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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEDICAL DEVICES ADVISORY COMMITTEE

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ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

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April 20, 2023

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Via Web Conference

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	Elizaveta Kon	Professor, Orthopedic Surgery, President, International Cartilage Regeneration and Joint Preservation Society	Milan, Italy
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	Seth Sherman, M.D.	Orthopedic Surgeon, Stanford University	Stanford, CA
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	John Foerster	NUsurface Implant Recipient	Denton, TX
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	Don Bennett	NUsurface Implant Recipient	Philomath, OR
	Rebecca Robinson	NUsurface Implant Recipient	Tombstone, AZ
	Mike Smith	NUsurface Implant Recipient	Birmingham, AL

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Call to Order

Dr. Smith: I would like to call this meeting of the Orthopaedics and Rehabilitation Devices Panel of the Medical Devices Advisory Committee on April 20th, 2023, to order. It's now 9:00 AM. I'm Dr. Harvey Smith, the chairperson of this panel. I'm an orthopedic surgeon. I work at University of Pennsylvania. I also have an affiliation with the Philadelphia VA Medical System. I note for the record that the voting members present constitute a quorum as required by 21 CFR part 14. I would also like to add that the panel members participating in today's meeting have received training and FDA device law and regulations.

For today's agenda, the committee will discuss, make recommendations, and vote on clinical information related to the de novo request for the NUsurface meniscus implant sponsored by Active Implants, Incorporated. The device is a polymeric disc shaped device implanted in the medial compartment of the knee to distribute load between the distal femur and proximal tibia and is intended to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected.

Before we begin, I would like to ask our distinguished committee members and FDA representatives attending virtually to introduce themselves. Committee members, please turn on your video monitors if you have not already done so and unmute your phone before you speak. I will call your name, and then please state your area of expertise, your position, and affiliation. Ms. Stacy Bonnell.

Panel Introductions

Ms. Bonnell: Hello and good morning. My name is Stacy Bonnell. I am a global leader of regulatory affairs for Nuvasive, acting in today's panel in the role of industry representative. I

currently serve the board of directors and the role of past president for the Orthopedic Surgical Manufacturer's Association, which is an industry advocacy group. Happy to be here. Thank you.

Dr. Smith: Dr. Amy Price.

Dr. Price: Hi, I'm Amy Price and I'm serving as a consumer representative today. And I have experience; I'm an editor with the British Medical Journal, a senior scientist with Stanford School of Medicine. And I also have personal experience with orthopedic devices due to a trauma in 2004. And I'm really excited to, to hear the views and to reason together about this product. Thank you.

Dr. Smith: Dr. Laura Porter.

Dr. Porter: Hello, I'm here as a patient representative. I've had bilateral total knee replacements. I have also on my left knee, had multiple surgeries. I had a tibial osteotomy, ephemeral osteotomy, an OATS procedure, cartilage transplant, a total knee replacement, and then a revision of my knee. So I have extensive orthopedic experience. I ended up with a total knee at 37, and all the prior surgeries were to prevent that from happening. Thank you.

Dr. Smith: Dr. Shelby Reed.

Dr. Reed: Good morning. I'm Shelby Reed. I'm a professor in the Department of Population Health Sciences at Duke University, where I lead the preference evaluation research group. I'm here today because I'm an expert in patient preference research.

Dr. Smith: Dr. Amy Cizik.

Dr. Cizik: Good morning. Thank you for having me. Amy Cizik. I'm an assistant professor in the Department of Orthopedics at the University of Utah. I'm here today to represent the views of patient reported outcome measurement in orthopedics.

Dr. Smith: Dr. Samprit Banerjee.

Dr. Banerjee: Hi, I'm Samprit Banerjee. I'm an associate professor of biostatistics in the Department of Population Health Sciences at Cornell University's Weill Medical College. I have done research in comparative effectiveness of hip replacement and knee replacement devices. And I'm here as a biostatistician.

Dr. Smith: Dr. Scott Evans.

Dr. Evans: Good morning. I'm Scott Evans. I'm a professor and chair of the Department of Biostatistics and Bioinformatics, and the director of the Biostatistic Center at the Milken Institute School of Public Health at George Washington University. My expertise is in clinical trial design and analysis. Thank you.

Dr. Smith: Dr. Ty Subhawong.

Dr. Subhawong: Good morning. I'm Ty . Subhawong. I'm an associate professor of radiology at the University of Miami. And my interests include both bone and soft tissue tumor imaging as well as cartilage imaging. Thank you.

Dr. Smith: Dr. Melvin Helgeson.

Dr. Helgeson: Good morning. I'm Mel Helgeson. I'm the professor and Director for Surgery at Walter Reed and an orthopedic surgeon.

Dr. Smith: Dr. Thomas Barber.

Dr. Barber: Good morning. I'm Dr. Thomas Barber. I'm an orthopedic surgeon and total joint surgeon presently in transition between jobs where I'm moving from Memorial Sloan Kettering to become a professor at University California San Francisco, and with expertise in registry oversight.

Dr. Smith: Dr. John Kirkpatrick.

Dr. Kirkpatrick: Good morning. I'm John Kirkpatrick. I'm an orthopedic surgeon at the Orlando VA Hospital.

Dr. Smith: Dr. Paul Manner.

Dr. Manner: Good morning. My name is Dr. Paul Manner. I'm a professor at the University of Washington. My area of clinical specialization is hip and knee replacement, and I also serve as senior editor at the Journal of Clinical Orthopedics and Related Research.

Dr. Smith: And Captain Raquel Peat.

Capt. Peat: Good morning, everyone. I'm Captain Raquel Peat. I'm a microbiologist as well as an officer in the United States Public Health Service. Currently, I am the director for the Office of Orthopaedic Devices here within the Center for Devices and Radiological Health. I have over 25 years of experience as a regulatory technical expert, as well as a manager and leader within FDA. Thank you very much for being here. We look forward to an exciting day.

Conflict of Interest Statement

Dr. Smith: Thank you. Dr. Akinola Awojope, the Designated Federal Officer for the Orthopaedics and Rehabilitation Devices Panel will read the conflict of interest statement.

Dr. Awojope: Good morning, everyone. I will now read the conflict of interest statement. The Food and Drug Administration, FDA, is convening today's meeting of the Orthopaedics and Rehabilitation Device Panel of the Medical Device Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of industrial 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 regulation.

The following information on the status of this panel, compliance with the federal ethics and conflict of interest law covered by but not limited to, those found at 18 U.S.C Section 208 are being provided to the participants in today's meeting and to the public. FDA has determined that members and consultants of this panel are in compliance with the federal ethics and conflict of interest law. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have a financial conflict when it is determined that the Agency's need for the particular individual's services outweighs a potential financial conflict of interest. Related to the discussion of today's meeting, members and consultant of this panel who are special government employees or regular federal employees have been screened for potential financial conflict of interests of their own as well as those imputed to them, including those of their spouses or minor children, and, for the purpose of 18 U.S.C. Section 208, their employers. These interests may include investment, consulting, expert witness testimonies, contract, credos, grants, teaching, speaking, writing patents and royalties, and primary employment.

For today's agenda, the panel will discuss, make recommendations, and vote on clinical information related to the de novo request for the NUsurface meniscus implant, sponsored by Active Implant, Inc. The intended use of the device is to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected. Based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, no conflict of interest waivers has been issued in accordance with 18 U.S.C. Section 208.

Ms. Stacey Bonnell is serving as an industry representative, acting on behalf of all related industry. Ms. Bonnell is employed by Nuvasive.

We would like to remind members and consultants that if the discussion involves any other product or firm not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participant needs 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 relationship they may have with any firm at issue. A copy of this statement will be available for review and included as a part of the official transcript. Thank you.

The appointments were authorized by Russell Forney, Director, Advisory Committee Oversight and Management staff on April 6th, 2023. I will now read the appointment to temporary voting status memo for the duration of the Orthopaedics and Rehabilitation Devices Panel meeting on April 28th, 2023. Laurel D. Porter, M.D., has been appointed to serve as a temporary non-voting member. For the record, Dr. Porter serves as a consultant to the Oncologic Drug Advisory Committee at the Center for Drug Evaluation and Research, CDER. This individual is a special government employee who has undergone the customary conflict of interest reveal and has reviewed the materials to be considered at this meeting.

I will now read the deputization memo. Pursuant to the authority granted under the Medical Devices Advisory Committee, charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and amended August 18th, 2006, I appoint the following individuals as voting members of the Orthopaedics and Rehabilitation Device panel for the duration of this meeting on April 20th, 2023: Shelby D. Reed, Ph.D.; Amy M. Cizik, Ph.D.; Samprit Banerjee, Ph.D.; Scott R. Evans, Ph.D.; PhD. Ty K. Subhawong, M.D.; Melvin D. Helgeson, M.D.; Thomas C. Barber, M.D.; John S. Kirkpatrick, M.D.; Paul A. Manner, M.D. For the record, these individuals are special government employees or regular government employees who have undergone the customary conflict of interest review and have reviewed the

materials to be considered at the meeting. These two memos have been signed by Dr. Jeffrey Shuren, March 27, 2023. A copy of this statement will be available for review and will be included as a part of the official transcript. Thank you.

FDA encourages all other participants to advise the panel of any financial relationship that they may have with any issues or firms.

A few general announcements, as follows. In order to help our transcribers identify who is speaking, please be sure to identify yourself each and every time that you speak. The press contact for today's meeting is Audra Harrison. Thank you very much. I'll hand it over. Back to Dr. Smith.

Dr. Smith: Thank you. We will now proceed to the FDA's presentation of the De Novo Program. I would like to invite the FDA to begin.

Overview of De Novo Program — Dr. Peter Yang

Dr. Yang: Good morning, everyone. My name is Peter Yang. I'm the Program Lead for the De Novo Program in the Division of Submission Support in the Office of Regulatory Programs, in the Office of Product Evaluation and Quality at the Center for Devices and Radiological Health at the FDA. I'm going to be presenting on the de novo program, helping you understand what a de novo request is. Just giving you some of the context for how the input that you're providing today on this submission will be used in FDA's decision making on this submission.

So just to give you a brief background into how the FDA classifies medical devices, medical devices that are reviewed by FDA are subject to one of three levels of classification. So risk-based classification process, Class I, Class II, or Class III. Class III are for generally the highest levels of risk in terms of medical devices. And so the classification that a device will have is dependent on the particular risk and the level of regulatory control that is needed for FDA

to ensure that those devices remain safe and effective. And so we'll start with the lowest level of classification and go to the highest level.

So Class I devices are subject to general controls. So any device that's Class I is subject to general requirements that are in place for a wide variety of medical devices. Things like registration and listing of manufacturing facilities to enable inspections, quality system requirements, which is basically good manufacturing practices, medical device reporting, that is reporting of adverse events to FDA, and prohibitions against misbranding or adulteration of the device. There are lots of devices for which just these general controls and there are other general controls here, I've just listed some of the most common ones, commonly known ones. These general controls provide for reasonable assurance of safety and effectiveness for the device. And devices that are Class I are generally exempt from FDA pre-market review. So FDA does not routinely review these devices.

Devices that are Class II are subject to the same general controls, but Class II devices are also subject to special controls that are tailored to the specific device technology and intended use. And so special controls will include things like specific bench testing requirements that are specific to the device technology, specific labeling requirements, and even specific clinical or post-market requirements. So to be legally marketed, devices that are Class II need to meet both general controls and special controls. They receive marketing authorization. They're cleared from marketing through the 510K process and demonstration of what we call substantial equivalence. And I think I'll have more on that in a subsequent slide.

Then there are Class III devices. So Class III devices are also subject to general controls, but then they're also subject to the pre-market approval process. And so the pre-market approval process requires a company to demonstrate reasonable assurance of safety and effectiveness for

the proposed intended use, sort of from first principle demonstrating that that device is safe and effective for what it's intended for. And so this includes a number of additional controls that are not available for Class I or Class II devices, so that includes things like reviewing ongoing manufacturing changes to the device, and approval of many manufacturing changes before they can be implemented, ongoing annual reporting requirements, and conditions of approval that are a little bit more robust than what you can get in Class II, including post-market requirements as well. So those devices are approved through the PMA process. So we have devices that are exempt, devices that are cleared, and devices that are approved.

So what happens if we have a device that is not classified? So something that is new or something that the FDA hasn't seen before. Then we arrive at the de novo process. Okay? So a de novo request is a type of pre-market submission, like a five 10 KK or PMA. So if granted, a de novo request allows a company to market a new device in the United States. But a de novo request is intended — so it's like a 510K or PMA, but it's intended for new types of devices that are low to moderate risk that are otherwise automatically classified into Class III. So here's what I mean by that. If FDA encounters a new kind of device that, by virtue of its intended use or technology, is different from other kinds of devices, the Federal Food, Drug, and Cosmetic Act automatically classifies that device into the highest level of risk, Class III, and requires that that device have a PMA in order to be legally marketed.

But as you can imagine, not every new kind of device that FDA encounters has the same kind of risk profile as something we would've reviewed through PMA. And so therefore, a de novo request allows a device to get onto the market because they're actually requesting that we formally classify the device for the first time into either Class I or Class II based on a determination of reasonable assurance of safety and effectiveness. So it's not substantial

equivalence, as we talked about for Class II devices in the 510K process. A company is not comparing themselves to an existing device that's on the market and saying, I'm as safe and effective as this other device that's out there. That's the substantial equivalence paradigm for Class II devices. Rather, they're saying, my device, from first principles, is safe and effective. And based off of that, we determine that the device can be classified into Class I or Class II.

If we grant the de novo request, we actually create a brand-new classification regulation for that device. And then that device becomes regulated through the 510K process if it's Class II. If it's classified as Class I, it's exempt. But more often than not, it will become a Class II device, and future devices will use the de novo device as the predicate comparison, and the comparators say, hey, I'm as safe and effective as the original de novo device. And so it will create a new sort of branch of devices that are of the same type as the de novo request that you're considering today. And so then future devices will ask FDA to determine that they're substantially equivalent and get onto the market that way. But the first of its kind device here, that's what we're doing in a de novo request. That's what you're considering this morning.

Okay. So a couple of things that we go through to make sure the device is actually new, because FDA obviously reviews a ton of different kinds of products. And so we have a couple of high-level criteria. I won't go into all of them here, but there's a couple. The criteria include, has to be a medical device. It can't fit into any existing classification regulation. So we have lots of regulations for different kinds of devices. And so it can't fit into any of those regulations. It's not substantially equivalent to any predicate device that FDA has ever reviewed. It is completely brand new. It also can't fit into an existing Class III regulation. So some devices are classified by regulation into Class III. They require a PMA. Some other devices are not officially classified as

Class III, but they're historically reviewed and approved through the PMA process, and so it can't fit into same type as something that's approved through the PMA process also.

Once we determine that something is a new type of device and therefore it's eligible for the de novo classification process, then, as part of any classification process, we have these three goals to meet. The first goal is to determine whether the probable benefits of the device outweigh the probable risks to health, sort of your standard benefit risk analysis. The second goal is to identify what the probable risks to health are for the device or product when used as intended. And then the third goal is kind of what we talked about, to determine the level of regulatory control that's needed to mitigate the risks that we identify. So if we only need general controls, again, that's Class I. If we need a combination of general controls and special controls, that's Class II. Assuming we meet all three of these goals together, that's what provides reasonable assurance of safety and effectiveness. And that's what allows us to grant a de novo request.

So the first part of our decision making is the benefit risk assessment. And so this is where we're definitely asking you to provide input today. The benefit risk assessment, of course, is based off the totality of evidence in the de novo request, and we assess probable benefits and probable risks of the device. And then we also assess additional factors in our benefit risk thinking. So for example, uncertainty. What's our inherent confidence that the data that we're reviewing is representative of what we're going to see in the real world? That includes statistical considerations, study design considerations, and so forth. Patient perspectives, whether that's looking at patient preferences or patient reported outcomes, looking at values and endpoints that are important to patients. And then the unmet medical need. What are the other devices in this space? What are the other treatment options for these patients? And how might this device meet an unmet medical need in this space?

We create a new classification regulation whenever we grant a de novo request. So that will receive its own federal regulation number, you know, 21 CFR 888 point whatever. We'll draft a new regulation name and then identification language, which basically includes the intended use and the key technological characteristics that are shared by all devices within that regulation. So it's a statement of what FDA believes to be a single kind of device, a single device type, with a shared intended use and technology among all the devices in the regulation.

We also create a risk mitigation table, and this is where we draft what the risks to health are for the device type. So not only for the device that you're considering today but all similar devices in the future. Risks to health are written from the patient's perspective, what the patient will experience. And then, and that's on the left side. And on the right side we have mitigation measures. These are categories of testing or other kinds of requirements, which together mitigate a particular risk to health. So for the risk of infection here, we have reprocessing validation and labeling. For the risk of adverse tissue reaction, we have biocompatibility evaluation. And then the particular risks and mitigations for any particular device are going to be dependent on that device's intended use and technology. And we have some backup slides. If people are interested, we can go through an example there. They're not in this main presentation, but if folks have questions, we can definitely give an example.

Next, we have special controls. Special controls are legal requirements for all devices in the regulation. They're written as part of the new classification regulation. And special controls are requirements that include, and they're not limited to, nonclinical testing requirements, bench testing, clinical validation requirements, labeling requirements, and some post-market requirements as well. I just want to point out here with respect to post-market authorities as special controls. Post-market studies are not intended to address pre-market questions. And by

that what I mean is, post-market studies are intended to address post-market issues. So things that are really a post-market concern or risk that can really only be studied in the post-market setting. Post-market studies are not intended to be used to bypass addressing a pre-market question. We do need to determine reasonable assurance of safety and effectiveness for the device before we grant a de novo request, before that device can be authorized. And that's what, all the special controls need to be met before we grant the de novo request. That's what we're saying there at the bottom bullet. It has to mean its own special controls. We need to make sure it actually belongs in this regulation. It meets all the requirements that we set for it before we can grant the de novo request and before we grant that device marketing authorization to sell their device in the United States.

So when a new de novo is granted, the device can now be legally marketed, of course subject to the special controls. But also when that de novo is granted, we send a letter to the sponsor saying, hey, you're ready to start marketing your device. We also established the brand-new classification regulation. And by doing that, the de novo device can now be used as a predicate device for future devices to be cleared through the substantial equivalence process. So if this device were be to be granted, another device could come in and say, I'm just as safe and effective as the de novo device, and I want to get into the market too, demonstrate that they're as safe and effective, and get onto the market. We will also publish a decision summary that provides transparency into our decision making and allows for folks to understand the decision that FDA made and also how the company met, how the device met the special controls so that future devices have a template, have an example, for how they could also meet the special controls with their own data. And then we will publish the new regulation in the code of federal regulations. The regulation is created when we grant the de novo request, but there's a separate

process to update the code of federal regulations. So it has to go through a separate process within the federal government.

So just to place the questions that we're asking today and the discussion that we're asking you to provide for FDA. The context for these questions is that we are asking questions today about the benefits and risks of the NUsurface meniscus implant. And so what we're doing in this panel is we're soliciting your input. You'll provide non-binding recommendations. You'll answer some questions. You'll clarify your thinking, and that will provide FDA with a lot of additional expertise and input to help understand whether or not to grant this de novo request. And if granted, FDA will go through the process of creating the new regulation, drawing up the special controls, and whatever's needed to help provide reasonable assurance of safety and effectiveness. And so your benefit risk discussion today will really play into that.

Dr. Smith: Thank you. And we will now proceed to the FDA's presentation on the Breakthrough Device Designation Program. I would like to invite the FDA to speak.

Breakthrough Device Designation — Ouidad Rouabhi

Ms. Rouabhi: Good morning. My name is Ouidad Rouabhi, and I'm the Assistant Director for Policy and Operations Team One in the Office of Clinical Evidence and Analysis within the Office of Product Evaluation and Quality in CDRH. My team oversees several CDRH programs, including the Breakthrough Devices Program, which I'll be discussing today. Our learning objectives for this session are to provide an overview of the Breakthrough Devices Program to review the criteria for breakthrough device designation, and lastly, to describe program features.

At a high level, the intention of the Breakthrough Devices Program is to provide patients and healthcare providers with timely access to devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. I'll talk more

about what qualifies as a breakthrough device in the slides to come, but the key thing to keep in mind is that for certain devices that meet the program eligibility criteria, FDA will expedite their development assessment and review.

The program guidance outlines the key principles of the program, which help to achieve that goal of more timely patient access. I won't go into each of these points, but I wanted to highlight a few key ones. The first is the opportunity for interactive and timely communication. Sponsors of designated breakthrough devices are able to receive feedback from FDA more quickly and collaboratively. This allows them to move forward with device development decisions more quickly while being reassured that the data that they plan to collect is consistent with FDA's expectations. Similarly, the program also aims to prioritize the review of marketing applications for designated devices, as well as aims to apply efficient and flexible approaches during review, such as enhanced opportunity for post-market data collection, all the while preserving the statutory standards for marketing authorization.

This last bullet is really an important one. The Breakthrough Devices Program does not change the statutory standards for marketing authorization. This means that sponsors of designated breakthrough devices are held to the same standards as similar devices that have not received the designation. Breakthrough device designation does not imply that the marketing application will be authorized.

There are a few things to note about the program. First, this is a statutorily mandated program under Section 515B of the Food, drug and Cosmetic Act, which was enacted following the passing of the 21st Century Cures Act at the end of 2016. The final guidance document describes the program's implementation and was issued in December of 2018. This is a very

useful document that contains all of the policy and process information that I'll be sharing with you today, and the link is listed here on this slide.

Lastly, this is a voluntary program, meaning that sponsors can choose to request the designation and they're not required to do so. Sponsors can request entrance into the Breakthrough Devices Program by submitting a breakthrough device designation request. If entrance is granted, then the sponsor will have additional mechanisms for feedback and interaction with FDA during device development as they're working towards their marketing submission. We'll talk about these more in the slides to come.

Next, I'll talk about the criteria for breakthrough device designation. There are a few eligibility considerations that a device must meet in order to be designated breakthrough. First, the program is only open to medical devices and device led combination products. Second, devices seeking breakthrough device designation must be subject to future marketing authorization via the PMA, de novo, or 510K pathways. Devices that are exempt from these marketing pathways would not be eligible for the program. Lastly, the device should meet the specific criteria outlined in the statute, including fully meeting breakthrough device criterion one, and one of the subparts of breakthrough device criterion two.

Because the designation criteria are the basis for all of our grant or deny decisions, we do take a thoughtful approach in ensuring that each criterion is met. Beginning with Criterion one, the device in its proposed indication must provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions. A device must fully meet this criterion in order to be eligible for the program.

Because decisions on request for designation are made prior to marketing authorization and a complete clinical data set is not required and may not be available at the time of

designation, FDA considers whether the sponsor has demonstrated a reasonable expectation that the device could provide for more effective treatment or diagnosis of the disease or condition identified in the proposed indications for use. Reviewers take into consideration whether the sponsor has demonstrated a reasonable expectation of technical success, meaning that we reasonably expect the device can be built and function as intended, as well as clinical success, meaning that a functioning device could more effectively treat or diagnose an identified disease or condition. Mechanisms for demonstrating a reasonable expectation of technical and clinical success could include literature or preliminary data.

The statute specifically calls out life-threatening or irreversibly debilitating human disease or conditions. So one thing that we do consider is whether the patient population or subpopulation identified in the proposed indications for the device are representative of that statutory criteria. We generally interpret life-threatening as a disease or condition for which the likelihood of death is high unless the course of the disease is interrupted. In the case of irreversibly debilitating, we consider the impact on such factors such as survival, day-to-day functioning, and the likelihood of progression to a more serious disease or condition if left untreated.

In addition to meeting criterion one, the second criterion requires that the device and it's repost indication should meet one of the following subparts in criterion two, either that the device represents a breakthrough technology, meaning that the device represents a novel technology or novel application of an existing technology that has the potential to lead to a clinical improvement, or that no approved or cleared alternatives exist, or that the device offers significant advantages over existing approved or cleared alternatives, or that the availability of which is in the best interest of patients. I won't go into examples for each of these today, but our

guidance document does talk about considerations for these subparts in more detail once a device enters the program.

There are a few different features outlined in the guidance that are useful for facilitating interactions with FDA. These are a few examples of features that sponsors can pursue within the program. Some of them you may have previously heard about. First, a data development plan is an optional map of the development process from entry into the program until the marketing submission and including post-market activities as necessary. The DDP is a high-level document that summarizes the plan, non-clinical and clinical testing, so that everyone is on the same page about data collection expectations. This can hopefully add predictability, efficiency, and transparency to the device development process in a way that's least burdensome. Next, the guidance discusses a sprint discussion, which is a highly interactive process to facilitate reaching rapid agreement on a single development issue. And lastly, regular status updates in between submissions, which can be useful for planning purposes.

There are a few items that I wanted to note at the marketing submission stage. First, it's important to keep in mind that breakthrough device designation must be requested prior to FDA receiving the marketing submission. This means that, as we mentioned previously, a decision on the designation request is typically made while the device is still under development and complete data has not yet been collected. During the review of the marketing submission, the program principles and benefits are applied, including those we mentioned earlier, such as expedited interactions and priority review, as well as senior management engagement and opportunity for pre-/post-market balance of data collection when it's appropriate. I want to note again that the statutory standard for marketing does not change. As with any marketing

submission, the review team reviews the totality of clinical and nonclinical evidence to make the regulatory decision.

In summary, the Breakthrough Devices program is intended to provide patients and healthcare providers with timely access to breakthrough devices. Devices are designated by making the statutory criteria and designated breakthrough devices can benefit from program features intended to expedite the development, assessment and review of these devices, both during device development as well as throughout the regulatory submission process. With that, we'll be happy to take any questions.

Q & A

Dr. Smith: I'd like to thank the FDA representatives for the presentations. Does anyone on the panel have a brief clarifying question for the FDA? Yes, Dr. Thomas Barber.

Dr. Barber: Just a quick question. By designation of de novo device it would seem to me, then, that the comparison for effectiveness would have to be conservative treatment as opposed to comparison to other existing devices that may not be identical but may be similar in the treatment regimen. An example from the past might have been surface replacement arthroplasty compared to total hip replacement where, as a surgeon, we would be weighing those alternatives, but here in a regulatory standpoint, we seem to be looking at the prosthetic in isolation as opposed to compared to other devices that while different may have the same effectiveness profiles, et cetera. So I'd just like to understand better how we are to evaluate that. Whether it has to be an isolation, or can we think about it with reference to other types of devices that may be different, but with the same principles.

Dr. Yang: This is Peter Yang with the de novo program. Great question. And I think it's a complex one. For FDA's perspective, we're not making a direct comparison to a device, because

our comparison would be much more thorough based on the intended use and technology. And so that's not what we're doing here. We're sort of doing an independent finding of safety and effectiveness. When you talk about benefits and risks, it's going to be in the context of alternatives.

So it's helpful to consider a device in terms of what other devices or treatments are out there for that condition and how does this device compare in its performance to that, comparing not only benefits, but the risks as well. And so I think it is helpful to kind of do this analysis in the context of other devices. But it is important to remember that you should still be thinking about this device on its own and whether or not, based on the data that you're seeing, it does demonstrate that the benefits outweigh the risks.

Dr. Smith: Excuse me, I was muted. Doctors, does anyone else have a question? If not, then we will proceed. We will now proceed to the sponsor's presentation. I would like to invite the sponsor to begin. I will 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 chair. The sponsor will have 90 minutes to present. You may now present your presentation.

Sponsor Presentation: NUsurface

Mr. Belaney: Hello, my name is Ryan Belaney. I'm the Vice President of Clinical and Regulatory Affairs at Active Implants. In our presentation today, I'll provide an introduction to the device and the indication statement, an overview of the implant design and regulatory history. Dr. Elliott Hershman will discuss the clinical need in patients indicated for the NUsurface implant, as well as the clinical studies and outcomes. Dr. Nogah Shabshin will provide

information about MRI findings in the clinical trials, and Dr. Deryk Jones will focus on the benefits and risks of both the NUsurface and non-operative therapy.

The proposed indication for the NUsurface meniscus implant is to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected. The indication for use is in patients with mild to moderate osteoarthritis, mild or greater knee pain, and cartilage present on the load-bearing articular surface. Each element needs confirmation from patient history, physical examination, videographic imaging, or visual observation.

The following contraindication and warning have been added to the instructions for use. Patients with extrusion of the medial meniscus five millimeters or greater are contraindicated for the device. Patients in which the height of the tibial spine is below 11 millimeters are at greater risk of device related adverse events.

The NUsurface implant is a biologically inert device made from a hydrophilic polycarbonate urethane, reinforced with ultra-high molecular weight polyethylene fibers. The NUsurface eliminates the concentration of forces in the medial compartment, distributing mechanical loads. This relieves pain and improves function and helps prevent cartilage degeneration.

The form and shape of the implant were developed from extensive MRI studies and morphometric computational models. The implant was designed with medical grade materials to replicate the material properties and shape of a natural meniscus. Here you see a comparison of the NUsurface implant and how it appears in the knee. From a superior viewpoint, the implant is not attached, allowing it to replicate the movement of the native meniscus. Because it is not

anchored, the procedure to implant the device is straightforward and does not damage bone, cartilage, or ligaments.

Pre-clinical testing included cadaver tests to confirm the implant could distribute loads similar to the natural meniscus. Kinematic evaluation using a robotic simulator showed good stability of the implant in cadavers. An in vivo sheep study demonstrated that the NUsurface and the PCU material could protect the cartilage.

The NUsurface implant was granted market authorization in the European Union under a CE mark in 2008. The first human clinical use began later that same year with an 18-patient pilot study. From 2011 to 2013, a multicenter trial enrolled 128 subjects in Israel, Belgium, Germany, and Italy.

The US regulatory history of the NUsurface implant began in 2008. Two 510K submissions comparing NUsurface to cleared metal meniscus replacements were not substantially equivalent. NUsurface was determined to be de novo 510K eligible. Two IDE clinical trials were approved to confirm benefit versus risk of the device, the randomized control Venus study and the single arm Sun study. Enrollment in Venus began in 2015. In 2017, the company met with FDA to discuss the data that would be included in its future de novo submission, at which time pulling the studies to create the Mercury study was first discussed. The statistical analysis plan for Mercury was approved in an IDE supplement in the spring of 2019 prior to the completion of either the Sun or Venus trials.

The NUsurface meniscus implant was designated as a breakthrough device in the fall of 2019 as treatment for a patient population with an irreversible debilitating condition with the potential to be more effective than current treatment options. The Mercury study results were submitted in July of 2020 as a de novo submission. The de novo was denied in June of 2021,

which was upheld on appeal in September of 2021 because of FDA's benefit risk assessment. This resulted in a discussion of a subpopulation that increased the benefit and decreased risks in the Mercury study. In June 2022, the company submitted the current de novo application with data from a subpopulation of the Mercury study.

Thank you for your time. And now, Dr. Elliot Hirschman will describe the patient need, current treatment options, and clinical outcomes.

Dr. Hershman: Good morning. My name is Elliot Hershman, and I am a New York City-based orthopedic surgeon at Lennox Hill Hospital, a part of Northwell Health. I'm the chairman emeritus of the Department of Orthopedic Surgery and an associate professor of orthopedic surgery at the Hofstra Northwell School of Medicine.

People today expect to live longer, more active lives, but greater longevity is increasing the burden of osteoarthritis on society. I've specialized for over 30 years in sports medicine, and my goal is to help my patients meet their treatment needs by providing the most effective, least invasive, and least morbid treatment options available. The NUsurface implant was designed to help those patients suffering from persistent knee pain caused by excessive loads on their medial compartment following previous meniscectomy surgery pain that is caused by damage to the subchondral bone and articular cartilage.

I am a consultant to Active Implants. I have been paid for my time and travel here today and have equity into the company, but do not have royalties or other interests contingent on the outcome of this meeting. I served as the medical director and principal investigator of both the Sun and Venus clinical studies, and I look forward to sharing with you the outcomes from the trials and thank you for your attention today.

Knee pain is the leading source of physical disability and impaired quality of life in industrialized nations. It is estimated that almost half of adults in the United States with diagnosed symptomatic knee osteoarthritis have had sufficient progression of osteoarthritis, such that if they were symptomatic, they would be eligible for knee replacement. Medical management without surgery is frequently sufficient, and over 15 million patients are treated with pain medication, physical therapy, bracing, and weight loss programs every year. As seen in this table, over 5 million knee injections are administered annually, and over two and a half million knee surgeries are performed each year, making knee pain the third most common reason for elective surgery following cataract removal and cesarean section.

Thinking about treatment in a hierarchical fashion, the first line of treatment for most patients with knee pain are the non-operative therapies described in the previous slide. The American Academy of orthopedic surgeons International Consensus statements and published guidelines all agree that non-operative care should be considered as the initial approach for treatment of non-traumatic knee pain. If these measures are unsuccessful, injection therapies can be a good next option. Injection treatment includes corticosteroid injections or hyaluronic acid injections.

A significant number of patients with traumatic knee injuries will, of course, require surgery. This would include, for example, ligament reconstruction, as for a torn ACL, articular cartilage repair for an acute full thickness lesion, and meniscus repair for an acutely displaced meniscus tear. In all these situations, our goal is knee preservation by restoration of injured anatomic structures. The goal of sports medicine surgery is to keep our patients healthy and active by repairing or reconstructing injured menisci or ligaments. For many of these knee

preserving surgeries, reoperations remain high. In general, these are situations and procedures that do not apply to the NUsurface population.

Injuries to the meniscus are quite common. An estimated two and a half million Americans annually have a meniscus injury. Many of these people are treated with arthroscopic surgery. Why are there so many meniscal injuries and meniscectomy procedures? The answer in part is the structure of the meniscus. The meniscus has a limited blood supply or vascular supply, and therefore poor healing potential when it is torn or damaged. Meniscal tears are often treated non-operatively, and this approach can certainly yield satisfactory results in many individuals. There are, however, patients that are unimproved by conservative measures, and these patients are generally offered arthroscopy with the intent to repair or remove the damaged meniscus through a minimally invasive approach. Every year, about 450,000 arthroscopic partial meniscectomies are performed on patients between the ages of 45 and 64 years old.

We recognize that it is important to preserve the meniscus and do whatever we can to maintain it at the time of surgery. However, it is frequently necessary to remove some of the damaged avascular tissue. Arthroscopic partial meniscectomy has satisfactory results, particularly in the short term. However, over time, pain returns in 15 to 50% of patients.

The population indicated for NUsurface are specifically these patients still symptomatic and in pain after a medial meniscectomy procedure. Why are musculoskeletal care providers focused on preserving the meniscus? Well, the meniscus plays a crucial role in the function of the knee, and it is important for protecting articular cartilage, supporting ligamentous stability, maintaining neutral leg alignment, and allowing for lubrication and transportation of cells in and out of articular cartilage. Biomechanical studies demonstrate that a normal meniscus distributes

the forces across the joint, lowering contact pressures. After a meniscectomy, the loads transmitted across the joint are concentrated over a smaller area, leading to higher forces.

Looking at the bottom image on the bottom right, the blue arrow represents the load from the femur as it is transmitted to the tibia. The green arrows located on the outside of the meniscus show an even distribution of the stress with an intact, functional meniscus. A partially or fully removed meniscus will alter the low distribution. The image on the bottom right shows a concentration of stress over a central location, illustrated in yellow and red. This concentration of stress leads to overload in that specific compartment of the knee. Symptomatically, this can lead to dull pain that some patients compare to a toothache.

