SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

April 20, 2023

9:00 a.m. EST

Attendees:

Chairperson

Harvey E. Smith, M.D.
Associate Professor of Orthopaedic Surgery
Hospital of the University of Pennsylvania
Veteran's Administration Medical Center
University of Pennsylvania School of Medicine — Philadelphia, PA

Industry Representative

Stacey E. Bonnell, M.B.A., RAC
Global Leader of Regulatory Affairs
Nuvasive, Inc. — San Diego, CA

Consumer Representative

Amy I. Price, Ph.D.
Senior Research Scientist
Stanford School of Medicine
Stanford University — Stanford, CA

Patient Representative

Laura D. Porter, M.D.
Medical Affairs Consultant & Patient Advocate — Cheverly, MD

Voting Member

CAPT Raquel Peat, PhD, MPH, USPHS
Director, OHT 6: Office of Orthopedic Devices
Office of Product Evaluation and Quality, CDRH, FDA — Silver Spring, MD

Temporary Voting Members

Shelby D. Reed, Ph.D., RPh
Director and Co-Founder, Preference Evaluation Research Group
Duke Clinical Research Institute
Duke University Medical Center — Durham, NC

Amy M. Cizik, Ph.D., M.P.H.
Affiliate Faculty, Surgical Population Analysis Research Core
Department of Surgery, University of Utah School of Medicine — Salt Lake City, UT

Samprit Banerjee, Ph.D.
Associate Professor, Division of Biostatistics, Department of Population Health Sciences

Weill Medical College, Cornell University — New York, NY

Scott R. Evans, Ph.D.
Professor & Founding Chair
Department of Biostatistics and Bioinformatics
George Washington University — Washington, DC

Ty K. Subhawong, M.D.
Associate Professor of Clinical Radiology
Director, Division of Musculoskeletal, Department of Radiology
University of Miami Miller School of Medicine — Miami, FL

COL. Melvin D. Helgeson, M.D, FAOA, FAAO
Director for Surgery
Walter Reed National Military Medical Center — Bethesda, MD

Thomas C. Barber, M.D.
Former Associate Deputy Physician in Chief, Perioperative Services
Memorial Sloan Kettering Cancer Center — New York, NY

John S. Kirkpatrick M.D.
Chief, Section on Orthopaedic Surgery
Orlando Veterans Administration Medical Center — Orlando, FL

Paul A. Manner, M.D.
Professor, Department of Orthopaedics and Sports Medicine
University of Washington School of Medicine — Seattle, WA

Designated Federal Officer

Akinola A. Awojope, DrPH, M.P.H.
CDRH, FDA — Silver Spring, MD

FDA Presenters

Peter Yang, Ph.D.
Lead, De Novo Program
Division of Submission Support, Office of Regulatory Programs, OPEQ, CDRH, FDA — Silver Spring, MD

Ouidad Rouabhi, M.S.
Assistant Director for Policy and Operations Team One
Office of Clinical Evidence and Analysis, OPEQ, CDRH, FDA — Silver Spring, MD

Travis Prest, Ph.D.
Lead Reviewer, Restorative, Repair, and Fracture Fixation Devices Team

DHT6C, OHT6, OPEQ, CDRH, FDA — Silver Spring, MD

Marc DeHart, M.D.
Orthopedic Surgeon
Medical Officer, Hip Arthroplasty Devices Team
DHT6A, OHT6, OPEQ, CDRH, FDA — Silver Spring, MD

Cynthia Liu, M.S.
Mathematical Statistician
Biostatistics Team 1, DCEA2, OCEA, OPEQ, CDRH, FDA — Silver Spring, MD

David Gebben, Ph.D.
Health Economist, Patient Science & Engagement Team
DARSS, OST, CDRH, FDA — Silver Spring, MD

Sponsor Presenters

Ryan Belaney, MSMBE
Vice President, Clinical and Regulatory Affairs
Active Implants — Memphis, TN

Elliott Hershman, M.D.
Orthopedic Surgeon, NUsurface Clinical Trial Investigator — New York, NY

Nogah Shabshin, M.D.
MSK Radiologist, University of Pennsylvania — Philadelphia, PA

Deryk Jones, M.D.
Orthopedic Surgeon, NUsurface Clinical Trial Investigator — New Orleans, LA

Open Public Hearing Speakers

Rene Verdonk, M.D., Ph.D.
Professor, Orthopedics and Trauma, Gent State University — Brussels, Belgium

