into the record by FDA by the Panel Chair. The indication that we would specify for the product that we wish to you consider today in your deliberations is the ReGen Collagen Scaffold that is intended for use in surgical procedures for the reinforcement and repair

of soft tissue injuries of the meniscus.

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 CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization. Also, the CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not a prosthetic device and is not intended to replace normal body structure or function or provide the full mechanical strength of the repair.

We're presenting clinical data today from a number of sources. One is a feasibility study that established the safety and long-term viability of the tissue. Another is a U.S. multi-center clinical trial, in which there were 162 patients. This trial was developed as part of an IDE in 1996 before the mesh category had broadened to include a number of these resorbable surgical meshes.

With relevant predicates established in the 510(k) pathway, we'll show that this device is as safe and effective as those predicates. Data confirmed that the device served as a surgical mesh

and that is provides a scaffold for the growth of new tissue and is as effective as any of the surgical meshes that have been cleared by the Agency.

Pre-clinical bench and animal testing have formed the basis of most FDA surgical mesh clearances, including meshes for new indications. Device-effectiveness is inherent in each device's ability to carry out its intended use. That intended use is to reinforce and/or provide a resorbable scaffold for tissue growth.

The recognized risks associated with surgery, tissue reactions, and infection are mitigated through ensuring biocompatibility and sterility of the device. Few surgical mesh submissions, including those with new indications include clinical evidence of safety and effectiveness. To give you an example of what some of these data, the clinical data, that was provided and was used as the bases for clearance of surgical meshes in new indications are several of these new indications in this slide.

The indication for reinforcement of rotator cuff had clinical data on five patients with three months of follow up. Patella, biceps, Achilles, quadriceps, and tendon repair had no clinical data.

Repair of anal/rectal and intracutaneous fistulas had 25 patients with three months of follow up. Urethral slings for incontinence and a non-absorbable surgical mesh to maintain the position of bone graft material had no clinical data supporting the clearance. A surgical mesh for use in sealing air leaks in the lungs had 26 patients followed through discharge.

Like other surgical meshes with new indications, ReGen CS surgical mesh is intended to reinforce soft tissue where weakness exists. ReGen submitted substantial clinical and pre-clinical data to the FDA demonstrating its device functions as a surgical mesh. To the extent that that data on the CS predicates exist, CS data shows that it is as safe as those predicates. Technological characteristics and indications for the CS do not raise new types of questions regarding its safe and effective use when compared to the performance of other surgical meshes.

I'd like to also make a comment regarding the FDA presentation just to highlight an issue that we feel is significant and needs to be considered in your deliberations today. There's a statement regarding the excerpt from the *JBJS* article that was submitted as part of the evidence in the 510(k) submission, which states, "The implant, ReGen CS, was

not found to have any benefit for patients within acute injury." That statement is taken out of context and is not in the context of a surgical mesh, but it is rather in the context of a publication, which was specifically intended to show a comparison of the CS device to partial meniscectomy and specific outcomes related to that comparison.

Today's deliberations need to be compared to the intended use of the device as a surgical mesh and not to a comparison to partial meniscectomy or surgical procedure. As such, we just wanted to alert you to that fact and to make sure that in your deliberations you understand that the comparison is to predicate surgical meshes and not to a surgical procedure that does not involve a mesh.

To speak to the idea and the concept behind surgical meshes and types of data that you would expect from surgical meshes, I'd like to introduce Dr. Stephen Badylak. Dr. Badylak holds an M.D., a Ph.D. in pathology, and a D.V.M. He's research professor in the Department of Surgery and director of the Tissue Engineering Institute at the McGowan Institute for Regenerative Medicine at the University of Pittsburgh. Dr. Badylak is a pioneer in the development of resorbable tissue scaffolds. I'll

turn it over to Dr. Badylak.

DR. BADYLAK: Thank you, John -- thank you. Good morning. Oh, thank you. The screen is a little farther away than I anticipated. I appreciate the opportunity to be here, and just for the record, I have absolutely no financial investment or will get -- you know, I have no vested interest in ReGen or the products that are being discussed today. So just so that's clear.

My intent today is to help to describe the mechanism by which surgical meshes are intended to perform their function regardless of their source or for the anatomic location in which they're intended to be used. We spent about 20 years looking at this particular issue and feel qualified to speak to the points I'm going to make.

Biological surgical meshes are significantly different than synthetic surgical mesh mainly in the point that -- to the point that synthetic meshes are intended to be a permanent implant. And, therefore, considerations about mechanical properties, material properties, and whether they can perform the function that they are intended to perform on Day 1 as well as 10 or 20 years afterwards, that's an important consideration

for a synthetic mesh.

A biologic mesh, however, is completely different. Even though one certainly needs to consider the mechanical material properties at Day 0, when it's implanted, so that it can perform the function that it needs, it's very important to understand the concept that this mesh will change almost immediately following implantation. It's not going to be the same device at one week, one month, two years, five years down the road. And, in fact, it's completely gone. So what one is left with at the anatomic site of placement is what the body replaces it with. And I think the real issue to consider is whether or not it can perform its function during that phase of remodeling.

Now, these collagen-based meshes are derived from a variety of tissues. There's so many on the market now, it's difficult to count, but they come from many species, pigs, cows, horses, sheep, and they're derived from -- they're composed of the components of the extra-cellular matrix, such as collagen, like -- the ReGen meniscus or their intact extra-cellular matrix. All of them are acellular. Some examples of these devices are listed, the Restore device, Permacol, Oasis, CollaMend, and,

hopefully, the ReGen Collagen Scaffold. These are all surgical meshes intended for the reinforcement of injured or missing tissues.

So there's a couple of main points I'd like to make for you. First, these meshes, these surgical meshes that are of biologic origin are intended to degrade, they're designed to degrade, that can be customized a bit by the methods of manufacturing. But they're not meant as a permanent implant, and that implies, of course, then that they're going to change during that process of degradation.

So in addition to the degradation of the scaffold material, one can expect a degree of cellular infiltration, and these will obviously be host cells. There's going to be deposition of new extra-cellular matrix by the host cells that infiltrate the scaffold. There'll be differentiation of these cells at the site of remodeling, organization of the new matrix. And this whole process is referred to as remodeling. So when I use a word remodeling, these are the components that I'm referring to.

The last point that I want you to think about during the next few slides is that the microenvironment of the implantation site is an

absolutely critical determinant in how well this surgical mesh is going to function. That includes biomechanical loading but isn't limited to that. For example, a surgical mesh to be used in the knee like the ReGen meniscus has a fluid environment. It's got a certain pH, it's got a certain oxygen tension, glucose concentration, which is different than an anal fistula, which is different than a ventral hernia, which is different than the shoulder.

So the individual sites are all different, and this is important because they define how well the surgical meshes are going to work. Let me continue this point by giving you an example of a typical material. In the middle there is a piece of extra-cellular matrix derived from a pig's urinary bladder. It's -- surgical mesh -- representative. I could be showing you their small intestinal submucosa, purified collagen, they would all look pretty similar. They're all acellular, and, in fact, they take on a lot of forms and shapes. And the reason they have these different forms and shapes is simple to make the surgeon's job easier.

Now, that doesn't mean that they're intended to look exactly like the native material. For example, the device in the upper left is ten

layers of small intestinal submucosa, SIS. That's the restore device used for orthopedic applications in the rotator cuff reinforcement.

The one below it, the -- let's see if can get this pointer to work here. There we go. This one here is four layers of SIS used as a sling for urinary incontinence in women with post-menopausal urinary stress incontinence, particulate forms of these same scaffolds could be made to turn them into three-dimensional shapes. They can look like tubes. It's all the same material.

A scanning electron micrographic view of some of these materials is shown here. On the left is this urinary bladder matrix. And you can see, on the surface, it's a very smooth surface. That's the basement membrane of the urinary bladder, and right below it is the tunica propria. There are no cells there. That surgical mesh looks a lot different than SIS, which has almost a laminated appearance, which looks a lot different than the collagen-based scaffold that has this pore-like structure.

But none of those structures look anything like their intended site in the body. And that's an important feature. And the reason is because they're not going to look even like this after a day or two

days. These meshes are meant to be temporary scaffolds to help perform the function of the injured tissue to reinforce it and then to stimulate remodeling response so that at the end of the day, what's left at the site is something that is better than what would have been there if nothing was used.