The meniscus itself is not the cause of the pain. The pain, we believe, comes from increased pressure on articular cartilage and the underlying subchondral bone. A damaged meniscus can also lead to thinning or loss of the articular cartilage, represented by reduced joint space. Over time, changes in ligament tension can occur, altered joint alignment can develop, and we often observe meniscus extrusion in these situations.

What can we offer a symptomatic, middle-aged patient that has had a previous meniscectomy and may not be a candidate for additional meniscus surgery or meniscus allograft transplantation? Well, treatment options are limited for this patient. Certainly, repeat arthroscopy most likely would be ineffective. Knee replacement, or arthroplasty, is not yet indicated for an individual with intact articular cartilage. Additionally, there is concern for total knee replacement in younger patients, as revision rates may be higher in this population. We can consider what treatment options are available for a 55-year-old patient with knee pain related to a history of one or more meniscectomies and mild medial compartment away.

Replacing the meniscus with another meniscus certainly makes sense. So when possible, a meniscus allograft transplantation may be the best option to replace a damaged meniscus. Meniscus allograft transplantation is the gold standard because key meniscus structures are restored, such as the meniscus rim and the anterior/posterior root attachments. At times, if limb varus alignment is an issue, a high tibial osteotomy can be performed concurrently to improve weightbearing forces across the knee. After recovery, patients can return to sports. However, additional surgical procedures for meniscus tears following meniscus allograft implantation are common. Reoperation rates have been estimated at up to 30%. Generally, meniscus allografts are a treatment reserved for younger patients.

This device corrects annual deformity greater than five degrees and uses a spring mechanism to reduce load on the joint operating like an unloader brace. However, it's internal and fixed to the bone, much like the hardware in a tibial osteotomy. This device was just cleared by FDA, with data from the IDE Clinical trial just published.

Next in the continuum of care is a joint replacement, either a unicompartmental arthroplasty or a total knee arthroplasty. The numbers of hip and knee replacements have been steadily rising each year, mostly because of the baby boomer generation's desire to be more active than any other previous generation. Today, about a third of cases are in patients between ages 45 to 64. The American Academy of orthopedic surgeons released a fact sheet during their 2018 annual meeting forecasting a 600% increase in the number of knee replacement procedures expected in the next 20 years. In an update released earlier this year, they estimated that orthopedic surgeons will need to double the joint replacement caseload to meet rising demand by 2050. But many middle-aged patients aren't ready for a knee replacement. They want to delay

this difficult procedure as long as possible. In addition, patients with viable intact cartilage are not indicated for arthroplasty.

Another significant concern is a potential need for revision arthroplasty in younger patients. This often leads arthroplasty surgeons to recommend delaying a replacement in the younger cohort of symptomatic individuals. Because of the current treatment landscape and lack of options, the proportion of younger patients undergoing total knee arthroplasty is increasing. And predictions state that the under 55 age group will be the fastest growing group by 2030. This trend clashes with recent data like the one from the most recent AAOS meeting, reporting that patients under 55 have worse total knee outcomes than those over 75. This report confirms it is in the patient's best interest to delay knee arthroplasty as long as possible. Knee replacement should be considered as the last surgical option in the management of osteoarthritis and should be indicated in patients with severe cartilage degeneration and advanced osteoarthritis.

In addition to having slightly poorer clinical outcomes, as this graph shows, younger patients also have a much higher risk of revision knee replacement when compared to patients over 70 with 50- to 55-year-olds facing a one in three lifetime chance of revision. The mean time to revision is reported as low as 4.55 years with a range of 4.07 years to 5.02 years. Delaying primary arthroplasty by five years could prevent 17% of total knee revisions. Additionally, once patients do undergo a knee replacement, they have a 33% chance of contralateral knee replacement within five years and a 40% likelihood by eight years from the time of their initial surgery.

The patient indicated for NUsurface is described in the yellow box, 55 years of age, mild to moderate cartilage degeneration with viable cartilage remaining, having had a previous arthroscopic meniscectomy with continued pain and disability. An important point to note is that

there is no new meniscus tear. This precludes a repeat meniscectomy as an option. This is a salvage population with limited treatment options and currently no ideal surgical option available.

AAOS has established the appropriate use criteria for this patient. When a patient has function-limiting pain that affects their function in a single compartment with mild to severe joint space narrowing, and no mechanical symptoms, the recommended treatments are shown on the right. Green check marks are weight management, physical therapy, knee bracing, pain management, and corticosteroid Injections. In red are arthroscopic meniscectomy or PRP injection. These are not recommended.

This image shows the gap in treatment options for the patient we have described. This patient has undergone one or more previous meniscectomies and is in pain. There is a treatment gap between meniscal allograft transplantation, or high tibial osteotomy and arthroplasty. I want to be clear that a patient with viable cartilage is not indicated for an arthroplasty.

The NUsurface is not the first artificial meniscus, and metal meniscus replacements are commercially available in the United States. But we know that metal meniscus replacements are not ideal because metal damages cartilage. Multiple studies report degeneration and wear of cartilage from metal meniscus implants.

NUsurface has been designed to reduce pain while protecting cartilage. In vivo and in vitro research confirm polycarbonate urethane is a cartilage friendly material compared with metal. NUsurface was designed to balance strength and stiffness. As we've seen with the metal meniscus, increased implant strength comes at the risk of damage to the surrounding tissue. On the left, once again, is the pressure distribution of a normal meniscus. In the middle, we see the concentrated stress in yellow and red as the result of a damaged or resected meniscus. On the

right is the stress distribution after implanting NUsurface. The low distribution no longer has yellow or red peaks, and green is distributed around the device, similar to an intact and normal meniscus. The image above the pressure distribution represents a finite element MA model, also calculating low distribution circumferentially around the NUsurface implant.

In summary, the principles of the NUsurface meniscal implant are: first, to mimic the physical and mechanical properties of a normal meniscus; and second, to more evenly distribute stress; and lastly, to absorb strain that would otherwise be transferred to the cartilage in the absence of a normally functioning meniscus.

Let's now discuss the NUsurface procedure. Under anesthesia, a tourniquet is applied above the knee. Bolsters are placed under the buttock and at the end of the table to support the heel when the leg is flexed during surgery. The leg is prepped, draped, and positioned for a knee arthroscopy. An arthroscopy is performed to evaluate the entire joint. This includes assessing the articular cartilage and assigning outer-bridge grades to any wear. Particular note is made of any exposed bone. If present, osteophytes are excised, the remaining medial meniscus is trimmed to create a two-millimeter vertical margin or rim around the periphery. Reparation is complete if the remaining meniscus is stable and horizontal meniscus fibers are visible, along with the drop-off of the medial tibial plateau. A four to centimeter medial parapatellar arthrotomy incision is performed to expose the medial compartment. A sizing trial is used to evaluate the correct size for the final NUsurface implant. The trial is implanted positionally between the medial femur and tibia. Correct placement and proper movement of the trial through the range of motion is confirmed by fluoroscopy. The trial implant is now removed with an extraction tool, and the final NUsurface implant is positioned in place. Final range of motion testing and measurement is

performed. The wound is closed, and after wound closure, a dressing and straightening immobilizer are applied. The entire procedure takes approximately 90 minutes.

The trial implant is radio opaque. Correct placement and movement of the trial implant through the range of motion is confirmed by intraoperative fluoroscopy. The NUsurface implant, however, is radiolucent postoperative evaluation is therefore performed using MRI. These figures depict the correct sizing and placement of NUsurface for a patient. This is a fluoroscopy video which was made while sizing the implant and testing the range of motion during a NUsurface. Notice how the NUsurface remains centered along the femoral condyle through the range of motion. Testing has confirmed that the NUsurface implant translates in the same manner as a native meniscus.

The NUsurface implant was first implanted in 2008 in a pilot study of 18 patients conducted in Europe and Israel. Results from the pilot study led to the 128 subject multi-center trial. This was also carried out in Europe and in Israel. In the United States, the NUsurface implant was investigated in two clinical trials. The first was approved in 2014 and was called the Venus trial. It is a randomized controlled study of 127 subjects comparing the NUsurface to the standard of care, non-operative therapy.

The Sun trial was approved in 2015 and is a single arm investigation in 115 NUsurface subjects. 30 experienced physicians in sports medicine with expertise in knee preservation participated in the Venus and Sun studies. Each investigator and institution is listed. You can see these were multi-center studies by design. Inclusion and exclusion criteria for the Venus and Sun studies were developed from the European MCT study. The major difference in the studies was the inclusion criterion in the US studies requiring a failed previous meniscectomy. The US studies also included a pain management ceiling, an intact municipal rim, and that subjects were

between the ages of 30 and 75 at enrollment. Exclusion criteria ensured that any focal cartilage lesions would not come into contact with the implant. Subjects were also excluded with greater than five degrees of knee angular deformity, knee laxity more than two on the ICR scale, patella component compartment pain, or an ACL reconstruction less than nine months before enrollment. The Venus and Sun studies also excluded subjects with a BMI greater than 32.5.

Here is the study design for the randomized controlled Venus trial. After confirming the inclusion and exclusion criteria and receiving informed consent, study subjects were randomized into two groups. The control group received the current non-operative standard of care for a patient without a surgical option. As mentioned, the non-operative control group had the option of injection therapies with corticosteroid or hyaluronic acid, pain management with over-the-counter or prescription medications, physical therapy, weight loss programs, and braces for the knee. The investigational group underwent arthroscopic surgery and implantation of a NUsurface. After treatment, follow-up visits occurred at six weeks, six months, 12 months, and 24 months. MRIs were taken at baseline, six weeks, 12 months, and 24 months.

The Venus study pre-specified primary and secondary endpoints at 24 months. The primary endpoint was a dual responder composite endpoint that required KOOS pain and KOOS overall improvements of 20 points or greater, confirmation of no MRI failure, and no surgical intervention to remove, replace, or reposition the implant. Surgical intervention to remove, replace, or reposition the device was defined as automatic study failure. For the control arm, any surgical intervention, including arthroscopy, was considered an automatic surgical failure. 20 point KOOS improvement is double the MCID of 10 points, validated in KOOS. In addition to the primary endpoint, secondary endpoints included individual KOOS measurements of visual analog pain scale and the IKDCSKEF, also known as the International Knee Documentation

Committee Subjective Knee Evaluation Form secondary points included six, 12, and 24 month measurements.

The Venus and Sun studies obtain data of high quality. Key baseline measurements that demonstrated no statistical difference included age, KOOS pain, KOOS overall, and cartilage condition. Venus and Sun had high follow up rates with greater than 95% of the expected follow up at each time. Point data was 100% monitored with independent clinical monitors. FDA audited four investigational sites and active implants with no major observations. Results from the Venus study met the primary endpoint with NUsurface superior to the standard of care controls with a P value of 0.029. NUsurface was superior to controls at all time points after six months. Analysis of the surgical events in the Venus study showed that NUsurface and controls were not statistically different at any time points. The responder rate of the NUsurface device was 81% at 24 months measured by the MCID of 10 point improvement in KOOS overall.

The Sun study rationale was to gather safety and probable clinical benefit data to support its future de novo regulatory submission, and to provide additional clinical data on the safety and effectiveness of the NUsurface. As a single arm study, the primary endpoint required 90% of the patients at one year to not have a device malfunction and no single device related adverse event in more than 10% of the subjects.

At a 2017 meeting, FDA recommended pooling Sun and Venus and confirmed that a 24-month endpoint was confirmed. Multiple submissions to the Venus IDE resulted in an app approved statistical analysis plan that merged Sun into the Venus study plan. The combined study is Mercury and included 242 subjects, 176 NUsurface and 66 controls.

All Venus Study success criteria were applied to the Mercury study as well. All Venus primary and secondary endpoints were applied to Mercury. The biostatistician was unblinded from data.

After the revised Venus statistical analysis plan was approved, the average patient was 50 years old with two previous knee arthroscopies, currently taking pain medicine or getting or getting injection therapy without a bridge grade two to three cartilage in the knee. The inclusion exclusion criteria identified patients with a degenerative meniscus and cartilage that is not indicated for arthroplasty as shown on the table. Major baseline characteristics such as age, BMI, and gender were not statistically different. In addition, baseline KOOS pain and KOOS overall values were also not statistically different.

In the total Mercury population, the NUsurface implant met the primary endpoint of superiority over control subjects with a P value of 0.013. The table on the left shows overall study success with propensity adjustments to account for differences in any baseline measurements between NUsurface and controls. Multiple propensity analyses were conducted after comments from FDA. All methods of adjusting the data concluded that the NUsurface device was superior to the controls. Secondary endpoint calculations were preset specified in the protocol, and results showed that all endpoints measured were superior compared to controls. Superiority over the controls was observed at six months, 12 months, and 24 months. These clinical data were submitted in a de novo application in July of 2020.

The analysis shows that there were five types of adverse events at a statistically different rate than controls. Of the five, four were device specific. One was related to the surgical procedure effusion. The device related adverse events resulted in three types of secondary surgeries. The first is repositioning of the original device back into the joint after an implant dislocation or rotation. This occurred in 2% of NUsurface subjects. The NUsurface device was permanently removed in 10% of NUsurface subjects and was exchanged in 20% of subjects. Although the exchange procedure has the additional risk of a surgical procedure, procedures did

not require additional tissue removal and proved to be faster at approximately 30 minutes for each procedure. Recovery was also faster than the primary procedure. This is unique in orthopedics, where revision procedure is typically more difficult and removes more tissue. Dr. Jones will speak about the outcomes of patients in whom the NUsurface was exchanged in his presentation.

The de novo application for the Mercury study total population was denied in 2021. Active Implants appealed this denial, which was upheld. This led to a discussion to identify a subpopulation with a better benefit risk profile. Data submitted in the de novo stratified the outcomes based on the number of meniscectomies a subject had undergone prior to enrollment. An equal percentage of subjects on both the control and NUsurface arms had undergone more than one previous meniscectomy, 30%. Patients with only one previous meniscectomy had much better outcomes compared to those with more than one in both arms.

This subpopulation significantly reduced the number of implant removals and exchanges while also increasing the rate of study success. FDA feedback was at the amount of meniscus removed in a meniscectomy procedure is too variable and more specific diagnostic criteria would be necessary to identify a subpopulation with better outcomes. Meniscal extrusion is a radiographic measurement that identifies a patient with more degenerative changes and a higher risk of failure. MRIs from the Mercury study were analyzed to determine the effect on outcomes in patients with significant meniscus extrusion. Meniscus extrusion is a common radiographic measurement.

Increased meniscus extrusion indicates a non-functional meniscus. The image on the left shows a normal meniscus with no meniscal extrusion. Load that is transferred through the femur can be distributed through this meniscus. The image on the right shows an extruded meniscus.

Load from the femur transfers directly to the tibia. An extrusion of greater than three millimeters is considered abnormal and is associated with meniscus and cartilage degradation. The Mercury study data indicates that a meniscus extrusion greater than five millimeters puts the patient at a significantly greater risk of implant removal or replacement. Meniscus extrusion greater than or equal to five millimeters had the most impact in the subpopulation.

As shown in this waterfall graph, meniscus extrusion at baseline is on the y-axis and each NUsurface subject on the x-axis. Green represents subjects that did not have a device-related second surgery, while red represents permanent device removals and yellow, a device exchange or repositioning. 28 subjects, or 15%, of the NUsurface population had meniscus extrusion of five millimeters or greater. Circled in the graph, these subjects had a high concentration of device related secondary surgeries by 24 months. Those that had meniscus extrusion less than five millimeters had a 23% device related second surgery rate. Excluding these 28 subjects significantly reduced the rate of permanent removals from 10.3% to 8.3%, and the rate of exchanges from 20.6% to 13.1%.

An image of the implant design is provided on this slide. The implant was designed for lateral edge engagement to the medial tibial spine. When a patient's anatomy has a lower-than-average tibial spine, there is increased lateral motion of the device. Patient morphometric information about the risk of a low tibial spine was presented to FDA in the 2020 de novo submission. The average tibial spine height was 11 millimeters in the Mercury study. When subjects with a lower-than-average tibial spine were excluded from the analysis, permanent removals are reduced from 8.3% to 6.9%. Implant exchanges or reposition further decreased from 13.1% to 9.7%. Methods to measure the height of the tibial spine are well described in the

orthopedic literature, but it is not something that sports medicine surgeons have paid much attention to.

How critical is the measurement to identify patients at a lower risk of a removal or replacement of NUsurface? Well, 28 NUsurface subjects in which tibial spine height was read as 10 millimeters were excluded from the analysis to yield a subpopulation of 74 subjects. Had they been included, the result would've been a subpopulation of 102 NUsurface subjects. In this subpopulation, there were nine removals, or 9%, and 11 device replacements, or 11%. These rates are comparable to the subpopulation of 74 patients, which were 7 and 10% respectively. Each of the 11 subjects in whom the device was replaced had a KOOS overall improvement of 20 points or more. Results following replacement are comparable to the subpopulation of 74 subjects.

Implanting patients with a tibial spine height measured at 10 millimeters does not make a significant difference in NUsurface outcomes. When both measurements are applied, the Mercury study reduces from 242 patients to 109, 74 NUsurface subjects and 34 non-surgical controls. With both subpopulation measurements applied, surgical feathers are reduced by 50% from 33% in the total population to 16% in the subpopulation.

To confirm the benefit risk profile in the subpopulation, the same radiographic criteria were applied to clinical data in the 128-patient multicenter trial. The MCT was a 24-month single arm clinical trial with inclusion exclusion criteria and follow-up visits similar to the Mercury study. Follow-up and MRIs were taken at the same points, and the average age and average body mass index of subjects in both studies were the same. The same definition of automatic surgical failure from the Mercury study was applied to MCT subjects. Results in the MCT confirm that the subpopulation reduces device related second surgeries. Just as in Mercury, only removing

subjects with meniscal extrusion five millimeters or greater, reduced the ASF rate significantly from 39% to 30%. Subjects with an extruded meniscus had an ASF rate of 77% in the MCT. In Mercury, the same excluded subjects had an ASF rate of 79%. Both the MCT and the Mercury subjects had tibial spine heights averaging 11 millimeters. The subpopulation criteria reduced the MCT study to 46% of subjects, which was similar to the reduction of the Mercury study reduction to 42% of the subjects.

This table provides the primary endpoint calculations for the subpopulation. The unadjusted study success rates at 24 months are at the top, followed by adjusted success rates based on propensity adjustments for any baseline differences. Results based on last observation carried forward are at the bottom of the table. The results were the same in all analyses. NUsurface was superior to non-surgical controls. The NUsurface subpopulation achieved three additional secondary superiority endpoints. Superiority was shown at 24 months in VAS pain, medial compartment cartilage condition, including both the medial femoral condyle and the medial tibial plateau, and the IKDCSKEF. Superiority in these secondary endpoints provide additional confirmation that the KOOS outcomes in the primary endpoint are adequately proving benefit over the standard of care.

In addition to superiority claims described in the last slide, a total of 10 secondary endpoints resulted in a P-value under 0.05. Marketing claims of superiority for the endpoints in orange will not be made because the hierarchical rank order ended at the fourth secondary endpoint. These data provide additional validation that the NUsurface device offers benefits compared to controls at the six-, 12- and 24-month time points.

The challenge from FDA regarding a subpopulation was to identify a population that increased the benefit risk profile of NUsurface. The subpopulation reduced device related second

surgeries by 50%. The subpopulation also improved NUsurface study successes from 45% in the total population to 51% in the subpopulation. NUsurface subjects were study successes at three times the rate compared to controls. When we started the US trials, we didn't have a full appreciation of the outcomes in patients in which the implant was replaced or the data to back up the anecdotal impression that patients did well following a replacement. The Mercury data helped to confirm this.

Decreasing the incidence of any second surgery is in everyone's interest, and patients with advanced degeneration of the meniscus clearly have worse outcomes. Realistically, the data show their knee joint cannot be preserved and we must be resigned to the inevitability of an early arthroplasty. For those with milder arthritic changes, however, it is not too late. NUsurface offers them the bridging procedure they clearly want and which the data show is in their best interest until they ultimately have reached the stage where arthroplasty is their only eye option.

I also cannot stress enough how important it is for this panel to understand the unique population that does not have an effective treatment option. The poor performance of the controls accurately reflects my experience in clinical practice. I thank you for your attention and I look forward to answering any questions you may have.

Dr. Shabshin: Hello, my name is Nogah Shabshin. I'm an academic MSK radiologist working at UPenn and at Kali Healthcare Services in Israel. I'm active in multiple societies, have published over 50 scientific papers and book chapters, and more than a hundred presentations and invited lectures. I had served as an editorial board member for skeletal radiology for seven years, and I'm a reviewer in multiple journals. You have just heard Dr. Hershman present the clinical outcomes of the Mercury study. In this presentation, I will discuss the MRI findings of the study.

The MRI protocol used in Mercury was designed to compare joint related MRI observations for the control and implanted arms over the first two years of therapy in order to evaluate two things, interval changes in the cartilage condition and changes in the joint, which might be relatable to the safety of the device. MR Imaging had several roles in the study. First of all, all candidates were imaged to eliminate those who had an exclusion criterion on MRI. MRI is considered as the best method for non-invasive evaluation of the joint structures. In some conditions, it is even superior to arthroscopy. For example, it is impossible for arthroscopy to evaluate the subchondral bone unless there's a full thickness cartilage defect and irregularity of the underlying subchondral plate. The subchondral bone and cartilage unit has drawn a vast amount of attention during the last decade with particular focus on the primary damage to the subchondral bone preceding the secondary cartilage defect formation. The MRI was also used postoperatively to evaluate and follow up on the device's position and integrity.

This is how the implant looks on MRI. It shows a dark signal on all sequences and has sharp margins. It is well delineated with a clear interface between the device and the surrounding joint structures. The device does not create any artifacts and therefore does not interfere with the evaluation of the joint structures. You can see the high quality of the cartilage imaging that allows us to visualize the cartilage layers. MRI was obtained at baseline and at 1.5-, 12-, and 24-month follow-up time points. To the best of our knowledge, there are no data in the literature on immediate and short-term MR Imaging following arthroscopy, and apparently, the Mercury trial is only study to include scans at six weeks. Studies were performed on 1.5-or 3-Tesla machines. It is important to mention that each patient was imaged on the same machine, using the same sequences and parameters at all time points.

The protocol used is in accordance with the ICRS recommended protocol for articular cartilage and contains the same sequences as used in CartiHeal's agility study that was recently cleared by the agency. The protocol included anatomical sequences in which the bright fat serves as a natural contrast and demarcates the dark soft tissues and cortex. Sagittal proton density is an excellent sequence for cartilage evaluation. We also used fluid sensitive sequences in three planes. These are the most sensitive for the vast majority of abnormal conditions in the musculoskeletal system in general, and for the cartilage subdural plate unit in specific. The protocol is the most commonly used in both research and daily practice. The sequences are available on any magnet, and therefore this protocol is the easiest to reproduce on multiple magnets and over two years. For us, it was important to achieve the most reliable longitudinal comparison within each patient and among our 21 sites throughout the study. This protocol was approved by the Agency in 2013.

This is how we evaluated the cartilage condition. MRIs were evaluated by two fellowship trained musculoskeletal radiologists with 20 and 10 years of experience. These are the same radiologists that performed the cartilage evaluation for CardiHeal. In case of a disagreement, a third reader was utilized. The radiologists were blinded to each other's reads and also to any patient's identifiers, treating surgeons, and clinical outcomes. The presence of a full thickness cartilage defect in the medial compartment was evaluated in both groups. This was a secondary endpoint in the study. We also evaluated cartilage in the lateral and patellofemoral compartments, although this analysis was not included in this submission.

We performed two statistical analyses. The first, comparative prevalence of full thickness cartilage defects at 24 months between the groups. And the second analysis focused on the disease progression in each individual throughout the study compared to baseline. Why did we

use full thickness defects as the measure of cartilage condition? Based on the scientific literature, full thickness defects provide the most reliable MR-arthroscopy correlation. The best inter- and intro-observer agreement, and the highest MR sensitivity. In terms of clinical relevance, full thickness defects are not only an early indicator for osteoarthritis but are also among the strongest independent predictors for new arthroplasty within five years.

On the right, there are two examples of full thickness defects in the medial tibial plateau of two different patients. On the superior image, there is a full thickness cartilage defect at the periphery. In the lower image, the full thickness defect is at the center of the medial tibial plateau. In both examples, the joint fluid reaches the bone through a full thickness defect. In the lower image, there is also subchondral bone edema indicating damage to the subdural bone.

As I already mentioned, we used two methods to compare the NUsurface and controls. First, we compared the prevalence of patients with full thickness defects in each group at 24 months and also relative to baseline. Second, we looked at subjects individually and whether they had a full thickness defect at baseline or at 24 months longitudinally. We classified each subject into one of four groups. Those who started and ended with no defect, started with a defect and ended without one, started without a defect and ended with one, started and ended with a full thickness defect.

A positive outcome was defined as ending the study without a full thickness defect. A negative outcome was defined as ending the study with a full thickness defect, and this is what we found. At baseline. The prevalence of full thickness defect was the same in both arms. At 24 months, the prevalence of full thickness cartilage defects in controls more than doubled, while there was no statistically significant change in the NUsurface patients. This means that at 24 months, NUsurface patients demonstrated superior cartilage condition compared to controls.

Controls had doubled the prevalence of full thickness defects at the end of the study, which is highly statistically significant.

Now, let's move on to the second method and see what happened in individual subjects in each group. The first group are patients of those who had a positive outcome, started without a defect, and ended that way. They did not progress. Half of the control patients that started without a defect did not progress compared to three quarters of the NUsurface patients who had no progression. The second group, in which there was a positive outcome, was especially impressive. There were eight implanted patients that started the study with a defect but ended the study without one. This was obviously a good outcome and was seen only in the NUsurface patients. There was not a single control patient in this group. Here, we see a NUsurface patient in which the cartilage has improved at 24 months compared to baseline. Here you can see that the patient clearly had a full thickness defect at baseline. At 24 months, the defect is filled and almost completely healed.

Now let's look at the negative outcomes. Some patients started without a defect but ended with one. This deterioration happened in almost 50% of the controls and in only 25% of the NUsurface group. This is an example of a rapidly progressive osteoarthritis under a non-operative therapy. At baseline, this patient had a meniscus extrusion, but the cartilage was intact. After only 1.5 months, almost all the medial compartment cartilage has been lost. There is severe bone [indiscernible]. On tier one, it is easier to see the flattening of the articular surface and the osteocyte formation in both the medial and lateral compartments. This illustrates how rapidly joint destruction can progress.

This is an example of deterioration of the cartilage and progression of disease in a control patient at baseline compared to two years. On the baseline MRI, we see post- meniscectomy

changes with a small residual meniscal body. There are no cartilage defects. The subcartilage bone is normal at the 12 months. There is pulmonary edema in the medial femoral condyle as well as flattening of the articular surface. As you can see, there is cartilage delamination with separation between the cartilage and the bone. We know that cartilage delamination can progress to a full thickness defect. Since this is sealed, the cartilage injury is sealed, it cannot be seen on arthroscopy and neither can this injured subchondral bone. At 24 months, this is now confirmed. There is now a full thickness defect with sharp margins. There is extensive bone [indiscernible] secondary to a new insufficiency fracture with damage to the subchondral bone.

And lastly, patients in the fourth group started with a defect and ended with one. Every control patient who started with a defect ended with a defect. However, in NUsurface patients, only half of those who started with a defect ended the study with one. In the other half the defect had recovered. When we look at the negative versus positive outcomes for positive outcomes, there was a significant predominance to the NUsurface group, while controls dominated the negative. And again, in this second method as well as in the first, the NUsurface was highly statistically superior to controls at 24 months. This is a patient in which the implant was exchanged after 53 months, and we can see in the MRI that the cartilage condition is the same as at baseline. There are no cartilage defects. Arthroscopy at the time of the exchange verified the MR observation that after four and a half years, the cartilage preserved and was in an excellent condition.

Joint observations other than the medial compartment cartilage were made to evaluate the safety of the device by ensuring that it doesn't cause any undesired effects on the joint. The following observations were assessed: bone marrow lesions, joint effusion, synovial proliferation, and MCL sprain pattern. Each observation is based on commonly used established

scales, which are well-documented in the scientific literature. This is an example of bone marrow edema in an implanted patient at 1.5 months after the procedure, which resolved completely by 24 months. Overall, we observed an increase in the prevalence of pulmonary lesions among implanted patients immediately after surgery. The transient nature of these lesions suggest that they're likely related to the adjustment to the new biomechanics of the joint post-implementation.

Additionally, reduced patient activity levels and resultant transient osteopenia may also contribute to the observed increase in bone marrow lesions at the 1.5 timeframe only. The remaining joint observations showed transient postoperative findings that reflected expected recent postoperative changes. We hypothesize that effusion and synovial proliferation are attributable to the surgical procedure itself. Regarding the MCL, the sprain pattern may result from minor stretching of the ligament post implantation.

The summary of the results: in terms of full thickness cartilage defects in the medial compartment, the implanted patients dominated the positive outcomes. The controls dominated the negative outcomes. 50% of controls developed new defects, while 50% of NUsurface patients reversed their full thickness defects and were defect free after two years. Based on existing literature, patients with full thickness cartilage defects are at high risk of progressing to knee arthroplasty in the upcoming years. Although at baseline both groups were similar, at the finish line, the NUsurface was superior. While the results of the studies suggest that controls are at higher risk for progressing to knee arthroplasty in the upcoming years, the NUsurface implant may delay this definitive surgery. In the long term, after 24 months, there were no undesired MR joint observations. Therefore, MRI confirms the safety of the device in the knee joint.

In conclusion, the cartilage condition in NUsurface patients is superior compared to non-operative care at two years. Those treated non-operatively are at a high risk of degeneration and therefore arthroplasty. MRI confirms that NUsurface is a safe device.

And now on a personal note, I've had the privilege of being involved in the development of two innovative knee devices over the past decade, Cardiheels Agility and the NUsurface. These devices target different patient populations, and my experience working on the one device strengthened my understanding and knowledge of the other. During my 30-year career in radiology, I've reviewed hundreds of thousands of MRIs and radiographs and injected relatively healthy-looking needs of patients, some of whom are quite young. Many of those are suffering from chronic pain, inability to maintain good physical and mental fitness, who end up undergoing knee replacement surgery because they have no other viable option. For those patients, I wish these innovations will provide a better future. Thank you.

Dr. Jones: Thank you, Dr. Shabshin. I'm Deryk Jones, head of Sports Medicine Cartilage Restoration at the Ochsner Sports Medicine Institute in New Orleans, Louisiana. I'm also a full-time professor of orthopedic surgery at Ochsner Clinical School and the University of Queensland Australia. I'm a consultant to Active Implants. I have been paid for my time in travel here today and have no other equity interest in the company, nor any royalties or other interests contingent on the outcome of this meeting. I'm going to talk with you this morning about the risk and benefits of operative use of the NUsurface implant as compared to non-operative care.

Before we consider NUsurface risk and benefits, we'll first look at the benefits and risk of the current standard of care, which is non-operative treatment, so we have something to compare NUsurface outcomes to. You heard Dr. Shabshin describe MRI findings for the control group, and Dr. Hirschman described the success rates for the control patients. 66 controls were enrolled

in the Venus trial. The failure rate was 78% in the overall population based on the criteria in the study protocol. 9 of the 52 subjects who made it to the 24 months were automatic study failures, a rate of 17%. 14 withdrew or were lost at follow-up. Full thickness cartilage lesions doubled at 24 months.

We have follow-up data for 12 Venus control patients who withdrew or were lost at follow up. Two subjects did not return after to being enrolled in randomized control. We combined the last observation for these 12 with scores for the patients who made it to two years to get a more accurate picture of the benefit they got from their therapy. Of the 12 patients with follow-up KOOS scores after baseline, five did not return after the six-week visit, or after the six months visit, and three did not return after the 12-month visit. You can see on the graph the mean KOOS scores were trending down.

Here are the mean improvement scores for the total control group of the patients who made it to 24 months. Mean improvement was 14.9 points. Using our last observation carried forward, however, mean improvement in KOOS drops to 10.3. There's not much in the literature to compare these results. There are very few rigorous trials of non-operative care in the salvage population. The clinical trials that do report outcomes are typically for a younger population with an acute tear. There are no results of physical therapy or injections in the literature for patients who have failed previous meniscectomies that we have been able to find. The Venus study confirms the poor prognosis for improvement in pain and function in control patients.

What about the risk we've recorded in control patients? Four had arthroscopic surgery, which was an automatic surgical failure in the trial. Five had more invasive procedures. The subpopulation included three of the subjects who had invasive procedures out of the subpopulation of 32 subjects. There is no statistical difference in the incidence of surgical

failures in the total control population compared to the subpopulations. In the total control population, there were 17% surgical failures. In the subpopulation, 10% were surgical failures. Patients in the control group tended to fail relatively early. Degenerative changes in the knee are not linear, and as Dr. Shabshin showed, the knee can deteriorate in a short period of time.

The literature reporting the detrimental effects of meniscectomy on the knee is very robust. Winter et. al performed an amended analysis of the literature, reporting the rate of arthroplasty patients following arthroscopic surgery. Of 12 general articles reporting outcomes from 1,678 patients in eight registries, reporting outcomes from greater than 372,000, patients met the criteria for inclusion in the analysis. The annual rate of patients undergoing TKA following the arthroscopy is 2.62% based on the meta-analysis. The annual rate of TKA following arthroscopy and older patients to bind is 50 and older was found to be 3.89%. The mean duration between arthroscopy and TKA being 3.4 years. These results are confirmed in an analysis of over 800,000 patients based on an NIH study as recorded by Abram in 2019. Based on these data, the annual incidence of TKAs recorded in controlled patients understates the TKA risk. Dr. Shabshin covered this topic in her presentation, but it bears repeating that the cartilage in patients undergoing non-active treatment can deteriorate quite quickly, and this leads inevitably to arthroplasty. This helps explain the high instance of TAs that Winter reported in patients who had undergone a meniscectomy.

A unique aspect of the patients enrolled in the Mercury study is that they were all surgical veterans. The patients enrolled the study sought out and participated in the trial because they had exhausted the currently available treatments, both surgical and nonsurgical, and they could see their trajectory towards a knee replacement and wanted to find some way to delay that. They're younger than 70, and they're aware of the limitations, risk, and dissatisfaction rates following

total knee arthroplasty. Consider, for example, a 40-year-old patient with a life expectancy of 85 years undergoing an arthroplasty. They likely need up to two revision surgeries in a lifetime, assuming a 15-year hardware lifespan. So they want to preserve their knee, and they place the highest value on maintaining their activities they of living, as well as being able to work and enjoy recreational activities.

These patients understand and accept that the realistic goal of knee preservation is to delay the degenerative process. We don't have a cure for this, and sometimes complete pain relief is not a realistic option. In the real world, treatment failure should be defined as a mismatch between the outcome and patient's expectations and satisfaction. So if my patient experiences two or more years without pain and they're satisfied with the result, this is a successful outcome for them and for me as well, even at the risk of a repeat operation.