Elizaveta Kon
Professor, Orthopedic Surgery
President, International Cartilage Regeneration and Joint Preservation Society — Milan, Italy

Christian Lattermann, M.D.
Chief, Sports Medicine
Brigham and Women's Hospital — Boston, MA

Kenneth Zaslav, M.D.
Professor, Orthopedic Surgery
Zucker School of Medicine, Hofstra University — Long Island, NY

Christopher Kaeding, M.D.
Executive Director of Sports Medicine
Ohio State University School of Medicine — Columbus, OH

Seth Sherman, M.D.
Orthopedic Surgeon
Stanford University — Stanford, CA

Lori Stogner Anderson
NUsurface Implant Recipient — Baton Rouge, LA

John Foerster
NUsurface Implant Recipient — Denton, TX

Debra Tongue
NUsurface Implant Recipient — Baton Rouge, LA

Tessa Lilley
NUsurface Implant Recipient Family Member — Smyrna Mills, ME

Carman Lilley
NUsurface Implant Recipient — Smyrna Mills, ME

Thomas Fazekas
NUsurface Implant Recipient — Dallas, TX

Laura Wood
NUsurface Implant Recipient — Colorado, USA

Steve Kistler
NUsurface Implant Recipient — Parker, CO

Don Bennett
NUsurface Implant Recipient — Philomath, OR

Rebecca Robinson
NUsurface Implant Recipient — Tombstone, AZ

Mike Smith
NUsurface Implant Recipient — Birmingham, AL

Press Contact
Audra Harrison
Press Officer, Office of Media Affairs, FDA — Silver Spring, Maryland

CALL TO ORDER
INTRODUCTIONS

Dr. Harvey Smith, the Panel's chairperson, introduced himself and announced the agenda for the meeting: to discuss, make recommendations, and vote on clinical information related to the De Novo request for the NUsurface meniscus implant sponsored by Active Implants, Inc. This 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. **Dr. Smith** prompted the Committee members to introduce themselves.

CONFLICT OF INTEREST STATEMENT

After introductions, **Dr. Akinola Awojope**, the Designated Federal Officer, read the conflict of interest statement and made general announcements, noting that Ms. Stacey Bonnell of Nuvasive serves as the industry representative. Dr. Laurel Porter, M.D., a consultant to CDER, serves as temporary non-voting member in this meeting. The following individuals were also appointed to serve as voting members, as authorized by Jeffrey Shuren on March 27, 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.; and Paul A. Manner, M.D. **Dr. Awojope** further announced Audra Harrison as the press contact for the meeting.

FDA PRESENTATIONS

Overview of De Novo Program — Dr. Peter Yang

Dr. Peter Yang of FDA initiated presentations with an overview of the De Novo Program. He summarized the classification system for medical devices and shared that devices can be Class I, subject to general controls and exempt from pre-market review, Class II, subject to general and special controls and cleared through the 510K process, or Class III, subject to general and special controls and approved through the pre-market approval (PMA) process. Devices that are novel and unclassified go through the De Novo process, as there are no predicate devices for which to claim substantial equivalence. Manufacturers seek to prove reasonable assurance of safety and effectiveness in order to gain classification as Class II or Class I devices for market clearance. When a De Novo request is granted, the device becomes a predicate device for future 510K clearance of similar devices.

After establishing that the device is novel and does not qualify existing regulatory standards, three goals must be met to grant a De Novo request: first, to determine whether the probable benefits of the device outweigh the probable risks to health; second, to identify what the probable risk to health are for the device or product when used as intended; and third, to determine the level of regulatory control that's needed to mitigate the risks that we identify.

Dr. Yang informed the Panel that the purpose of today's meeting is to consider benefits and risks of the device and additional factors such as real-world use, statistical considerations,

study design considerations, patient perspectives, and unmet medical needs. Panel input will provide important expertise to guide FDA's decision on whether to grant the De Novo request.

If the De Novo request is granted, a new classification regulation is established under 21 CFR that defines the new device type with its shared intended use and technology. A specific risk-mitigation table, which outlines risks to patient health and regulatory mitigation measures, is produced for the device type. Special controls are also established for the device type, such as nonclinical testing requirements, bench testing, clinical validation requirements, labeling requirements, and some post-market requirements.