Now, let me give you an example of one fact that I indicated was critical in the remodeling process, and that's mechanical loading. This was a study that has been done a couple of times, most recently, this summer. I'm going to show you two pictures here. On the left is a remodeled scaffold, and on the right is the same scaffold that's remodeled. The only difference is mechanical loading. These scaffold materials represent the small intestinal submucosa of a pig that was used to reinforce and, in this case, actually replace large segments of missing urinary bladder in a dog model.

In the case on the left, the mesh was placed and replaced 50 percent of the dome of the bladder, and the catheter was removed immediately so that the bladder saw filling and emptying six to eight times a day like it normally would for 28 days. The same -- material in the same application by the same surgeon was placed there in the specimen on the

right. The only difference is that the catheter was left in place so that the bladder never filled, never experienced the mechanical loading. And this type of experiment can be repeated in a lot of different ways. The point is that the simple, one factor being changed, and that is mechanical loading, dramatically affects the remodeling process.

And when considering the ReGen Collagen Scaffold, I think this is important because this scaffold is placed in a site where different types of forces will dictate the remodeling. You've got compressive forces, you've got tensile forces, and it's in an environment of course that -- and it's attached to an intact rim. These forces will dictate the type of remodeling that occurs for this surgical mesh just like the environment including mechanical forces dictate the remodeling for any surgical mesh that's used.

Now, let me move on here. This is an important slide. This is a biopsy specimen from a patient that was treated for a rotator cuff reconstruction with the Restore device. And this specimen was taken six weeks after surgery when a second surgical procedure in the shoulder area for a different indication was needed, and the surgeon took

a biopsy. Let me show you a higher magnification of that. But at low magnification, you can see that this looks nothing like the SIS material that was implanted. And the reason is it's been very significantly remodeled in a very short period of time. And there are vascular or at least tubelike structures and new matrix in here, and under high magnification, you can see that this material has got mononuclear cells imbedded within a new matrix and these probably blood-vessel-type structures are there.

You show this to any pathologist, and they'll have a very difficult time interpreting it, because they're -- we -- I'm a pathologist -- are trained for pattern recognition, and so this is some type of whatever, fibril vascular granulation to whatever. It'd be a very generic sort of a phenomena. And yet this material turned into a very functional reinforcement for an injured rotator cuff with an absolutely perfectly good clinical outcome and by MRI, normal rotator cuff tissue.

Every surgical mesh for every application will go through a phase where it will look like this. And you're going to see other slides from the following presenters that show you very similar

patterns of remodeling in the surgical -- in the collagen scaffold used for the meniscus that end up with very good outcomes. So this remodeling process is absolutely critical in your considerations.

The final example I want to give is a publication that we had in *JBJS* about a year ago. And what you're looking at are six -- a one-week remodeling result of six different biologic materials. The one in the upper left is autologous tissue, an autograft, in other words. This happens to be a body wall model, but you could think of it as a hamstring for an ACL or a middle third patellar tendon. That's an autologous tissue being remodeled. The four over here on the right all represent commercially available 510(k)-approved surgical meshes for orthopedic soft tissue repair, and Graftjacket is cadaveric human tissue that's not regulated but rather considered as a transplant.

The point is that every one of these meshes at one week has a very robust cellular infiltrate, the only difference being the pattern of infiltration, and that's because of the different manufacturing processes that these meshes -- to which these meshes are subjected.

Now, the following slide represents the

outcome at 16 weeks. So four months afterwards, one can see that the cellular infiltrate is significantly mitigated, and there's been remodeling into acceptable tissues for the given applications that there were. So all of these surgical meshes, even though they're processed differently, they're still composed of extra-cellular matrix or components of extra-cellular matrix. They undergo the same remodeling process, and the outcome is dictated by their location in the body and the rapidity of the remodeling process.

So, finally, I'd like to leave you with the following points. This is really the heart of what we're talking about here. All surgical meshes of biologic origin, as far as that goes, synthetic origin, elicit a very robust cellular response. This is exactly what we want to happen. If this doesn't happen, there's no remodeling and the entire advantages of a surgical mesh with biologic origin are missed. The remodeling process will differ for every surgical mesh, but it's clear that the resorption of these products is associated with a constructive remodeling process. And, finally, microenvironmental factors including mechanical forces such as those that are seen in the knee are

absolutely critical determinants in the remodeling process and the downstream results.

I thank you for your attention. There'll be a chance for questions and answers, and I'll be available for it any time. Thank you.

MR. DICHIARA: I'd like to introduce our next speaker, Dr. Vincent Vigorita. He's a professor of pathology and orthopedic surgery at the State University Health Science Center at Brooklyn, and chairman emeritus at the Department of Laboratories, Lutheran Medical Center in Brooklyn, New York. Dr. Vigorita is an orthopedic pathologist, and he's going to talk about histologic findings following animal studies and human clinical trial biopsy specimens.

DR. VIGORITA: Thank you, John. Dr. Mabrey and members of the FDA, I was invited to interpret slides for ReGen Biologic. I have no vested interest, stocks, or anything of that nature. I have received a consultation fee for interpretation of the slides, much as I do from the hospitals I serve for interpretation of breast biopsies and malignant bone tumors.

In the canine study, the object was to assess the ability of the collagen scaffold to remain

attached to the host rim and provide a resorbable scaffold for tissue in-growth and to assess the type and progression of tissue in-growth. And what we found was that there were mechanical characteristics which proved sufficient to maintain attachment of the scaffold to host meniscus rim in the animal model and that the collagen scaffold functions as a tissue scaffold and disappears over time, as we'll see. The newly formed tissue shows a predictable evolution of early angiogenesis, which Dr. Badylak just showed us nicely, comparably, in these other models, with a reparative type of tissue evolving into fibrochondrocytic meniscal-like tissue.

And the first slide shows you a piece of the collagen meniscal implant scaffold, which is seen here as this pale pink, surrounded by tissue and an occasional giant cell on the surface, resorbing the collagen scaffold. Actually, that was a rarely observed event. Most of the time, as you see in this second picture, we noticed the collagen scaffold literally blending in and assimilating into the host tissue without a surface cellular reaction. Notice also here, this is an angiogenic phenomenon similar to what was just discussed by Dr. Badylak.

There was deposition of mature

fibrochondrocytic matrix identical to what's seen in the meniscal tissue shown here. You can see the nuclei and lacunar space, as much as we would expect to see in fibrocartilage, and the collagen scaffold is blending into this host tissue. This is an important slide, on the bottom here, because it's demonstrating a host meniscal tissue, integration with the now dissipating, assimilating fragments of collagen scaffold.

In addition to the canine study, I was asked to interpret slides from a second-look biopsy in patients obviously in the clinical study. I had 136 biopsies to be examined. Eighty-one had sufficient collagen scaffold to form the basis of the slides that I will show you. However, it's worth mentioning the remainder of the tissue samples that did not contain collagen scaffold did have tissue and did not show any adverse cellular reactions.

What we see in this picture is abundant fibrochondrocytic in-growth, and it's replacing the now assimilating and literally disappearing collagen scaffold. And as we saw in the canine model, here is a picture from a human biopsy specimen showing the host meniscal tissue literally integrating with the collagen scaffold, which, as you can see in these

very fine filaments, is assimilating into the host tissue.

Again, there was evidence of angiogenesis, of the microenvironment of remodeling that Dr. Badylak was discussing in his examples, and, on occasion we would encounter some inflammation, and this is an example of that occasional observation, where we have the scaffold with adjacent inflammation showing a disappearing scaffold as we see right here.

So the conclusions. Most importantly, I think the results are very consistent with what I saw in my interpretation of the canine study. And, in addition to that, the collagen scaffold did provide a meniscal-like fibrochondrocytic matrix, which, to my eye looks like meniscal, normal meniscal tissue. This tissue integrated well into the host meniscal rim as was also demonstrated in the canine model. The collagen scaffold became imbedded in newly formed tissue and really became the dominant tissue on the slide as over time we see that the collagen scaffold is literally disappearing.

There were no clinically significant adverse reactions, although I did show an occasional patient who has some inflammatory response, which I think in most instances represents that

microenvironment remodeling that in a rare circumstance may represent some reaction to the collagen scaffold, much as we pathologists often encounter, for example, in a cellular reaction to an embedded suture.