So let's look at the risk reported in the 74 patients in the subpopulation. The AEs in the subpopulation mirror the AEs in the total population, but at lower rates. The rate of infusion was higher in NUsurface subpopulation compared to controls. Study failure was 49% along with the 74, or 17%, were acute study failures. There were no patients lost at follow-up. Here, it bears to mention in which there was a statistical difference compared to controls as in the total population, for specific to the device, the fusions resolved by 12 months has occurred in the total population. Device related adverse events resulted in three types of second surgeries. The original device was repositioned in the joint after an implant dislocation or rotation in one NUsurface subject. It was permanently removed in 7% of NUsurface subjects and was exchanged in 8%.

Let's focus on the safety profile, the replacement surgeries. There were fewer AEs in the replacement procedures, and this makes sense. Speaking from personal experience, these were

faster and easier to perform since the medial compartment had previously been prepared during the initial surgery and the patient's medial compartment had adjusted to the first implant. This allowed the patient's recovery to get faster. Other investigations have confirmed the same experience in their patients. Procedures took on average 30 minutes to perform. Once again, post-operative recovery was faster than after the primary procedure. This is unique in orthopedics. Typically a revision, procedures more difficult due to scar tissue formation, loss of bone, and soft tissue destruction. These issues are not encountered during replacement or repositioning of a NUsurface implant.

We have KOOS overall scores for six of seven patients in which the device was replaced or repositioned. The KOOS improvement was excellent. 5 improvements are greater than 20 points in overall score. Of the five patients in which the device was permanently removed, three went onto arthroplasty with two unit compartments and one total knee arthroplasty, and there was no statistical difference in the incidence of arthroplasty in subpopulation between the controls and NUsurface. Looking at the probable risk of TKA, the cartilage data Dr. Shabshin presented provides evidence that you are at much higher risk of an arthroplasty with non-operative treatment than NUsurface.

How does the instance of secondary procedures and NUsurface compare to other procedures in which we preserve the knee joint. As you see here, it compares quite favorably. Meniscal allograft is probably the most relevant because NUsurface may be considered a synthetic alternative to allograft. The reoperation for meniscal allograft transplantation is 45% at two years. All joint procedures to preserve the joint have a high rate of second surgeries. FDA recently cleared a new treatment for correcting angular deformity in the knee as an alternative to HTO, which Dr. Hershman showed in one of his slides. By two years, the implant had been

removed in 11 of 81 subjects for pain, discomfort, or deep infection, a rate of 14%. Permanent removals in the NUsurface subpopulation were 7% by comparison.

You see rapid improvement in KOOS overall scores, and the benefit is of long duration. Mean KOOS overall improvement is 22.7 points in the NUsurface subpopulation. Referred to a study by Cats in my discussion of outcomes published in the literature for non-operative care. In that same article, he reported mean and KOOS pain improvement scores of 26.8 after a first-time meniscectomy procedure. NUsurface KOOS pain improvement was 24.2 and post meniscectomy knees. NUsurface compares favorably to the 10.3-point improvement in controls measured by last observation carried forward by analysis. When we look at the benefit of measured by MCID as refined in the KOOS instrument, 75% were responders. On the right you see scores, the scores, when you include scores for patients in which the implant was replaced, they are the same. Secondary outcomes instruments show the same response rate as KOOS. These include Vas, WOMET, and IKDC.

This slide reiterates the benefit of cartilage preservation in NUsurface patients that we measured in the MR slides that Dr. Shabshin went over. Preserving cartilage is a significant benefit of NUsurface.

To summarize the benefits of NUsurface, you see improvement by six months, and the results last. This improvement is confirmed by multiple outcomes instruments. Three-quarters of the patients improved by at least the MCID and KOOS overall score. NUsurface acts to preserve the cartilage.

When Sun was merged into Venus, the primary outcomes variable from the Venus protocol became the primary outcomes variable from Mercury in the Combined Statistical Plan. The safety endpoint based on a device malfunction rate as described in Sun was not applied to

Mercury. It is a unique challenge, however, to determine safety in a randomized trial in which a surgical treatment is compared to non-operative therapy. Few surgical treatments would anticipate a rate of adverse events low enough to compare favorably to non-operative therapy, especially when the surgical treatment is an implanted device. But the outcomes showed that the only clinical aid that was statistically different in the NUsurface group was anticipated and without sequela. Failure of the implant or replacement or repositioning for any reason was factored into the success criteria. The data showed that patients got excellent clinical benefit from the implant as long as it was intact and in place.

So what happened to patients in which the implant failed? The data also showed that the implant could easily be replaced, and patients got comparable benefit from the second implant that they got from the first implant. They did have to undergo another procedure, and it is for everyone's benefit that we minimize the number of repeat procedures. Can we further mitigate that risk? In the original de novo, we analyzed trends as surgeons gain experience with the procedure and the rate of second surgeries will lower after the first three cases. We understand the importance of surgeon training to ensure good results. The device fails in essentially two ways. It can come into contact with bone, which abrades the polymer. This can be mitigated as surgeons gain experience to ensure the implant doesn't contact bone. Or it can tear when it is subjected to heavy impact loads. There's little we can do about this mode affair other than warn patients of the potential risk to the implant that may result from high impact activities. I had that happen in one of my patients who was playing basketball regularly. I told him to stop doing that. I gave him the option of replacing the implant, and he agreed because he was ecstatic with his function. He continues to function at a high level, but he did stop playing basketball.

It can be useful to pool potential candidates for procedure to gaze the level of risk that they would consider acceptable for a probable benefit. We conducted seven such surveys of focus groups. The last survey we were able to include the actual outcomes of the Mercury study, and the respondents came from a large pool of 100,000 individuals. This analysis closely matched demographics in the respondents with the study demographics and to identify patients with knee pain.

Here are the results, analyzed according to FDA's guidance document on PPI surveys. 93% of the respondents thought the benefit of use outweighed the risk. The uncertainty of the finding was between 88% and 96%, meaning an overwhelming majority of the simulated patients that closely matched the Mercury clinical study found the benefit of the NUsurface device to outweigh the risk. Patient perspective information may also be obtained from patient reported outcomes measures. Seven questions in the PRO instruments used in Mercury provide valuable data regarding patient perspectives, which is a evaluated, measured patient perspectives in the treatment of knee pain. NUsurface treated patients had statistically higher values for KOOS quality of life and Walnut emotion scale. As you can see, this was for both the entire population and the subpopulation at three different time points. NUsurface patients were satisfied with their outcomes, quality of life, and emotional state compared to the patients who had mostly the standard of care.

Imagine a middle-aged patient comes in complaining of knee pain. They've had a meniscectomy in the past. They go out for a course of physical therapy and come back, and then we find they've got early radiographic evidence of osteoarthritis upon MRI in only one compartment of the knee. I could suggest that a uni-compartmental replacement could alleviate their pain. This may sound like a fantastic offer to the patient, solely from a pain relief

perspective and has obvious appeal to someone who has been experiencing escalating pain knee pain for some time. But what if I told the patient I could just remove all the sensory feedback from the painful knee through the process of internal knee amputation, where I cut on all knee sensory components and replace these components of metal and plastic parts? Based on both descriptions, it sounds like their knee pain will be addressed, right? So any difference in the relative appeal between these two offers highlights the importance of a thorough and informed patient consent conversation.

Clearly there is little doubt that TKA is the appropriate choice for end-stage intervention for knee OA among elderly patients, alleviating pain and improving function. However, results decline if the patient is less than 70 years of age, is overweight, has less severe joint space narrowing, or display symptoms of depression or anxiety. NUsurface patients understand this, and these patients overwhelmingly chose to undergo repeat NUsurface procedure when given that option. This is probably the most valuable data that you can have on patient preference, perception, awareness, whatever you want to call it. These patients all have the unique experience with the NUsurface procedure, recovery and pain relief, and the decisions to repeat that should speak for itself.

You'll be asked to vote on one question as you consider the evidence we presented to you. Do the probable benefits to help of the NUsurface meniscus implant outweigh the probable risk when used in patients in accordance with the proposed indications for use? Let's consider who these patients are. Previous surgeries have not improved their symptoms. Previous surgeries have placed them at risk of degeneration of their cartilage, which places them at greater risk of a TKA. In granting breakthrough designation for NUsurface, the FDA recognized that this patient

population had debilitating disease and needed a more effective treatment option, which clinical trials confirmed that outcomes from non-operative therapy in this salvage population are poor.

NUsurface benefit is superior to the standard of care, was apparent in the Venus trial and in the Mercury trial, both in the total population and the subpopulation. It was effective in revision surgeries as it was in the first surgery. For the risk for NUsurface, MRI data support the conclusion that the implant protects the cartilage, confirming the findings of preclinical research. Preoperative risk of NUsurface were comparable to risk reported from meniscectomies, which are well characterized in the medical industry. There was a lower incidence of adverse events in the replacement procedures, and the rate of second surgeries is comparable to or lower than the rate of commonly performed joint preservation procedures. We believe the data before you constitute valid scientific evidence that in this salvage population, the probable benefits of NUsurface outweigh the probable risk. Thank you for your attention and we look forward to answering any questions you may have.

Q & A

Dr. Smith: I would like to thank the sponsor's representatives for the presentation. Does anyone on the panel have a brief clarifying question with the sponsor? Yes, Dr. Kirkpatrick.

Dr. Kirkpatrick: I got a little confused because I heard early that outer bridge four was a contraindication, and yet the data presented, a lot of the MRI showed that there was a large proportion of both groups that had full thickness cartilage defects. Just wondering if the sponsor could clarify their definition of full thickness and outer bridge four and help me understand how there's such a large proportion of full thickness defects in the selection. Thank you.

Mr. Belaney: Thank you, Dr. Kirkpatrick. I'm Ryan Belaney. And first off, I would like to thank the panel for dedicating their day to discussing the NUsurface device. And yes, that's a great

question. Because in our indication statement, grade four cartilage lesions are allowed if they have a certain size, a limited size, and the location of that lesion. And what we're really trying to exclude from this study is having bone contacting the NUsurface implant. And that is the intention of grade four cartilage lesions in that exclusion. I can bring up the slide that shows the indication statement. Or Dr. Kirkpatrick, does that answer your question? I need the —

Dr. Kirkpatrick: Dr. Kirkpatrick you please Need on mute please. Thank you. Oh, this clicking. So anyway it would be nice to fully understand what you're saying. If I saw the device right, it is thicker on the edges, but it encompasses an entire surface of the joint. So if you have a full thickness cartilage defect, it's automatically going to be in contact with the device, is it not?

Mr. Belaney: That's correct. If there's a peripheral cartilage defect that would not come in contact, then that would be allowed. Or if it's centered on the condyle where it would not come in contact with the edge of the implant. Now we can bring up a slide showing the implant. Or we can also bring up the inclusion exclusion criteria from Dr. Hershman's presentation. And I think that can help explain this. That would be great. Thank you. So when we look at exclusion criteria, number one, we see evidence of grade four articular cartilage loss that has a size limitation. So if focal lesions are above 0.5 centimeters, those are excluded from the study.

Dr. Kirkpatrick: Okay. A as a follow up, can our radiographic experts help us understand if that is a realistic threshold to be able to determine on an MRI?

Mr. Belaney: Absolutely.

Dr. Shabshin: Hello and thank you. The decision on eight millimeters of a full thickness defect being the threshold was based on the R and D during the development of the device in some trials. That's how we saw that lesions that were smaller than eight millimeters didn't really contact the implant. The concern was that if there will be too much contact with the implant or

contact, I mean, contact of the implant and the bone, between the implant and the bone, then it will cause tears. Therefore, we excluded those large full thickness defects.

Dr. Kirkpatrick: Thank you. And is that size determination based upon the MRI or is it based upon clinically at the arthroscopy time?

Dr. Shabshin: Clinically in arthroscopy. This is from the early stage of the development.

Dr. Kirkpatrick: Thank you.

Dr. Shabshin: Thank you.

Dr. Smith: Dr. Paul Manner.

Dr. Manner: Yeah, thanks for very interesting presentation. With respect to the Venus study how many patients were approached versus how many patients ultimately enrolled?

Mr. Belaney: I'm sorry, I missed one word that you said there. Could you please repeat your question?

Dr. Manner: Yeah, of course. Yeah. So in the Venus study in particular, how many patients were approached for participation versus the number, the total number enrolled?

Mr. Belaney: Absolutely. In our executive summary to the panel, we have a flow chart that shows the accountability table for the Venus study. So when patients or subjects were first, there was advertisement, and over 12,000 subjects came to Active Implants looking to be in the Venus study. Now, after assessing bone on bone contact or whether they were truly eligible for the study, I believe it's over 200 subjects made it to the point of radiographic assessment of whether they were included or not. So radiographic and physical assessment by the clinician ensured the inclusion/exclusion criteria into Venus was appropriate. And from that point on, the 66 and the 61 subjects were randomized into the two arms of the Venus trial.

Dr. Manner: Okay. Thanks.

Dr. Smith: I believe Dr. Cizik was next.

Dr. Cizik: Yeah, thank you. This is Amy Cizik. There was a lot of talk about the average patient, 50 years of age. Could you provide a little more on age range that was in this study? I've looked through the executive summary, had trouble locating that. I'm sure it's there, but. And do the indications have an age criteria or not?

Mr. Belaney: Well I know you're not asking this, but in the clinical study there was an age range. And the range, the average was 55, and the range included subjects that were 30 years old all the way up to 70 years old. Dr. Hershman can provide more insight onto exactly who the patient is and what they typically are of age, but what, how that range also is more than just this 50-year-old or 55-year-old patient.

Dr. Hershman: Thank you. Yes, the age range that we saw in the group ranged from a group at 30 up into 70s. And many of these patients were at a stage where they had challenges with respect to their clinical situation. And that is why we enroll them into this study.

Dr. Smith: We have three more panelists with their hands raised. Dr. Banerjee, I believe you're next, sir.

Dr. Banerjee: Hi. Sorry, I have a very, sort of a more detail-oriented question.

Mr. Belaney: Great.

Dr. Banerjee: First the clarifying question. In your Mercury dataset and in the subpopulation of the Mercury dataset, in both instances, you performed propensity score adjustments. Is that correct?

Mr. Belaney: Yes, that is correct.

Dr. Banerjee: The second question is slightly more detail-oriented. In the sponsor executive summary, you have presented the distribution of propensity scores, but you have categorized it as

low and high propensity scores. Is there a definition for that category? What does low mean and what does high mean?

Mr. Belaney: Absolutely. Our biostatistician is on the line. And I'll open up the mic to Dr. Fred Haler.

Dr. Haler: Hi, I'm Fred Haler. I'm a biostatistician consulting for Active Implants. The propensity score was divided based on the median. So there's high and low, and that's what we used for adjustment.

Dr. Banerjee: Thank you. I believe we have two more panelists, Dr. Barber, then followed by Dr. Reed.

Dr. Barber: Hi, I'm Dr. Tom Barber. And I just had a question for you about the BMI and the BMI range in the study populations. As a total joint surgeon, as I sort of look at the data, that's an awfully low average BMI for patients with osteoarthritis of the knee. Maybe it's my population, but what I see is a low population with exclusion, I know, of greater than 32. But I wonder whether there's not a bias towards small, you know lower BMI patients. And second secondary question to that, is there a mechanical and absolute contraindication towards the larger patients, or was that just a choice of the study?

Mr. Belaney: Thank you. Yes, you are correct that the upper limit of the exclusion criteria within the study was 32.5 BMI. And we had an equal distribution across the under 25, 25 to 30, and 30 to 32.5. The current indication statement does not discuss the BMI, but in the contraindications, there is a limit of 32.5. So yes.

Dr. Smith: Dr. Reed.

Dr. Reed: Hi. I have two questions, one in regard to the patient preference study that was conducted. My questions pertain to who were the patients enrolled in that study, and how were

they identified? It just says that they were similar to the people who participated in the study, but there's no information about how they were identified and recruited. So that's my first question. My second question pertains to the subgroup of patients, based on the height of the tibial spine and the meniscus extrusion or whatever. When was that subgroup identified? Was it completely a post hoc determination? And were sensitivity analyses conducted to vary the criteria that defined that subgroup?

Mr. Belaney: I will start by answering your second question and then I will pass to a colleague for your first question. So the subgrouping of the Mercury study, that occurred after the total population of the Mercury study, in discussion with the Agency about improving the benefit risk profile, I would like to remind all on the panel that the Venus study alone met the threshold of superiority as well as the Mercury combined study met the threshold of superiority. And that is important when we think about the subpopulation from a study that has met that threshold. Now, for the first question, I'll introduce Dr. Rick Treharne.

Dr. Treharne: Yes. Dr. Reed, we had an outside group that does surveys for a living help us with this. And they had a 10,000-patient data set that they could pick from. And for this particular study, they went to another agency that had a hundred thousand people from the general population who answered all kinds of questions. And one of them was about whether they had any heart problems, hearing problems, joint problems, and that sort of thing. The ones that said they had joint problems, they were queried as to which joint, and the ones that said that it was their knee, those ones were then screened to see if they had knee pain. And if so, they would be part of the pool that would be selected from to try to match the clinical study patients as closely as possible. These were not patients; these were general population people that volunteer for these surveys. And knee problems are so prevalent that that was very easy to find patients,

people, who had this kind of knee problem that matched our clinical study. Does that answer your question?

Dr. Reed: In part. But just to confirm, these are just people who reported knee pain. They weren't people who had previous meniscal surgery or met the criteria for the study?

Dr. Treharne: Right. There was no further level of detail provided about that. Just knee pain in general. Okay. Thank you.

Dr. Smith: I would like to remind everyone, a quick update on time. We're running over, but we have two pending questions, so let's address these questions. And then, reminder, we'll have to shorten our break time. We'll reconvene at 11:35, but I think it's important we have everyone's questions addressed. Dr. Subhawong is next. And then his questions followed by Colonel Helgeson.

Dr. Subhawong: Hi, Ty Subhawong, musculoskeletal radiology. I noted that most of the failures in the control arm were due to PROs, and I wanted to know if you had data on analgesic use between the two arms and viscosupplementation and steroid use injections into the knee in the control arm.

Mr. Belaney: So, as you know, the non-operative control arm has the option of corticosteroid injection, hyaluronic acid injections, and those were prevalently used throughout the control arm. As far as answering the initial question about that, I would like to provide a more complete answer with some information on that after, perhaps, our lunch break, and we can talk about that, answering that question more completely.

I would also like to finish answering the last question at the risk of our break being shortened. I would like to make it clear that the subpopulation, the tibial spine height and meniscus extrusion, those were radiographic criteria that had been identified at the beginning of

the total population Mercury study. And in fact, tibial spine height was discussed with FDA in the first de novo submission back in 2020. So I just wanted to make it clear that these were measurements that we could see improve patients even during the first de novo submission.

Dr. Smith: Colonel Helgeson.

Col. Helgeson:Thank you. My question's about the adverse events and trying to focus on some of the adverse events. And then, one of the significant findings was the effusion. And my question was whether or not the effusion was based on clinical exam or knowing that you have the MRI data available, if you utilize the MRI to do something more quantitative than the binary effusion that we can see on clinical exam.

Mr. Belaney: Thank you. Yes. In the executive summary, effusion, where the effusion described was through our adverse event collection. But we also did measure effusion radiographically. And I will bring up our radiologist, Dr. Shabshin, to discuss effusion rates. I can also describe that, and it was in the executive summary provided by FDA, that effusions were attributed to surgical procedure and they did occur early and resolved with time. Dr. Shabshin?

Dr. Shabshin: We analyzed the results of the presence of joint effusion at all time points. We did see higher numbers of joint effusion in, obviously it was just in the implanted patients, because they had a surgical procedure. So at six months after the procedure, we did see an increased number of patients with joint effusion. However, at 24 months, there was no difference between the groups. Does that answer your question?

Col. Helgeson:Yes. I guess I was also kind of, on a secondary question, wondering if there was any difference in the pain in those that had effusions and those that did not have effusions. More of a clinical question. I know we have got to get on break. We can maybe defer that.

Dr. Shabshin: Would you like to answer question?

Mr. Belaney: When we looked at effusions, I mentioned that these appear to be transient and related to the procedure. So when we look at one-year and two-year pain rates, there was not an increase due to, in the subjects that had effusion.

Col. Helgeson:Thank you.

Mr. Belaney: You're welcome.

Dr. Smith: Thank you everyone.

Dr. Shabshin: Just a quick, just a quick slide, if you would like to see, on the transient joint effusion. Miles, would you like to project it? We'll do this after the break. Thank you. Thank you everyone.

Dr. Smith: We are now going to take a break. We're going to shorten the break for a five minute break. It's currently 11:32, almost 33, so we'll return at 11:38 AM.

Dr. Smith: It is now 11:39 AM, and I would like to call this meeting back to order. FDA may now give their presentation. 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 chair. FDA will now have 90 minutes to present. FDA, you may now begin your presentation.

FDA Presentation: Overview of NUsurface De Novo Request

Introduction — Dr. Travis Prest

Dr. Prest: We'll be discussing the de novo request for the NUsurface meniscus implant from Active Infants, LLC. My name is Travis Prest. I'm a biomedical engineer in the Restorative, Repair, and Fracture Fixation Devices Team within the Office of Orthopedic Devices. I am the lead reviewer for the de novo submission associated with the NUsurface meniscus implant. The

review of this submission has included a large interdisciplinary team, of which you will hear from a subset of our team today. As lead reviewer, I'm providing an introduction and a brief regulatory background. Our medical officer, Dr. Marc DeHart, will provide an overview of the meniscus in knee pain before introducing the device and its intended use. He will then give a walkthrough of the clinical background studies and data sets. Our statistical reviewer, Ms. Cynthia Liu, will provide a presentation on the statistical considerations. Dr. David Gibbon will present on the provided patient preference information. Finally, Dr. Marc DeHart will provide closing remarks on the benefit risks considerations.

The NUsurface meniscus implant was deemed eligible for the de novo classification. It was determined that it did not fit into any existing regulations, that it does not have a previously approved pre-market approval, and that it presents a low to moderate risk profile. Devices classified under the de novo request may serve as predicate for future devices, which can be appropriately regulated through the 510K program. Therefore, FDA carefully considers the benefit risk profile of these devices in the determination that there is a reasonable assurance of safety and effectiveness. The de novo request under review includes both nonclinical and clinical data. However, the focus of today's meeting is limited to the discussion of only clinical data.

We will be asking the panel to discuss several topics during this meeting, including: to consider the patient population that would benefit from this device in consideration of the available alternative non-surgical surgical treatments, to comment on the adequacy of the overall clinical success criteria, and the clinical significance of the device-related subsequent secondary surgical interventions, as well as the overall success rate of the modified Mercury dataset and its impact on the benefit risk determination. We will also ask the panel to consider the contributions of the patient preference information and to discuss the impact of the proposed risk mitigation

strategies on the clinical reproducibility, particularly the accurate identification of the target patient population. Finally, we will ask the panel a voting question on whether a favorable benefit risk profile has been demonstrated for the subject device for its proposed intended use. I'll now hand the presentation over to our medical officer, Dr. Marc DeHart.

Clinical Background and Data Sets — Dr. Marc DeHart

Dr. DeHart: Hello, my name is Marc DeHart. I'm an orthopedic surgeon in adult hip and knee reconstructive surgery, and I have a certificate of added qualification in sports medicine. I'm going to present the clinical background of the NUsurface clinical studies.

The knee meniscus maintains the health of the knee joint by predicting joint cartilage through the distribution of load, shock absorption, stabilization, and lubrication of the joint. The medial meniscus is normally well fixed to the tibia through three ligament attachments, two connecting anterior and posterior horns to the inside knee at the center of the tibia, and the tibial collateral ligament, which holds it fixed in position at the far medial outside between the medial femoral condyle and the tibia. The loss of the important functions of the meniscus can increase pressure on the cartilage surface and potentially lead to condyle damage. When meniscus function is lost, degenerative changes to the knees frequently occur, and that leads to osteoarthritis.

There's a growing level of evidence regarding pain associated with meniscus pathology. High level randomized controlled trials have shown arthroscopic partial meniscectomy for pain alone is not statistically better than a dedicated physical therapy program or placebo surgery. Also, arthroscopic management for arthritis has not been shown better than a placebo. The results from studies like these were used as a rationale to justify a non-operative control group.

We commonly see meniscus tears on MRIs that are asymptomatic, and experience shows the more meniscus you remove, the greater the arthritis seen later. So it makes sense that meniscus pathology and arthritis are commonly associated. As an orthopedic surgeon. Farina's article from JBJS in 2021 is a little humbling. This research group found that even when orthopedic surgeons think the pain is consistent with meniscus symptoms, there was a greater association with arthritis changes in the knee than actual meniscus pathology.

There are several surgical options for symptoms we believe come from the meniscus. We recognize symptoms are what drive patients to doctors. We also know that successful surgery is related not only to those subjective symptoms of pain, but also identifying objective findings that surgery can successfully address. With pain and a repairable tear of the meniscus, we try to fix the meniscus with sutures to prevent meniscus tears from worsening and to preserve meniscus tissue. We hope that this will decrease the rate of arthritis and delay arthroplasty in the future. Sometimes a meniscus tear causes pain and a mechanical block or reproducible mechanical symptoms. And if it's not repairable, we can sometimes fix the block by simply cutting out the mobile fragment that causes trouble. Collagen augmentation devices are available to replace partial losses of meniscus tissue, and these are sutured down to the remaining meniscus. Some studies have shown symptomatic benefits, but follow up at 20 years, they demonstrate few adverse events, but no difference in outcomes for pain. With major absence of meniscus, meniscus allograft can replace an entire meniscus in younger patients by firmly sewing the new tissue into its normal position.

The device under study was a rubber light polymer disc intended to provide a meniscus like function. The sponsors hoped that it would improve symptoms and delay additional surgeries from arthritis, surgeries like knee replacements. The device is a non-anchored inter-

positional spacer that is not fixed in place with suture or cement and relies on its shape for its position. It's made of polycarbonate urethane called Bionate and was reinforced around the rim with stronger ultra-high molecular weight plastic fibers. However, to make space for this device in the knee, a near total meniscectomy is performed as part of implantation.

The indications for use are provided by the sponsor and they read: the intended use of the NUsurface meniscus implant is to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected. The indication for use is in patients with mild to moderate arthritis, mild or greater knee pain, and cartilage present on the load-bearing articular surfaces. Each element needs confirmation from patient history, physical examination, radiographic imaging, and/or visual observation.

The clinical study history of this device began outside the US with a feasibility study, and then in 2011, they began a study called the Multi-Center Trial, or MCT, at seven sites in Europe and Israel. This was a single arm trial of patients who had meniscus tears and those who had previous meniscectomies. It used a different version of the implant, but we bring it up here because the sponsor uses it to validate anatomic selection criteria for the final dataset used in this de novo. The Venus 2012 study is the only randomized trial performed by the sponsor with the final implant. In 2015, the Sun trial was a single arm trial to have more patients to evaluate safety issues. So let's go through these a little more carefully.

The Venus was a prospective, randomized, one-to-one, parallel arm, multi-centered interventional superiority trial. The sponsor compared a group of 61 subjects randomized to receive NUsurface device surgery with their specific post-operative physical therapy routine to 66 group of non-operative controls who continued the usual non-operative treatments that included whatever the patient and the surgeon desired. This is the only randomized trial of this

device, and therefore the only study that provided a control group. These controls are used for the Mercury and modified Mercury dataset used for the regulatory submissions. Important limitations include 30% of the control subjects were lost to follow up or withdrew from the study by 12 months. Overall success was to be based on a composite endpoint, including patient reported pain and function, as well as the absence of surgery that the sponsor felt was related to the device. We'll get into the details about endpoints later.

The Safety Utilizing NUsurface Meniscus Implant study, or the Sun trial, was a prospective, single arm, non-randomized trial with the intent to follow for at least 24 months, with an additional option to see longer term data at 60 months. It reports the observations of 115 patients who received the implant, and the vast majority of the data presented to the FDA was limited to 24 months. Sun trial had two drivers. One was to make the NUsurface numbers more robust because of slow enrollment in the Venus trial. The second important reason was to answer safety concerns seen in the prior studies. The Sun trial was meant to be a safety trial, and this study contributed the most patient numbers to the data sets we will look at.

Prior to enrolling for this safety trial, the sponsor provided the following safety hypothesis. The sponsor says, “The most crucial study hypothesis is that the NUsurface meniscus implant subjects have a safety rate less than or equal to 10%. The null hypothesis is that the NUsurface meniscus implant treatment is not safe and has a malfunction rate greater than 10%.” The final report of this trial showed 37% of subjects had device damage, 20% had displacement of the device, and a smaller number had adhesion arthrofibrosis with limited range of motion and mechanical symptoms.

From the two studies we have previously mentioned, the sponsor created two data sets used for their de novo submissions. The footnote identifies that the Mercury dataset wasn't a

separate trial. It was actually the data pooled from both the Venus and the Sun Trials. This dataset included 176 subjects who were to have device implantations and 66 subjects who were to be non-surgical controls. The modified Mercury dataset was a selected group of subjects to address the 37% surgical failure rate seen in the Mercury dataset. This modified group excluded subjects with meniscus extrusions of five millimeters or more, and those who had tibial spines that were shorter than 11 millimeters. This group had 74 subjects who received the device and 35 non-surgical control subject.

The primary inclusion criteria for the studies included having at least one prior partial meniscectomy, but also having maintained at least a rim of meniscus that needed to be available to help contain the device. They had to report knee pain by the KOOS score, and the pains had to be at 75 or less, and the patients needed to be between age 30 and 75 years of age. The patients also had to be willing to be entered into either arm of the study. Now remember, this would only be relevant for the Venus derived patients, because the Sun group all expected, and all received surgical treatment.

Key exclusion criteria include a long list, but the most clinically relevant for our discussion include exclusions related to arthritis. More severe degrees of arthritis were excluded from the study. No evidence of grade four arthritis, loss greater than half a centimeter squared, was allowed. No lateral compartment pain, and grade three or four cartilage score was allowed. No patellar compartment pain or articular cartilage damage graded two or more in this compartment was allowed.

It is also important to understand, in the NUsurface group, arthroscopic screening was allowed. The sponsor created the term ‘bailout’ to identify a subject who has found, in arthroscopy, to have pathology that would exclude them from the study. These patients were

removed before randomization. Other exclusions included: no malalignment where an osteotomy would be appropriate was allowed for this population, no ligament laxity or recent ACL operations were allowed, and no obesity greater than a BMI 32.5 would be allowed.

The next quick series of slides are going to cover the procedure used to place the NUsurface device. Key steps to the placement of the device included a meniscectomy and the screening arthroscopic evaluation of each compartment to confirm the lack of arthritis. Osteophyte removal and notchplasty. A trial was inserted for sizing, and then trial was assessed. And then final placement of the device.

So the first part after the subject passed the arthroscopic screening and entered the study was a near complete meniscectomy that's required for the device placement. The sponsor's instructions note that you must remove as much of the meniscus as possible, leaving no more than a two-millimeter margin around its periphery. The images below are the sponsor's, and they identify the degree of meniscus removal recommended. This near complete meniscectomy creates uncertainty regarding the long-term knee health for every patient who receives the device. But what is clear is that this may have a great influence on the health of the knee if the device fails and must be removed.

Unlike a normal medial meniscus, the NUsurface meniscus implant is not anchored, and its design includes a raised lateral bridge, a rim around the device to help keep it inside the joint. This lateral bridge is for placement between the tibial spine and the medial femoral condyle in the notch region. Another important part of the procedure includes removing bone spurs, which may impinge or catch the device. The pictures from the sponsor identify this region and the resulting exposed bone that is seen in this notch region. There is uncertainty if this can be

effectively accomplished without providing a larger amount of exposed bone that may also catch or abrade the NUsurface device.

After arthroscopy, the incision is enlarged to four to eight centimeters. A trial is inserted and used to test the sizing. They state a goal is to avoid overhang. Stability is tested by ranging the knee and looking for motion that is free and smooth to look if any anterior liftoff, as seen with range of motions greater than 90 degrees. The sponsor stresses the importance of not having adequate space for the anterior lateral wall of the implant, because the device may be damaged. And we'll discuss this point a little more later.

Once you've selected the trial, the final implant is placed. And the pictures below from the sponsor identify an example of ideal sizing of the implant and good positioning of an implant. Notice the lateral aspect of the device. Between the medial femoral condyle and the medial tibial spine, which provides containment for the unfixed interpositional device. While orthopedic surgeons understand this, for the rest of the panel, it's important to note that this region between the tibial spine in the femoral condyle is a location where no normal tissue is usually found.

Specifically regarding the control group, this was a non-operative control group, so blinding is not possible. Nearly all non-operative options were allowed for the control group. This includes everything from over-the-counter drugs, prescription drugs, exercise, and physical therapy to cortisone shots and hyaluronic acid injections. The statistics team will talk later about the statistically significant differences between the groups, but there were some clinically relevant differences between the NUsurface and control populations. For example, the control population had 10% or more frequent experience with cartilage surgery, previous lateral meniscectomies, or having more than one medial meniscectomy. In addition, the control

population had 10% or greater rates of treatments that included physical therapy, bracing, steroid injections, and non-steroidal anti-inflammatory drugs. On the other hand, the NUsurface group had 10% or higher rates of treatment with activity modification and analgesics like Tylenol.

A second important clinical point is that unlike many other non-operatively controlled studies on meniscus surgeries, no formal physical therapy protocol or specific regimen of care was prescribed for the control group. They were free to pick with their surgeons what kind of usual customary care they'd received. Now, this is different from the NUsurface subjects who had surgery and a specific program of early activity restrictions, pain medicines, and a formal physical therapy protocol. The lack of an official treatment protocol may have created outcome differences between the NUsurface group and the control group.

The study patient assessment schedule is shown in this slide. Patients were screened, and outcome measures and images were taken at baseline and planned for six weeks, 12 months, 24 months, and 60 months. The study was initially considered for a longer five-year period to understand the long-term follow-up, but long-term trials are challenging to capture patients. There were limited amount of five-year results available, and the majority of comparisons we will present include two-year data.

Study endpoints were a composite of three endpoints. Subjective panel reported outcomes using KOOS survey instruments, MRIs that look for structural failure of the device, and the absence of secondary surgical interventions. The definition between the secondary surgical and intervention was different between the two groups. A secondary surgical event that the sponsor identified with the device is called an automatic study failure. Any surgical intervention in the control group was counted as a failure, and we'll speak more to this point later.

For the endpoint of the KOOS instrument, the Knee Injury and Osteoarthritis Outcome Score, which is a validated patient reported outcome measurement commonly used to assess knee related injuries and treatments. This study focuses on KOOS pain and the KOOS overall score, which also includes the pain score. The minimal detectable change for the KOOS subscales range from about 14 to 19.6 for younger individuals and 20 for older individuals. To provide some clinical context on the value of these KOOS pain scores, randomized controlled trials on partial medial meniscectomies and their control groups from the literature range between 24 and 31. The value of 86.2 was felt to be an acceptable patient state by the sponsor.

The study endpoint for MRI was used to verify if the NUsurface implant had subluxed, rotated, or torn, and might confirm that additional surgery would be needed to remove the device. As we will discuss in the retrieval portion of the study, these devices had a fairly consistent pattern of failure. They could dislocate posteriorly, anteriorly, rotate various degrees, and they could tear. However, in the course of the study, only one patient or one subject failed exclusively by MRI. In most cases, when the device failed by MRI, surgery was also needed. So the MRI data is not particularly important.