Finally, although I wasn't focused on the biomechanical properties, the lack of adverse events between the host tissue and the new fibrochondrocytic tissue, that is, items such as cystic degeneration or bursa-like formation, supports a conclusion that the remaining collagen scaffold is not biomechanically acting in an adverse fashion. Thank you.

MR. DICHIARA: Thank you, Dr. Vigorita. I'd like to introduce Dr. Kenneth DeHaven, who is going to be talking about meniscal surgery and clinical outcomes. Dr. DeHaven is a professor of orthopedic surgery at the University of Rochester, School of Medicine and Dentistry. He also is a past president of each of the following organizations, the American Academy of Orthopedic Surgeons, the American Orthopedic Society for Sports Medicine, and the Arthroscopy Association of North America. He is a pioneer in the field of meniscus repair surgery. And Dr. DeHaven was an investigator in the clinical trial for the last ten years. He implanted 19 CS devices

into patients. Most of those patients are now out to seven years follow up.

DR. DeHAVEN: Thanks, John, and good morning, everybody. I want to make it clear that I also have no vested interest to whatever in either the company or the product. My travel expenses are being reimbursed for being here, but I'm not being paid for my time.

As mentioned, I'm here to try to highlight the clinical outcomes and some things about the procedure itself. Certainly, there has been an increasing consensus in the last couple decades that it's important to conserve as much meniscus tissue as possible because the loss of meniscus tissue has definitely been tied to increased stress on articular cartilage and long-term degenerative changes. And illustrative of this is the fact that the number of meniscus repairs has been increasing, but when there is an irreparable injury to the meniscus, the only thing available today to have tissue where the meniscus had to be removed is allograft meniscus transplantation.

Now, partial meniscectomy has been one of the most successful orthopedic procedures we have for short-term results. But it leaves the patient with a

permanent loss of meniscus tissue, and, certainly significant potential for long-term degenerative changes.

It's been mentioned repeatedly already what the requirements are for the use of this particular collagen scaffold. The reason that the intact meniscal rim is so important and that the anterior and posterior horns being present are important is that these are what allow the hoop stress resistance function of the meniscus, which is the key biomechanical function. So the intact peripheral circumferential fibers are there, and they are anchored into the tibia both anteriorly and posteriorly. So the implant is not having to sustain hoop stress. It is the peripherated and the horns, and that's the same for partial meniscectomy.

So, in a sense, the only difference between partial meniscectomy and the implants are that with the implant there is the potential for in-growth and replacement tissue because of the scaffold effect. But it also permits a more conservative partial meniscectomy, and this diagram is a bird's eye view of medial meniscus with this area back here representing preparation for insertion of an implant. So notice that there is a squared off resection here

of the damaged tissue.

Now, the dotted -- the dashed line shows the type of tapered, contoured procedure that would be done typically for partial meniscectomy. But -- and if you left these kind of things without any support, they would be stress risers for more tearing and could directly damage articular cartilage. So that is the important reinforcement function of the implant as a surgical mesh, and it allows preservation of more of the natural meniscus tissue that's not torn.

The relook part of this study gave us the opportunity to see that the tissue growth is impressive, and here's an illustrative case with the irreparable posterior tear here. Here is with the implant in place. You can see the sutures holding the implant to the rim back there. And then one year post surgery, you can still see the sutures back here. All of this is now the regenerated tissue that's replaced the implant. You can't see the implant, and you can see that it's very difficult to tell where the anterior horn stops and the regenerated tissue begins.

So the quality of the tissue was impressive and is impressive, and there has recently been a case

to allow us to see even more impressive durability. This is an 11-year relook surgery because of a lateral compartment problem just a few weeks ago, 11 years. This is one of the first patients in the study. So all of this tissue remains intact, and the fusion with the anterior horn remains intact 11 years out.

So, again, the reason for having intact peripheral rim and anterior horns, it's -- but the second point is it's important to realize that there is with the implant restricted weight bearing for the early weeks after surgery to allow an opportunity for healing to take place and this tissue integration to get well underway and that this is similar to labeling of predicate meshes, which also recommend limits on activities over a specified period to facilitate the tissue incorporation. It's also important to point out that the rehabilitation following the implant is very similar to that for meniscus repair and that it's not like rehab for partial meniscectomy.

So a few details about the study. I had 26 surgeons at 16 sites, 162 cases of implantation, 75 in acute cases, where they had the partial meniscectomy and the implant at the same operation,

and 87 were chronic cases, where they had had one and up to three previous partial meniscectomy procedures before receiving the implant. And the relook was for two things, to assess the new tissue growth at one year and to get specimen for biopsy that you just heard the results of. They have also been followed at regular intervals for pain with a VAS scale, function via Lysholm, activity level with the Tegner scores, and global self-assessment. And the patients have been followed up through seven years with a mean of 4.9.

This slide illustrates the important point that there was significant increase in tissue at one year for all patient populations, both acute and chronic. And this is an aggregate figure here. I mean, 43 percent of the meniscus tissue was remaining at the time of surgery. There was 73 percent total tissue at the relook, which means a tissue gain of 70 percent on the mean. If we stratify it by acute versus chronics, the chronics had a little less tissue remaining, had about the same total tissue at the relook, which added up to a 97 percent increase in tissue. And on the acute side, less had to be removed, so there was 51 percent remaining. Again, the total tissue was the same, and the increase was

43 percent. All of these are highly statistically significant differences.

This tries to summarize the other clinical data, the pain data. And this is for all patients in the study that received implants. The pre-op pain score mean was 35, had improved to a mean of 14.5 at the longest follow-up, and the mean change in score was almost 20. Lysholm, 63.3 mean pre-op, 83.6 mean post-op, and another 20-point increase. Self-assessment showed similar increase at less than half, 43 percent, rated themselves as normal or nearly normal pre-operatively. And at the longest follow-up, almost 85 percent consider themselves to be normal or nearly normal. And the Tegner activity scores had a mean of 6.7. At pre-op, it had dropped to 3, which is activities of daily living level of function before the surgery, and was up to 4.5 mean at the longest follow-up.

So conclusions from the multi-center trial that the implant patients had significantly more tissue filling the defect left by a partial meniscectomy and that the patients had statistically significant improvement from their preoperative levels of pain, Lysholm, Tegner Activity Level, and self-assessment. These clinical outcomes complement

the data establishing the performance of the CS as a surgical mesh, and are comparable outcomes to partial meniscectomy; again, one of the most highly successful procedures for the short term, but maybe not in the long term.

There are some published papers to draw attention to. One is the feasibility study to establish tissue durability. Second, *JBJS* article that just came out this past summer, which I'm a co-author. And then European publications that have shown that the procedure is safe and effective in over 2,000 cases in Europe. And that while we're not really looking at -- well, we'll come to that.

This gives a little more data about the feasibility study. It was a single surgeon, eight patients, mean follow-up of almost six years. And each patient had a relook at either six months or one year and again at a mean of 5.8 years in all patients. And that showed that approximately 70 percent of the meniscal defect was filled with new tissue, and the amount of new tissue growth had remained constant between that first relook at six months to a year and at the second relook at nearly six years. And this documents the durability of this tissue.

The histology showed the same picture that we heard out two pathology experts talk about with one important difference is that in the 5.8 year biopsies, none of them showed any remaining implant fragments. Those were all gone by that time. Again, the patients all improved in pain, Lysholm, self-assessment, and Tegner, and, as I mentioned, complete resorption of the scaffold in tissue samples and no complications. So that was the feasibility study.

In our *JBJS* article, we compared the results with the CS to the partial meniscectomy control population. Both acute and chronic patients showed all of these improvements that I have already mentioned, in pain, in activity level, in Lysholm score, and self-assessment. But in the acute patients, the controls also showed similar improvements. That was the basis for no benefit in the acute, but that was only in the comparison, but the acutes had all the same improvements as the chronics in terms of what we're here to consider today.

However, there were two things that were shown to demonstrate superiority in the chronic group to partial meniscectomy controls in the chronic arm of the study, and that is that they regained more of

their lost activity level than the chronics did, and they had a lower reoperation rate that was related to meniscus symptoms when compared to chronic controls.

The Tegner Index is something that needs a little explanation. This is something that we utilize to rate the activity level profile of each patient. And so we included the pre-injury Tegner score, the pre-surgical score, which documented the amount of lost activity that they had, each individual patient, and then what it was at the longest follow-up, and expressed -- how much of was lost was regained is expressed as a percent, and that's the Tegner Index. I know there have been questions about the Tegner Index, but it has been separately validated for use in assessing meniscal injuries with the authors listed.