An important difference when comparing the secondary surgical interventions that would be considered automatic study failures is that the definition differed between the NUsurface and the non-operative controls. For example, the NUsurface implant count did not include all secondary surgeries if the sponsor was uncertain if they were device related. Some cases of patients with a NUsurface device received surgery for adhesions but were not counted as automatic surgery failures. On the other hand, control patients had no restriction of specific indication or contraindication for their surgery. An example would be, even though angular

deformity that was severe enough for an HTO was an exclusion criteria, a patient had an HTO in the control group and was counted as a failure.

In addition, cases with persistent pain in the control group who underwent arthroscopic treatment during the study and were found to have degrees of arthritis that would've excluded them from the NUsurface group, were also counted as control group failures. An endpoint that doesn't rely on differences of indication and may provide a more apples to apple comparison might be patients whose arthritis progressed to the point of needing an arthroplasty, but the study was not powered for this endpoint. Secondary endpoints included a host of other subjective patient reported outcome measurements at six-, 12-, and 24-month time points. Secondary endpoints also included an analysis of cartilage lesions that was limited to full thickness cartilage lesions in a smaller subset of MRIs that were available.

The patient reported outcome results have some limitations we'll get to, but make no mistake, valid evidence of cartilage growth would be viewed very favorably. The sponsor's findings of cartilage condition bears further discussion. Valid semi-quantitative MRI methods exist to evaluate knee arthritis progression. Examples include whole organ MRI scoring, known as WORMS, and MRI osteoarthritis knee scores, known as MOAKS. What these semi-quantitative methods include, which is not included in this secondary endpoint claim, is an evaluation of the whole knee. This would include articular cartilage lesion evaluations that looked at both depth and the area of the lesion. It would include bone marrow lesions and cysts. It would include osteophytes. It would include synovitis and effusion, the signs of irritation or inflammation in the knee, and it would include meniscus changes over time, things like extrusion and tears. These semi-quantitative approaches were not used. The cartilage analysis is limited and prevents making cartilage preservations or regrowth claims.

This graphic demonstrates the Mercury data results. So the Mercury dataset is the bigger study, and this can provide context for the modified Mercury dataset, which we will discuss later, and is the prime data set for this de novo. Overall success for the composite endpoint was 45% at 24 months. This means that outcome scores were met. They had no automatic study failure by 24 months. Subjects could fail by failure of the device and leads to surgery, and this occurred in 34% of the Mercury dataset. And this exceeds the safety hypothesis. Subjects could also keep their device but fail from not meeting the outcome score goals. And this occurred in 24% of the Mercury dataset group. At the bottom, you can see 55% of the subjects failed by either surgical failures or by not meeting the outcome goals.

In response to this 34% rate of automatic study failures from surgery, the sponsor provided a table to classify failures. They classified the failures by fatigue, surgical technique, arthritis progression, implant stability, patient related trauma, and general complications such as infection and fibrous adhesions. Each of these categories was then determined to be device related or not related. There is uncertainty in the relevance and reliability of their classification technique. The sponsor hypothesized that the automatic study failure rate could be lowered with mitigation strategies.

So let's talk about some of those mitigation strategies. These included a much more detailed surgical technique to address surgeon error, adequate osteophyte removal with new instruments, which included especially designed rafts to ask access the notch, better evaluation of the patient, not anatomy and notchplasty as needed, a stricter avoidance of patients with more severe arthritis patient education to avoid uncontrolled traumatic events, and a restriction of patient postoperative activity level, better instructions for the surgeons on sizing the implant and increased choices for implant sizing, a change in the material properties of device, and

limitations to the patient population who had single versus multiple prior meniscectomies. The selection based on anatomical differences was also suggested femoral condylar thickness versus height, and differences in the notch size and shape, the meniscus extrusion, and the tibial spine height.

And after reviewing their populations who had had automatic study failures, the sponsor selected the last two anatomical differences to identify a subpopulation with a lower surgical failure rate. The sponsor provided these graphs after applying the exclusions of meniscus extrusion greater than five millimeters, and then with both the meniscus extrusion criteria and tibial spines shorter than 11 millimeters. The criteria were also evaluated in both the original pooled Mercury dataset and the multi-centered pilot trial data. These graphs show similar decreases in the automatic study failures in both groups.

The rationale for meniscus extrusion meniscus extrusion is a measure of the or original meniscus health. It can result from a rupture of the meniscus root, but this was a contraindication for this study. The meniscus extrusion in this study serves as a surrogate for the amount of arthritis inside the knee. Less extrusion is generally associated with less arthritis. This colorful water waterfall graph shows the outcomes in colors based on the measures of meniscus extrusion on the vertical graph. At about five, you can see they're much more colorful, yellow and red on the right, compared to primary green on the left. The red and yellow bars are patients who had automatic surgical or study failures with the devices removed. The yellow bars represent cases where the surgeons and patients elected to replace another device inside the knee.

Selecting a healthier population with less arthritis creates greater uncertainty regarding the benefit risk balance. The selection of patients with less arthritis may increase the risk of a

procedure that requires a near total meniscectomy for placement of the new implant. These patients may have more to lose when study failures occur and the devices removed.

The second exclusion criteria was subjects with shorter tibial spines. It's recognized that the device's lateral bridge is required for stability of the unfixed interpositional design. The sponsor hypothesized that the taller spines would better prevent surgical failures. 11 millimeters is close to the population's average spine height, and the sponsor felt that patients with taller than average spines would have fewer failures. The sponsor did not provide a separate waterfall graft for failures based on ranges of spine height.

The method and evaluation of the results raise uncertainty regarding these two measurements. Two raters were used, and when there was a disagreement, those subjects were excluded from the analysis. This disagreement was present in 19% of those images looked at. Rater uncertainty decreases the clinical relevance of these measures. It may make the measurement less valuable for the surgeon in the field if we can't agree on what 11 millimeters is when measured. In addition, there were differences in the results between groups where agreement existed versus those that had disagreement and were excluded. The sponsor's selection of the agreement only group provided more favorable results for the NUsurface group. The population where raters had uncertainty had a higher surgical failure rates, up to 39%, compared to those in whom the raters agreed, which was 28%. The technique and its analysis raised a potential question of bias because the exclusion lowered the automatic surgical failure rate.

So now let's focus on the modified Mercury dataset. This is the subset from the larger Mercury dataset. We will talk about the safety results and then the effectiveness results. First, we will discuss the safety assessments that include adverse events, those the sponsor felt were associated with the device, secondary surgical interventions, and the secondary surgical

interventions that were counted as automatic study failures in the composite study success criteria. We will also briefly look at some of the retrieval analysis data provided by the sponsor.

The number of patients with adverse events in the index knee, or possibly related to the implant, were higher in the NUsurface group compared to the control group. About twice as many NUsurface subjects had adverse events than the control subjects. NUsurface adverse event counts were 124 compared to the control group events, who had 14. The sponsor divided the results for the modified Mercury dataset differently than their prior de novo. The modified Mercury results are divided into uncorrectable, correctable, expected device effects, and knee adverse events. This had the effect to split adverse event numbers into different categories, which each has a smaller event count.

Adverse events at index knee are possibly related with larger percentages, include subjects that had noise, also described as mechanical symptoms, which included clicking, popping and squeaks. It also included 27% of the subjects who had reported effusions compared to one patient in the control group. The following adverse events that may be device related, but because of uncertainty, the sponsor did not attribute it to the device included adhesions, arthrofibrosis, and limited range of motion. None of these events were found in the control group. These adverse events create uncertainty regarding the long-term safety of the device. Clicking, popping, and effusions are signs of knee irritation, and often of worsening arthritis. The sponsor also recognized that progression of arthritis may also lead to device failure.

The next topic is serious adverse events. The largest category of serious adverse events was device issues relating or that resulted in secondary surgical events. In 24 months of the study, 17% of the modified Mercury subgroup had at least one operation to remove the initial device. Operations were done for device damage, dislocation of the device, or rotation of the

device. Some subjects experienced more than one of these categories, and some subjects had secondary surgeries on the new devices that were used to replace the initial device. 25% of the patients who had their devices removed received an arthroplasty in the 24-month timeframe of the study.

The retrieval analysis creates uncertainty in the root causes claimed for the device. The pattern of abrasion and fractures occur in the lateral aspect of the device that sits in a location where no tissue normally exists. Lateral overload from this design feature may be an alternative explanation for the failure seen. Further evidence of the possibility of the lateral overload hypothesis is seen in this retrieval case where a subject returned with symptoms. MRI on the far right shows bone edema underneath that lateral bridge region in the area where no tissue normally exists. At arthroscopy, you can see that there was a resulting lesion down to bone in the area where this overload occurred. And then finally, you can see that the device is not yet fully ruptured.

So the safety summary. Automatic study failures due to surgery were lowered from [audio lost, 152 seconds] [From Script of slides that was read: 34% to 17% and continued to exceed the safety hypothesis. Adverse Events and Serious Adverse Events were numerically higher in the NUsurface group. Retrieval analysis showed a consistent pattern of abrasion and tearing in the non-anatomic section needed for fixation. Effectiveness Assessments included Patient Reported Outcomes, Absence of Device Related Secondary Surgical Interventions, absence of MRI failure and then we will discuss overall success rates. 62.1% of subjects met the primary endpoint for KOOS improvement compared to 17.9% of the control group. 83 percent of the NUsurface group did not require any device-related surgery compared to 90 percent of the control group. The definition for secondary surgical intervention was different between the

groups. One subject in the NUsurface group failed by MRI and had not undergone secondary surgery. For the control group, MRI failure was not relevant. To summarize overall] surgical success. 51.4% of NUsurface subjects met the composite endpoint. 16.1% of control subjects met the composite endpoint. Again, the main driver of composite endpoint study success was the patient reported outcome score differences in the NUsurface group and the nonsurgical control group, neither of which could be blinded. The sponsor suggests cartilage preservation, and in some analysis, cartilage improvements. However, evidence presented was limited and creates uncertainty. The analysis was limited to full thickness cartilage lesions. The MRIs available from both groups had a great deal of missing data. 35% was missing from the control group, and 17 percent of the MRIs were missing from the NUsurface group. Some analysis used last observation carried forward for their missing data, which would be inappropriate for arthritis evaluation over time.

In their initial analysis, the sponsor described concerns regarding the evaluation of tibial cartilage and noted that the thickness of tibial cartilage was technically beyond the capability of MRI scans to produce reliable data and no measurements were possible. Further evidence of uncertainty regarding the cartilage or progression of arthritis conclusions is created from the retrieval analysis, which reported progressive osteophytes and full thickness cartilage lesions that were attributed to device failure.

Using the composite steady success criteria, NUsurface has greater composite endpoint success. 51% of NUsurface subjects met success criteria compared to 16% of non-operative controls. The main driver of failure for the non-operative control was the lack of patient reported outcome improvement. The study design has unblinded patients. The NUsurface group received something new, the effects of surgery, of formal physical therapy protocol, and postoperative

appointments. The control group, those who remained in the study, continued their usual routine without a formal regimen of care.

With that, we'll wrap up the initial clinical considerations. The next section we have for the panel is a discussion of the statistical considerations provided by Ms. Cynthia Lu.

Statistical Considerations — Ms. Cynthia Liu

Ms. Liu: Hello, my name is Cynthia Liu, and I am a statistical reviewer in the Office of Clinical Evidence Analysis. Mr. Van Orden was the original statistical reviewer for the de novo application, and I am the statistical reviewer who will present the statistical considerations and limitations for the NUsurface meniscus implant data sets for the panel.

You have just heard Dr. DeHart's clinical presentation. Now I'm going to express some of my concerns from the statistical point of view. The Mercury dataset consisted of data from the Venus and Sun Studies. The Venus study was a prospective randomized two arm non-surgical-controlled trial, enrolling 61 NUsurface subjects and 66 control subjects between 2015 and 2018. The Sun study was a prospective, non-randomized, one arm trial, enrolling 115 NUsurface subjects between 2016 and 2018. The idea of combining the data from the Venus and Sun studies was proposed in 2017 while the two unblinded studies were still ongoing. After the last patient was enrolled in June, 2018, a propensity score analysis was performed to check whether or not the two studies could be combined.

Then, the statistical analysis plan for the combined dataset was finalized in early 2019 and approved by the Agency based on the limited information given by the sponsor at that time. According to the sponsor, the database lock occurred on June 30th, 2020. So, a total of 242 subjects from 20 different sites were in the Mercury dataset, where 176 were in the combined NUsurface group and 66 in the control group.

Since the combined Mercury dataset consisted of data from a randomized Venus and a non-randomized Sun, it is important to ensure that baselines between the combined NUsurface group and the control group were balanced. While reviewing the first de novo submission, the FDA noticed that among 122 baseline variables reported for the Mercury dataset, 14 of them had a nominal P value of less than 5% when comparing the combined NUsurface group and the control group. Therefore, similarity of the two study populations appears to be questionable.

As Dr. DeHart mentioned earlier, there was uncertainty or bias in the results due to missing data. As you can see from the table here, the control group had very high rates of missing data for various endpoints. Although the NUsurface group had only 2% of primary endpoint data missing, the KOOS PRO, which was the sole driver for the overall success, as Dr. DeHart pointed out, had 13% of the data missing. Together with 35% missing KOOS in the control group, it is unclear in which direction the results will shift if all of the missing data had been probably accounted for.

Sensitivity analysis using last observation carried forward and multiple imputation techniques to examine the impact of missing data on the primary endpoint results were conducted. The last observation carried forward technique is a single imputation method that assumes missing completely at random, whereas multiple imputation technique assumes missing at random. With the effectiveness endpoints heavily relying on the PRO measures in an unblinded setting, and as the missing data between the two treatment groups may be due to various reasons, it is unclear if the two missing data handling techniques were suitable.

Recall that two radiographic variables, meniscus extrusion and tibial spine height, found in the Mercury dataset were used to identify a modified patient population with a lower secondary surgery rate. The five-millimeter cut off value for meniscus extrusion and 11-

millimeter cut off value for tibial spine height were obtained through some analysis on the MRI measurements read by the raters. Therefore, the modified patient population included subjects from the Mercury dataset who had a meniscus extrusion of less than five millimeter, and a tibial spine height of 11 millimeter or greater at baseline. In other words, except for subjects being excluded by both raters, subjects who had a disagreement between the two raters, such that one measurement was below the threshold value and the other above, were also excluded from the modified patient population, as is shown in the green colored boxes of the table here.

Please note that the percentage of inter-rater disagreements was nearly 20% in both treatment groups. With this high rate of disagreements between the raters, it raises an uncertainty in data analysis, since it is unclear in which direction the results will shift if subjects with the disagreed MRI images are included in the analysis.

Since a subpopulation from the Mercury dataset was defined, a modified Mercury data set was therefore created, which consisted of 74 NUsurface subjects and 35 control subjects. Please note that the modified Mercury dataset included only about 45% of the Mercury subjects after applying the two hypothesized risk mitigation criteria and excluding the disagreements. The modified Mercury dataset also has some of the Mercury dataset's problems. Among the 55 baseline variables reported, prior cartilage surgery, physical therapy, and steroid injection appear to show imbalance between the NUsurface and the control groups. It is noteworthy that there were 122 baseline variables reported for the Mercury dataset, while only 55 baseline variables were reported for the modified Mercury dataset. Since the modified Mercury data asset was not generated from a randomized trial, any unbalanced and/or clinically important baselines should be accounted for in a model for the outcome analysis. There was no pre-specified analysis plan for the modified Mercury dataset.

As described in the clinical report document, a propensity score analysis was performed to account for some baseline differences. But it is unclear to the FDA how the propensity score analysis was implemented. Specifically, the logistic regression model for propensity scores appears to include prior cartilage surgery and sterile injection intervention through a model selection process, as I will show in the next slide. Also, the outcome analysis was adjusted for two propensity score strata, as opposed to five that is commonly used. And it is unclear if the baselines were balanced between the two treatment groups within each of the two propensity score strata.

This table describes the sponsor's basis for the propensity score adjustments. No other information was provided to the FDA for further evaluation on the appropriateness of the propensity score method. As you can see from the yellow-colored text in the table here, the model selection process started out with all variables with a statistically significant P-value of less than 0.05, then added additional variables that became statistically significant in the adjusted analysis, then removed the variables with the worst P-values as long as no statistically significant effects reappeared. From the descriptions here, it is possible that the selection of baselines may have been influenced by a knowledge of the observed outcome.

The missing data pattern observed in the Mercury data set said was also observed in the modified Mercury data set but in a lesser degree. Although the primary endpoint data missing at 24 months was only 3% in the NUsurface group and 11% in the control group, the KOOS PRO, which was one of the components of the primary endpoint and a major contributor to the overall failure in both treatment groups, had 11% and 20% missing in the NUsurface group and the control group, respectively. In fact, similar missing data rates at 24 months were also observed for all other PRO secondary endpoints, which may have therefore impacted their outcomes.

As in the case of the Mercury dataset, the assumption for the missing data handling technique such as last observation carried forward, may not hold, because reasons leading to missing data may be different between the two treatment groups and the missingness may not be completely at random.

Finally, let me sum up the statistical limitations of data analysis for the modified Mercury dataset. The modified patient population was defined based on the two hypothesized risk mitigation criteria found from the Mercury dataset. It included about 45% of the 242 Mercury subjects, so the sample size was not large, especially in the control group where only 35 subjects were identified. There was no agreed upon pre-specified analysis plan for the modified Mercury data set. The analysis plan pre-specified for the Mercury data set was not followed, either. Although using the propensity score technique to account for baseline differences to mimic a randomized controlled trial is reasonable, the validity of the sponsor's propensity score model is questionable. As mentioned earlier, the propensity score model used for the analysis of the modified Mercury dataset was not pre-specified. It is unclear if all potential clinically relevant baselines were included in the model. It is also unclear if the selection of the baseline variables was based on an outcome free approach and if all clinically relevant baselines were balanced between the two treatment groups after the propensity score analysis.

Any of these uncertainties, if not addressed, may bias the results. Also, due to the small simple size in the modified Mercury dataset, it is unclear if the propensity score method is applicable, as the propensity score model may not adequately accommodate all the clinically important baselines. Although the missing 24-month data rates in the modified Mercury dataset were not as high as the ones in the Mercury dataset, the 20% missing for all the PRO measures in

the control group makes the interpretation of the effectiveness comparative results in an unblinded setting very difficult.

In summary, with the modified Mercury dataset being created from the Mercury dataset, along with the statistical uncertainties that I just mentioned, it is challenging to draw a sound conclusion based on any statistical inference. This concludes my presentation. Next, Dr. Gebben will give a presentation regarding social science and patient preference. Thank you.

Patient Preference Information — Dr. David Gebben

Dr. Gebben: I am David Gebben. I am an economist trained in stated preference research, of which patient preference are a type. At CDRH, is part of the patient science and engagement team. I am a subject matter expert in patient preference methodology. For over a decade, CDRH has been committed to bringing the patient's perspective and experience into our regulatory efforts. In 2016, CDRH issued a guidance document on the role that voluntary patient preference information can play in the regulatory decision.

PPI is defined in the guidance as, quote, "qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions." Patient preference information is not the same as patient reported outcome or other clinical trial endpoint or outcomes. These measures assess different things, are used at different points in medical device evaluation, and are interpreted differently. As you heard, the Knee Injury and Osteoarthritis Outcome, or KOOS, results in a score and measures pain, physical function, and quality of life. Whereas a patient preference study would not result in an overall score, but instead assess the relative value that patients place on a treatment profile or its alternatives.

Patient preference studies need to be well designed and implemented in a way that allows for useful information to be generated. A well designed and well conducted patient preference study can provide valid scientific evidence regarding patient's risk tolerance. This may inform FDA's evaluation of a device's benefit profile during the review process. The CDRH PPI guidance lays out the features that can assist in the determination of whether a study is of high quality to generate valid scientific evidence. Well designed and conducted patient preference Studies include the following features: established good research practices, effective communication with minimal cognitive bias, and robustness of analysis and results.

Since patient preference studies are a type of social science research, they should also follow established good research practices like obtaining informed consent and IRB approval prior to fielding the study. In addition, a good study will have effective communication and benefit risk information with minimal cognitive bias. And of course, the study will need to include all relevant information that a patient would be expected to need to know and understand in order to make an informed decision regarding treatment options. Finally, it is expected that a study would be conducted in a way where the analysis yields interpretable results, and the analysis is in alignment with the accepted methods in the published literature. And when those components are present in a patient preference study, it can provide information about what benefit risks tradeoffs are acceptable from the patient perspective. These studies are not typical opinions surveys. Instead, they follow an experimental design that takes careful planning and methodologic expertise to implement correctly.

The sponsor conducted their first patient preference study before engaging with FDA on the study. Hence, FDA was not able to provide feedback on the PPI study protocol or analysis plan. FDA evaluated the results from the study and relayed concerns to the sponsor related to the

design conduct and analysis of the study. The sponsor conducted multiple studies, each time attempting to address FDA's concerns by designing the next study to address different questions and using different methods. However, FDA's feedback on key concerns were not reflected in the study protocols conducted and analyzed by the sponsor. Therefore, despite feedback provided by the FDA for the prior six studies, the current study has many of the same concerns noted by the FDA from the prior studies, such as inadequate presentation of the risks, biased presentation of benefits and risks, and unclear educational materials, critical features of well-designed and conducted studies along with sponsor studies. Limitations will be discussed in further in the following slides.

Patient preference studies are social science experiments, and as such, standard ethical principles and practices of human subject research apply as outlined under good clinical practices guidelines 21 CFR parts 50 and 56. In accordance with standard PPI research methods and principles, informed consent is expected to be obtained and IRB approval sought. The sponsor chose not to obtain informed consent or seek IRB approval for the patient preference study. The proposed study objective was to determine how much additional risk of reconstructive knee surgery patients would accept in exchange for pain reduction relative to the neurosurgical treatment option.

For a study participant to make an informed choice about treatment options, the educational materials accompanying the survey instrument should be complete. The educational material in the NUsurface survey did not adequately reflect the risk of other secondary surgical procedures like a NUsurface removal or replacement. The PPI guidance states that a feature of good survey, good study design, is effective communication of the benefits and risks. When the educational portion does not clearly communicate all relevant information, the resulting data is

likely to be biased, leading to an underestimating the minimum acceptable benefit, or overestimating the maximum acceptable risk for a treatment option. This bias results from respondents not having the necessary information to weigh the relevant features of a treatment and its alternative. By not presenting all relevant information about the risk in the survey, it may be challenging for the results from the PPI study to inform the benefit risk assessment.

In the educational material, the sponsor provided respondents, "benefits are in green, and risks are in red." This could influence or bias a subject's response because of the positive and negative connotations associated with the red and green colors in US culture. Red is often meant to convey a warning or sign to stop, while green has the opposite meaning. Benefits and risks should be presented in neutral colors, for example, blue or orange.

To avoid this cognitive bias, in the educational portion of the survey, the sponsor only showed a percentage to communicate the risk. Good research methods for PPI studies include accounting for challenges respondents might have in understanding probabilistic data, also called numeracy, multiple formats for presenting numerical data, such as presented percentages, pictographs, and text, may help different respondents better understand the numerical risks and benefits. For example, risks should be presented as a percentage, 10%, a numerical 10 out of 100, and graphical or pictograph presentation, a grid of 100 boxes with 10 shaded in, to communicate the same information. That presentation format for probabilities should be consistently used throughout the entire survey. This is to reduce the cognitive burden on the respondent and reduce the measurement error in the survey. If the probabilities are not presented in an easily understood and unbiased manner, this could create an over-acceptance of risk or an under-reporting of the needed benefits. When a study is constructed without effective

communication of risks and benefits, respondents may be unable to make informed decisions. This results in potentially skewing the actual preference estimation, potentially leading to bias.

The sponsor used a threshold technique to determine at what point the potential additional benefits of the NUsurface device compared to no surgery outweigh the associated risks of the NUsurface device. In the example on the slide from the NUsurface PPI study, the benefit was determined to be a 25% reduction in pain, which the sponsor equated to a 25 point pain score improvement of one disability level. The risk is defined as the chance of an unplanned reconstructive surgery of the knee. The initial starting point for either treatment option was a 25% chance of improvement on the pain scale and a 10% risk of unplanned reconstructive surgery, with the NUsurface device without a change in the profile for the no surgery option. From this starting point, either benefit or risk would increase or decrease in 5% increments depending on which option was chosen. For example, if the no surgery option was chosen, the next question would show a 30% chance of improvement in pain and keep the 10% chance of unplanned knee reconstructive surgery. The respondent would then be asked to choose. Respondents were not presented with probabilities in multiple formats as previously described, nor were respondents educated about the complete benefit and risks associated with the surgery or no surgery option. These two methodologic flaws would likely bias the results.

The analytic approach is also important for patient preference studies. Once respondents choose the point at which they would switch from one treatment option to the other, the data is analyzed using proper econometric techniques to estimate the sample threshold. The accepted way to estimate that sample threshold is through an interval regression, which the sponsor did not do. The analysis the sponsor performed was not consistent with the published literature of

acceptable approaches. As a result, the patient preference information presented by the sponsor is unclear.

For example, the results presented in Table 22 from the sponsor's executive summary and which were not previously presented to the FDA for review do not represent the sample estimate of the threshold or the maximum acceptable risk. The sponsor previously indicated in the de novo submission that the preference data for study seven were analyzed using an analysis of variants and linear probability model. However, this analysis approach would not be able to provide the information they labeled as average preference. Instead, to generate a sample preference value, the sponsor would have to conduct an interval regression. This analysis was not performed by the sponsor. The column 95% minimum calculation is unclear based on the information the sponsor has provided.

As previously mentioned, the sponsor did not perform an interval regression. Therefore, no sample level estimate of preference was calculated. Without an initial point estimate from the interval regression, the meaning of the 95% minimum calculation is difficult to understand. Therefore, the information expected to be related to the minimum acceptable benefit and maximum acceptable risk in the last two columns is not generated using accepted methods in the published literature.

PPI Guidance recommends that high quality patient preference studies include analysis that ensures the appropriate interpretation of the collected data, also referred to as robustness of analysis results in the PPI guidance document. Since the sponsor did not conduct an analysis consistent with accepted statistical approaches, the results are challenging to interpret as robust.

In addition, the sponsor stated that, quote, "The PPI studies ask different questions and collected data by different means." Close quote. Therefore, data from the different studies are not comparable or poolable, which is what the table from the sponsor implies.

In summary, the qualities of the patient preference studies conducted by the sponsor did not appear to be consistent with those described in the Patient Preference Information guidance. When considering all PPI studies conducted by the sponsor, including the current PPI study, the concerns identified by the FDA in the previous six studies are still present in the seventh study despite repeated interactions with the agency, the PPI studies were not designed or conducted in a manner consistent with accepted PPI research practices or methodologies. The sponsor did not obtain informed consent or IRB approval, which is standard for human subject research. The study results were likely biased in favor for the NUsurface device. The risks and benefits were not fully described when the treatment options were presented, which includes omitting the risks of secondary surgical procedures. The benefit risk information was not presented in a neutral patient-centric manager that would be easily understood by all respondents. The analyses did not provide the needed information for assessing a sample threshold estimate. Patient preference information has been provided to support the benefit risk determination. Please comment on the design and execution of the current PPI study, study seven. Please discuss the contribution of the PPI studies to the final benefit risk determination. Thank you.

Benefits and Risks Summary — Dr. Marc DeHart

Dr. DeHart: Thanks, Dr. Gebben. With that, we'll move on to a summary of benefits and risk. Again, I'm Marc DeHart. I'm the orthopedic surgeon and the medical officer for this submission. Let's start with a summary of the benefits for the NUsurface meniscus implant. Patients may experience an improvement in pain, function, and quality of life, as measured by the KOOS pain

and overall score, as well as various secondary endpoint assessments at 24 months. The percent of patients meeting the outcome goals were higher for the surgical group than the control group. The average improvements lasted the two years of the study. The magnitude of improvement exceeds the minimally detectable difference for the KOOS scores.

Patients may experience an improvement in pain and keep their device in place or need a surgery to replace or reposition the device. 51% of NUsurface subjects in the modified Mercury dataset met the composite success criteria 24 months compared to 16% of the non-surgical control subjects. When compared to the non-operative control group, 62.1% of the NUsurface subjects met the patient reported outcome goals compared to 17.9% of the controls. 83% of NUsurface subjects retain their device for two years compared to 90% of the control group who avoided further surgery.

The summary of the risks. Patients may not experience any improvement in pain or function, and some pain scores worsened. 38% of NUsurface subjects did not experience outcome score success. The NUsurface meniscus implant may become damaged or become dislocated, rotate, and lead to additional surgery. 49% of subjects did not meet the patient-reported outcome goals for pain or function, or needed a surgery to remove the initial device. 17% of the selected modified subgroup needed removal surgery by 24 months, and other patients needed additional surgery. This exceeded the safety hypothesis. 12.5% of NUsurface subjects experienced noises including clicking, popping, and squeaks, which may portend device related mechanical integrity or positioning issues.

The NUsurface implant and the sub-total meniscectomy required to implant the device may accelerate osteoarthritis disease progression. 4.2% of the arthroscopically evaluated NUsurface subjects in the modified Mercury Dataset needed a joint replacement, either a total

knee or a uniknee, by 24 months due to disease progression versus 1 out of the 31 nonsurgical control group who received no arthroscopic screening. Of the 12 subjects whose NUsurface device was removed, 25% went on to have a knee arthroplasty by 24 months. NUsurface subjects experience more adverse events and more serious adverse events than the control group. 41.6% had serious adverse events compared to 12.9% of the controls. 13% of NUsurface subjects experienced adhesions, arthrofibrosis, stiffness, or limited range of motion compared to 0% of the nonsurgical control group.

Additional considerations regarding uncertainty. There's uncertainty, lack of understanding, about the root cause of implant-associated secondary surgeries and adverse events and which subjects are at increased risk for these surgeries. Long-term consequences of device use and the associated near complete meniscectomy may need longer than 24 months to access their end result. Large amount of missing data from a limited non-surgical control group and limited amount of MRI data from both groups provide uncertainty. The magnitude of outcome scores, while meeting goals, are in the same range as KOOS scores from randomized controlled trials for partial arthroscopic meniscectomies and their sham arthroscopic surgery and non-operative controls. Types of surgery required by subjects in the nonsurgical control group suggest there may be differences in the screening between study arms, arthroscopic screening of cartilage in the NUsurface group, that led to bailouts in this group. This study was not designed to evaluate cartilage preservation and regrowth. Arthritis progression analysis was not sufficiently robust. The design and contact of the patient preference information were not in alignment with accepted practices described in published health preference literature.

Additional considerations, proposed risk mitigation. Modifications to the labeling related to meniscus extrusions included a contraindication that patients with extrusion of the medial

meniscus of five millimeters or greater should be a contraindication. The labeling also includes a warning: patients in which the height of the tibial spine is below 11 millimeters are at a greater risk of device related adverse events.

And that sums up our talk. Thank you for your time and attention. In the next section will move toward panel questions, for reference.

Q & A

Dr. Smith: I would like to thank the FDA speakers for the presentation. Does anyone on the panel have a brief clarifying question for the FDA?

Capt. Peat: Dr. Smith, before we move to the questions, I invite all FDA presenters to turn on your camera please, so you can answer the questions. Thank you.

Dr. Smith: Hey, Dr. Cizik, I believe you're first.

Dr. Cizik: Yeah, I didn't catch this, so I don't know if the FDA's able to answer this, or if it goes back to the sponsor, if we'll have another opportunity. I'm a little confused about a KOOS overall score. How was that calculated? Because it's not recommended. And so I'd like to know what that was. And also to clarify, too, that it required both an overall and a pain. So they were like double counted in that 'and' category. So I'm confused about that.

And secondly, and I'm sure Dr. Reed might want to comment on this as well, I just do want to clarify if it was a population based preference study. So like if they used MTURK, you wouldn't necessarily need informed consent or an IRB as that went out. I mean, again, I don't know how they actually conducted this study. I heard them say they used other people, but I mean, that would not be a concern if it was a population based, you know, census type study. So I just want to give them the benefit of the doubt on that and maybe allow them to respond to that as well.

Capt. Peat: Thank you so much. Dr. DeHart, do you want to take the first question from Dr. Cizik?

Dr. DeHart: Yeah, Dr. Cizik, a great question. And yes, the pain score is a subpart of the KOOS overall score. The KOOS score is pretty well accepted in sports medicine literature, and we go for that. Initially, you know, we would've liked to have some objective performance measure, something besides just pain.

But the KOOS overall score does include pain, a quality of life measure, some activity level things. But I understand your —

Dr. Cizik: I'm aware of that. I know what's in it. I'm saying it should not be calculated according to Deus who, who wrote that. So I'm just, I'm just wanting to know, was it summed up and added and divided? That's what I'm trying to understand. Did the overall include all the subscales? And I think that's, you're saying yes, it did.

Dr. Cizik: Yes. It's supposed to, it's supposed to contain all the subscales. That's correct.

Dr. Smith: Dr. Price. I believe you're next.

Dr. Price: Hi. I think it would be great to see the subscales if that's possible. The, because that could have a reference on how we, the decision is made. And also, I had concerns because I thought I heard the sponsor mention that there was some kind of arrangement with the FDA where they combined the two trials. And I can see that there's serious methodological challenges with an combining a randomized and a non-randomized trial. And so I'm wondering if the FDA could address maybe their initial involvement. And I heard the objections, and I think that, you know, I mean, that they're considerable. So yeah, I would just like to know if it's possible.

Capt. Peat: At this time I'm going to invite Dr. Fraser to answer these questions regarding the PRO. Dr. Frasier.

Dr. Bocell: Hi, my name's Fraser Bocell. I'm a psychometrician and clinical outcomes assessment reviewer with a patient science engagement team at CDRH. So in response to Dr. Cizik's comment, yeah, we acknowledge that that is not common practice for a total score to be calculated. And at the same time, yeah, that you've got the pain measure from the KOOS and a vast pain score that we're looking at. And so the interpretation of the overall score is challenging, because that's not common to the literature and hasn't been researched a lot. So that's something that we wouldn't put a lot of weight in. We'd be looking at the individual subscales instead. And I apologize Dr. Price, I missed your question.

Dr. Price: Oh, okay. In the sponsor's initial presentation, I heard that there was some kind of a combination with the two trials that became the Mercury trial, and that, that's how it came across was so that it kind of had the blessing of the FDA. And yeah. What I'm also hearing is they are combining a non-randomized and randomized trial, as we know can produce significant methodological question, especially in terms of bias and in terms of safety. So I'm just wondering a little bit more about the background of that or if there's something that that I heard wrong or came to an erroneous conclusion on.

Dr. Bocell: Oh yeah. Thank you for repeating that. I'm actually going to turn that over to Dr. DeHart and Dr. Liu to address that.

Dr. DeHart: Yeah, I'm going to turn it over to Cynthia, because she's way smarter on stats than I am. But I agree. There's been, there was a lot of controversy about how to put that together, but we were faced with a problem, or the reviewers at the time. There have been several sets of reviewers that have looked over this over many, many years. One of the issues was how do you get enough patients to really look at safety and try and get a large enough population? Cynthia, are you prepared to talk about that now?

Ms. Liu: I guess I could. Okay. So, well, I don't know the exact history of how those two were proposed to be combined. But I do know that, for the safety evaluation sake, we want more subjects. So we kind of maybe suggested that the sponsor can look the dataset, two datasets, together. Correct me if I'm wrong, Dr. DeHart. So to examine whether the Venus studies could be combined, we told the sponsor that you need to check whether the two study populations were similar enough in order to be combined. Then the sponsor proposed propensity score method to examine if the two studies could be combined. And they proposed a very limited information for us at that time. And the limited information appears to be reasonable to us, basically just say propensity score analysis.

So the sponsor had an independent statistician to look at 18 baseline variables in the Mercury dataset and somehow choose 11 of them in the end to, in the propensity score model, as a predictors of assignments to Venus to examine whether the two studies can be combined. Then the propensity score obtained were ranked, and the population was subdivided into five nearly equal strata. And the sponsor propensity score analysis report concluded that there were no significant differences in propensity scores between the two studies within each stratum, indicating that the two study populations were generally similar and the propensity score strata could be used as a covariate to eliminate any potential differences between the two studies.

But however, since the propensity scores were obtained based on the probabilities of being assigned to one of the two studies, not being assigned to one of the two treatment groups, and the outcome analysis was to examine the difference between the two treatment groups, not a difference between the two studies, the FDA noted that the propensity score strata would not be useful for the outcome analysis. So the sponsor in the end revised the statistical analysis plan for

the Mercury dataset, and the final outcome analysis was analyzed using a dichotomized based like KOOS sports recreation variable as a covariant in the model instead.

However, as I mentioned earlier in the presentation, while reviewing the first de novo application, the FDA noticed that there was some baseline differences between the two treatment groups. So similarity of the two-study population appears to be questionable to us. Thank you.

Capt. Peat: Thank you, Ms. Lu. I also want to give some time for Dr. Gebben to expand on that response as well.

Dr. Gebben: Yes. I'd like to clarify for Dr. Cizik. The patient preference information. It is very standard, even when using market panel data, to obtain an informed consent as part of the process of collecting the data. So even if the sponsor chose to use a market panel or Amazon Turk, as you mentioned, it would still be pretty standard procedure within the research field to obtain informed consent.

Dr. Smith: Thank you. I'd like to make a quick comment and some clarifications. There's four hands raised, including mine. I just wanted to respectfully note to the sponsor that during this portion of the question and answer, the sponsor is not to answer questions in this portion. And the order of questions will be myself, Dr. Banerjee, and then Dr. Barber.

The question I wanted to ask. A lot has been made in both presentations, both MRI measurements and MRI findings, chondral defects, tibial spine height. However, in these studies, the MRIs were performed at two different field strengths, 1.5 and 3 Tesla, and I haven't seen any data about the resolution of the boxes. Was the field of view standardized across patients? Was the image matrix anisotropic? What was the slice thickness? And what is the resolution of the boxes? Because I question if one can accurately make these measurements on these clinical MRI images. And there may be an inherent degree of uncertainty across the patient population. And

also when these MRI data tests were reconstructed with a zero fill to higher resolution, what was the smoothing algorithm? And then we saw some coronal images and the other presentation were as clear longitudinally. The coronal images were in different plains, as evidenced by different morphology of the condyles, different appearances of the notch, and different visualizations of the muscles.

And then also, on the one image we saw of a reported resolution of a coronal defect that was a non-weightbearing posterior femoral condyle. And we already know from the literature on tendons and cartilage that T2 weighted imaging you have in what's called a magic angle effect around 55 degrees, which confounds the measurement of T2 intensity as you go about a curbed surface of anisotropic tissue around that angle. And just the amount we've referenced MRIs across this meeting, I think we need to really have a better understanding of what was the MRI protocol and how accurate is that data, and are these measurements even feasible to make on the data that's being presented?

Dr. DeHart: Hey. Yeah, they asked me to speak up a little bit here, but your point is well taken. Again, the MRI and the cartilage issues in the major dataset were secondary endpoints. And when the proposal was initially out, we were primarily looking for the device malposition and tearing. And these MRIs can show that very well. We had several series of slides to show you on the retrieval that got canned because of amount of time. But the bottom line is even the sponsor, in the first response regarding the Mercury dataset, was concerned about the overall ability of the MRI to be able to look at the cartilage in a successful way. And I tried to quote that in the presentation. They made no claims on the tibial side in the first presentation. In the end I'm not an MRI specialist and so I can't answer all of your difficult to answer questions on the, the pixels.

But if any of the FDA people have more experience on that and want to weigh in, please feel free to join.

Capt. Peat: Dr. Coyne, do you want to expound a bit on this particular question?

Dr. Coyne: Yeah. In a way, I don't possess the direct expertise to address your question, Dr. Smith. I would say that, you know, just from a high level, this is — the issue that you raised is just factoring into the uncertainty of some of the conclusions that were presented and, you know, both received from the sponsor and FDA. And that we have just invite the panel to just consider the degree of uncertainty associated with the measurements and factor into how this contribute to the overall benefit risk profile of the device.

Dr. Smith: Thank you, sir.

Capt. Peat: Thank you so much. May I also add that later on this afternoon we would love to hear from our panel member that is a radiologist, Dr. Subhawong, so that this is something that can be deliberated later on. Thank you.

Dr. Smith: Dr. Banerjee, I believe you are next.

Dr. Banerjee: Hi, Sam Banerjee. So I have two clarifying questions for the FDA. One, sort of a procedural question for the chair, Dr. Smith. The clarifying questions for the FDA, one, is regarding missing data handling. Clearly the LLCF, or last observation carried forward, is not appropriate in this case. But I saw that it was mentioned the multiple imputation was used, but I could not find anything in the sponsor, the summary or the FDA summary regarding multiple imputation. Could you provide more details on how it was done, was it done on the outcome, and et cetera?

The second question is regarding the inter-rater disagreement. And I just want to mention that the inter-rater disagreement, the failures in the inter-rater disagreement failure rate was

higher than the included ones. However, this difference was, according to my calculations, not statistically significant, although it still is inappropriate to remove the disagreed measures on tibial spine height.

And the third question is a procedural question. I had a lot of comments about the propensity score and the modeling. I wonder if this is the right forum or the deliberation section is the right forum to address those issues.

Dr. Smith: I defer that to Captain Peat.

Capt. Peat: I would say for that latter question, it can be something where we could discuss in the afternoon during the deliberation timeframe. Ms. Liu, do you want to go ahead and answer that particular question, followed by Dr. DeHart? The first two questions I should say, rather.

Ms. Liu: I think, I believe the first question is about the multiple imputation methods. Maybe this afternoon the sponsor can answer better than me. I remember in their finalized statistical analysis plan they, or in their clinical study report, I'm sorry, the statistical analysis plan say they will use five imputation datasets, but in the clinical report, they say they generated the 20 imputation datasets. So that's the difference I found. But since more is better, we didn't raise any question about that. But I think they also use regression-based model, including several variables, which I can't remember on top of my head right now. I can probably give you information after lunch, or the sponsor will have a better information for you for that. And the second question about disagreements, sorry, would you please repeat that again?

Dr. Banerjee: So, so the failure rate in the disagreed ratings was higher than the ones that were agreed upon and included in the analysis. So that difference was about, it was 39% versus, I believe, 28 or something percent. So that difference was based on the data provider was not

statistically significant. I that I was trying to confirm whether that is the case and whether it was taken into consideration.

Ms. Liu: I think that was based on tibial spine height, quite, only —

Dr. Banerjee: Yes. Right. So the disagreement on measuring the tibial height.

Ms. Liu: Yeah, tibial spine height is about 20% disagreement in both treatment groups. And the 28% versus 39%, you were, that was for the automatic study failure rate. Right? So the modified Mercury assets, the automatic study failure rate was around 34%. And even if the sponsor used tibial spine height criteria alone, it reduced to 28%. But if the disagreements were included back to the datasets, then it raised the study failure rate to 23%. It's not actually 39. 39, it's only the subgroup of disagreements. But if you add a disagreement to the 74 subjects, then the automated study failure rate, I believe it's around 23%. Did I answer your question?

Dr. Banerjee: Sure. Thank you.

Ms. Liu: Okay. Maybe I can get you more information after lunch.

Dr. Smith: We have one more pending question, although, Captain Peat, you referenced earlier, you called on Dr. DeHart.

Capt. Peat: Yeah. Dr. DeHart, do you want to expand on that, or you think the response is sufficient? I just want to make sure that we have a better understanding regarding the disagreements that were done with the inter-raters and why that presents itself with uncertainties that we present, we brought to the panel members.

Dr. DeHart: Yeah, so I think the most important part is that there's a bell-shaped curve in the tibial spine height in humans, and right in the middle is about 11. So it was unclear to us how they decided which side to go. There were some medical officers who felt, well, a taller tibial spine would cause more fractures because the pressure between the medial femoral condyle and

the tibial spine would pinch it. And some thought, well, maybe we could agree with the sponsor that a shorter tibial spine height would be a problem because the device would slip out of place. So the clinical relevance of that was that it's hard for orthopedic surgeons to be sure about that measurement, and the statistical part that just turns out that, without the waterfall graphs to see where the failures happened, without dividing the tibial spine height into millimeters of difference, it's challenging for us to be able to say, does that make sense? Do we agree with the rationale in a clinically and statistically significant way? Alls we saw was the statistically the difference, and it favored the sponsor.

Dr. Smith: Dr. Barber.

Dr. Barber: Yeah. Hi, it's Tom Barber speaking. Just a question. And we saw one MRI in the presentation with the fracture of the implant that demonstrated or looked like it demonstrated some bone lysis. And I know polyethylene has been shown to have bone lysis issues in the past. And was that specifically looked at as part of the MRI reviews with regard to all of the patients, whether they had any bone license or not?

Dr. DeHart: Yeah, that's a great question. There was a pathology response that was done, but not of the entire population that we got to see. There was a histopathology evaluation where they looked at MRIs, and they found bone spurs and increased size of arthritis lesions. They also noted that there was some Bionate particle debris identified in that population. Now, the Bionate particles aren't as toxic as some of the other particles, like the metal-on-metal stuff that you're familiar with and I'm familiar with. But they did show particulate wear debris, and the synovitis looked like it was responding to that particulate degrees. They did markers on the synovium to look at macrophages and inflammatory cells, and they were elevated. And so in that review they, they were able to identify some particular debris.

But the biggest serious adverse event was the failure of the device. It dislocated and it fractured, and that's what causes the secondary surgery and removal of the device. But if you take that device out and you've already taken out all of the meniscus, there's going to be a large impetus from the orthopedic surgeon and the patient to say, hey, we went through this to get this spacer in there. We better put another one in there, because otherwise I have no meniscus at all. And so there's a big impetus to do the second operation once the device failed and is removed.

Dr. Smith: At this point, we are a little over time. I don't see any other pending questions. If there's no other pending questions, we'll now break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any members of the audience. We will reconvene at 2:00 PM. Thank you.

Open Public Hearing

Dr. Smith: It is now 2:00 p.m., and I would like to resume this panel meeting. We'll proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the panel to present data, information, or reviews relevant to the meeting agenda. Akinola Awojope will read the Open Public Hearing disclosure process statement.

Dr. Awojope: Both the Food and Drug Administration, FDA, and the public believe in transparent process of information gathering and decision making. To ensure such transparency at the Open Public Hearing section of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual presentation. For this reason, FDA encourages you, the Open Public Hearing speakers, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any companies or group that may be affected by the topic of this meeting.

For example, this financial information may include a company's or group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, everybody encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationship. If you choose not to address these issues of financial relationship at the beginning of your statement, it will not preclude you from speaking. I'll now hand it over back to Dr. Smith. Thank you very much.

Dr. Smith: Thank you, Dr. Awojope. FDA has received 18 requests to speak prior to the final date published in the Federal Register. Speaker number one, your audio is now connected. The first speaker is Rene Verdonk, M.D. You may begin.

Dr. Verdonk: Good day, ladies and gentlemen. Let me introduce myself. I'm Professor Emeritus at the Gent State University in Orthopedics and Trauma. Now I'm a consultant at the University Libre in Brussels, ERASMUS University Hospital. It is widely accepted that partial-meniscectomy leads to early onset of osteoarthritis; and the aim of replacing the meniscus are, of course, to reduce pressure pain; to prevent the degenerative changes; to avoid or reduce the risk of osteoarthritis; and to restore optimally the mechanical properties of the knee joint. And the idea is not new. It's been around since more than 70 years.

This is the NUsurface Synthetic Allograft Meniscus. It's a niche product for middle-aged chronic patients, post partial meniscectomy. And today, according to the current commendations, the current standard for meniscus replacement is MAT, is meniscus allograft transplantation, indicated in patients with a history of total meniscectomy; pain localized in the medial lateral compartment; stable knee; no malalignment, very important; and articular cartilage, with only minor evidence of degenerative changes. This is the indications suggested by IMREF, the International Society, where it suggests that it is indicated in patients with a history of total

meniscectomy; pain localized and in the meniscus efficient compartment; again, stable knee; no malalignment; and articular cartilage that is with minor evidence of degenerative changes.

When I first became aware of the NUsurface meniscal implant through research at my institution, evaluating the kinematics of the implant using the MRI, I have an interest since then because I saw the potential offered of an artificial meniscus to our patients. This is one of the papers that we published in evaluating these kinematics. The other papers are listed here, as I was an investigator in European multicellular clinical trial where, again, experience on the matter. This is the NUsurface, our bibliography on the matter. And, of course, you can look at this more closely. And the indications for the NUsurface are almost similar to meniscal allograft, except for age. It is indeed for middle-aged patients with medial compartmental knee pain; no axial malalignment; no instability; early OA, no more than ICRS grade three; and my experience has taught me that the device is safe and easy to revise. And this is one of the cases. I just want to close up and suggest is any follow-up where you can evaluate the status of the cartilage and medial compartment, which remains intact for 10 years. Thank you very much for your kind attention.

Dr. Kon: Good morning. I'm Elizaveta Kon. I'm an orthopedic surgeon and associated professor of orthopedic surgery from Humanitas University Milan, and I'm also current president of ICRS, International Cartilage Repair and Joint Preservation Society, which is a premier forum of international collaboration in cartilage research worldwide. And we have an objective to promote appropriate recognition of the research in the treatment of degenerative disease and the conditions, and the integration between basic science and clinical practice, trying to bring the innovation inside to the clinical practice to the health of our patients, trying to work with the laboratory agencies to promote the new technologies and innovations for our patients.

So our leadership share this views, and we have been discussed and supports what I am going to say, but we really recognize a critical role of the meniscus and the meniscal loss will bring to the deterioration and impairment of the joint from a biomechanical and biological point of view. And it's our responsibility to create something which will help our patients and researchers to make our patients work and walk and do sports and do whatever, even with the meniscal loss, to have them live a normal life, even if they are middle-aged patients and not eligible for the meniscal allograft transplantation, which is the major procedure which is now used to cure the meniscus loss, which is a really complicated surgery, sometimes requires more surgeries and universally recognized to be a bridge procedure, which is bringing these patients from meniscal loss up to the total joint knee replacement sometimes.

But you really have this big gap where patients, we don't have the right age for meniscal transplantation. They're probably too old but are still very active. We need something minimal invasive and not burning, bridge burning as a knee replacement procedure maybe to bring them and to guarantee them good quality of life. And we really think that NUsurface is the device that can bridge this gap. And several members of ICRS have participated to the NUsurface implant clinical studies, and also a lot of submissions have been done during the ICRS congresses and during the different ICRS meetings from the beginning of 2009.

And so it's really, we think the NUsurface provide our patients with a reasonable alternative and helps to address the significant unmet clinical need for this many patients to creating them the bridge following arthroscopic loss of the meniscal arthroscopic meniscal surgery they face up to having a knee replacement of the, as much far away as needed. So that's why we commend this panel to work in considering this application and to recommend the approval of this device. Thank you for your attention.

Dr. Lattermann: Good afternoon. My name is Christian Lattermann. I'm the Chief of Sports Medicine at the Brigham and Women's Hospital in Boston. I wish to present regarding my personal experience as a clinical investigator in the Venus clinical trial. I do not have any financial interest in the outcome of the advisory panel's recommendation or the FDA's final decision, and I've received no financial support.

The NUsurface meniscus implant is made from polyurethane, and it's an artificial device designed to relieve knee pain and restore function similar to that of the natural healthy meniscus. This implant provides an alternative to using fresh frozen donor meniscus transplantations in patients who have suffered meniscus loss and have significant knee pain and swelling, and this implant actually works. We have done clinical trials on this over the last several years showing significant differences between the implant receiving patients and those that were treated in the control group. So that is really not a discussion today.

What is this discussion today is the fact that there is a significant failure rate of some of these implants at in the vicinity of about 17%. Now that sounds like a lot, and particularly for me as a sports medicine surgeon, that sounds like a lot. However, if you compare it to failure rates of comparable implants that are currently on the market, this is actually not outside of the ballpark. The active fit implant has an 18% failure range with a range of up to 31%. And the CMI, which is also a meniscus substitute implant, has up to 11% failure rates reported in the literature. And if you compare to the actual meniscus transplant itself, meniscus transplantation has an almost 60% secondary surgery rate after the original procedure. That is not necessarily a failure; however, it is a re-operation, and that is really what is at stake here.

So if you really compare the NUsurface implant to the true competitors in the field, so to speak, it does not compare badly at all. In fact, it compares favorably. And the underlying

problem is the following: You have significant wear on the tibia. That comes with the territory, and that's what these patients do. And when you put that implant in -- this is a patient of mine where I had to take it out. You saw the tear right here. But look what happened underneath the tear. The articular cartilage is fully protected, in fact, looks better than it looked before the surgery.

So this implant really works. It does have a failure rate, no question. You have to understand that there's about 15% of patients that may have to have a re-surgery. However, compared to the allograft meniscus transplants, it compares favorably. None of these patients were worse off. The contrary, they significantly improve. So let's not miss this opportunity and make NUsurface available for our patients. Thank you.

Dr. Zaslav: Hi. My name is Ken Zaslav. I'm an orthopedic surgeon focused on sports medicine in New York. I'm currently a professor of orthopedic surgery at the Zucker School of Medicine, Hofstra University, and full-time faculty at Northwell Lennox Hill Hospital. I'm currently the Co-Chair of the Biologic Association based here in Chicago. I'm the past president of the International Cartilage Repair Society based in Zurich, Switzerland, and I'm currently the Director of the Center for Regenerative Orthopedic Medicine at Lennox Hill Hospital. I have no financial interest in the outcome of the panel's recommendation or the FDA's final decision today.

So I was an investigator in the randomized Venus trial, and I enrolled, I think, 26 patients. I know there's been some concern over the re-operation rate. And, of course, we'd all like to reduce any chance that a patient needs another operation; but we saw something very interesting. In those that we had to replace an implant, we found that the implant was not only not harmful to the cartilage, but seemed to be chondro-protective, meaning that we were

maintaining the smooth joint surface preventing progression of early osteoarthritis. This is a pretty important finding, in fact, that the NUsurface could potentially be chondro-protective, which means it could be disease modifying.

So the patients that we went in a second time always had smooth surface, no progression of any wear. Whereas in my case, 12 of my 26 patients were randomized to the control group, which received non-surgical care. And nearly one-third, between a quarter and a third of those, went on over the two-year period to have progression of the full thickness cartilage defects that they started with. So even though they had some early improvement in their pain, they had increasing changes on MRI. So I believe, based on my experience, that the NUsurface is a safe device and has the potential to reduce pain and improve the quality of life of the patients that I gave it to but also perhaps slow down or prevent any progressive wear of the, on the articular surface, prevent progression of OA during the time the implant's in.

By the way, when we had to repeat the implant, removing the old implant due to a tear or a subluxation, putting in a new implant was a very quick and easy procedure, went much faster than the initial procedure. And post-operatively, because the patients were used to having an implant in that medial joint and, therefore, used to having something that size in, they were off crutches within one week and had full range of motion returned within two weeks. So it was a very easy revision surgery.

So, overall, I think the treatment fills a void in the options currently available to treat middle-aged patients who are, at the moment, stuck to just having NSAIDs – and, as we know, taking NSAIDs increases the progression of arthritis, is not chondro-protective -- and waiting until they can have an arthroplasty, and many of these patients don't need an arthroplasty yet. So I thank the committee for their work here today, and I urge you to recommend approval of the

NUsurface. And I'll be happy to answer any questions by email or text. Thanks very much for listening to me today and inviting me here.

Dr. Kaeding: Hi. My name's Chris Kaeding. I'm an orthopedic surgeon. I'm a full-time faculty member at Ohio State University School of Medicine. In fact, my official title is Executive Director of Sports Medicine. I was fortunate enough to be the first surgeon to implant the NUsurface implant in North America at the very beginning of that controlled trial. I quickly became a big fan of this implant.

And, you know, the indication for it is that patient, typically that 30- to 60-year-old patient that's starting to have some increasing knee pain, they've got some early arthritis, they've lost some of their meniscus either from a tear or a meniscectomy, and we don't have much to offer that patient currently. We just maybe give them some injections. We tell them, take ibuprofen, and we tell them, you've got early arthritis. You lost your meniscus, you know, it's just going to get worse and worse and worse. When it's bad enough, you do a knee replacement. That's how we kind of currently treat them.

So this implant kind of fills that void in our spectrum of knee care that we have that I just described. These patients can bear weight right away. The pain relief is very rapid. They go back to very active lifestyles. The downside, as we all know, is that these implants can crack at some point, the fatigue fail. And at some point between, typically between 3 and 10 years, they have to have an exchange done.

What's nice about this implant, it's the only orthopedic surgery I know of, if you repeat it, do the exchange, that second surgery is technically easier for the surgeon. It's easier for the patient. They have less pain, and the recovery is faster. And the prognosis for the second surgery we do is as good as the first one.

And the two exchanges that I did, I took a very close look at the articular cartilage in that medial side of the knee, and I compared to my initial, when I put the implant in for the first time, and I hate to say the cartilage looks better, 'cause that's a little, but it didn't look worse. And there's some evidence, as I think you guys know, that shows that this device is actually chondro-protective. It protects the cartilage and helps slow the progression of the arthritis, so relieves pain and slows your arthritis. This is ideal.

The downside is you have to do the exchange. But one of the patients I did an exchange on was a firefighter. And he told me, without me prompting him, he said, Dr. Kating, if I had to have this exchange done every three to five years for the rest of my life, I'd do it because I was off crutches in two or three days. I was back to work in a couple of weeks. And my knee feels fine.

So I'm a big fan of this implant. I think it helps us fill a void in our knee care, and without it, we've got a big segment of patients in our society with knee pain that we don't have much to offer. There's no other good alternative. So I'd love to answer any questions. If somebody has any questions for me, feel free to reach out to me. But I think this is a great opportunity to increase our knee care for our patients in American, American society. Thanks.

Dr. Sherman: Hi. I'm Seth Sherman from Stanford University, and I'm honored to be here at this FDA public panel discussing NUsurface. I was not a site PI in the NUsurface study. I do not have any financial interest in the ultimate outcome of this FDA panel decision. However, I do have a critical need for better treatment options for my middle-aged patients with symptomatic meniscus deficiency.

In 2023, we are all trying to save the meniscus. We know the ramifications of meniscectomy, including, in our study, where we showed that patients were more likely to

undergo future surgery after meniscectomy, including meniscus transplant or total joint arthroplasty. Despite this, a lot of patients are having partial-meniscectomy around here and around the country and world, and a subset have symptomatic meniscus deficiency, which is a very challenging problem that I see every day.

For those young and active patients with symptomatic meniscus deficiency without arthritis, we can perform meniscus allograft transplantations. And this is a good but not great solution that is relatively time tested over decades. However, in our study that we looked at, there was a 58% re-operation rate at one year. Note that this was a low complication rate overall in the short term and a low conversion rate to uni-compartment or total joint arthroplasty. But, nonetheless, this is something to keep in mind that these are bridging procedures. They don't last forever, and we accept a knee joint preservation approximately a 20 to 30% chance that there might be a re-operation at some point to get the outcome that we're looking for.

For the older patients with arthritis, those patients get a total joint arthroplasty when they have symptomatic meniscus deficiency. Now, younger patients really don't fare well with total joints. They'll likely require multiple revisions within their lifetime, and so we feel that it's better to offer these bridging procedures until they're at an age or an activity level more appropriate for arthroplasty. This led to the article that myself and my colleague wrote in Orthopedics Today, identifying this tweener population of middle-aged patients with symptomatic meniscus deficiency after partial meniscectomy and how they might benefit from a technology such as NUsurface artificial meniscus implantation.

There's basically no real treatment options for these patients in 2023. They're not good candidates for meniscus transplant. Maybe they're too old. Maybe their joint's a bit too narrowed. Maybe they have cartilage wear on both sides of the joint. They're not bone on bone and not

good candidates for total joints. Maybe they don't have significant malalignment and are not a candidate for unloading or osteotomy or other procedures that we have in our armamentarium.

And so I think that NUsurface fills a void for these tweeners. It's a bridging procedure for this challenging and growing population. It's technically straightforward for surgeons of differing skill levels, relatively easy rehabilitation and recovery timeline. And the evidence that I have carefully reviewed does support its approval. This fills a gap in my knee joint preservation portfolio, and I'm excited about the prospect of using this procedure to help my patients. I thank you very much for your kind attention.

Ms. Anderson: Hi. My name is Lori Stogner Anderson. I'm 53 years old. I'm from Baton Rouge, Louisiana, and I have had the NUsurface meniscus implant for the past seven years. When I first got injured, I had a tennis accident, shortly after I had a scope and a repair that failed. The next nine months was spent with steroid shots and pain meds and things that were not controlling my pain.

I got a little depressed. I was unable to play with my grandchildren, work out, things like that. It also affected my job. I was a construction project manager at the time. Trying to walk construction sites was not, just wasn't working. Wearing a knee brace for almost a year and just, even things around the house, cleaning the house and just different things like that, I was unable to do. I also gained about 30 pounds which is also not fun and also puts more strain on your knee. I was not eligible to get a full knee replacement or even a partial. So my only option was just to wait, just to be in pain. I didn't think that was a significant option.

So the meniscus has, the replacement has worked out great. I had less therapy than I did with the scope, less pain. I had full range of motion very quickly. And today I'm still doing great. It's been seven years. I'm back on the tennis court. I have new grandbabies to play with in the yard. We

play games and ride bikes and just, you know, have a blast, things that I didn't think I was going to be able to do with them, which is very disheartening when you're a young grandma like I am.

I think the FDA approval is essential to people that, that don't qualify for the full replacement or that is just looking for a less invasive alternative. It was wonderful for me. I can't say enough great things about it. I don't, I no longer wear a brace. I'm not in pain. I don't take any pain meds. It's, I have a brand new knee. Just got back a couple of weeks ago from Belize and did cliff diving and fishing and cave diving, a waterfall hike. So that would not have been possible without my knee replacement or my meniscus replacement.

Mr. Foerster: Hi. My name is John Foerster. I'm 50 years old, and I live in Denton, Texas, and I am a NUsurface implant recipient for six years. Six years ago, I was looking for options. I had injured my knee playing sports. I played soccer and football most of my life. I had a late start with children and realizing that I needed an option so I could be able to keep up with them. I was faced with trying to find something. The options were not, there weren't any. It was either a knee replacement or continue in pain.

When I found out about the NUsurface study, I was excited. I understood it. It made sense to me, and I went ahead and did it. Where I'm at today, I'm living my life. I'm able to keep up with my kids, coach their teams, go on ski trips and continue to run with them and be right there by their side. I did not want to be that dad stuck on the sideline.

The FDA really needs to look at this as an option for us players that, I call myself a player 'cause I played sports and I will continue to play sports, but the FDA needs to look at this as an option for us to continue our young-adult lives. Again, I'm 50. I can run like I'm 30, and the option should be allowed.

Ms. Tongue: Hi there. My name is Debra Tongue. I'm 53 years old, and I've had the NUsurface implant for seven years. I tore my meniscus, and because of the pain that I was in, my doctor went ahead and did a meniscectomy. After the meniscectomy, I, surprisingly to me, I had more pain than I did before. So my activity level just completely stopped. I couldn't do anything. I couldn't do even a small bend in my knees without pain. I couldn't go up or down the stairs in my home without turning sideways because of the pain. It was very frustrating. And so I went back to my doctor, and he gave me three options: Essentially I could, A, just live with the pain and not do anything; B, I could get a total knee replacement, which I didn't want to do. The doctor even said that I was really too young to do that. And then my third option was to enter into the clinical trial and get the NUsurface implant. So that's what I did. I got the NUsurface implant seven years ago.

And since that time, I live a normal life. I can do anything that I want to do. I don't have any pain in my knee at all. A couple of years ago I did get a replacement meniscus. I just, you know, just a freak thing. I dislocated the one that I had. I didn't have any pain when it dislocated, but I knew something had happened. I felt something shift, and actually terror came over me because the first thought into my head was, oh my gosh, these did not get FDA approval. I'm not going to be able to get another meniscus. And so I was really terrified of what life would be like for me without this implant. So a couple of years ago, I got my second implant and actually, I feel like it's even better than the first.

I have a normal life. I work in retail. I'm on my feet all day long, very active, and I have zero pain. And it's for that reason that I think that the FDA really does need to approve the NUsurface meniscus implant for people just like me who don't really, are too young for a knee replacement and don't really have any other good options. This is really life changing.

Ms. Lilley: Hi, my name is Tessa Lilley. I'm a clinical research coordinator for Dr. Brian McKeon in Boston. And my dad is actually a patient that received the NUsurface implant. My dad, prior to enrolling in this study, he was really concerned about the need for a total joint replacement, which he had been told by other surgeons in the past. This was really concerning to him because he felt like it was going to impede his way of life as far as activities go, as well as his work. Additionally, he just was really uncomfortable with losing his natural anatomy and having metal put into his body. And so he enrolled in this NUsurface trial, and since he hasn't looked back. The implant has allowed him to continue coaching baseball and hockey, maintaining the farm that he lives at. And he would be the first to tell you, actually, that if the NUsurface implant was approved today, he would have it done in the other knee.

From a clinical research coordinator point of view, we've really seen a great impact with the NUsurface implant. Patients who received the implant have come back with an improved quality of life, reduced pain, and they've been able to delay the need for invasive surgery. And I think it's important to know that the implant isn't designed to replace a total knee arthroplasty, but just get these patients along their course before it's absolutely necessary. And I think this really addresses a gap in care in the orthopedic world that we have today. A lot of these patients aren't ready for a total knee replacement. Their cartilage isn't quite gone. They're still maintaining their long leg alignment. And so this NUsurface implant is able to assist in that.

Research we have done has shown that the implant maintains joint space, cartilage, and prevents collapse of that medial compartment. And patients younger than 60 that do get a total knee done, they usually require, well, 35% require a revision, and I don't think this is the best outcome. And so I think the NUsurface implant, having been approved, would address a big gap in healthcare.

Mr. Lilley: Hi. My name is Carman Lilley. I live in Smyrna Mills, Maine. I'm currently 62 years of age, and I am a retired Maine State Trooper, and I have received a NUsurface meniscal implant. I was injured in 2014, in a line of duty accident, and I had my meniscus, was torn and flipped over on itself and had to be removed. After recovery, I was in extreme pain. I'd been refused by two doctors to do a partial knee replacement. I was told that I was too young. I was in a pretty tough place because I was in such pain and wanted to return to work. I was kept on light duty because I was not fit to return to full duty.

I was then referred to the NUsurface implant study that was being run out of Boston, and I was fortunate to get in and to receive a NUsurface meniscal implant. Recovery was very quick. I went back to the road full duty, more fit than before any of my meniscus injury. I was involved in another line of work injury, a severe impact. I was struck by a vehicle in a high-speed chase, and I was, it cracked and spun. And that was in 2017, and it was replaced, and I was retired in 2019 after 25 years.

Since retiring, the NUsurface implant has allowed me to return to a normal lifestyle that I don't think I would've received by having a partial implant. I assistant coach two baseball teams, assistant coach two ice hockey teams, keep a hundred acre farm running, and do carpentry work and do all the things that one would want to do in retirement. It’s my opinion that the FDA should approve this. This is a perfect fit for someone in my position that was too young to have a knee replacement, and the rehab is much quicker and easier. And I think this is a really good thing and very glad that I did it six years ago.

Mr. Fazekas: Hi. My name is Thomas. I'm from Dallas, Texas, and I have had the NUsurface implant for six years. In 2008, I'd injured myself salsa dancing and had a knee arthoscopy, which worked out well. I went back to my active lifestyle of dancing, hiking, doing the things that I

liked to do. But by 2016, that had worn out and I was in a lot of pain. And I couldn't really do the things that I wanted to do without limping, without hurting. So I started looking at my options, and about the only thing that was available to me was a total knee replacement, which I didn't want to do because of the trauma associated with that kind of surgery. So I looked and found a NUsurface implant study, applied to it, and eventually I was accepted to the program.

I had my surgery, and it was just as easy as a knee arthroscopy. I was back to work two days later. Seven weeks later, I woke up and I was pain free and fully mobile, and six years later, I'm still pain free, fully mobile, and I can do all the activities that I want to do. I'm so grateful to be part of this clinical study because it's pretty miraculous that I don't even think of my knee anymore.

I think the FDA should approve this because it's a bridge between a knee arthroscopy and a full knee replacement without having the cost and complications of a full knee replacement. Should I ever need another operation on my knee, I would hope that the NUsurface knee implant has been approved because it is the only option for me.

Ms. Wood: Hi. My name is Laura Wood. I'm 55 years old. I'm from Colorado, and I've had my implant for five years. I have currently had several meniscus injuries and surgeries. I have lived in pain for pretty much most of my adult life. I've had to stop doing a lot of the activities I used to do. Horseback riding, hiking, even walking was painful. It's affected my job and my abilities to do what I do at work. I was not a candidate for knee replacement, and so I didn't really have a lot of options on what I could do to help my situation. I did finally hear about the NUsurface implant and decided I was going to give it a try.

I have been totally happy with it. I've had some replacements, but the recoveries are very mild, easy. I was back to work in like two to three days. I can happily say that I am pain free. I

have no issues. I'm back to living my normal life. I do all the things that I couldn't do on a regular basis now, and I would do it all over again.

I do recommend that this be approved by the FDA. It's a great product. There's a lot of people out there who don't have the choices like this to be able to have a knee replacement or be able to do anything with their knee. And their only options are either live in pain or, you know, hopefully have something like this as an option for them. So I strongly recommend that the FDA passes this and approves it.

Mr. Kistler: Hi. I'm Steve Kistler. I'm 55, from Parker, Colorado. I've got the active implant, meniscus implant, in my right knee. I've had it about five years now. Prior to having the implant put in, I was experiencing severe pain, which was affecting my day-to-day getting around, even my work. I was having a hard time staying on my feet all day. I found myself wearing a brace, and even then I was not confident on whether the knee would hold me up. Because when I did hit bone on bone, certain positions while walking, it was just like a knife going right into the joint, and it would almost drop me to the ground. I went in to see what my options were for this, and when I found out about the implant, I was a hundred percent into it over a complete knee replacement.

And because it’s a lot less evasive, recovery time was quicker. And if a simple implant cushioning that joint would keep me from having a complete knee replacement, I was a hundred percent into that. So I went ahead and did it. After the implant was in, I went through a couple weeks of physical therapy. I was back to work. I was doing things that I never thought I would be able to do with the confidence with that knee. I, me and my wife went up to Hanging Lake, which is about a six mile uphill climb, hike, pretty strenuous hike, and I did it with no problems. The knee performed a hundred percent. Since then, I'm back to work. I'm going on hikes. I go

camping, fishing, things I love doing, and the knee has been trouble free. I have nothing but good things to say.