And the Tegner Index is merely a mathematical calculation using a validated scale, and there is no need to have separate validation of the index. And the index, the difference between just using pre-op Tegner and post-op Tegner is that the index takes into account the pre-injury level of function. And the potential for recall bias, we feel, was addressed by the fact that all patients were asked to recall their pre-injury level at the

same point in the trial whether they were implant patients or controls.

The reoperation rate for meniscal symptoms and chronic CS patients was significantly lower than in the controls, 9.5 percent compared to 22.7, a statistically significant difference. The same definition meniscal symptoms relating and being the reason for the intervention were used in both CS and partial meniscectomy patients and also for all acute and chronic. So they all have been calculated using the same definitions.

So conclusions I'd like to concentrate on from the clinical data is that, first of all, this is more clinical data that's been collected on a CS than any other cleared surgical mesh currently available. 170 patients between the multi-center trial and the feasibility studies with almost six years follow-up. The device provides a stable interface with the host rim resulting in a mean of 70 percent increase in tissue to reinforce the remaining meniscus rim and the meniscus horns.

The data shows that the tissue remains viable and durable through at least 5.8 years. And we have that one case now at 11 years. The CS patients improved significantly from their pre-

operative pain, function, self-assessment, and activity levels. And the outcomes were comparable to partial meniscectomy except that the CS patients have the added benefit of more tissue and that both acute and chronic patients benefited from an increase in tissue and increased outcomes. Thank you.

MR. DICHIARA: I'd like to introduce our next speaker, Dr. William Montgomery. Dr. Montgomery will talk about safety from the clinical studies. Dr. Montgomery did his training at the Hospital for Special Surgery in Orthopedics and is a sports medicine surgeon. He's an orthopedic sports medicine surgeon at the San Francisco Orthopedic Surgery Medical Group. He's chief of training at the San Francisco Orthopedic Residency Training Program. Dr. Montgomery?

DR. MONTGOMERY: Good morning. So I'd also like to state that I was a clinical investigator but I had no financial interest in ReGen or the device.

Safety is obviously very important, and, as Dr. DeHaven has mentioned, because of the IDE study, the multi-center study, we have more safety data than -- with this device than any other surgical meshes that are there on the market at all.

And if we go ahead and look at serious

adverse effects -- events. An adverse event is broadly defined in protocol as any event that is not of benefit to the patient. And that includes every report, every report of pain, swelling, et cetera, regardless of whether it's anticipated or not. And that includes any typical expected complaint. And it's too broad of a category to be compared with complications in literature or databases.

A serious adverse event is defined as an adverse event which is fatal, life-threatening, permanently disabling, unexpected, or results in hospitalization. And that includes pain, swelling, paresthesias at a time point -- excuse me -- at a time point which can actually be compared with other ones in the literature.

So SAEs were evaluated as a basis of comparison to predicate meshes. And the sources for that would be literature, predicate product labeling, and FDA, MDR, and MAUDE databases. Safety data collected under the IDE study included all SAEs, not just those related to the operative knee.

So comparison to the predicates. The types of incidence of SAEs and SDAEs, which would be serious device-related adverse events, occurring in the CS group are comparable to those occurring with

predicate meshes, and the best predicate mesh to compare that to would be with the surgical meshes of the shoulder. But, in addition, 18 percent of the CS patients had SAEs -- this is in the IDE study -- 6 percent of CS patients had serious device-related events.

If we look in the literature for the use of surgical mesh in hernias, the complication rate ranges from 7 to 57 percent. If we look at the literature for the shoulder, it has little bit more than is what on the slide, but the reintervention rate, which is really the reoperation rate, ranges from 20 to 26 percent versus 8.8 percent in the CS. And the explant rate was actually 16 percent, which is comparable to 3.7 percent for the CS. So we don't really need to compare for safety the CS with partial meniscectomy, but we have a nice study which actually gives an idea of what the safety profile is like.

The results from the CS study showed no statistically significant difference in the rate of SAEs between the CS and the partial meniscectomy groups even though the collagen scaffold patients experienced an additional relook surgery and biopsy at 12 months post placement. And there's no statistical difference was shown on either a per-

patient basis or per-event basis or per-event basis either cumulatively or at any time point between -- through a mean of 4.9 years up to seven years. And this is an excellent indication of safety. No other mesh has been compared in such a manner to surgery without mesh. And the *JBJS* publication of the CS study reported 7.5 percent of CS patients and 7.3 percent of the partial meniscectomy control patients had an operative knee-related SAE that required some sort of treatment, meaning that there was no difference at all.

At relook procedure, it was noted that 16 percent of the patients, 20 or 22 patients reported that the collagen scaffold was not firmly attached to the meniscus, and there has been some concern from the FDA with regards to this. But this did not mean that the implant was loose. Rather, it may not have been firmly attached along the entire interface. And if we look at these 22 patients, 17 of these patients showed an average of 20 percent tissue gain with a mean total tissue of 64 percent. Only three of them showed no meniscal growth at all, and two of them were explanted cases.

The lack of the firm attachment to the entire rim does not translate into failure of the

device or failure of the device to provide increase tissue within the defect. Literature on other mesh devices point out that areas of the mesh that are not in direct opposition to the host tissue will resorb without providing an adequate interface for integration and tissue growth, such as in the shoulder and a hernia. And this typically is without any type of complication.

So we have some additional results from the collagen scaffold study. During relook surgery, there were no observations of damage to the articular surfaces that appeared to be the result of the device. Probing of the tissue at relook showed that the issue to be -- was pliable and similar to the native meniscus. A histological examination showed no evidence of a negative tissue reaction to the implant material, with tissue developing into fibrochondrocytic, which is essentially meniscal-like tissue. Results of immunology study also showed that there was no evidence of clinically significant humoral immune-mediated response to the collagen scaffold.

There is also the results from the early feasibility study with eight patients. Again, we had 5.8 year follow-up. No unanticipated adverse events;

no significant complications; relooks showed no damage to the articular surfaces related to the use of the implant. And we did have some radiologic assessment at pre-op, one, and two years which showed no significant progression of Fairbanks changes, essentially, it'd be arthritis, and no noteworthy changes in joint space or axial alignment.

When we look at our European experience, we have over 2,000 of the CS devices implanted. The complaint rate, which is what they use in Europe, is 0.31 percent and none of which indicated a significant safety issue. And publications of the European experience indicate no complications associated with the use of the device.

In conclusion with regards to the safety, the clinical data with up to seven years follow-up demonstrated long-term safety of the collagen scaffold for its proposed intended use. Adverse events were not unexpected and were consistent with those associated with predicate surgical meshes. Data from 141 relook procedures and 136 biopsies showed the CS device provided a scaffold for meniscus-like matrix production by the host with no damage to the joint or adjacent articular surfaces caused by the implant. There is no evidence of

immune response, no evidence of negative histological reaction to the implant material.

Even compared to partial meniscectomy, which does not involve a mesh, does not treat the meniscus loss, and did not require a relook surgery and biopsy, there was no significant difference in SAEs at any time point. And then safety data provide reasonable assurance that the CS device is as safe as legally marketed surgical mesh predicates. No new types of safety or effectiveness questions were raised when compared to predicates with the same intended use of soft tissue reinforcement and providing a scaffold for replacement by the patient's own tissue.

Now, we've talked about predicates, and I'd like to go into a little comparison of the shoulder using a mesh in the shoulder and using a surgical mesh in the meniscus. So the most easily used comparison would be the DePuy Restore Surgical Mesh, and that's used essentially for rotator cuff repairs. And the specific FDA-cleared indication for the Restore Surgical Mesh is for the use in general surgical procedures for reinforcement of soft tissue where weakness exists. The device is intended to act as a resorbable scaffold that initially has

sufficient strength to assist with soft tissue repair but then is replaced by the patient's own tissue. 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 limited to the supraspinatus, which part of the rotator cuff, during rotator cuff repair surgery.

So when we look at this for purposes of substantial equivalence, there are a number of similarities between the shoulder and the knee. The shoulder joint is not a weight-bearing joint. However, the primary force on the rotator cuff is tensile. Likewise, the primary force on the meniscus is also tensile. Now, the FDA Panel package suggests that the use of the surgical mesh in the shoulder and the knee are quite different, but I have to disagree with this, being as they both have the majority being tensile forces going across them. The tensile force in the shoulder is higher, as much as an order of magnitude higher than the meniscus, but the shoulder also sees compressive forces similar to the meniscus in the knee because of impingement of that rotator cuff against the acromion.