I would recommend this implant to anyone that is experiencing that type of pain where the joint isn't so bad that they, you know, where they can get this implant and put their life back on track. But it's definitely a positive thing. I think the FDA should approve it. I think it's a lot less invasive procedure, and it has given me everything I expected out of it.

Mr. Bennett: Hi. My name is Don Bennett. I'm 66 years old, and I live in Philomath, Oregon. I have had the NUsurface implant in my left leg for about five years now. Before the implant, I was in constant pain. Every time I moved, my freaking knee hurt. So this has been a blessing. I probably spent close to five years in constant pain like that from my basketball playing.

I've had, counting the NUsurface surgery, eight surgeries on my knees. I'm much better now. No pain. You know, this is a much better option for me than the total knee replacement was. The results have been amazing to me because of the freedom I've had now with no pain in my knee. I can do anything. It was impacting the way I worked, the way I walked, the way I did everything before. Now I'm back to being able to move where I want, when I want, how I want, and not have to worry about excruciating pain in my knees.

In my opinion, the FDA needs to approve this method just because of that. It was so dramatic on the difference from my pain levels to where they are now with no pain. It was phenomenal. It's about time we caught up with Europe. They have been doing this in Europe for quite some time and had good success, and we need to get onboard and get this approved as well.

Ms. Robinson: Hi. My name's Rebecca Robinson (phonetic). I'm from Tombstone, Arizona. I'm 44 years old, and I've had the NUsurface meniscus implant for six years. Before I received my meniscus implant, I was active in soccer and softball, and I ended up with three

different surgeries causing a lot of pain and swelling in my knee, limiting my ability to do my normal activities and my daily job of teaching music. I had such pain and swelling in my knee that I couldn't squat or kneel down and help my students with their instruments.

I didn't have a lot of options at that point. I was told because of my age that I was not a candidate for a knee replacement, and I knew I didn't want to have a knee replacement anyways. Because of my age, I would end up having to have a second one, possibly even a third one as I aged. So when the option came for me to get the meniscus NUsurface implant, I knew this was going to be the best option for me. I really didn't have anything to lose.

Since I received my implant, I have been able to increase my activity levels and have lost 50 pounds due to the increased activity levels. I may not be able to play soccer or softball again, but I can walk and hike unlimited miles. I can stand all day and teach, I can kneel and squat and help my students again.

One of the things that I did have an issue with was my meniscus implant did fail at one point, and the option was there for me to receive a replacement. And I knew this was going to be my choice no matter what. The recovery after the replacement was super fast, and it was a super easy process to be able to just take out the damaged meniscus implant and put a new one in. I would gladly do it again if it failed at some point. I knew it was a great option for me.

I do believe that the FDA should approve this meniscus implant because there are so many other patients that are dealing with the same situation that I am that are in that age bracket that they're not eligible for knee replacement and don't want to go to that route anyways. I know of so many people who have reached out to me and asked for more information on when this might be approved and available, and I know that there are so many people that can benefit from this without having to have that drastic knee replacement done. So thank you.

Mr. Smith: My name is Mike Smith. I'm 59 years old. I live in Birmingham, Alabama. I'm looking at the NUsurface product as a solution to solve the knee pain that I have in my knee. I went through a sports related injury in high school, had a torn meniscus. 2009, I went through arthroscopic surgery to trim part of that off. Over the years, the knee has continued to hurt a little more and more, so it got me searching on the internet.

In 2015, I found the NUsurface product and saw that it was just a component that you basically install a new man-made meniscus into where your meniscus was worn out. I thought this made all the sense in the world, so I kept researching it, found out that the clinical trials were already passed. Wish very much I could have been included in that. I would've stepped right up and been part of the clinical trials, but now I understand that it's awaiting FDA approval.

So I've been searching this product for over eight years. I've even driven to Memphis, Tennessee, and met with the company because I was looking for solutions. You know, what can I do to get this done? I did find out that they'd been performing this type of procedure over in Israel and Europe, many countries, for, I think, about 11 to 15 years. And I've considered going over there to have the surgery just because the quality of life that it would make for me, the change.

So the NUsurface product seems like a great idea to just replace the component that is worn out in my knee. I don't want to do a total knee replacement. As I said, I'm too young for that. I don't want the immobility that comes with it. I don't see the risk, the downside risk to getting just the meniscus replaced. If it were to have a problem after that, I've always got the total knee replacement. But my hope is that the FDA will approve this so that I can have the surgery and have it done on my knee and get back to my daily life.

I've had the most pain since about 2015 or '16. I actually walk with pain every day. It's limited me on my exercising. I like to do outdoor hikes, running, things like that. I can't do running anymore for sure. Hikes. I know if I'm on a long hike, I know I'm going to pay for it the next day. So my hope is that the FDA will approve this product, and it'll be a minor surgery on my knee and basically put it back to normal. I just don't see the need to go for a total knee replacement and replace a bunch of components in my leg that are good. I simply have a worn out meniscus. My hope is that NUsurface will see their way to approve this product, and I can have a lifestyle for the better.

Panel Deliberations

Dr. Smith: I now pronounce the Open Public Hearing to be officially closed. We will proceed with today's agenda. We will now begin the panel deliberations. Although this portion is open to public observers, public attendees may not participate, except at the specific request of the panel chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist to identify the speakers. During the next hour, we will open up the floor to questions for both the sponsor and the FDA. Is the sponsor and FDA prepared to respond to the panel's questions posed this morning?

Mr. Belaney: Yes.

Capt. Peat: This is Dr. Peat. Yes.

Dr. Smith: Does any panel member have a question or comment for the sponsor or FDA?

Dr. Kirkpatrick raised his hand.

Dr. Kirkpatrick: Thanks. If I understand correctly, this is our time to be able to ask the sponsor or the FDA team of questions that we are unclear on, right?

Dr. Smith: Yes, sir.

Dr. Kirkpatrick: Okay. Thank you. One of the criteria for indications for this is a total meniscectomy, and a second one is it's to be with osteoarthritis. My understanding of the pathophysiology of knee arthritis after a medial meniscectomy is that it starts right away. Can the sponsor help me understand two things: One is, is this for the patient that is 35, 40, 45 playing basketball and has a partial meniscus tear that is resected, but then you go ahead and do a total meniscectomy so you can do the implant? Or does that patient have to wait 5, 10, whatever years until there's radiographic evidence for osteoarthritis and then get the meniscal implant? And just, in my mind, what I'm thinking is, you know, a big bucket handle in a 45-year-old sounds like an easy decision for doing it, but do I have to wait for the arthritis to develop before I can do it?

Mr. Belaney: Thank you for the question. I think Dr. Deryk Jones would be appropriate to answer this. Dr. Jones.

Dr. Jones: Thank you. Thank you, Ryan. This is Deryk Jones from Ochsner Health down in New Orleans. Yes, the indications are for post meniscectomized knees, either one or two previous meniscectomies having been performed with early cartilage wear. So we wouldn't want to wait for full thick, full blown bone on bone pathology before we put the implant in. You would lose the benefit of the implant.

So the indications per the study, and I think the best indication in my experience with the implant was to put it in patients who had a previous one or two meniscectomies with cartilage wear that was grade two or three, lesions that were not contacting the periphery of the implant, with well-maintained lateral compartment, well-maintained ligamental structures, well-maintained patella frontal compartment. So, you know, those are the highest level patients that would get the best benefit for this.

The one patient that did play basketball, I did, I told him not to play basketball. He decided to play basketball, played it for two years, and then tore, while playing basketball, high level basketball on a regular basis. I then, I gave him the option of proceeding with other treatment options. He was so ecstatic with the response and the activity level he obtained with the first implant, he begged for the second implant. We put the second implant in. He has not played basketball. He still has the implant in now, six years later.

So those are the ideal candidates. We would not want to wait until there's bone on bone pathology to have that happen. This is not for the acute meniscus tear that is going to be removed, and then we put the NUsurface implant in immediately. No. We would do the meniscectomy we typically would perform, and, as we know, some of those patients actually do well for some time. If they then have symptoms develop, we know what's going on. Then going in back for a second meniscectomy in that patient would be an incorrect move, in my mind. I would put the NUsurface in at that time. Thank you.

Dr. Kirkpatrick: Thank you.

Dr. Smith: Dr. Cizik.

Dr. Cizik: I'm struggling with the indication of function and trying to understand a little bit more, again, back to the KOOS and not seeing the subscale scores post. I'm looking in the executive summary. I see baseline difference, the baseline characteristics for pain, and, again, this overall, but it would be helpful to see the subscale scores, especially related to function. So I don't know if you have that available, but that would be, to me, critical data for –

Mr. Belaney: Absolutely. And I can also, in answering your question here, address your question about KOOS overall. So in 2012 is when we started the process of getting an IDE approved, known as the Venus study, and that is where, working with the FDA, the discussion of

the primary endpoint involving both KOOS pain and KOOS overall to include function. So what you see on your screen here is the five components that make up the KOOS questionnaire, and KOOS overall is an average of each component's score. So, in this instance, you can see the thickest dark blue bar, that represents KOOS overall and how that compares to the five other subsets of KOOS. Does that answer your question completely? Good. Thank you.

Dr. Smith: I believe, Colonel Helgeson, you're next.

Col. Helgeson:Thank you. This is Mel Helgeson. The question I had, and maybe from both the FDA and the sponsor, I think that the FDA presented a significant argument for the issues within the methodologic component of the study, in the Venus study, and the Sun, and I think there was a lot discussed about the statistical analysis, but I was still a little bit confused about the informed consent issues. I think that there was a little bit of a discussion about the concerns with the informed consent process and being able to present the appropriate risk in doing the informed consent prior to surgical intervention or the randomization.

But to go back to the initial IDE study and the initial applications in 2012 to '14, were some of these methodologic concerns conveyed back in that timeframe? And was anything changed based off of those concerns?

Mr. Belaney: Thank you. I'm going to –

Capt. Peat: Thank you. That's a very good question. I'm sorry, I thought you said both the FDA and the sponsor. I'll defer to the sponsor, and then we'll pick up after that. How's that?

Dr. Helgeson: That sounds good. Thanks.

Mr. Belaney: Thank you, Captain Peat. Thank you for the question because in the last Q&A session, we did raise our hand because, Dr. DeHart, you are correct. There has been different reviewers and different staff working on this device. We, however, were there. So there was a

question about the combination of Venus and Sun and the methods that go along with that. And the combination of Venus and Sun, the conversation really began in October of 2017 at a meeting at FDA, and the discussion was about having two studies with the same inclusion and exclusion criteria and the opportunity to bring those two together. There were multiple IDE supplements, and ultimately in 2019 there was an agreed upon statistical analysis plan from the Venus study that allowed the Sun study to merge into Venus.

Now, you also asked a question about some methods that were part of the Venus protocol and non-surgical care, and I appreciate the opportunity to clarify that as well. The IDE for Venus and the IDE for Sun were both discussed with the Agency. The IDE for Venus took quite some time because it is difficult to identify a comparator to the NUsurface that's a surgical option. The ideal comparator is what we have, the standard of care, non-operative care. So I do want to make it clear that the protocols were developed with the Agency.

Now your last question, I believe, about informed consent. I don't believe that there was a question about informed consent for the clinical trials. Now, I did hear discussion about informed consent for the PPI surveys. Can anyone on the panel clarify if there was a question about informed consent in the clinical trials?

Dr. Helgeson: I'm sorry. It was for the PPI.

Mr. Belaney: For that question, we're going to have Janice Hogan (phonetic) address that? No. Yeah, she -- oh, rather, Rick Trejan (phonetic). Thank you.

Sponsor Trejan: Yes, that was exempt from, uh, having the need to informed consent or IRB approval. According to 45 CFR 46.104, that allows surveys of the general public as long as they are not identified and they're not young, they're not children, and they're not put at any

liability. So general surveys are exempt from needing IRB approval. Does that answer your question?

Dr. Helgeson: Thank you.

Dr. Gebben: May I have an opportunity to respond?

Capt. Peat: Yeah. I wanted to make sure, you had a multi-pronged questions, Colonel, so let us just get an opportunity, as well, to respond to those questions. First, we'll start out with Dr. Gebben to address the questions surrounding the PPI.

Dr. Gebben: Thank you, Dr. Peat. Regarding the exempt status of a patient preference survey, yes, it is true that often these surveys are exempt, even when they are general subjects, general population. However, exempt does not mean you do not have to get IRB approval. You need the IRB board to determine that you are exempt. That is also different than getting an informed consent. Those are two pieces of the exemption that need to be covered. This is very critical, because we are still talking about human subjects research. Does that clarify the question, Colonel?

Dr. Helgeson: Yes, I think that's very helpful. I think there certainly is some disagreement here between the FDA and the sponsor, and I think that does help.

Capt. Peat: Yes. Thank you so much. And also too, let's not forget, regarding the patient preference information, we do have a final guidance document that's out that speaks to these merits of having informed consent and all the outlined information that should be included in the study. I also wanted to make sure we give an opportunity for Dr. Prest to speak a little bit more regarding the history with the IDE and what was agreed upon; because I do remember, Colonel, that you mentioned whether or not there were agreements that were done, a priority to the study actually being started. So I just wanted to make sure that we addressed that as well. Dr. Prest.

Dr. Helgeson: Yeah, that's probably partly because I'm naive to that and new to this process. I don't know what the understanding was during the discussions back in the beginning of this. So thank you.

Capt. Peat: No, it's a fair question. So we could go ahead and just expound on that, Dr. Prest.

Dr. Prest: Yes. Thank you. I think what I can comment on is that we have, we did review the strategy based on, you know, early data or early plans and early information. I believe that there is, I believe that Mrs. Liu had commented before the lunch break about some of the changes that have occurred, as well as, you know, the uncertainties with the data now that we've, you know, that we've received it. I think that some of them were, some of these differences between the two groups that weren't, weren't part of the original discussions as, that we had discussed when we had originally reviewed this strategy of combining. And so I think some of the uncertainties that we've discussed today are things that were not previously part of that original discussion around the strategy of combining.

Dr. Smith: We have three pending questions. But before we move on, I wanted to ask if the sponsor had any other comments on this current question?

Mr. Belaney: Absolutely. Thank you for the opportunity. I would like to, Dr. Prest brought up some of the statistical uncertainty, and I would like to address some of the statistical uncertainty that was presented in the FDA's presentation. I think the first on our screen we'll see. It was discussed that there was both agreement, total agreement, total exclusion agreement, and disagreements. So this table that you see, this is from the FDA's executive summary. And what I would like to ensure that the panel understands is that, first, the ICC, the correlation coefficient value, for both meniscus extrusion and tibial spine height were above 0.8, 0.9, and 0.82 for the NUsurface group.

And if we took total disagreement and included that into a subpopulation, we would have a subpopulation that would be 101 subjects, rather than 74 NUsurface subjects, and that would still meet the level of superiority at a P-value of 0.002. Now, if we included that group, the FDA is correct that the ASF, the automatic study failure rate, would increase, but that increase would be 23% in the worst-case scenario of all disagreements. And if we split that down the middle of disagreements, that would represent a 20% ASF rate in the NUsurface arm.

So I would also like to address the comment about missing data, especially missing 24-month KOOS data. So both in the NUsurface and in the control arm, FDA presented that there were 23 missing data points. It's very important to know that, for example, in the NUsurface arm, 18 of those 23 missing data points were implants that were permanently removed. That would not be appropriate to present at the 24-month time point as you're determining study success. And as the same goes for the control arm, there were nine control ASFs, along with the 14 loss to follow-up patients. That accounts for the 23 missing. So the missing data is explained in that way. So thank you.

Dr. Smith: Dr. Peat, I believe the FDA has additional comments.

Capt. Peat: Oh, yes. Thank you so much, Dr. Smith. I'm going to have Dr. Coyne go ahead and expound a bit more regarding the IDE study and the conduct of it and FDA's feedback that surrounded that particular study.

Dr. Coyne: Yes. Thank you. So the sponsor did present this morning that, regarding the pooling of the two data sets from the Venus and Sun study to form the Mercury data set, was done under an IDE supplement. Now we, and certainly under the current way we approve IDE supplements, if they, for the most part, if there are no issues regarding the study subject protection measures or, you know, protecting the health and wellbeing of the study, of the

participants in the study, or informed consent issues or matters like that with regard to study design, that's usually, we would note that via recommendations communicated as study design considerations.

You know, as Dr. Prest was referring to, there was some interactions regarding that when, you know, at the time when that particular supplement was approved, but there were also some of the concerns or issues that FDA believed needed to be addressed and were also, would've been communicated at that time as well.

Dr. Smith: Dr. Peat, does the FDA have any other comments on this question?

Capt. Peat: I just want to check. I think I see Dr. Gebben. Do you want to expound on anything else regarding this feedback for the PPI or no?

Dr. Gebben: The guidance document. Sorry. The HHS regulations from OHRP point out that it is not up to the principal investigator to determine an exemption for the review. It is up to an IRB board to make that determination. So I just wanted to make sure that that was clarified.

Capt. Peat: Thank you very much. Thank you, Dr. Smith.

Dr. Smith: Thank you, Dr. Peat. Now, before we move on to the next question, I'd like to return to the sponsor and inquire if you have any further comments on this question.

Mr. Belaney: Not at this time. Thank you.

Dr. Smith: Thank you. I believe the next question is Dr. Barber.

Dr. Barber: Hi. Yeah, it's Tom Barber speaking. I have two questions that are unrelated, so I'll ask one at a time. The first one it regards activity level and the fact that we've heard a lot of different description of activity levels from both patients and physicians. And when I hear the recommendations around activity level post-surgery, it sounds very similar to me to the recommendations that would occur with a total knee replacement. So, and I've had patients with

total knees that play basketball and other things when I told them not to, so I'm just sort of wondering where you see the differences. And do you see a functional difference between somebody with this implant and a total knee replacement, for instance? And what's the perspective on that?

Mr. Belaney: Thank you for that. I think Dr. Hershman would be perfect to answer this question.

Dr. Hershman: Thanks for that question. We would agree that high impact activities should be discouraged for patients with the NUsurface device. We understand what the recommendations are for arthroplasty patients. We also understand that arthroplasty patients sometimes follow these directions and sometimes don't. But for NUsurface, it's our feeling that high impact should be avoided, and we do make that recommendation to this cohort of patients.

Dr. Barber: Great. Thank you. The second question I had is that there, we're talking about a very culled group of patients here that are, you know, low BMI, you've got a height of the tibial spine, you've got no extrusion, and, to your own admission, it's reducing the number of patients by 50%. So we've got this culled group, which is great. Now, how are we going to ensure that surgeons in the future putting this in are going to follow the recommendations around these types of things? One of my concerns is that most of these measurements require an MRI, and yet in many circumstances, an MRI, over the age of 55, for instance, is not recommended and may not be approved by insurance, for example. So how do we ensure that we get this done appropriately, and it gets done in the appropriate patient? I guess is what I'm saying.

Mr. Belaney: Thank you for that. So when we consider what the two radiographic measurements are, a meniscus extrusion is a very common measurement that is done for inclusion in this study or to receive the device. And tibial spine height, as well, is something that

we've provided training on and the ability to repeat the measurements that the radiologists that measured this subpopulation can continue to successfully create. So I would like to call up our radiologist, Dr. Shabshin, just to talk a little bit about the radiographic process of measuring extrusion or measuring tibial spine height.

And I would also like to note, as she's walking up here, that Dr. Jones would also like to provide a response to your first question, but we will get to that if there's time.

Dr. Shabshin: So this is how the tibial spine height is measured. Excuse me just a second. So, first of all, we look at the coronal, T1 and T2. Then the evaluator should select the slice -- it's working -- should select the slice, the slice in which the medial tibial spine is the highest. Then draw a vertical line along the tip of the cortex in the medial spine. Find the deepest point of the medial tibial plateau cortex. Draw a horizontal line that intersects with the tibial spine vertical line, and then measure the height of the tibial spine line between that horizontal line and the tip of the tibial spine. And this is how the tibial spine is measured. Now that's, that's okay? Okay.

Mr. Belaney: Would it be okay for Dr. Jones to provide his response to patient activity as well?

Dr. Smith: Yes, please.

Dr. Jones: Thank you. One of the things I wanted to note is, yes, they can go back and play basketball with the risk of the total knee. I have patients trying to do that as well. However, the risk if the total knee replacement fails versus the risk if the NUsurface fails are significantly different. As we've heard, the NUsurface can be replaced. The patient can be told not to do that activity. Total knee replacement is revised, the patient certainly will never even try to do that and will have less function. We've burned additional bone, additional bridges in a young patient. So the differences between the two are significant, regardless of what they go back to do. One's revision is very easy. One revision is very hard. I do both procedures. Thank you.

Dr. Smith: Thank you.

Mr. Belaney: I believe there was one final statement about MRIs for patients above age 55, and Dr. Hershman would like to address that. Microphone's on.

Dr. Hershman: Yeah. You know, we certainly acknowledge that in patients with significant osteoarthritis, MR may not be indicated. But for patients particularly like in our cohort who have x-rays that show good joint space preservation, MR can be helpful. Just like getting CT for patient specific instruments in arthroplasty -- and I am not an arthroplasty surgeon, but my colleagues tell me that that's what they do -- we can get MR for surgical planning if we need to do that in terms of considering patients for NUsurface. So that's how I would address the issue of obtaining MR in this population. Thank you.

Dr. Smith: The next question is Dr. Porter.

Dr. Porter: Hi. Laura Porter. I am the patient representative for the panel, and I just wanted to share a little bit of my personal history and then ask a couple of questions. I had my very first scope of my left knee when I was 28 after playing softball. By the time I was 38, I had a total knee replacement. In between there, I had multiple scopes to go in and clean it up. I had a femoral osteotomy to straighten out my leg. I had a tibial osteotomy to remove the pressure from my knee. I had a cartilage transplant and Oats procedure, and then a total knee replacement at the age of 38. And the reason that I had the knee replacement, I was in medical school. I was needing to stand a lot, and I was unable to do that. I asked my doctor to do my knee replacement. He was waiting for me to turn 40, he said, but I couldn't wait any longer.

And since my knee replacement, I've had at, seven years later, I had to have the spacers replaced. But I haven't had to have a revision. And it's the best thing that I ever did, even at that age, was to have a total knee replacement. Because even though I've had a few problems since

then, you know, I've gained quite a bit of weight, but it still has given me a different, it's changed my life in my ability to function.

So my question is: you surveyed people, I think it was, what is it? The PPI, the survey that was done. You surveyed people with knee pain, but nobody that had had knee surgery before. So I think that comparing that is not, you know, if somebody hasn't had the surgery, they're not going to know what they would be willing to do. And I think that that's something that's important to keep in mind.

Also, you said that you stopped, you analyzed the data at two years, but what about after that? You know, how long does it take before it fails? I know we heard people talk about their, you know, seven or six years, but I think that, you know, it's ultimately, from my opinion and my experience, I need to have a knee replacement ultimately, you know. And I'm not sure that waiting and prolonging the pain and the agony, okay, which it was, is worth it, and that's my personal patient opinion. Thank you.

Mr. Belaney: Thank you very much for your comments. To your first question about interviewing or rather surveying patients that are in knee pain rather than previous surgery, the intention of that survey was to identify patients that matched this non-operative control group and that do not know the complete risk of surgery like you do. You have quite an experience with that, and thank you for sharing your story.

As far as data beyond two years, I do want to make it clear that the endpoint for the study is at the 24-month, two-year time point, and all data that's been provided to FDA are up to that two-year endpoint. Now, on your screen, I will show KOOS pain scores for subjects that are, as you know or may not know, the Sun study has a 60-month, five-year endpoint. So we do have some evidence of the NUsurface device and the KOOS pain improvements beyond two years. So

when you're looking at this graph, on the Y axis is improvement in KOOS pain, and as you go across the right, you see different months. If you could show the next slide please. We also show that KOOS overall, and it's a very similar graph. You may not have even noticed that the graph just changed, but it's a similar trend for all KOOS components.

And, lastly, you asked about how long would this device last and how long -- if you could go to the next slide, please. We do have a Kaplan Meyer curve of permanent NUsurface removals in the subpopulation, and where you see less than 10% at the two-year time point that Kaplan Meyer curve shows a linear trend out to five years. Thank you.

Dr. Smith: Thank you. I believe the next question is Dr. Subhawong.

Dr. Subhawong: Hi. Ty Subhawong. Sorry. I have three questions or points of clarification: So, the first, I want to circle back to giving the sponsor the chance to address the use of analgesics and other interventions in the control arm. The second question has to do with the FDA and independent readers. Did the FDA have any radiologists or orthopedic surgeons measure? Because what I saw it looked like it was the sponsor's readers, or the MRI findings, the measurements of the tibial spine height extrusion and the cartilage defects. And then the third question has to do with on radio, on plain films, is there any way to detect the position of the implant, or are they imperceptible on radiographs? Is there any radiopaque marker that's been embedded into the implant?

Mr. Belaney: Excellent. Thank you. I will handle the first question, and then Dr. Shabshin will handle the second and the third questions. And I'm glad you asked so that we could come back to this topic. So on this statistical table, the Mercury study did ask subjects of their drug use for pain at every follow-up time point. And what we see is that it's similar in the control group, in the Venus group or in the Sun group, for any of these drugs. Listed down, I recognize that this is

a small graph, but listed down are at baseline narcotics, NSAIDs, acetaminophen, salicylates, hyaluronic acid, or others. So I hope this helps answer your question. Dr. Shabshin.

Dr. Shabshin: Thank you. I believe your question was whether the implant is radiolucent, correct?

Dr. Subhawong: And specifically whether, I understand that it's predominantly radiolucent, but is there any radio-opaque marker in it or is there any way to identify it on a radiograph, or can you only confirm its position on MRI?

Dr. Shabshin: So for the trial, we can see it on the radiograph. It's radio-opaque, but the device, in general, is not radiopaque and it can be seen on MRI.

Dr. Subhawong: So just to confirm, you would not have to get an MRI to confirm correct positioning of the implant. You could follow it radiographically.

Dr. Shabshin: We confirm the position in the surgery. So when they do the surgery, they can see the position, the surgeons. And then if there is a concern about the device after the surgery, MRI is a great tool. We can see, we can evaluate the position and any complications on MRI. We could see all the complications on the MRIs. Could you --

Dr. Smith: Dr. Peat.

Dr. Shabshin: Could you –

Dr. Smith: Excuse me. Go ahead.

Dr. Shabshin: Could you please repeat the third question, or was,

Dr. Subhawong: It would probably be for Dr. Peat, I guess, and that was whether FDA had any radiologists review this, the MRIs?

Dr. Shabshin: No. Okay. So actually the measurements were done, excuse me. Yeah, it was done by two of, two radiologists from the sponsor's side. No FDA radiologists.

Capt. Peat: Great. I'm going to turn it over to Dr. Prest, the lead reviewer, regarding this question about the MRI.

Dr. Prest: I can just, this is Travis Prest. I can just confirm that we didn't independently do our own analysis. We, you know, any of the comments we've made based on the integrator disagreement was based on the information that was provided by the sponsor and the two raters that they used to provide those measurements.

Capt. Peat: Great. The image is not typically something that we actually get submitted to FDA for us to do any form of adjudication. The key concern here is, when we do look at the data, there was differences in the integrators and how the sponsor actually adjudicated those disposition, whether the person is considered a success or a failure.

I want to digress for a quick second so that I can have Dr. Bocell go ahead and answer some questions regarding the KOOS score, because I know that seems to be a big area surrounding some of the comments that have been made by the panel members.

Dr. Bocell: Yeah. So one thing I can speak to is it, it looked up, on the graph that was shown by the sponsor just now, and going out to 68 months, I hope everybody noticed that the sample size was 28 at 60 months. And so there's quite a bit of attrition there that can be biasing on that. And then if it's helpful, y'all had asked earlier about the different subscales and the activities of daily living, the sports and recreation function. There's not something that we would consider to be just general physical function, as in like general kind of your ability to move around and walk and perform those activities. Instead the developer chose to break it up into activities of daily livings, or your ability to do things that you would normally go about in your daily life, and sports and recreation function, which is specifically the difficulty you experience doing different sport related activities. So those are the closest we get to those concepts.

Dr. Smith: Dr. Peat, does the FDA have any more comments on this particular question?

Capt. Peat: No, we do not. Thank you.

Dr. Smith: And before we go to the next question, I'd like to ask the sponsor if they have any follow-up.

Mr. Belaney: Thank you. Yes. I would like to address the comment about function measurements because we've spent quite a bit of time talking about the KOOS measurement tool. And that's appropriate for the primary endpoint. But I would also like to describe that in the secondary endpoint, we did have other measurement tools that agree in both pain and function. So if you could please bring up slide number, stop. Slide number 43. Here we go. So this was in the presentation this morning. But what I want to draw your attention to are the two boxes at the bottom. And this is broken up into our 20 secondary endpoints that were measured in the entire Mercury study. But what's important here is that we're looking at the different tools that were also in agreement with the KOOS score.

We have VAS. We know that's a pain based. IKDCSKEF. We have some individual KOOS composites, as well as EQ-5D and IKDC. So the intention of this study was to look at more than just KOOS scores to understand if these patients were achieving benefit. And as you can see from the results, whether it's the Venus study, the entire Mercury study, or the subpopulation with the Mercury study, the NUsurface outperformed the controls.

Dr. Smith: Thank you. Does that conclude your response, sir?

Mr. Belaney: Yes, it does. Thank you.

Dr. Smith: Thank you. I think we have three pending questions. It’s myself, then Dr. Reed, and then Dr. Price.

I wanted to make a comment or question. There's been a number of populations and subpopulations discussed, and I understand the study as it was designed in partnership with the FDA, helping the questions in the design of it. And there is sort of an as-treated analysis. You do attention treater analysis. Without getting the statistics, I'm not a statistician. The concern I have is for that population who ultimately had implant removal and they, you don't have the two-year data on them. Presumably, they sort of exited the trial at that point. And so for that population, if you have a relatively younger person with a meniscal injury, they undergo an almost total meniscectomy, have the implant placed, and then the implant is removed, and now two years later they don't have a meniscus and don't have the implant, I questioned, I know the data may not be there, but my question to be born is that person better off after that than if they just used a media on motor brace? And when we're sort of excluding the failures, are we really getting an accurate representation of how this compares to non-operative management?

Mr. Belaney: Thank you for that question. I believe that Dr. Jones would be appropriate to discuss, in the real world, if a situation with a young patient like that were to arise, what are his opinions of that.

Dr. Jones: Yeah. So once again, I go back to the, thank you for the question. I go back to the indications for the procedure. Once again, these are people who've already had the previous meniscectomy. This is not the acute tear. I remove it and I put this in, or I remove the entire meniscus and put this in. So these are people who've had one or two meniscectomies, and I would submit that in most of those cases, there's limited functional meniscus remaining.

As I believe Dr. Hershman showed in his talk, the load on a tibial plateau is significant at that point. That's why they're having symptoms. Yes, they could use an unloaded brace and buy time; however, the NUsurface implant provides a functional improvement in pain and function while it

does buy them time. Whereas, the unloaded brace, and this is something that I have personal experience with myself, is a bit of a problem. It's a headache. Whereas the NUsurface, as you can hear from the testimonials, is not. Now if it is pulled out, you are left with a joint without a meniscus. That is true. But you can either put the NUsurface back in or proceed with what you would do normally in that situation, osteotomy, meniscus transplant. Because the cartilage has been maintained, we have not burned any bridges in that situation.

Once we do the uni-compartmental, we know that bridge has been burned. Next thing is a knee replacement. Once we do the high tibial osteotomy, we know we're going on to partial replacement at minimum. So we haven't really burned any bridges. I do understand the concern about the subtotal meniscectomy. We've been taught as orthopedists not to do that. However, this is people that already had that meniscectomy and what's left behind is not functioning. So these are not the acute meniscus tears where you remove everything, go back to subtotal meniscectomy, and then put the NUsurface in. That is not the scenario. The scenario is to put this in people that are having symptoms after previous meniscectomies, and the meniscus is not functioning well at that time. So different scenario really.

Dr. Smith: Oh. Thank you, sir. To clarify my question, with all due respect, is: the one hypothesis is they've had a partial medial meniscectomy, and then they have, effectively, a total meniscectomy minus the rim. And then we're saying if it gets extruded with, that's where we are. But I would respectfully submit, if we don't have the data of that group who was pulled out of the study when it failed, do we really know that, we don't really know how they were doing. And is it possible that that group is doing worse than a group who had a partial meniscectomy and then still had pain and then had an unloader brace? I just don't know. Unless I misunderstood something, I don't know if we know how those, for lack of a better word, total failures turned out

because they don't have any two-year data for them, and yet the percentage of people that had a total failure was not small.

Dr. Jones: Thank you. Excellent question. Thank you for that clarification. I think, Ryan, can you provide the data?

Mr. Belaney: Yes.

Dr. Jones: We do have some data there. There's not complete lack of data in that group, so I think we have that data for you, so provide that to him please. I think that's a great question. I understand your concern, and I think we have that data for you.

Dr. Smith: Thank you, sir.

Mr. Belaney: Thank you for clarifying that question. And I would agree completely with you that it would not be appropriate to exclude patients that had the device removed. So I would remind that the study success was based on a composite endpoint that included both the KOOS PRO benefits, along with the risks of surgical failure, including this removal. So when we look at the overall study success, that's taking into account both the benefits and the risks. So if you were a subject that had that device removed, you are not, that data is not excluded. What I would like to invite is Dr. Hershman to discuss the three subjects in the subpopulation that did have either a uni-compartment or a total knee arthroscopy. And I think he can answer some of your question about what happens to a patient after NUsurface.

Dr. Hershman: Thank you. So we did have three patients who went on to additional surgery, following removal of their implant. This is one of our subjects described on this slide who, at the baseline, at the time of implantation, had a BMI of 30.8. Their implant was exchanged at 203 days for a rotation issue, and then continued to have problems and ultimately underwent a uni at 481 days. And his surgeon actually commented that in the intervening time, the patient had put

on an excessive amount of weight and was now beyond the BMI criteria at the, compared to the outset when he was first implanted. And for that reason, underwent a uni-compartment replacement rather than a replacement of his NUsurface.

We have the next subject who was very active and also had a replacement at 259 days. That replacement stayed until 589 days. And at that point, because of a shared decision-making conversation between the surgeon and the individual, it was elected at that point to also go ahead with the uni, because of the patient preference.

And the third patient that we have was a firefighter with a BMI of 29.1. At a six-month visit had their implant removed at 300 days after it was dislocated posteriorly. His osteoarthritis did progress. And at that point, he was not a candidate for a replacement of the device. And so he underwent a total knee replacement.

So this is an example of some of the individuals that had an issue with their device, went on to a different type of procedure, and the kind of conversations that occurred between the investigators and the patients in terms of deciding what approach to take as they went forward in their episode of care.

Dr. Smith: Thank you sir. Dr. Peat, does the FDA have any comments on this question before we move forward?

Capt. Peat: Yes. Thank you so much, Dr. Smith. I wanted to make sure that we queue in slide 82 and ask Dr. DeHart to opine on it. The key facet here is the sample size is very low for us to make inferences as to what is going to happen in the general public. Equally, the fact that they're missing data goes back to some of the comments that were made by you, Dr. Smith. And so we wanted to just expound a little bit more on some of the data that we've reviewed and our understanding of the risk. Dr. DeHart.

Dr. DeHart: Sure. We'll take the –

Capt. Peat: AV, please queue in slide 82 of our earlier presentation.

Dr. DeHart: We'll address Dr. Smith's comments about the missing data first. So you're correct. The data that might reflect poorly on the NUsurface device from the devices that failed was excluded, not part of the study, and that was by design. Also, data from the patients who were in the control group who eventually got surgery, which apparently they really like and patients want to have, that data wasn't included either. Both of those could swing the results one way or the other.

The problem with, when we measure pain as a main outcome, and we're using a non-operative control group, the placebo effect is really quite important, and that difference can't be seen in this study. Although it was discussed with the sponsor during the IDE process, it was felt that it was not an option for the surgeons participating in this study to do an arthroscopic evaluation of every patient to equally screen that population. Remember the population that had the NUsurface had a screening arthroscopy before they were included in the study. If they had more arthritis, or if they had other pathology that wasn't recognized on plain films or the MRI, they were excluded from the study. And the subject, the sponsor called those bailouts, and that made up about 13% of the patients who actually approached the study.

The control group didn't have that same screening procedure, which makes it a challenge sometimes to know what was causing their symptoms, because it's very challenging for orthopedic surgeons to define whether the symptoms are coming from the meniscus tear, the lack of the meniscus tear, or some other pathology inside the knee joint. And so it makes it hard to compare those two populations.

Dr. Peat, I still don't see the slide that you were trying to get them to pull up.

Capt. Peat: Yeah, we're actually trying to get that up with our AV folks. Is it possible you could just walk through the slides really quickly until we are able to share?

Dr. DeHart: Sure. Well, at least we could talk about the overall failure aspects of the study, and approximately 50% of the patients who entered the study failed. Some failed by having additional surgery, but some failed because they didn't have an adequate pain response. And that gets to the magnitude of the pain response that we're looking at. There have been several studies that have had non-operative control groups in the past. Some of them have even had sham surgeries - just simple arthroscopies and the amount of pain relief that we actually see reported in this study is the same magnitude as a sham surgery or a well-controlled, well-planned physical therapy program. And while the populations are a little bit different, some of the literature studies have arthritis of grades two or three.

So the summary of the risks that we have are that the implant and the sub-total meniscectomy required may accelerate the arthritis. And why that's important that in every study group that we've looked at with this device and had that near total meniscectomy, there have been a high rate of arthroplasties in the folks where the device had to be removed. And though this study is not powered for that, we are not comparing that, but it's hard for us to look at that. For example, in the last study that they picked, the study group had exclusions because the people with a lot of arthritis were excluded, and then they also narrowed the population down again by arthritis severity because they picked the patients without significant meniscus extrusion, which is another surrogate for arthritis. Even after both of those screening levels, 25% of the patients who got this device and failed, ended up with an arthroplasty.

And I'm not sure if there's any other points you wanted to bring up, Dr. Peat?

Capt. Peat: No, this is good. Thank you so much.

Dr. Smith: A quick point of clarification. Procedurally for Dr. Peat, we're approaching time on our agenda. We have three pending questions, and I also wanted to circle back with the sponsor before moving on to the next question. How should we handle this? Are we able to extend time, Dr. Peat, or do we need to close that after the sponsor's reply?

Capt. Peat: Yes. Let's go ahead and give another five minutes. So by 4:45 we close out. So if the sponsor can be succinct in their return, then we can go to another question.

Dr. Smith: Thank you.

Capt. Peat: Mm-hmm.

Mr. Belaney: Thank you, Dr. Peat. I will do my best to be succinct. There's a lot of information that Dr. DeHart just provided. The first thing I would like to talk about, not what's on your screen, but first the discussion about NUsurface or controls that had surgical failure and those results swaying the study either way. I want to be very clear that the success of the study included the failure of the surgical treatment. So if a subject did have a surgical failure, that is taken into account into that and does not sway the results of the study.

There was discussion about missing data, and this is a slide that Dr. Jones presented this morning. And what I want to make clear is there were 14 control subjects that were lost or withdrawn from the study. And what we can see on these control subjects are 12 of them remained at six weeks, 7 at six months, and 3 at 12 months. And they were all having negative KOOS overall scores. So the subjects that were lost, the last time point that we were able to capture data on them, they were not doing well.

What I would also like to address is the question about if a NUsurface subject had an exchange surgery, that data is not available. Well, the data actually is available. And if you look at the bar graph on the right, these are the 66 NUsurface subjects that included the six exchanged

NUsurface implants. And you can see that the responder rate is similar to whether the exchange patients were included or excluded.

And, finally, I would like to bring Dr. Hershman up to quickly talk about the sham surgery, as well as, Dr. DeHart, I appreciate the effort by the agency to find literature that is comparable to this NUsurface group, but I want to stress this is a very unique population. These are patients that have already failed non-operative care, surgical care, and non-operative care again. And it's very difficult to find literature that is comparable to the control data and the NUsurface data from the Mercury study. Dr. Hershman.

Dr. Smith: Before Dr. Hershman starts, I'd like to, we have a hard stop at 3:45 is my understanding. So obviously I want to give you the opportunity to respond, but please be succinct if possible.

Dr. Hershman: I'll just say that, just quickly, that at the time that we put the IDE together and we sat with FDA, we talked about sham surgery and we talked about non-operative controls, and the study that we came up with is the study that you see today.

Dr. Smith: Thank you. On that note, we have about 45 seconds. There were some hands up, but is there any quick comments or statements to make in the next 40 seconds? Otherwise, unfortunately, we have to adjourn this portion of the agenda. Dr. Price? Dr. Bonnell? Dr. Reed?

Dr. Reed: I'll save my comments for the FDA question period.

Dr. Smith: Okay. On that note then, we're scheduled for a five-minute break at this point. Dr. Peat, are we still going to proceed with that break?

Capt. Peat: Yes, sir.

Dr. Smith: Okay. Thank you. And we are going to move to break, and we'll resume in five minutes at 3:50.

FDA Questions

Question One

Dr. Smith: At this time, let us focus our discussion on the FDA questions. Panel members, electronic copies of the questions have been emailed to you and are posted on the FDA website. I would ask that each panel member identify him or herself each time he or she speaks to facilitate transcription. Please show the first question.

This is panel voting question one: patient population. Based on the modified Mercury dataset subgroup analysis, the sponsor has identified a target population that includes patients with mild or greater pain, mild to moderate arthritis and previous meniscectomy and meeting inclusion/exclusion criteria, specifically the exclusion of patients with meniscal extrusion greater than 5mm and tibial spine height less than 11mm.

Please comment on what patient populations would benefit from this device, in consideration of available alternative non-surgical and surgical treatments. Please comment on the clinical relevance of the sponsor's modified target population.

I would, yes, Dr. Barber.

Dr. Barber: Just from my perspective, I think it would be awfully hard to apply these criteria in actual practice. And I think that we're not going to necessarily treat the same population that has been elucidated in this study, because I think that surgeons would expand the criteria and use it in a different way. So I'm concerned that we have a very defined culled down patient population that is not the population that we're going to see treated in the real world.

Dr. Smith: Thank you. Dr. Price.

Dr. Price: Hi. Yes, my concern is the area of a lot of people get heavier as they get older, and there was a large emphasis on the BMI being under a certain, and with each extra, you know,

BMI point, there's extra pressure on that specific disc. And so as people get older, because we gain weight as we get older, I'm concerned about those effects and, even more specifically, for the slippage aspects. So if it slips for whatever reason, even in a small way, that increases the pressure and the likelihood of it breaking down. And I'm wondering if the sponsor, if that could be addressed in some way in this question or if, perhaps, there has to be some way to anchor this.

Dr. Smith: Ms. Bonnell.

Ms. Bonnell: Thank you for the opportunity. I just wanted to comment on some of the recent considerations, especially regarding the patient population here and whether or not it could be elucidated in the real world. And I think that the data needs to drive the label. I think it's been limited to reflect the dataset that we've seen here today. And that dataset does meet FDA's definition of valid scientific evidence, even that's partially controlled and where we don't have direct exact frequency matched control. So where the data's going to drive that label, on and off-label use, is not necessarily something that FDA or the sponsor can control, right? So our label and our risk mitigators are things that we can control. Real world practical use, that falls to the clinicians, which are not regulated by the staff here.

Dr. Smith: I don't see any other hands raised, so I was going to ask some members of the panel some questions. Dr. Subhawong, as our radiologist, do you feel that these criteria are clinically relevant? I mean, we discussed earlier questions about how accurate is the MRI. We're trying to measure 11mm of height or tibial spine. Are these things that are clinically relevant from a radiology standpoint? Or is it going to, I can leave it at that. Is it clinically relevant from a radiology standpoint, these measurements?

Dr. Subhawong: Sure. Thanks, Dr. Smith. I did have a chance to, again, review the MRI protocols that was provided in the sponsor's summary. And it looks like a pretty standard clinical

MRI protocol was employed, so they didn't use 3D acquisitions with, you know, high spatial resolution that allow some of the more kind of fine-tuned quantitative cartilage imaging that you see in some of these longitudinal cartilage studies. But I think it's a clinically relevant protocol that allows detection of the size, high-grade cartilage defects that were used as exclusion criteria. And I think that doing the measurements of medial meniscus extrusion and tibial spine height as suggested seems reasonable.

Dr. Smith: Thank you. Dr. Reed, you have your hand up.

Dr. Reed: Yes. Thank you. Shelby Reed. I just wanted to comment on the fact that when I read the executive summary, I was struck by what appeared to be relatively broad inclusion criteria, in regard to pain, for this, you know, to be indicated. I understand that people had to have, you know, previous meniscectomy, but they also could just have mild osteoarthritis and mild pain. And that really gets at the heart of, you know, the benefit risk, the trade-off here that is relevant to what we're discussing today.

Dr. Smith: Thank you. Dr. Helgeson. Excuse me. Colonel Helgeson.

Col. Helgeson:Yeah. I also have some concerns about this targeted patient population. It is all done after the fact, and it seems very arbitrary to select 11mm. I think, like it was alluded to, that's at the middle of the bell curve of tibial spine height, but it's a relatively arbitrary number that I am not sure is very well understood why that number makes any sense. I think the meniscal extrusion probably makes a little bit more sense, but, you know, what's the difference between 3mm, 4mm, 5mm, 6mm? The study's certainly not going to be powered to figure out any differences there. So I may, I am concerned about the inclusion of this targeted population.

I also know that in the, I think in the presentation by Dr. Hershman, he did state that there, the patients with only one meniscectomy did better than those that had more than one. And so that

wasn't included in the target population here for this analysis. But it just seems like there's a little bit of a concern I have with the very specific population. I don't know how well that would be able to be applied. And I share some of the previous concerns.

Dr. Smith: At one point, Dr. Kirkpatrick had his hand up. I don't see him on right now. If he's not available right now, I was going to ask our statisticians, experts Dr. Banerjee and Dr. Evans. Hi, Dr. Kirkpatrick. You had your hand up?

Excuse me, sir, you're muted.

Dr. Kirkpatrick: So sorry. I'm so sorry. I'm getting my buttons mixed up all the time. Anyway, echoing Dr. Barber's comments on the specific indications, I think it's going to be very tight indications, and I think the relevance of their target population is high because they kind of change things to include what would make it better. But it's not an easy population to figure out, so thanks.

Dr. Smith: Thank you, sir. One quick comment to our statistics experts, Dr. Banerjee and Dr. Evans, with respect to the clinical relevance of the modified target population, and there's been some varying statements made about data being included or excluded, do you feel that we have a good handle on the target population and the statistics that were presented?

Dr. Banerjee: I have some doubts, particularly related to the comment made by Dr. Bonnell earlier, about the BMI exclusion. I think BMI more than 31.2 or 32.5 was excluded. That really excludes a major chunk of the population who might benefit from, who might have this problem and might benefit from it. So the representation of the population is challenging here.

Dr. Smith: Thank you, sir. Dr. Evans, did you have any comment regarding?

Dr. Evans: Yes. Thank you. Before I made the point, I did just want to thank the sponsor and the FDA for their thoughtful and helpful presentations. I understand the complexities associated with today's proceedings, and I appreciate your efforts to understand the data.

I do have concerns about the quality of the evidence that's presented and would like to make one or two points, particularly related to a question that Dr. Reed asked this morning, and Colonel Helgeson just made a point related to it as well. Perhaps the biggest issue I see is that I struggled to identify a clear distinction between hypothesis generation versus confirmation with regard to subgroup identification and the ultimate estimation of what happened in that subgroup. My understanding is that the data that served as the basis for the identification of the subgroup is also presented as part of the ultimate evidentiary analyses. If so, then the presented analyses are really subject to the multiplicity issues that are associated with the post-talk analyses that gave rise to the subgroup, which may play into the point Colonel Helgeson just made about some of the arbitrary nature of how the subgroup was defined. And so with these blurred lines of hypothesis generation and confirmation, you know, I'm unable to really establish a clear foundation for how you control errors in a way. Because you may be looking at many subgroups, and then you're reporting, in a targeted way, the positive ones you found, but without context of how that arose. And so I think that's an important point and plays into the identification of the population that is being proposed.

Dr. Smith: Thank you. Dr. Cizik and Dr. Manner, do you have any comments related to this question?

Dr. Manner: Yeah. Dr. Manner here. You know, my concern really here, I think, echoes what Dr. Barber had mentioned, which is by the time you slice down all of the disqualifiers for using this, the number of patients that you are going to be able to offer this to becomes vanishingly

small. You know, in terms of disqualifying patients that have a tibial spine height of 11mm, well, the average woman has a medial spine height of about 9mm. So almost by definition, if you're setting a limit of 11, you're going to be excluding the majority of women from using this device. You know, I also have concerns about the yield strength of the polycarbonate urethane that they're using here. I didn't see any concerns with or, you know, data with that. And I'm not enough of an engineer to have a strong feeling about it. You know, with respect to the clinical criteria, I'm just not seeing a huge patient population that this is going to help really make a difference for.

Dr. Smith: Thank you, sir. Dr. Cizik.

Dr. Cizik: I just echo that this is a very specific population and appreciate that the surgeons that do have to do this, we know that it could be expanded very easily in the general population. We know that that could happen, and I understand that's not the point here, but this is a very specific population, so I agree.

Dr. Smith: Thank you, Dr. Cizik, Dr. Subhawong.

Dr. Subhawong: Thanks. I just wanted to make one additional point. I'm kind of taking maybe the other side of this, which is that we see these patients in clinic. We do ultrasound guided injections a lot, offering patients who don't want surgery, who aren't at the point of surgery yet but have significant knee pain, we do steroid injections, hyaluronic acid injections. And the data on these injections is pretty weak. And, in fact, a lot of the data's emerging, and we shouldn't be doing so many steroid injections, that it's chondro-toxic and it leads to accelerated osteoarthritis. And the hyaluronic acid data maybe shows that while you achieve statistically significant effects, the clinical magnitude, the magnitude of the effect is almost below the threshold of being clinically meaningful. So we, you know, don't have a lot of options to offer

some patients that might fall into this category. So we have to tolerate some weakness in the data. You know, we don't get a perfect trial design. But there does seem to be, you know, some strong signal on the KOOS pain scores.

Dr. Smith: Thank you, sir. Dr. Peat, regarding question one, the patient generally, excuse me, the panel generally believes that the clinical patient population would likely be a relatively small subset relative to the general population, but there is a general consensus that there may be a small subset of patients that would benefit from the device. However, the panel also has some concerns about the statistical analysis that's been presented. And also the panel did voice some concerns regarding the ultimate biomechanical strength and risk of deterioration of the device that perhaps has not been fully elucidated in the discussions. Dr. Peat, is this adequate?

Capt. Peat: Yes, it is. Thank you so much. The responses are sufficient, and thank you for summarizing as well.

Question Two

Dr. Smith: Thank you. In that event, we are ready for the next question. Question two: clinical success criteria and secondary surgical interventions. Overall, clinical success for the modified Mercury dataset was defined as improved KOOS overall and KOOS pain positive MRI and no automatic study failure. The statistical analysis plan for the modified Mercury dataset predefined automatic study failures as secondary surgical interventions to permanently remove the device and revisions to reposition or replace the device. 17% of NUsurface subjects experienced a device-related secondary surgical intervention, and 25% of these subjects had more than one secondary surgical intervention.

Please discuss the adequacy of the overall clinical success criteria and the clinical significance of the secondary surgical interventions related to the device. Please comment on the classification of the secondary surgical interventions and automatic study failures. Colonel Helgeson.

Col. Helgeson:Yeah, I guess I'd start by saying that when we're looking at something like arthritis and meniscectomy, it seems that the long-term outcome is the ability to avoid a knee replacement at a specific age. And so the problem I have with these specific secondary surgical interventions is we're not, we're not tracking it beyond 24 months. And I know that that was the design of the study, but anytime we look at a problem like this, it seems that the more relevant secondary surgical intervention should be the long-term knee replacement numbers. And that's just the limitation of their study, given that it's only out two years. So that would be my biggest criticism of this specific criteria.

Dr. Smith: Thank you. Dr. Barber.

Dr. Barber: Just two quick comments: The first is that when we look at these revisions and, or excuse me, when we look at the complications and the issues, I want to make sure we look at it with reference to what's going to be done in the future. Because if it does fail, you're thinking about a total knee replacement. You're thinking about moving forward. And with many of these complications such as the adhesions, the arthrofibrosis, the one infection, would make a subsequent total knee much more difficult. And so I have some concerns that there's a fairly high percentage of these potential complications. And that's just one of the things I'm thinking about. And the other thing that sort of pushes me the wrong way, if you will, is there's a lot of consideration that total knee is, going to total knee is a failure. Well, it's not, you know, it really works well. And yet we're not seeing, or I'm not hearing that these folks have a significant, greater amount of function than you'd get with a partial total knee or a total knee. So, I mean,

we're just sort of saying that it's a failure to do a total knee, and I don't buy that. I'm sorry. So I'm just sort of, I'm not quite ready to get in on this one. I just think that there's a high rate of complications and issues that are concerning to me, and I'll just leave it at that. Thanks.

Dr. Smith: Thank you. Dr. Kirkpatrick.

Dr. Kirkpatrick: I unmuted without talking first, cool. I kind of boil it down into how I present this dataset and results to a patient, which would be, I can give you a 50% chance that I can give you 20% relief of your knee pain, but you'll also have an almost 20% chance of having to go back to the operating room. So, overall, I think the adequacy of their success criteria were defined reasonably well, but I don't think they're enough to make a big difference in between the non-op and the operative. And I do have concerns about subsequent revisions.

Dr. Smith: Thank you. Dr. Subhawong.

Dr. Subhawong: Thank you. There was a comment made about, you know, ideally there would've been apples to apples comparison, using the need for total arthroplasty as an endpoint. And while we don't have that, we do have the cartilage, you know, the progression of the cartilage defects, the high grade cartilage defects, in the control arm, and the apparent chondro-protective effects of the implant, which, you know, it's small data. It’s limited, but that could serve as a pretty good surrogate for a reduced need for arthroplasty in the implant, in the patients who received an implant. And I just wanted to make one other comment, which was that, you know, there was, I heard talk about this being almost like a disease modifying agent. But that is, the FDA, if it approves this device, would not approve it as a disease modifying agent, correct? Like it wouldn't get that kind of designation?

Dr. Smith: Dr. Peat, may you offer a comment on that?

Capt. Peat: At this point, it should be deliberation amongst the panel members, and then we'll provide our recommendations later on.

Dr. Smith: Does anyone on the panel have a comment with regard to Dr. Subhawong's question? I myself, I don't know the exact answer, so I don't want to speak incorrectly.

Dr. Bonnell: We can offer an industry perspective, but it hasn't seen any substantiation for that claim, Dr. Subhawong, nor did I see it in the executive summary, so I don't think that it's a claim that's either sought, nor substantiated at this time.

Dr. Subhawong: Okay.

Dr. Smith: Dr. Cizik.

Dr. Cizik: Yeah, I just want to come back to, I mean, again, I'm here to represent patient reported outcomes and how we interpret them and use them. And, I mean, Ruse, who developed that measure, said that the aggregate score is not validated and should not really be reported. Right? The subscales are reported. You can do it, it says for an RCT, you can aggregate it as a primary outcome. But then in this, in the statement before, it says it's not validated for that. So, I mean, again, to me, when we're talking about orthopedic devices and there's pain and functional issues, I just, it would've been nice to see, I mean, we did see that graph. I would've liked to have seen it in the executive summary to see more of the functional side of it. And, again, we heard from people that were, you know, this does seem to be like this very active population. And so seeing the sport and those kind of data just would've been easier to make some functional, better functional criteria. I guess that's what I would've preferred to see in the clinical success criteria, as opposed to this overall and pain alone.

Dr. Smith: Dr. Manner.

Dr. Manner: Sorry. Just had to unmute there. So there are a couple of issues here that I have: First of all, to my way of thinking, any re-operation, particularly for an investigational device, should be considered a failure. You know, when we do surgery and we have a complication, which, you know, let's say we define it as a return to the operating room for any reason, we don't then say, oh, well the patient had a success, even though, you know, because two years later they were feeling pretty good in spite of the fact that we had to take them back to the operating room two or three times. Well, no, that's not a success. That's a failure.

My other concern has to do with the fact that these really are cherry-picked patients, and their surgery is performed by cherry-picked surgeons. And if this is the best that they can do with, you know, if this is the best that we can see with every possible advantage given to the device, it's almost a guarantee that what you'll see in real practice is going to be substantially worse. And you're going to be extending the indications to patients that probably don't fit the mold, and you're going to probably have surgeons doing it who do not have, necessarily, the expertise of the designer surgeons. So classifying return or secondary surgical interventions as an automatic study failure, I think, is completely appropriate. And I think that's correct.

Dr. Smith: Thank you. Dr. Peat, may we ask the FDA to re-state the indications for use of this device?

Capt. Peat: Sure. No problem. So within our presentation we talked about the proposed indications for use. And so this product, NUsurface meniscal implant, is to improve pain and function and the medial compartment of the knee in which the medial meniscus has been resected. The indications for use is in patients with mild to moderate osteoarthritis, mild or greater knee pain, and cartilage present on the low bearing articular surfaces. Each element needs confirmation from patient's history, physical examination, radiographic imaging, and/or visual

observation. We do not evaluate this particular product as a cartilage preservation product, simply because that is not the data that was presented at hand. We have to go with the data that has been presented to see whether or not it supports the proposed indications for use.

Dr. Smith: Thank you, Captain.

Capt. Peat: Hope that helps.

Dr. Smith: Thank you, Dr. Peat. If I may make a quick comment and then I was going to ask Dr. Barber this question as well, regarding the second part of this question, the comment on classification of these SSIs as ASFs, Dr. Manner felt that was appropriate. Dr. Barber had been discussing earlier about, I got the sense that maybe he didn't agree with that, and I just wanted to make sure I had an accurate understanding of the consensus of the panel regarding that point. And then also, Dr. Barber, uh, your hand is up.

Dr. Barber: Yeah, just to go back to your question, remind me, I'm not exactly sure what you're asking.

Dr. Smith: So the question the FDA's asked us is in the Mercury dataset, if the, in the statistical analysis plan, if an individual underwent a secondary surgical intervention to permanently remove the device and revisions or reposition, then it was automatically classified –

Dr. Barber: -- as a failure. And I agree with that a hundred percent. It should be a failure.

Dr. Smith: Thank you.

Dr. Barber: It should be a failure. The other point I was going to make though, is in the FDA guidance document that was just read, it stated that the indications would be mild to moderate osteoarthritis, but we've, as Dr. Kirkpatrick pointed out earlier, but we've said that those should be excluded. So I'm like, I'm a little torn, you know, as to those indications because if it's mild to moderate RFC arthritis, why aren't we doing a uni-compartmental knee? That's, sorry.

Dr. Smith: Thank you, sir. Are there any other comments on this question? Yes, Dr. Banerjee.

Dr. Banerjee: A quick comment about the classification. I'm pretty sure everybody is understanding this, but, you know, when you classify a secondary intervention as a failure, you know, you cannot change the endpoint post hoc. That was part of the end point. And now I think the argument is being made that the secondary intervention is not that invasive. It's quick. It has, it's not a bad outcome, but I think, you know, once the endpoint was discussed by the sponsor and the FDA together, and the endpoint cannot be changed at this point.

Dr. Smith: Thank you. Are there any other comments on this question? Dr. Peat, regarding question two, the panel generally believes that there is a lack of consensus regarding the adequacy of the overall clinical success criteria, significantly regarding comparison beyond two years to other surgical alternatives. Also, the clinical significance of the secondary surgical interventions were felt by the panel to be appropriately classified as automatic study failures.

Capt. Peat: Thank you, Dr. Smith and the panel. Your responses are sufficient. Thank you.

Question Three

Dr. Smith: We will now go to question three: Subgroup analysis. The sponsor provided a subgroup analysis intended to identify a modified target population with a reduced rate of secondary surgical interventions from the unmodified Mercury dataset. The modified Mercury dataset involves the exclusion of meniscal extrusion greater than 5mm and tibial spine height less than 11mm.

Please comment on the overall success rate of the modified Mercury dataset. Please comment on whether the modified Mercury dataset provides sufficient information to understand whether the device improves pain and function in the medial compartment of the knee in which

the medial meniscus has been resected. Please comment on the strengths and limitations of the study design elements of the Mercury dataset and modified Mercury dataset. Please comment on the benefit risk profile for use of the NUsurface meniscus implant in alternative subgroups. Are there any additional subgroups in which the NUsurface meniscus implant would have a favorable benefit risk profile?

Would anyone like to raise their hand to start, or should I, yes, Dr. Kirkpatrick.

Dr. Kirkpatrick: With regard to the pain and function out of the dataset, it does improve pain in a proportion of the patients and made the overall numbers look good enough to say yes, but that was only a 20 point difference on the KOOS out of a hundred. So how much it is, it's hard to say.

The different datasets utilized, I think it was appropriate to have a non-surgical control because I don't have an issue with that part of it. The benefit risk profile is where it gets down to a very challenging decision because it seems to hit a home run in some patients and strike out in others. And the home runs, is it worth it to go through the potential of a removal of implant or a readjustment of an implant or a conversion to a knee replacement? I don't think the device speeds that. But the question is, can we really pin down the right people that are going to get the benefit risk profile to their advantage?

And then, are there additional subgroups? It's kind of hard for us as outsiders to determine that. I don't, I didn't see anything obvious to think of, to be able to say this would be a big difference as far as a new population to look at with a different risk profile. Thank you.

Dr. Smith: Dr. Reed.

Dr. Reed: My question, I don't think that we saw this in the executive summary, but my question relates to whether there was a differential treatment effect among people with higher or lower pain levels at baseline.

Dr. Smith: Does anyone on the panel have a comment or response to that inquiry?

Dr. Cizik: I didn't see that either. I mean, I am, I'm a little more familiar with spine instruments than I am some of the knee ones, but it's a valid point because we do see, even in spine patients and on these PROMS measures that, depending on where people start, right, depends on where, how much improvement they can make. I was also, though, going to comment, just to play devil's advocate, 20 points is above the MCID. So you can detect that. And so that's reasonable that we're seeing change and, clinically important change, and it's above the minimal detectable change as well. So, I mean, that is valid, but I agree we did not get to see some of that information, which would've been nice.

Dr. Reed: Well, I would add that it seemed like the patient testimonials, like none of those people at baseline seemed to describe mild levels of pain or, you know, mild, impairments in their function. They all seemed to be quite dramatically impacted before. So that was one reason for my question.

Dr. Cizik: I agree with that, and I think it would've been, I mean, even just also seeing a simple VAS score would've been interesting as well. And just seeing did people make two-point change on those as well. But, yeah, and back to the indication where we're seeing mild indications, but the testimonies were very clearly people without mild.

Dr. Smith: Colonel Helgeson.

Col. Helgeson:I guess to the question about whether or not I think that the modified Mercury dataset provides the information to make that determination, I think I would go back and, and

excluding criteria of 5mm and the tibial height of 11mm, I think I'd go back to the, our previous comments about how they came to that dataset, the post hoc analysis, to arrive to those two numbers. I mean, we don't have that data. And I don't know if they did do the analysis that sometimes people do where you look at 10mm and 11mm and 12 mm, and you just keep looking till you find one that works. That certainly introduces a lot of risk there. We didn't get that information, so that would give me some pause on whether or not I can make a determination on that.

As far as some of the other questions in this, underneath this non-voting question, I would say that if you're going to look at other additional subgroups, I don't, I don't know how you would be able to do that. Certainly we, in this dataset, don't have any information that we can make any sort of determination on that. But for the benefit risk profile question in other subgroups, I just don't know without having additional information on the data, we just don't have the granularity to make that determination.

Dr. Smith: Thank you. Dr. Barber.

Dr. Barber: Yeah, I would have similar comments. I don't think we have the granularity in data. To me a lot of this would be around functional status before and after. And I don't think I have all that information. As far as subgroups that would do well from this, I think that the way they've defined the Mercury dataset, the refined dataset, is almost too specific, in my mind. And I don't like the way it's been, it's been done. And, you know, even with this more limited dataset, that should be the best of all possible worlds. I mean, my God, you've got a patient population that would be perfect for this, and they're not still, they're still not getting good results. So I'm just concerned about that. And I also continue to have concerns about how this would be applied

in real life. I just don't see that these criteria would be followed religiously. And so there would be, certainly, some degradation in results as we go out to the community.

Dr. Smith: The next comment will be Dr. Price, and then I was going to ask Dr. Porter, as our patient representative, as well.

Dr. Price: Thank you so much. So the one comment was on the study design and the methodology, and I believe that the FDA made a very good case for the shortcomings there. And they gave a very plausible explanation for like the de novo. It's like, it's also a new thing. And I feel that we need to be cautious because basically we're extending policy that will make an effect for the kind of procedures that are allowed to go forward in the future just by implication. If this goes to with those limitations, I'd certainly give it some thought.

And I also have the concerns about the placebo effect because the control group, they really did nothing for them. And so they are just going to be a group of like, really dissatisfied patients compared to the other ones that have, you know, the brand new, the brand new treatment. And those in the control group would also feel, if they complain loud enough, that they would possibly get the brand new treatment, like as a consolation price or the, or whatever.

And so I have concerns because methodological issues that seem small, they’re not small, and they, and they really have the capacity to bring bias. And we may not see it in this small population, but when it's rolled out to a large population, that's my concern. And I know it's a non-voting question, so I'm just giving my thoughts. Thank you.

Dr. Smith: Thank you. Dr. Porter, as our patient representative on the panel, may we ask for your input?

Dr. Porter: Yes. I agree with the comments that have been made so far. I feel, I think one of the, one of my main problems that I have is the fact that, from what I could see, the study was

supposed to be extended longer, but they stopped it at two years. So my concern is did they stop it at two years so that they could meet their parameters, and did they adjust the 5mm and the 11mm heights for the enrollment so they could meet their parameters, you know, that they want to show. And so I feel like, you know, if, like everybody said, if this was, this is an ideal population, they're not overweight, they're, you know, not having severe knee problems, it should be successful in more than 90%, in my opinion. And it isn't. And that's my concern. And what was also said about, you know, I feel like the biggest gift I got was having a total knee replacement at the age of 38. And, you know, so to look at it as not wanting a knee replacement, you know, I think that dangling that over somebody's head with all the negativity that goes with it can influence their decisions also. Thank you.

Dr. Smith: Thank you. We have two pending comments, and then if there's nothing further after that, I was going to recapitulate our summary for Dr. Peat. Dr. Subhawong.

Dr. Subhawong: Thank you. I think, with regard to the first point, the modified Mercury data seems to provide good evidence about pain relief. But I think a lot of us had questions about the comparator arm, and that was, you know, really we, we were using a, maybe a flawed comparator, and I think we would've all liked to see like a sham surgery. But you're left with the data we have from these two studies. And I think, at least, even though it's small dataset and it's kind of been extracted and kind of curated to meet certain definitions, at least in my mind, it does provide pretty compelling evidence that there is pain relief with this implant.

And the other point I wanted to make was with regard to the surgical, the failure rate of 10%, I think was set high priority, I just wonder if, you know, if you presented to patients it ended up being something like 20 to 30% needing to, to have an additional surgery, but given that it's a, a free floating implant and they're not having to anchor anything into bone, I think that's a risk that

patient maybe should be able to discuss with their, with the physician. And so that, that we may tolerate somewhat higher rates of re-operation with a device like this, that isn't as difficult to insert.

Dr. Smith: Thank you. Ms. Bonnell.

Ms. Bonnell: Thank you for the opportunity. Just reorienting the panelists that we are looking at a de novo eligible device that is likely to be Class II, moderate risk, not a high risk or Class III device. The metallic resurfacing implants that are promulgated under Class II currently don't have a clinical special control. So when we look at the clinical data that's been available to us, whether or not it meets the FDA's definition of valid scientific evidence, again, of which that definition includes partial, uncontrolled studies, you have to look at the robustness of that data and its control.

There was a prior comment here regarding the control in terms of those patients who received conservative care. And I actually appreciated earlier in the afternoon when they talked about their protocol modifications during the investigation, and the modifications were for the investigation group, but not the control. And I think actually the control great gives this panel a unique perspective of real-world performance of what those conservative care patients are experiencing. I think the proposed labeling is a salvage or a rescue situation, and you heard in the public panel, detailing those patients who did have a positive experience and they kept using the term bridging, right?

So this is an alternate intervention before you would get to any, any other sort of a total knee arthroplasty. And so while I don't know the, if a total knee arthroplasty, to earlier points, is a detriment, you know, I think that arguably there's some meta-analysis and literature there that can be discussed. I do think that the control data gives that unique caged animal versus wild animal

perspective, and you have to look at this as the benefits for a particular subset of patients, rescue patients. I think that we can't dismiss that there are notable benefits for that small cohort.

Dr. Smith: Thank you. Dr. Peat, regarding question three, the panel generally believes that there was data presented that did show there is an improvement in pain in the modified dataset. However, the panel did raise some concerns about the criteria of the modified dataset and the extrapolation of those results to a more general population.

With respect to the study design characteristics, some members of the panel felt that it was appropriate to have a non-operative control. Other members of the panel felt that a sham surgery control may have been more beneficial. With respect to the benefit risk profile for the use of the implant, the panel's consensus was that there was a lack of, the panel's consensus was that the data presented was insufficient to reach a conclusion. And with respect to additional subgroups in which the implant would have a favorable benefit risk profile, the panel also had a consensus that the data presented was not adequate to reach a conclusion.

Some members of the panel did note that there may well be a small segment of patients for whom this may be beneficial. Dr. Peat, is that adequate?

Capt. Peat: Thank you, Dr. Smith and panel members. That is adequate. Thank you.

Question Four

Dr. Smith: May we please advance to question four: Patient preference information. Patient preference information, PPI, has been provided to support benefit risk determination. Please comment on the design and execution of the current PPI study, study seven. Please discuss the contribution of the PPI datasets to the final benefit risk determination. Dr. Reed.

Dr. Reed: Shelby Reed. Since I'm here to present on, weigh in on the patient preference study, I, you know, I'd like to take a little bit of time. Dr. Gebben presented, you know, and I

agreed with his comments, in regard to, you know, concerns about the, of the analysis of the data, as well as presenting the survey information in such a way that it may have inflated the perceived magnitude of benefit and minimized the, you know, risks that were shown. So just to sort of provide a summary, they used a video script to provide background information to the participants.