The use of a surgical mesh in the shoulder and the meniscus are similar. The Restore device in

the shoulder does not replace the rotator cuff, does not provide the full mechanical strength of the repair. They use sutures or anchors to do this. The collagen scaffold device in the meniscus does not replace the meniscus and does not provide the full mechanical strength of the repair. Sutures, meniscus rim, and horns do this. And both have new tissue growth.

So I'd like to describe a little bit of the use of the Restore surgical patch so you know exactly what's going on. This is a picture of it, just a drawing, and you can see the patch with the little sutures covering a repair of the tendon. And the Restore patch is placed over a large area of the rotator cuff, not only the suture line. And unlike Restore, there are meshes such as the BioBlanket, which are specifically labeled for suture line reinforcement. That's not the case with the Restore patch.

This an in vivo picture, same type of patch. You can see the sutures around it and it's covering the entire surgical procedure, the whole repair, not just the suture line. The surgical technique indicates that the Restore should be used if the tendon is thin, delaminated or frayed,

essentially, if it's a weakened tendon. The intent is to allow tissue growth into the deficient area not only to reinforce the suture line. Therefore, adding mechanical strength is inherent in its use as a surgical mesh in this procedure.

In this next picture, this is from the labeling of the Restore implant, and the Restore implant is also labeled to fill gaps where the coverage of the humoral head is incomplete. And, as you can see from this picture, you can see the little hole in the tendon that the labeling for the Restore patch means that it can be used to fill defects.

So the surgical mesh reinforces soft tissue. The FDA has indicated the Restore mesh or Restore mesh is not used to repair the rotator cuff. Yet, the labeling and use of the device show the intention to provide a scaffold for tissue growth to reinforce the deficient tissue and aid in the repair. And the FDA has indicated that the Restore mesh does not add mechanical strength. However, the purpose of the resorbable mesh in the shoulder and in the knee is to add tissue volume that reinforces the deficient tissue and adds mechanical strength. Thank you.

MR. DICHIARA: Thank you, Dr. Montgomery. I'd like to summarize and provide some conclusions

based on the data that's been presented. The bench testing and animal studies show that the CS device functions as any surgical mesh to reinforce the meniscus following partial meniscectomy. This is new indications just like the new indications that I mentioned before.

The device provides a resorbable scaffold that is replaced by meniscus-like fibrochondrocytic tissue similar to other surgical meshes that are resorbable scaffolds. The clinical data from a single center feasibility study and multi-center trial show that the CS is as safe and effective when used as mesh in the meniscus as has been demonstrated for other legally marketed predicate devices. And this is shown both for acute and chronic patients, as has been seen in the clinical outcomes data and the data regarding the amount of tissue growth.

In all cases, the benefit for both chronic and acute patients is a significant increase in tissue within the meniscal defects which reinforces the meniscus and allows the surgeon to preserve more of the native meniscal horns plus the statistically significant improvement in all of the clinical outcomes measures that were discussed. The clinical data that we've presented, we believe, clearly shows

that the device is as safe and effective as other legally marketed predicate devices. Thank you.

DR. MABREY: And thank you. I'd like to thank the Sponsor's representatives for their presentation.

Does anyone on the Panel have questions related to the Sponsor's presentation? And I will begin with Dr. Spindell

DR. SPINDELL: Just one question. In the clinical study, the large clinical study, did the control group, the partial meniscectomy, did they have relooks as well or just --

MR. DICHIARA: The control group did not have relooks. It was not felt to be necessary to relook the control group because the purpose of the relook was to determine that the device provided additional tissue and filled the meniscal defect and also functioned appropriately, didn't cause any damage to articular surfaces. In the case of a partial meniscectomy, the literature is well-known that, you know, the meniscus, once you do a partial meniscectomy, does not substantively regenerate itself.

DR. SPINDELL: Thank you.

DR. MABREY: Anything else? Ms. Dalrymple,

questions?

MS. DALRYMPLE: Well, I enjoyed the presentation. I guess, when I was reviewing the information, I was just wondering, there was a question about the weight-bearing with the knee, but I know that you had a lot of people in your clinical study. I was just wondering how you address that specific to how much time it took for them to rehabilitate. Like, I noticed that there was a longer length of time in one of the studies overall to regain full activity. And can you speak a little about that?

MR. DICHIARA: Yes. Just like with any of these resorbable surgical meshes, when you use them, they need to be able to fill in and to heal, as opposed to a partial meniscectomy. In a partial meniscectomy, all you do is cut out damaged tissue, so there is no healing response. You have just taken everything out. In a case where you do, say, a meniscus repair or something else, I'll let Dr. DeHaven talk about that.

DR. DeHAVEN: Yes, in the specific case with an implant, for the first week, the patient was not to be weight-bearing at all, just using crutches and barely touching down. And then for the next five

weeks to be still using crutches with just partial weight-bearing, gradually increasing so that by the sixth week point they would be off the crutches. In addition, they had some limits in motion in the very early-going so that there would be minimal risk of dislodging the sutured implant. And then -- so that was to provide the best opportunity for healing and integration.

This is exactly the same as what I've always done with meniscus repair cases of minimal weight-bearing but motion early on to help stimulate and help allow healing to take place. And then for both of these procedures, you need to allow time for maturation of this new tissue so that it doesn't get destroyed with excess loading. So, again, it's parallel with a meniscus repair patient where we're repairing their own meniscus and that it's a very gradually increasing type of rehabilitation so that no truly serious heavy loading would take place until approximately six months. And the basic science has shown us that that's enough time for the maturation process and then gradually increase from there. So that's a vastly different return to function, but it's expected because it's a very different procedure.

MS. DALRYMPLE: Okay. Thank you.

DR. MABREY: Dr. Propert?

DR. PROPERT: I have two questions which I hope are quick. The first one has to do with this Tegner Index. I'm still trying to understand exactly what this is. Is this correct that it is simply the percent change in the activity scale from pre-injury to post-op?

MR. DICHIARA: No, that's not.

DR. PROPERT: Or from pre-op to post-op?

MR. DICHIARA: No, it isn't. Actually, I'll let Dr. DeHaven talk about that because he was involved in developing that.

DR. DeHAVEN: Now, it uses all three points.

DR. PROPERT: Okay.

DR. DeHAVEN: It uses the pre-injury activity level. Then to the preoperative level, that number went down.

DR. PROPERT: Um-hum.

DR. DeHAVEN: So for each patient, that creates the lost function. Then, at the longest follow-up we have the third Tegner score, which shows how far back they came, and the index is simply what percent of the lost function has been regained by the

final follow-up, and that's expressed as a percent of regaining the lost function.

DR. PROPERT: So I see from the title of the paper, "Developing the Original Scale," that it was validated for responsiveness to change, but has this particular mathematical construction been validated for responsiveness to clinical change?

DR. DeHAVEN: Well, as I've mentioned, it's simple math using a validated instrument.

DR. PROPERT: Okay. My other question, and it may be easier to answer this later, is I noticed on your clinical outcomes slide you had some patients lost to follow-up, and it would help me -- especially the 20 patients who were lost before the relook, and it would help me to understand why they were lost.

MR. DICHIARA: Yes, we'll have to go back and get that data for you, but, you know, one of the things is that the lost to follow-up, you have to realize that the term of the actual study, the endpoint termination, was originally two years. The data that we're presenting is all of the clinical data. Past two years follow-up, the patients were followed by questionnaire through seven years so that when you went to questionnaire versus having patients come in for visits, there's a natural patient loss.

DR. MABREY: Thank you. Colonel Kragh?

COL KRAGH: Can you clarify for me whether the indication will include acute?

MR. DICHIARA: Actually, that's something that we would like you to discuss among yourselves. We've presented the data on the combined acute and chronic. From the standpoint, our position has been, and, you know, and still remains that as a surgical mesh, the device is intended to reinforce soft tissue. If that's the intention and both groups have an increase in the amount of tissue, which reinforces the native meniscus, then it's effective for both groups. Again, you would want to look at, you know, those both groups to see if there's a change in outcomes as a result of that, did those patients also improve, and we showed that there is a clinically significant improvement in all of the outcomes measures both for the chronic and the acute. So we would like you on the Panel to consider that information.

COL KRAGH: So --

DR. MABREY: Colonel Kragh, that question is going to be addressed this afternoon --

COL KRAGH: Okay.

DR. MABREY: -- as part of the FDA

questions.

COL KRAGH: Okay. That's all I have.

DR. MABREY: No, go ahead. I just wanted to let you know we're going to specifically address that this afternoon. Dr. Kelly?

DR. KELLY: I have two questions, sir. One is why were acute patients even included because I think it'd be difficult to ascribe any improvement from the scaffold or differentiate that from any improvement from the meniscectomy itself. And, actually, when someone has a partial meniscus tear, they're going to get better after the surgery just from the resection. So I think it's very, very difficult to discern what effect the scaffold had versus just the meniscectomy.

MR. DICHIARA: I'll let one of the clinicians, Dr. DeHaven, address that issue of why you would want to use this in acute patients.

DR. KELLY: I'm having difficulty with why even including that data, because if someone has a partial meniscus tear, if you do a Tegner pre-op or Lysholm pre-op, they're going to get better by just simply resecting the meniscus acutely.

DR. DeHAVEN: Yes, it's true, and it was clear at the very onset that, you know, particularly

in a two-year window, partial meniscectomy is hard to beat. It's a very good operation. And so in a sense, we were hopeful that the implants would do as well clinically as the partial meniscectomies in the first two years because they had a more conservative aftercare, et cetera. And that also the thinking was if there is going to be significant additional tissue, why not make that available to the acutes if that's going to be helpful in the long run. It's going to take long-term data to really prove any chondroprotective effect. But at least we know the tissue is there. But it was in the chronic arm that gave the best opportunity to see what impact the implant would have on the ongoing symptoms of somebody with a partial meniscectomy who wasn't doing well.

DR. KELLY: The question I have, Dr. DeHaven, is just an overview of the recent literature, there seems to be a trend, at least for the shoulder, that xenografts elicit more of an immune response, inflammatory response than allogeneic tissue. There seems to be some winds of change that perhaps the more processed and the more foreign the tissue is, the more inflammatory response that may be evoked. How do you explain the paucity

of inflammation from a xenograft tissue?

DR. DeHAVEN: Well, I personally have not been involved with the xenograft approaches. I know the early attempts were pretty disastrous and that I guess they're refining what they do to it, but I'm really -- I don't know -- Bill, do you have any information on that?

DR. MONTGOMERY: Well, I think a couple things. Just with regards to the xenograft, if you're going to put a xenograft meniscus in -- so let's say you had some sort of pig meniscus, or something, that you wanted to put into the person, even though the body is going to infiltrate this with its own cells, there is still going to be a large portion of that xenograft remaining, and that's probably where some of the response comes from. When we're using a resorbable scaffold such as this, it's been so washed out it's really just the collagen that's there and then there's a couple other little ingredients with regards to it, and most of that gets absorbed -- I think it's getting absorbed before there's any type of response to it. So I think that's the difference between putting something where the majority of it remains or for -- at least for a long period of time versus going to be resorbed in a

short period of time.

The other thing is with regards to the acute and chronics. And, again, we included all of them because we were hoping in the long term, since we're going to have long-term follow-up in this that we're helping people in the long run, even the acutes. When we first did this study and looked at it and all the surgeons sat down and discussed it, our best hope for the acute arm was if we were equal at two years, or probably even five years because that's still a short period of time, to partial meniscectomy, were in good shape. As long as we're not worse, because bottom line is in acute arm, partial meniscectomy do great in the first two years often to five years.

The chronic arm was the ones that people already -- their pain was not because of meniscus tear. Their pain was because of deficiency in the meniscus. So it's a different group. So they're already the ten-year out meniscectomy, you could say. So if that arm looked better, than that was going to be a good thing because those are people who already are deficient from the meniscus.

COL KRAGH: Thank you.

DR. MONTGOMERY: Did I answer that?

COL KRAGH: Yes.

DR. MONTGOMERY: Okay.

DR. MABREY: Great. Dr. Endres?

DR. VIGORITA: Could I add one additional thing to that because the question that was asked is very important for all these surgical meshes, allogeneic and xenogeneic. And this issue has received an incredible amount of attention especially in the past two years in the field of regenerative medicine, people working with all of these surgical mesh materials.

And this goes probably a little bit beyond what you'd want to know, but it's all good news for the surgical mesh community in that when they're -- it's the processing, basically. By decellularizing them, you get rid of all of the major epitopes, antigenic epitopes that cause an adverse immune response. Every one of these surgical mesh materials that's put in that's not autogeneic, which is virtually all of them, are indeed recognized by the host as not self.

But what we've learned particularly in the past two years is that there are two arms of an immune response to these sorts of tissues. One of them, it's called M1TH1 and M2TH2. Every one of

these meshes elicits an M2TH2-type response, which is what -- immunology would call accommodation or tissue remodeling. It's the opposite M1 that gives you the adverse immune-type response or adverse immune responses that you -- most people think about. So the issue that you're -- the question you're answering is certainly very important, but the news is all good in terms of safety.

MR. DICHIARA: I'd like to make one comment, too, regarding your questions about the acute patients and benefit. You have to remember that when we're looking at this as a surgical mesh for a 510(k) while, you know, you as a clinician will look at it compared to a partial meniscectomy, the goal of a surgical mesh is to be able to compare it to a predicate. Did it show the same benefit as a shoulder mesh to reinforce the shoulder? The shoulder mesh with five patients certainly never showed -- what they showed as the endpoint with five patients and three months follow-up is that with those patients, the patients improved in pain and range of motion at three months with five patients.

So what you're looking at is a comparison between the function of this device as a surgical mesh to reinforce soft tissue and not the ultimate

clinical outcome. Of course those clinical outcomes are important, as you mentioned, from the safety standpoint. You certainly wouldn't want to put this device, grow a lot of new tissue and have a worse clinical outcome. That's not a good result for the patient or the company or for anybody. So --

LTC SHAWEN: Dr. Mabrey, may I go ahead and ask my question? It relates to --

DR. MABREY: Yes, please.

LTC SHAWEN: -- by Dr. Kelly. When we're looking at the relative cellularity of these meshes, it was mentioned that they are acellular, when more recent data shows that SIS grafts are not totally acellular when compared to some of the other grafts. And I would like at least a commentary on the relative acellularity of this graft that we're looking at and then looking at the SIS graft and just a comment since that was made that they are acellular.

MR. DICHIARA: Absolutely.

DR. VIGORITA: You're absolutely right in terms of the term acellular, and I think it requires clarification by everybody making these grafts. So the attempt is you lyse the cells, you get rid of all the debris, and I think anybody would understand that

it's virtually impossible to get rid of all of the debris.

There's an article coming out in the *Journal of Surgical Research* next month where we compared about a half a dozen commercially available meshes that are all called acellular, including the Restore device. And every single one of them has got measurable amounts of DNA. We went further. We even looked at how big are the pieces of DNA that are left in the material. And virtually all of them are less than 200 base pair, which will cause no antigenic response at all. And so the issue -- so the point is, it's not those cellular remnants or the nuclear remnants that are present that are causing the host response that you see.

And the other part of this is how much of the host response is actually that overlap between remodeling and inflammation. As I pointed out, we want a robust cellular infiltration and those mononuclear cells that are infiltrating them aren't necessarily indicative of a problem. In fact, they're part of the remodeling. They assist in the degradation, and what we've recently shown also is that many of these cells actually stick around and become part of the new tissue, because where did the

fibrochondrocytic cells come from that were -- they were the host cells. And they didn't come from the adjacent cartilage only. They came from these cells that were infiltrating it.

So your point is very well-taken, that I think one of the things we need to look at in all of these meshes is when someone says they're acellular, it needs to be a little bit more quantifiable. In terms of the ReGen meniscus, we've looked at that, and of all of the surgical meshes that are available, ReGen is in the lowest 25 percent in terms of the amount of nuclear material as measured by a PicoGreen assay that we could come up with.

So, you know, in comparison to other surgical meshes, it's no different. In fact, if you wanted to look to the range, it's on the low side of the amount of material that we can measure.

LTC SHAWEN: John, may I make -- also one other comment would be is there any thought of looking at when we're talking about a cellular mesh that is placed into tissue and that is extra-articular versus intra-articular. I think that we probably need to make a differentiation because the immune response is most likely different intra-articularly versus into the tissue itself.