So some of my concerns, and it might be useful to take a look, is how they, they describe the benefit in terms of being a 25% reduction or 25% reduction in the proportion of people who improved one disability level. That's difficult for your average person to understand. And my concern is, you know, how many of the people actually interpret that as simply a 25% reduction in pain. On the flip side, when they were presenting risks, that was presented as the percentage of people who would have reconstructive knee surgery. And in the training materials or the slides that they were showing during the script, it said to relieve pain, which isn't really a risk. It's almost presented as a benefit. So I think that's, you know, it's very difficult, I think, and they did not show any information that gave me confidence that people understood what was being conveyed.

And it becomes even more challenging to understand it when it goes down to this survey, they no longer presented as a, you know, a percent chance of reconstructive surgery to relieve pain. When they went to the actual choice questions, it flipped to presenting that as more pain. So there are a lot of concerns the way that the information was presented to patient.

Another major concern I have is that in presenting the pain information, they seem to conflate pain and disability. And actually, if you, you know, want to take a look, on page 69 of the executive summary, it shows a pain disability scale that I assume maps to the KOOS pain PRO.

And, you know, KOOS pain really, you know, targets things that people can do and that, and it doesn't represent the pain scale as they have described it here.

And they have conflated pain and disability sometimes for the different levels, representing mild, moderate, severe, and extreme disability. They sometimes describe pain in terms of having to put ice on a knee. And then sometimes they describe it in terms of what people can do. You know, particularly I'm concerned about the extreme disability where it is described as people either being bedridden or in a wheelchair to get around. And I'm sure if you ask an amputee that is, or a person who's paralyzed, that means very different things to different people. So I don't think that there is any good psychometrics done to present this scale. So that is the major concern for me. So it makes it impossible to really relate this patient preference study to the PRO results that came from the clinical data.

In addition, there are a lot of bad practices in terms of risk communication. I've highlighted some of them. Yeah. There are a number of concerns. I just, I guess I'll stop there unless there's more time and people want to know more.

Dr. Smith: Thank you, Dr. Reed. Dr. Kirkpatrick.

Dr. Kirkpatrick: Thank you. I agree with the FDA's concern about the research oversight. Surveys are indeed a research tool of human subjects and subject to IRB oversight, even if the IRB finds it to be an exempt study and does not require consent. Whether that affects the question of its validity, I'd have to leave up to the FDA. But in my institution, if you proceed with a study that does not have IRB oversight and it's deemed to be human subjects research, the principal investigators generally are disciplined, and the study is shut down. The PPI studies that I read through in the appendix seemed very complicated. I'm not sure my patients would understand how to take that survey. And with that, I rest my concerns about the PPI.

Dr. Smith: Thank you. Dr. Porter.

Dr. Porter: This is Laura Porter. I agree with what Dr. Reed said. You know, the definitions, I mean, we all know they came up with the pain scale to make it easier to assess pain. And I don't know if that really has done that. And, you know, pain is a subjective thing. So, you know, I can tell you that I can't get out of bed in the morning. That's, I think, more realistic than having a pain on a scale of 1 to 10. But I think that my biggest concern is that they did a survey, and they used this as evidence. They did a survey of people that have never had surgery who just say that they have knee pain.

But did they, and I didn't see this, did they assess the amount of knee pain these people had before they surveyed them? So is there any indication about how bad their knee pain was when they surveyed them about what their choice would be as far as surgery?

Dr. Reed: I didn't notice that. You know, one additional thing is that they, you know, typically in these studies, they'll be sort of a reference condition where everyone sort of would be, you know, assume that you have this, this sort of level of pain, so that we can sort of have a common starting point. And so, again, that question, because people probably have varying levels of pain that would influence their responses to the patient preference study.

Dr. Porter: Sure.

Dr. Reed: And if that wasn't measured, you know, it should have been measured and should have been considered as part of the analysis.

Dr. Porter: I want to say another thing too, and this is a little off topic, but I think it's pertinent here. But I'm a metastatic colon cancer survivor. I was diagnosed 20 years ago and given an 8% chance of living five years. And before that, I said that there were certain things that I would never do. Okay? I would never go on chemo that only gave me a 2% chance of

surviving. You know, I would never do this, I would never do that. And I truly believe that until people are put in an actual situation, they don't know what they're going to do. And as far as, you know, take this however you want to take it as far as this knee device is concerned, but, you know, I just, I wanted to bring that up.

Dr. Smith: Thank you, Dr. Porter. Dr. Cizik.

Dr. Cizik: Yeah. I just want to play a little devil's advocate in why I started this conversation about IRB approval for a preference study. I got the impression they used a vendor. And, again, a lot of this was done, it seems like, at sites that were private sites and outside, but the preference study, to me, did not seem to, it was not recruiting patients. So I'm just, again, I don't have all the details, but if it was done as market research, I think, you know, again, we can't hold it against the sponsor not knowing how, right? These were not patients, is my understanding, that were not recruited. And that being said, the other thing, and Dr. Reed can comment to this too, I think often when we do preference studies, we want societal preferences. So we want people who are agnostic to the condition, right? To make these type of decisions from a preference base that, again, is including people who, who aren't influenced by the fact that they have the condition. Now that being said, I have issues with the methods as well. We didn't really see a framework of a discrete choice experiment or a best worth scaling. And I know there's a document by the FDA on the guidance that I think was clear that the FDA felt was not followed. So I do, I'm just trying to, you know, be a little bit that we don't know all the circumstances or we're not given the information that sometimes these things, a lot of us on here are at universities and so we are very used to IRBs and those, but we don't know that process. So I'm just trying to play a little bit of, you know, we could, we don't know how these people were recruited. But, again, there are methodologic issues for sure.

Dr. Smith: Okay. Dr. Manner.

Dr. Manner: I actually have a question. They mentioned a few times or, in the executive summary, mentioned this was the seventh PPI. Why was that? And what happened to the first six? Does anybody know? No? Okay. Okay. I'm, Dr. Peat, or does that, do we know any of that, why they did six previous PPIs, and then they only reported this one? Okay.

Ms. Bonnell: This is Stacey speaking on behalf of industry representative.

Dr. Manner: Yes, thanks.

Ms. Bonnell: I think the other six PPI studies are highlighted on page 66 of the executive summary. I recall it from the presentations from today. And also, if I recall, FDA had shared that there was back and forth in terms of the criteria which should be included in those PPI evaluations. But the, all seven respondents and the proportions that they captured are on page 66 of the executive summary.

Dr. Manner: Okay. Okay. I apologize. Thank you so much.

Capt. Peat: I wanted to thank you so much, Stacey. So let me just make sure I give you some clarity. Each time we got feedback, we got their protocol for the PPI study, we provided feedback. But just remember what was indicated before. The sponsor had already started their PPI study. And so instead of coming back to FDA to address our responses, it was never necessarily addressed. And so they were already down the border of seven, the seventh turn. And yeah.

Dr. Smith: Dr. Price. Dr. Price, you're muted.

Dr. Price: Sorry. Thank you. Thank you so much. I agree with what everyone has said so far. And the other thing that I would add is there's no indication that since these are patient preference, patient interests, there's no indication that these were built with patients. And, um, so

we don't know if that is true to any kind of patient experience because, also, they didn't survey patients. They surveyed people with knee pain, as Dr. Porter said. And so if we, if we're not representing, letting the patients, giving the patients their own voice for their own experience, then how accurate can that measure be? And so I just pushed you back a little bit on that because Mechanical Turk (phonetic) survey, or whatever it is, is not patient experience.

Dr. Smith: Thank you. Ms. Bonnell.

Ms. Bonnell: Thank you. Speaking on behalf of industry representative, I saw the sponsor present these PPIs. We've talked tonight. I don't disagree with the commentary that we've just had about these seven PPIs. But I didn't see that they were positioned as primary objective evidence. I saw them being provided as a complementary or supplementary. So I just keep that in, in the framework, that the clinical evidence is their primary evidence from which to draw your conclusions.

Dr. Smith: Thank you. If there's no further comments from the panel, I was going to summarize for Dr. Peat. Dr. Peat, regarding question four, the panel generally believes that the PPI data sets up significant methodological issues, which limited their applicability for drawing conclusions, particularly with respect to the final benefit risk determination. Specifically there was concerns regarding the aliasing of disability and pain and also the ways, and also the ways in which the datasets or the questionnaires represented to patients.

Also, some members of the panel raised concerns regarding if it was appropriate for the sponsor to proceed with these PPI without first receiving a formal exemption from the IRB. Others noted that it's possible this was more of a market research and that perhaps, as these things were done with the eye of market research, perhaps the sponsor was not aware or did not need to have an

IRB exemption, but I believe the majority of the panel had concerns regarding the lack of IRB approval for exemption prior to proceeding with this

Dr. Peat, is this adequate?

Capt. Peat: I'm actually writing down some additional notes. Thank you, Dr. Smith, as well as the panel members. Your responses are sufficient for us. Thank you.

Question Five

Dr. Smith: Thank you. In that event, we are ready for question five: risk mitigation. The sponsor has identified several key considerations in risk mitigation, including the appropriate selection of patients, e.g., exclusion of meniscal extrusion greater than 5mm and tibial spine height less than 11mm, and a more detailed surgical technique, e.g. the ability to precisely identify the appropriate device size and implant the device. The sponsor reported inter-rater disagreements over the meniscal extrusion and tibial spine height exclusion criteria. How might these factors impact the clinical reproducibility, particularly the clinician's ability to identify patients that would benefit from the device?

Does any member of the panel wish to raise their hands, or would it be more conducive if I sort of call it out or started the discussion? Yes. Colonel Helgeson.

Col. Helgeson:I'll speak up. So I, it's a little odd to me that the inter-rater reliability wasn't higher between these measurements, because they do seem like very simple measurements that most people could agree how to measure. But at the same time, if they're, that the data that they reported was that it wasn't, then I would be concerned moving forward that this would be a patient population that would be hard to define for the average surgeon in making a determination whether or not they would meet the criteria for this implant. And I don't know, there's probably a difference between 11 and 5mm at tibial height, but there's probably not a lot

of difference between 11 and 10mm of height. And I know that that is taken into consideration in the analysis, but there's going to be a, it's going to be harder to define this population if there's not reliability in that measurement. I just don't understand how it's hard to measure.

Dr. Smith: Thank you, Colonel. Dr. Barber.

Dr. Barber: Yeah. Just to go further on your point, Colonel, it's that, you know, if we're just seeing inter-rater problems within radiology, you add some orthopedic surgeons to that, and, I think, the reliability is going to go down rather considerably. Only because, you know, the precision at which you're going to measure the tibial height and the extrusion and where your starting point is, et cetera, will be difficult because I'm not sure that all of the radiologists around the country are going to be instructed on exactly how to do those measurements. So it's going to end up, probably in a lot of places, in the orthopedic surgeon's lap. So that's my only point there.

Dr. Smith: Thank you, Dr. Barber. Dr. Subhawong.

Dr. Subhawong: Thank you. I'll second what's been said. For medial meniscal extrusion, that's something I regularly comment on, and I think most radiologists, you know, at least musculoskeletal radiologists, feel comfortable measuring. But I don't routinely measure tibial spine height, so I can see a lot of variability coming from that measurement that could be problematic.

Dr. Smith: Are there any other comments from the panel on this question?

Dr. Cizik: I just wanted to highlight Dr. Manner's comment about tibial height in women and the exclusion criteria there. I think that's important to reiterate.

Dr. Smith: Thank you. Colonel Helgeson.

Col. Helgeson:Yeah, I was just going to go back to the expanding the patient population that would be eligible for this would be up to the discretion of the surgeon. And if you have an

unreliable measurement, that measurement will, if they're looking to do the surgery, would be suddenly easy to manipulate that measurement to make somebody eligible for the procedure or not eligible for the procedure, which then calls into question whether or not it would be applicable for the general population.

Dr. Smith: Thank you. Ms. Bonnell.

Ms. Bonnell: Great. Thank you for the opportunity. Just in response to that comment, I think it's important just to reiterate that the data does drive the label in the intended patient population. To the last point, this is not intended for a broad population; that the subpopulation that was presented, at least herein and then the executive summary, was demonstrated to reduce the potential for second surgeries by at least 50%. So they met that endpoint, and then they continue to be that endpoint for this subpopulation. So definitely not broad, needs to be constrained, but the point for that off-label use, that's at the discretion of the treating physician. For manufacturers, we have the responsibility to mitigate those risks to the degree that we can, using the tools at our disposal predominantly with labeling and with training.

Dr. Smith: Are there any other comments from the panel before I summarize for Dr. Peat? Yes, Dr. Subhawong.

Dr. Subhawong: I just wanted to make one comment. Maybe the surgeons can speak to this better than I can, but, you know, using that medial tibial spine height, I wonder if they ever saw MRI data that the implant was extruding in that direction. Because it seems like it's, if it's free floating there, it's going to slide around. I just wonder if that was one, you know, you have so many variables collected. It's a small patient population. You're doing a post hoc analysis. You just choose one that kind of cuts down your, you know, the number of displaced implants. But do the surgeons feel like that that medial tibial spine height would be kind of a clinically relevant,

you know, measurement of, or at least does a really adequate function or, you know, adequate morphological barrier to an implant like this slide around in the joint?

Dr. Smith: I was going to make a comment to that, Dr. Subhawong. And this goes to some comments made earlier, which not to sort of get too much into the weeds, but it, excuse me. I may have missed a point. The concern I have about tibial height measurements is, on these MRIs, I don't even know what the coronal sliced plane thickness was, and we have the end plane resolution, but it's not clear at all to me that you can accurately measure 10 verses 11mm of height. With the resolution of these MRIs, the coronal slice must have been at least 3mm thick. And so you get symmetric, you get significant volume averaging across the boxes. And so I don't believe, frankly, and correct me if I'm wrong, Dr. Subhawong, that you can accurately measure within a millimeter the tibial spine height on a coronal MRI. And so it's somewhat of an arbitrary measurement that's being thrown out.

When we make patient specific implants, we don't make them up of MRIs. We make them up of high-resolution CT scans. And to that note, also, I think it's important that we focus that this arbitrary, well, I would say arbitrary, height of 11mm was a post hoc analysis that was done to then refine the subgroup. It wasn't an a priori decision, and I have some concerns about how they came out with that height in the first place. Are there any other comments from the panel?

In that event, Dr. Peat, regarding question five, the panel generally believes that the inter-rater disagreements over the measurements was a significant concern for reproducibility and clinical applicability. Our radiologist expert on the panel noted that typically tibial spine height is not something that is measured. They do measure, routinely, meniscus extrusion, but there is a concern amongst the panel members that this measurement will most likely need to be made by

the surgeons in the office, who may not have the same expertise as clinical radiologists in that measurement.

And, also, some members of the panel voiced concerns regarding if this measurement can be made accurately on a coronal MRI image. And, overall, there was some concern regarding if these measurement factors will impact the clinical reproducibility due to the inherent heterogeneity in the measurement itself within their own study observations.

Dr. Peat, is this adequate?

Capt. Peat: Thank you again, Dr. Smith, as well as the panel members. This is adequate, your responses. I appreciate it.

FDA Summation

Dr. Smith: Thank you. And for a point of clarification, Dr. Peat, should we move now directly to the FDA and sponsor summations? At this time, the panel will hear summations, comments, or clarifications from FDA. You have 10 minutes.

Capt. Peat: Thank you so much. I'll start off. I really wanted to say thank you to the panel. I know this has been a very long day. So just to give you a quick recap, the NUsurface meniscus implant is a first-of-a-kind polymeric meniscal implant device. And the sponsor had originally submitted a de novo with the Mercury dataset, and that Mercury dataset comprised of Sun, as well as the Venus studies.

Once we had reviewed that original PMA and, in response to the feedback from us about their clinical datasets and FDA's inability to evaluate the benefit risk profile, as well as our lack of understanding of the effectiveness risk medications that were put forward by the sponsor, the sponsor then submitted, provided a subgroup analysis to identify a population that has fewer secondary surgical interventions. So the information that we are putting forth here today is FDA

has analyzed the data. We've interpreted the data, and we're still having a lot of concerns related to the safety and effectiveness, as well as the benefit and risk.

So today we brought to your expert opinion to address the following: The patient population that would benefit from this device, and we are also in consideration of available alternative non-surgical and surgical treatment. We also asked you to ponder the adequacy of the overall success, clinical success criteria and the surgical significance of the SSI related to the device. We asked you to think a little bit more in dialogue about the overall success rate of the modified Mercury dataset for which this de novo was put forward and its impact on the benefit and risk determination.

Equally, we asked you for the contributions of the patient preference information studies, as well as how they should assist with benefit and risk determination. Next, we ask you the impact of the proposed risk mitigation strategies on the clinical reproducibility, particularly as it relates to accurate identification of the target patient population. And, finally, whether or not there's going to be a favorable benefit risk profile, if this product is granted, whether or not this information has been demonstrated for the subject device for its proposed intended use.

So I know today was a very long day, and, again, I just want to emphasize our thanks. And as you go into deliberations on our voting questions, we will be asking, regarding our, the benefit and risk profile. So thank you so much again. I'll turn it over to Dr. Smith.

Sponsor Summation

Dr. Smith: At this time, the panel will hear summations, comments, or clarifications from the sponsor. You have 10 minutes.

Mr. Belaney: We want to thank the panel for the thoughtful review and feedback today. We've presented the culmination of over 17 years of work from this device, from preclinical testing to

clinical evaluation. Four clinical studies have been performed from the early feasibility testing that began in 2008 through pivotal studies presented today. In total, over 400 patients were enrolled in these studies. This is a large body of evidence relative to most devices that FDA has cleared to date through the de novo process, including other approved orthopedic implants. We believe the total body of evidence gathered over the entire development of the NUsurface supports that there is benefit to patients that outweigh risk, meeting the standard for de novo clearance.

We acknowledge that every study can always be more perfect. Looking at the study, we started years ago with multiple rounds of prior FDA review, discussion, and approval. We performed the best studies we and our experts could design to characterize risk and benefit, taking into account the FDA's feedback. We have extensive interaction with FDA about choice of control endpoints, follow-up duration, and statistical methods, including dozens of interactions over multiple years. The two-year study duration is consistent with FDA guidance and numerous other orthopedic device approvals.

FDA cited multiple sources of uncertainty. We want to clarify a few points that we believe reduce uncertainty. We want to clarify that we know the 24-month outcome for over 90% of our enrolled patients. We have data showing that variation in measuring the tibial height of a millimeter or two does not significantly impact our outcomes. Thus, while there may be some variation, it does not introduce significant uncertainty with respect to outcomes. We achieved superiority in the overall population and in the subpopulation with propensity adjustment by multiple methods and without adjustment. The tibial height and meniscus extrusion criteria were validated in the separate MCT dataset.

As expected over a project of this duration, many of the personnel involved today were not involved in the original IDE design and may have preferred something different, as well as some of the panel members. We recognize that it is important input. Nonetheless, we do not believe it is appropriate to move the goalposts now compared to the IDE study designed with FDA input in 2012 or 2015, applying FDA guidance or views that were not available at that time.

We designed a study that met our pre-specified primary endpoint for superiority with a large between group difference in favor of the NUsurface, both in the original population and in the subpopulation. As you have heard from our clinical advisors and from patients, there is an important unmet need for additional treatment options, such as NUsurface, that allows patients to maintain activity and provide pain relief. I will let Dr. Jones comment on that.

But the key points that we would like to highlight, taking into account the panel's questions and discussion, are the following: NUsurface was clearly superior to the controls on the pre-specified primary study endpoint. This was true in both the original population and in the subpopulation for which we are seeking clearance. NUsurface also showed superiority on multiple secondary endpoints, again, in both the overall population and the subpopulation. This included multiple validated measures of pain and function, as well as cartilage status. If secondary surgery is required, it is straightforward. The radiologic data demonstrates that cartilage is generally preserved at a minimum. These benefits are achieved with minimal impact on the patient in terms of offloading rehabilitation and limitations on activity.

Our procedure, like all knee procedures, carry some risks, including risk of re-operation. The rate of re-operation is comparable to or lower than other devices that have been approved by the FDA, including recently approved knee implants, and is similar to or lower than other accepted techniques such as meniscus allograft. As you have heard in the public session, even

patients who had undergone a re-operation believed that the device was a good option for them. These are important considerations in weighing risks relative to benefit. Patients who meet our eligibility criteria have no options today that offer them the same combination of a potential for significant relief in pain and function and minimal rehabilitation or time away from work and activity. The panel heard repeatedly from patients and doctors who want this choice available. We do not think our product is for every patient. Some patients may choose a total knee arthroplasty if they're eligible. Many patients, as you heard in the public session, did not choose that option. Each patient can discuss with their clinician the relative benefits and risks of the available treatments and make a shared decision about the best option.

We, as the manufacturer, are committed to working with FDA to develop labeling materials that clearly explain the risks and benefits of treatment so the patient and clinicians can make informed decisions. Active Implants is committed to ensuring appropriate training as an additional risk mitigation. We have learned over years of experience what types of patients are most likely to benefit from NUsurface. These patients represent a well-defined group, and we will provide training to ensure that eligible patients are correctly identified. Note that there were 20 women included in our subpopulation, not just men. Importantly, we are seeking clearance only for a specific indication, and our understanding is that this is the only population that the panel is being asked to evaluate.

Our commercial experience in Europe, where we have already launched the device, provides additional support that this can be done safely and that our training is effective, as you heard from the European surgeons in the public session that are already using the device. We, like everyone here, want to see the best patient outcomes possible. Many of us have family

members and friends who are living with knee pain, and we want them to have the best array of options available, including our device, but with the right device for the right patient. Considering all of the options, we will incorporate the panel's feedback going forward, considering all the points we have discussed today, and we look forward to the panel's recommendations. I will turn to Dr. Jones for the last word.

Dr. Smith: Excuse me.

Dr. Jones: Thank you, Ryan.

Dr. Smith: Excuse me, Dr. Jones. Sorry. I will remind you about the time. You have about two and a half minutes left.

Dr. Jones: Thank you very much, Dr. Smith. Yes. Thank you very much for the time today. I just wanted to reiterate some of the things Ryan just talked about. We don't intend to replace total knee, merely to delay it. This is a device that everyone, not everyone's eligible for. We know that. However, we do want this in our toolkit. This is something surgeons and patients want as an option, and we think we deserve that option and to provide that to our patients. We can train clinicians. I've done this already in the trial, and I feel it's important to train the clinicians appropriately, as I've done with other procedures, and we can do this.

It is a needed option. I feel that's something that the patients have voiced a true need in their armamentarium, things they want to have available to them, and that was demonstrated today by the testimonials. The NUsurface does spare a bone. It does spare soft tissues. Revisions are easy. The revision rehabilitation's easy, and the primary procedure has a very quick rehabilitation. So unlike total knee arthroplasties and other procedures, this is not a tough revision. It's certainly not a tough case to recover from. Thank you.

Representative Summations

Dr. Smith: Thank you. Before we proceed to the panel vote, I would like to ask our non-voting members, Amy Price, our consumer representative, Stacey Bonnell, our industry representative, and Dr. Laura Porter, our patient representative, if they have any additional comments. Dr. Price.

Dr. Price: Sorry. I think I'm muted still. Oh, no, I'm not. Okay. I kind of agree with both sides. I mean, I think that it's an excellent opportunity for a select population, and it would be good to give them a chance. I think there's probably some things that could be improved, but does that need years and years more to fine tune it or, you know, I mean, that's something that you'll all vote on. So I appreciate the effort that's gone into it, the 17 years in development and what's being done so far, and the carefulness on both sides to deliberate it. Thank you.

Dr. Smith: Thank you, Dr. Price. Ms. Bonnell, do you have any comments?

Ms. Bonnell: I do, and thank you for the opportunity. I just want to highlight the collaboration between the FDA and the sponsor. A significant amount of work has gone in and it looks like in tremendous earnest to make sure that innovative products are available here to our US patients in a timely way to advance patient care. I do think that it's important to recognize that this is an additional tool within a continuum or an armament of products that are available to patients that are suffering with knee pain. We're all patients, and so no one solution will fit all patients. This is a subset.

I think I'd like to also highlight the difficulty of being able to define parameters years in advance. And so I, again, highlight both to the FDA reviewers, and I know that there's been changes along the way, but their inputs and to the sponsor for trying to accommodate those. From an industry

perspective, it also highlights the difficulty of being able to nail down the perfect patient subset and the ideal patient analysis that would then demonstrate reasonable safety and assurance. I took away from this a great amount of information in terms of benefit risk, and the reasonable benefits seem to outweigh the risks for this potential subset of patient populations; not a broad set, a subset. So to that degree, I want to highlight the difficulty of coming up with that proper defined subset through all of these years and making sure that we're making diligent decisions in the best interest of patients. So thank you for the opportunity.

Dr. Smith: Thank you, Ms. Bonnell. Dr. Porter, do you have any comments?

Dr. Porter: Just a couple. I think that for this small subset, and it seems that it is a small subset, that it may be a reasonable, may be reasonable. But my concern is also, you know, I don't know about, I know that different drugs can be used off labels. But is this something that will be protected and not be able to be used off labels, so to speak, or fudging measurements or expanding things that shouldn't be expanded and that it would get, it would be used in patients that it was definitely not intended for? So I think that that's a concern for me.

Vote

Dr. Smith: Thank you, Dr. Porter. We are now ready to vote on the panel's recommendation to the FDA for the de novo request for the intended, for the intended for use of the NUsurface meniscus implant. The panel will vote on one question relating to the benefit risk profile of the device. Dr. Akinola Awojope will now read two definitions to assist in the voting process.

Dr. Awojope: The medical device amendment to the Federal Food, Drug, and Cosmetic Act as amended by the Safety Medical Devices Act of 1990. All the Food and Drug administration to obtain a recommendation from an expat advisory panel on designated medical devices filed with the agency. The de novo classification request must stand on its own merit, and your

recommendation must be supported by safety and effectiveness data in the de novo request or by applicable public available information. To grant a de novo request, the FDA must determine whether general controls or a combination of general and special controls can provide a reasonable assurance of safety and effectiveness.

The definition of safety and effectiveness as follows: Safety as defined in 21 CFR Section 860.7(d) (1): There is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefit to health from use of the device for its intended uses and conditions of use, when accompanied by adequate direction and warnings against unsafe use, outweigh any probable risk.

Effectiveness as defined in 21 CFR Section 860.7(e) (1): There is a reasonable assurance that a device is effective when it can be determined, based upon the valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and condition of use, when accompanied by adequate direction for use and warned against unsafe use, will provide a clinical significant result.

The panel members, we will now begin the voting process. I will read the voting question. Each of the voting members have received an electronic ballot to respond to. Once I read the question, please vote, and I will tally the votes and read them into records.

The voting question: Based on consideration of the clinical information provided, do the probable benefit to health of NUsurface meniscus implant outweigh the probable risk when used in patients in accordance with the proposed indication for use? Please vote now. Yes. No. Abstain. Wait 5 to 10 seconds. Thank you very much. We may now begin the voting process.

Ms. Bonnell: Dr. Peat, I think it might be appropriate just to reiterate that the vote is taking place on the proposed indications for use and –

Capt. Peat: I'm sorry, Ms. Bonnell, we've already started the voting process, so I have to turn it over to Dr. Smith to address.

Ms. Bonnell: You're on mute.

Dr. Smith: Yes. Ms. Bonnell, what was your comment?

Ms. Bonnell: Just the procedural effect. I think it's important that we reiterate to the voting members that we're voting on the proposed on-label indications for use and that any other considerations, as recently presented, should not be considered when the vote's taking place.

Dr. Smith: And Dr. Banerjee, you have your hand up?

Capt. Peat: I want to –

Dr. Banerjee: I heard that we were getting an electronic ballot. I'm not sure where to find that.

Capt. Peat: Yes. I want to remind everyone that the DFO had an opportunity to read over the voting question. And so we really want you all to deliberate on the question at hand.

Unknown Speaker: Dr. Smith, can we go ahead and take a up to 15 minute break for the voting process?

Dr. Smith: Excuse me?

Unknown Speaker: If we can take a break now so we can go offline from the webcast, and we can go into the voting process and go into the backstage process like we talked, we discussed earlier.

Dr. Smith: Okay. So we'll take a 15-minute break and reconvene at 5:37.

Dr. Cizik: But the voting members go backstage, correct?

Dr. Awojope: The vote has been captured. I will now read the official vote into record. The panel voted 2 yes, 6 no, 1 abstain that the probable benefit to the health for the use of this NUsurface meniscal implant outweigh the probable risk of the proposed indication.

Vote Results

Dr. Smith: Thank you. I would like to note for the record, after the voting questions were read and the voting had begun, some comments were made by some members, and those comments may represent a conflict of interest. I will now ask the panel members to discuss their votes for the official record. If you answered no, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer. Please state your name, your vote, and please state the reason why you voted as you did. As we're virtual facilitates, I could call on individuals by name as we go across the screen since we're not in front of each other at a table. I'll start with Dr. Price. Actually, excuse me, Dr. Price is a non-voting member. Dr. Barber. Excuse me.

Dr. Barber: Dr. Tom Barber. I voted no because I saw the failure rate as too high in an absolutely ideal population with a select group of surgeons, and I don't feel that labeling or other minor changes would make a difference, as I just feel that the implant's not, doesn't provide the effectiveness and safety that I would like to see.

Dr. Smith: Thank you, Dr. Barber. Dr. Cizik.

Dr. Cizik: Could you state again what were the three criteria?

Dr. Smith: Yes. I'll re-read the statement. If you answered no, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer.

Dr. Cizik: This is Dr. Amy Cizik. I voted no. I do think a change in indication would, or sorry, in labeling would help. I struggled with 'to improve pain and function.' I felt that the data did not support what we were presented in the executive summary. I would like to have seen more functional data presented. And, again, the indication for use. I, again, the data that was presented and the indication currently as it's worded to me did not link well.

Dr. Smith: Thank you. Dr. Helgeson.

Col. Helgeson:I share some of the similar concerns that were already expressed. I don't think that changing the labeling or the restrictions on use would be recommended from my opinion. The data that initially was presented on the Mercury study is probably still the most relevant given that the modified Mercury data subset is difficult to interpret whether or not that truly represents a difference in the difficulty we had in defining that group of 5mm extrusion and 11mm of height, I think really is difficult to focus in on a specific subgroup analysis and then, and by default makes it more difficult to apply to the population.

Dr. Smith: Thank you. Dr. Subhawong.

Dr. Subhawong: Ty Subhawong. I voted yes. I thought that the, even though there was a narrow patient population, they did demonstrate significant benefit for patients with regard to KOOS pain scores. And taking into account the automatic study failures, I still thought that the benefits outweighed the risk in this patient population.

Dr. Smith: Thank you. Dr. Evans.

Dr. Evans: I voted no. I had concerns about the quality of the evidence that was presented. I don't think there's a foundation for inference or error control, given that the data that's served as the basis for subgroup identification is the data that was, is presented for evidence, but without the context of multiplicity of the way the subgroup was, subgroups may have been evaluated, I think that introduces considerable uncertainty regarding replicability of the evidence.

I was concerned about the different success criteria and different arms and the inconsistencies in which the way ASF was evaluated in the two groups. I think that makes comparative analysis challenging to interpret the prevalence of the missing data, but also its

differential presentation between arms concerned me that there may be an unobserved signal that could be hidden by missing data.

I was concerned about the quality and the conduct of the patient preference studies. And I thought the risks were notable. There's considerably more adverse events with some such as effusion greatly increased and concerns about function in the form of restricted mobility and so forth and long-term risks around accelerated arthritis disease progression. I just thought the quality of the evidence needs to be stronger for the benefits to outweigh the risks, and label changes would not affect my vote. Thank you.

Dr. Smith: Thank you. Dr. Banerjee.

Dr. Banerjee: Hi. I voted no. Some of the reasons have already been stated before, but I'll state them for the record. Again, the same reason as Dr. Evan said. I voted no because of the quality of the evidence, issues with the study design. The selection of the two variables that made the modified Mercury dataset were correlated with outcome making. Understanding the benefit, hard dress, hard to interpret the estimate of the benefit. There were concerns about the propensity score analysis. There were concerns about the handling of missing data. And, taken together, I don't think labeling changes would make a difference, but I should provide this as, I should say this as a context that I'm really sympathetic to both the sponsor and the FDA for this long journey. And it has been a really, really complex trial with very good intentions from both sides, but, unfortunately, we have to follow the evidence and read the evidence, and that's where my vote comes from.

Dr. Smith: Thank you. Dr. Manner.

Dr. Manner: Paul Manner. I voted no. I had concerns about the highly selective nature of the patients involved. I also had concerns about the highly selective nature of the surgeons involved.

And my concern here was that even in the best of circumstances, the efficacy demonstrated by this device was not, was not acceptable in terms of the risk that potentially would be taken. And I think it would be a virtual certainty that the effectiveness would be far lower in the real world.

Dr. Smith: Thank you. Dr. Kirkpatrick.

Dr. Kirkpatrick: I've been involved in panels for, since basically the late '90s, and this was the most difficult decision that I've faced. I voted yes. I agree with all the critiques. I do believe there's enough valid scientific evidence to tilt the balance slightly on the go side instead of the risk side. I do think that there should be a consideration of post-market studies. The easiest one that I can think of is keeping record of any implants that are replaced, because I think that's something that they should be able to be tracking. Otherwise, there might be some other tracking to make sure that they're capturing the other types of failures. But, overall, I thought it was filling a very specific niche for a problem that we don't have any other good solution for.

Dr. Smith: Thank you. Dr. Reed.

Dr. Reed: Shelby Reed. I abstained. I was torn. I was, I do believe that there is an unmet need and few options for people in this situation. I really considered voting yes because, although the benefit isn't as great as I would want it to be, and I had a lot of, you know, shared the concerns with regard to the analysis, the different definitions and things that have already been stated. But on the risk side, the risk was primarily, you know, re-operation, which people seem to tolerate, or moving on to arthroplasty, which is, you know, just a delay in the inevitable. So that risk, you know, didn't seem to loom as large for me.

So, you know, being asked to vote on the suggested label was what was difficult. I think it's too broad, including people with mild pain and with mild, you know, functional limitations.

That really gave me pause. I'm concerned about scope creep and this device being used widely among, you know, clinicians and patients who may not have engaged in shared decision making.

Closing Comments

Dr. Smith: Thank you. I would like to thank the panel, FDA, the sponsor and all of the Open Public Hearing speakers for their contributions to today's panel. Dr. Peat, do you have any final remarks?

Capt. Peat: Yes. Thank you. I know I've said it throughout the day how much we thank you for your deliberation and time, as well as your recommendation. It has been a very long journey, and this predates me as well. I really want to thank the sponsor for all of their hard work, as well as the presentation that was done by our public speakers, and then as well as FDA.

I know for behind the scenes there was quite a few fury of activities just so that we can make sure we provided the information in an unbiased manner. But as we note, we look at it from the totality of the information as provided, and at the end of the day, we still have to make sure that we make our determination of benefit and risk. So, again, I know I stand before you and exiting for the rest of the day. Thank you again.

Adjournment

Dr. Smith: Thank you. This meeting for the Orthopedics and Rehabilitation Devices Panel is now adjourned.