DR. VIGORITA: Well, I think it's different in every location. For example, the immune response and that overlap between immunity and inflammation is going to be different in an anal fistula plug location where there is contamination, certainly, in addition to that, as well as to a rotator cuff, where you've got part of it -- the inside of the joint and part of it not is -- in comparison to the meniscus is totally intra-articular except where, you know, it attaches to the soft tissue, which, again, is different than a ventral hernia. So each one of these locations has got a different immune response.

And so these considerations -- the considerations being given to the ReGen meniscus should really be no different than were given to any of the other surgical meshes when considering these sorts of responses.

DR. MABREY: Okay. Dr. Endres?

MR. DICHIARA: I'd like to make another comment about that. I don't know if you noticed, but in the 510(k), actually, we did a study on the cell-mediated humoral immune response, and we did blood testing throughout the study, and they showed that there was no response above the --

UNIDENTIFIED SPEAKER: On the ELISA test,

correct.

MR. DICHIARA: Sure. And Dr. Vigorita can comment on the histology, because that's also important in looking at local cellular reaction.

DR. VIGORITA: Well, I have little to add from Dr. Badylak's comments. Obviously, to the morphological eye of a pathologist, diagnostic pathologist, this material is very acellular. But as I mentioned, there are additional processing steps including radiation which can impact on that, and as far as cellular infiltration, the infiltration would appear to be at least in two locations coming into the pores. One would be from the residual fibrocartilaginous meniscal rim, and the other is clearly coming from synovial tissue, which, incidentally, as you know, is very active from an immunological point of view in general, in reaction to the viruses we might be ingesting right now.

DR. MABREY: I thought I'd wait until you got up again.

MR. DICHIARA: Thank you.

DR. MABREY: Do you have another question? Do you have another answer for us?

MR. DICHIARA: No, no.

DR. MABREY: All right.

MR. DICHIARA: Ready for another question.

DR. MABREY: Dr. Endres?

DR. ENDRES: Yeah, I got a few questions. You mentioned in the paper that one of the exclusion criteria was abnormal alignment and this was judged by the weight-bearing axis on standing AP radiographs. Were these long-leg alignment films or just regular weight-bearing AP radiographs?

MR. DICHIARA: I'll let Dr. --

DR. ENDRES: And do you recommend long-leg alignment films pre-op?

MR. DICHIARA: Sure.

DR. DeHAVEN: We discussed that before the study ever began, and we recognized that that would be ideal but that, from a practical standpoint, from multiple sites, getting is it a single-leg weight-bearing, is it both legs, how do they do it. So we decided to make the compromise of using the axial alignment on standard weight-bearing AP views, which we at least were able to get. And were looking for people that were going to tremendously overload the medial compartment and wanted to exclude those. So, you know, it's not as accurate as a true mechanical axis, but under the circumstances, we didn't think we were going to really have a consistent thing to

measure the mechanical axis.

DR. ENDRES: I think sort of along those lines, I think in the paper it says that all of these surgeries were done on the medial meniscus, is that correct? And, if so, is it -- would this device be indicated for the lateral meniscus as well although none of them were done on the lateral meniscus?

DR. DeHAVEN: That's true. This particular IDE study was for the medial meniscus.

DR. ENDRES: Another technical question. I think --

MR. DICHIARA: I would like to respond to that. You know, we have no reason to believe that it would be any different, and, as a matter of fact, the product that's distributed in Europe is indicated for both lateral and medial, and they're devices implanted in patients, and, you know, we have been collecting data in Europe on lateral as well as medial patients.

DR. ENDRES: Okay. And I think all of the procedures were done with an inside out technique. Did that involve a formal longitudinal incision posterior to the MCL with a use of a popliteal retractor?

MR. DICHIARA: I'm not a surgeon, so I'll

let Dr. DeHaven --

DR. DeHAVEN: Yes, it did.

DR. ENDRES: Could you also do this with an all-inside technique or would you recommend --

DR. DeHAVEN: You could now with the fast-fix device. We've shown that to ourselves in a cadaver workshop. But it's no longer available. It was only available in the study. So, in Europe, they're routinely using the all-inside, particularly the fast-fix, because it is pretty easy to do vertical sutures, which are most of the sutures. But at the anterior horn and the posterior horns, they're horizontal, but it's adversatile. And so it would -- I think the way it would be done if it's cleared would be with a reliable all-inside device.

DR. ENDRES: Just a couple quick questions about --

DR. MONTGOMERY: Let me just comment on that. When we first started -- I mean, this has been a ten-year-old study. So when we first started this, the standard of care was either an outside in or an inside out, so we did a standard inside out repair. Before it got cleared in Europe, I worked with some of the European surgeons in the lab, and we did them all-inside using a fast-fix. And then we took the

knees apart to look to make sure that we thought that we had good fixation. It actually worked great. So the majority of the cases and probably all of them now in Europe that are being done are all done on an all-inside technique, and it's been validated in the lab as well as now in vivo.

DR. ENDRES: And so is it just vertical mattress sutures at the rim or do you have to do anything --

DR. MONTGOMERY: We use vertical mattress along the rim, but then when you attach it to the anterior and posterior horn, you use a horizontal --

DR. ENDRES: Okay.

DR. MONTGOMERY: One or two horizontals in each one of those.

DR. ENDRES: Okay. And then just a couple quick questions about scores. Why do you think that there was no statistically significant difference in the Lysholm score, the pain score, or the patient self-assessment score?

MR. DICHIARA: There was a statistically significant difference from pre-op in all three --

DR. ENDRES: But between the control group and the surgical group, I think -- I have the paper right here. It says --

MR. DICHIARA: That's right between the partial --

DR. ENDRES: Correct.

MR. DICHIARA: One comment. I'll let Dr. DeHaven address that, but one of the comments is, again, from the standpoint of a 510(k), the comparison isn't clinical outcomes to partial meniscectomy. The standard would be comparison to predicate devices for safety and effectiveness, and the effectiveness would be, you know, its intended use to reinforce tissue. But I'll let Dr. DeHaven address that.

DR. DeHAVEN: Yeah, this was true. The clinical data of the pain and self-assessment and Lysholm were not statistically different in the chronics or the acute, but it's a very good example of why the Tegner is so important because -- and there is a statement in the FDA package that says the Tegner cannot be used without the Lysholm. But it's really the other way around. The Lysholm score has no meaning if you don't know the functional level.

So in the chronic patients, they had the same clinical symptoms, but to do that, they had to have a lower level of activity. And the only way that comes out is looking at it with the Tegner. And

the Tegner -- you know, the Lysholm, I'm sure you're well-aware, was developed in Sweden. And they realized that data was meaningless without the activity level. And then they came up with the Tegner Scale subsequent to that.

DR. ENDRES: The last question. I would assume that the Tegner scores, the pre-injury and the pre-operative Tegner scores, were equivalent in the control group and the surgical group. Is that correct?

DR. DeHAVEN: Yeah, I don't have the exact details, but I think the pre-op -- do -- yeah, they were very similar.

DR. ENDRES: Okay.

DR. DeHAVEN: But, again, using this index approach, you accommodate for that as well.

DR. ENDRES: Thank you.

DR. MONTGOMERY: Just one more comment on the -- why the results weren't that different was, again, it's a five-year study. And what we're going to be looking -- what we're hoping is in the long run, in the 10 to 20-year or even further out, that that's where we're going to see the difference where those scores will hopefully be better with the implants.

DR. MABREY: Dr. Potter?

DR. POTTER: Actually, I have three questions. With your assessment of tissue regeneration, you used a measuring device, a measuring tape placed arthroscopically so the surgeon could assess the amount of tissue regeneration. Do you have any reproducibility data on that?

MR. DICHIARA: I'll let the surgeons talk about how they measured it.

DR. DeHAVEN: Yeah, actually, the measuring device was used at the time of implantation to measure the defect so you knew how large to make the -- how long to make the implant. At the second look, there were some confounding factors. One was just like with meniscus repairs, there's some synovial overgrowth, and so the determining where the original meniscus-synovial junction was and comparing that to what we saw at the second looks was very difficult. And the thing that was consistent between the surgery picture and the one-year picture were the sutures. So we could then interpolate tissue within the sutures, tissue beyond the sutures, as regenerated tissue.

DR. POTTER: Did you actually measure it arthroscopically or just eyeball it?

DR. DeHAVEN: Well, we could measure it at the anterior horns and at the posterior horns in terms of whether it matched up to the native tissue or not. But beyond that, it was an estimate.

DR. POTTER: Okay. Two more questions. I applaud your use of objective MR assessment in both your feasibility study and your European study, but I had some questions regarding the methodology. In your feasibility study, you used MR to assess again meniscal regeneration. You used a T1-weighted pulse sequence, which arguably has very poor contrast between the fibrovascular response and the synovial fluid, and then you also used a gradient echo sequence, which is also going to be very degraded in a post-operative setting, particular around all the non-absorbable suture. In that paper, there was really no methodology specifically expressed about how you sized the meniscus. Was this a segmentation algorithm? How was that done?

MR. DICHIARA: I'll let our radiologist discuss, you know, the methodology. A couple of comments, though, first --

DR. POTTER: Um-hum.

MR. DICHIARA: -- is one MR in the multi-center clinical study was originally part of the

protocol. When FDA required the actual relook arthroscopy, the MRs would -- they were dropped from the protocol. Number of reasons, but just of course multiple sites, ten years ago, it was not the standard of care to do MR and was not always easy to have done.

The other thing is that there is an animal study that was done, which we presented to FDA early on, which compared histologic results to the actual MRI results in a dog model. And while we could see some differences, it wasn't elucidive enough to be able to define tissue maturation, and, therefore, we had biopsies with direct histological examination rather than using MR.

DR. POTTER: Okay.

MR. DICHIARA: Okay. Dr. Ho? Dr. Ho is a radiologist who was involved with reading the radiographs from the study.

DR. HO: My name is Charles Ho. I'm a radiologist by training. I was a radiologist consultant on the feasibility study and on the multi-center trials. I did review the imaging studies that were done in both of those. I was paid a consultation fee for each exam I reviewed, and I also did make an investment in a private placement funding

for ReGen in 2003.

Having said that, in terms of the feasibility study, that was done a number of years ago. That was at a single site, single center, and so the imaging studies were controlled, at least reproducible on all the patients. Having said that, I did not set up the imaging study. I would not have chosen T1 or gradient echo sequences, but that was what I had to be able to look at. In terms of estimating how much tissue was regrown, based on the imaging sequences I had, I compared the pres and the posts, and that was how I was able to -- that's the only evaluation I could do.

DR. POTTER: Did you get a meniscal volume by segmentation or just kind of eyeballing?

DR. HO: This was subjective.

DR. POTTER: Subjective?

DR. HO: This was subjective.

DR. POTTER: Okay.

DR. HO: In terms of the multi-center trials, the -- we did request specific imaging protocols for the radiographs and the MRI, but with 16 centers, we found that we could not get any of the centers to adhere to that protocol. And so it was requested subsequently once we realized we had the

second looks that we have direct visualization and biopsy. ReGen did request -- the FDA to remove the imaging arm of the multi-center trial and the FDA did approve that.

DR. POTTER: Okay. Stay up there one more.

DR. HO: Aha.

DR. POTTER: For the European trial, you state that MR showed evidence of biocompatibility of the collagen implant. What were your MR criteria for assessing biocompatibility?

DR. HO: The European trial, I did not review those studies, so I do not know specifically what to say about that.

MR. DICHIARA: Those are published literature. We had nothing to do with those studies. Those were investigators in European --

DR. POTTER: But you do state them in your 510(k). You refer to them in --

MR. DICHIARA: Yeah, we included them as published literature, and, you know, those are experiences that -- the device has been for sale in Europe since 2001, so those were publications that we just cited because of the information that they contained. We don't have the details of the MR. You know, if that were -- we could always, I'm sure, go

to those investigators and get the information, but, no, that was not under our control, those studies.

DR. POTTER: Um-hum.

DR. MABREY: Dr. Kadrmas?

MAJ KADRMAS: Just a few quick studies, or real quick questions. One, first of all, on the technique. It says -- it's indicated with tears that extend at least to the red/white zone. Just for my understanding, so that's the central peripheral portion of the tears -- to the red/white zone, the anterior, the posterior horns are formed into --

MR. DICHIARA: I'll let the --

MAJ KADRMAS: -- radial tears extending to the red/white zone? Is that correct or do you excise the entire anterior/posterior horns to the white/white zone to implant the meniscus?

DR. DeHAVEN: No, absolutely not. We used the probe as a measuring device to measure how close to the meniscal/synovial junction is the tear and up to five millimeters, we consider that the red zone and that the red zone stops at five millimeters on the medial meniscus. So the red/red zone is the peripheral five millimeters of the meniscus.

So it has come up that the implant patients had more meniscus removed than the control patients

on a mean, and the implication was that we were excising extra tissue just to put the -- good tissue to put the implant in. That's absolutely not the case. If a patient randomized to implant had a minor tear that could be treated with a partial meniscectomy without getting anywhere near the meniscal/synovial junction, that's what we did and they were excluded.

So the depth of the preparation was determined by the depth of the tear. And then at the anterior horn, we didn't really remove any anterior horn. We made a square cut back to the depth of the tear because this facilitated anchoring the implant, and it was going to -- it was stabilized by the implant. Normally, you would contour it so you would take out tissue maybe up to, you know -- the anterior horn. It's fairly small to begin with. But on the posterior side, it was the same.

So squared-off cuts anteriorly and posteriorly at the anterior and posterior extents of the tears, taking it back as far as the tears went, and then if it was within the peripheral five millimeters, then it met the criteria of being in the vascular zone.

MAJ KADRMAS: So -- thank you, sir. This

is part of a sub-question with that. Cited the numbers at second look arthroscopy, 16 percent of the implants --

DR. DeHAVEN: Sorry to interrupt you. One second. Just about the red/red, red/white, and all the white/white zone, when we left the posterior and anterior horn, theoretically, we're leaving white/white zone, okay? And, again, theoretically you think, well, how does it heal there because there is no blood supply. And they did. We saw a number -- I had some that healed 100 percent, looked like a normal meniscus when we went back in. And that most likely was cellular infiltration from the synovial fluid that went in and allowed that area to heal. We did initially leave that part basically for fixation, because we wanted to have a solid fixation in the anterior and posterior horns, but we did see good healing in that area. Not all the time, but we did see some that healed all the way in. Thank you. Sorry to interrupt.

MAJ KADRMAS: That kind of falls into the second question, which is 16 percent were cited as not firmly attached at second look arthroscopy. Were those attachments not attached to those anterior peripheral horns, or anterior and posterior horns, or

were they --

DR. DeHAVEN: That had to do with the way that the questions were asked. For each of the surgeons, we had actually a huge notebook on each one of the patients, and when we did the relooks, we had a bunch of questions, what the tissue felt like, what it looked like, what percentage we thought was the re-healing, and then there was a question about the healing on the periphery. And there was basically fully integrated, not at all, and then there was this broad zone, which was partially. And that could mean that you put your probe in, it felt a little soft in one little spot, maybe it didn't heal in, or there was a gap in one of the horns. Sometimes we had one that would heal on the anterior horn, not on the posterior horn or vice versa, but all along the rim.

So there were various different types of healing that all got packaged into that -- those 22 patients. And that's why when you look at them, they're not all failures by any means. I think two were explants, three didn't have any tissue growth, but I think 15 of them still had -- or 17 still had up to I think average of 20 percent regrowth of tissue. Some were much more than that, but the mean was 20 percent. But that was just sort of a big

package of the in between patients, and they all got included in that one category.

MAJ KADRMAS: Okay. Thank you. The second question is just kind of a -- thing throughout the papers if you could just clarify a little bit. One of the benefits you cite in your paper with this compared to partial meniscectomy was the partial meniscectomy reoperation rate of 22 percent, which is -- in a separate section, you cite average reoperation rate of menial meniscectomy in multiple studies of 12 and a half percent. Why the discrepancy between 22 percent reoperation rate with the partial meniscectomy and the multi-center study and the 12 and a half percent in the literature?

MR. DICHIARA: One thing is, first of all, comparing the reoperation rate between partial meniscectomy and the device is not the comparison to, you know --

MAJ KADRMAS: Sure.

MR. DICHIARA: -- predicate surgical meshes, but I'll let one of the clinicians talk about that.

DR. MONTGOMERY: I can't remember the exact ones that were quoted in there, but that was an average taken from probably a low, 5 percent, to a