Breakthrough Device Designation — Dr. Ouidad Rouabhi

Dr. Ouidad Rouabhi, Assistant Director for Policy and Operations Team One in CDRH's Office of Product Evaluation and Quality, provided an overview of the Breakthrough Device Program, a program intended 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 while preserving existent statutory standards for marketing authorization. In order to be designated a breakthrough device, the device in its proposed indication must provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions. FDA requires the sponsor to show a reasonable expectation that the device could provide for more effective treatment or diagnosis of the disease/condition. Additionally, the device must either represent a novel technology or novel application of technology, or it must offer significant advantages over existing alternatives, or the availability of the device must be in the best interest of patients.

As part of the Breakthrough Device Program, sponsors are given additional mechanisms to work with FDA for the approval of the device, such as a Data Development Plan (DDP), sprint discussions, and regular status updates between submissions.

Q & A

Dr. Thomas Barber asked whether, when assessing De Novo devices, the Panel is to draw comparisons to different device types that may have similar applications. **Dr. Yang** responded that it can be useful to draw comparisons for contextual considerations in benefit risk analysis, but that ultimately, the device's safety and efficacy is being considered on a standalone basis.

SPONSOR PRESENTATION — ACTIVE IMPLANTS, LLC

Next, **Ryan Belaney**, Vice President of Clinical and Regulatory Affairs at Active Implants, introduced the NUsurface device and its indication, design overview, and regulation history. He stated the indication: to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected in patients with mild to moderate osteoarthritis, mild or greater knee pain, and cartilage present on the load-bearing articular surface. It is contraindicated in patients with extrusion of the medial meniscus five millimeters or greater, and patients with a tibial spine height below 11 millimeters have greater risk of device-associated adverse events.

The device is made from a hydrophilic polycarbonate urethane and reinforced with ultra-high molecular weight polyethylene fibers to replicate a natural meniscus. The NUsurface eliminates the concentration of forces in the medial compartment by distributing mechanical loads. Thus relieving pain, improving function, and helping to prevent cartilage degeneration. The implantation procedure is straightforward and does not damage bone, cartilage, or ligaments. Pre-clinical cadaver testing confirmed the load distribution capability of the implant and its overall stability. A sheep study demonstrated its ability to protect cartilage.

NUsurface obtained market authorization in the European Union in 2008 and has been the subject of human clinical use trials in the EU. US FDA granted NUsurface breakthrough device status in 2019. Its De Novo request was denied in June 2021, and study designs were altered to include patient subpopulations more representative of high patient benefit and low risk as a result of the initial denial.

Dr. Elliott Hershman, an orthopedic surgeon and clinical trial investigator for NUsurface, described hierarchical treatment approaches for the prevalent condition of knee dysfunction. He pointed out that NUsurface is intended for patients who are still symptomatic and in pain after a medial mastectomy procedure. He provided data on the prevalence of meniscus dysfunction in younger and older adults and emphasized the drawbacks of metal meniscus replacements, which cause cartilage damage, a problem not observed with NUsurface's polycarbonate urethane. Overall, he positioned NUsurface as: able to mimic the physical and mechanical properties of a normal meniscus, able to more evenly distribute stress, and able to absorb strain that would otherwise be transferred to the cartilage in the absence of a normally functioning meniscus. The device is appropriate for older patients with mild to moderate cartilage degeneration who have viable cartilage remaining after a previous arthroscopic meniscectomy and who experience continued pain and disability post-meniscectomy.

The replacement procedure for NUsurface takes about 90 minutes and begins with a sizing trial implant to correctly fit the NUsurface device, implanted between the medial femur and tibia and confirmed with fluoroscopy. Once the trial is removed, the implant is inserted, and its location should be confirmed with MRI.

Dr. Hershman presented results from the Venus clinical study, which 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 Sun study, focused on safety and effectiveness data to support the De Novo request, was merged with the Venus study to form the Mercury study, which included 242 subjects, 176 NUsurface and 66 controls. This study met the primary endpoint of superiority over control subjects with a P value of 0.013. All secondary endpoints were similarly superior to the controls. Adverse events included four device-specific adverse events and one related to surgical procedure effusion. Adverse events resulted in three types of secondary surgeries: repositioning of the original device back into the joint after an implant dislocation or rotation in 2% of

NUsurface subjects permanent removal of NUsurface in 10% of subjects, and device exchange in 20% of subjects. Uniquely, the recovery for the replacement surgeries were faster than for the primary procedure.

The Mercury study was rejected for the De Novo application in 2021, causing reselection of a more suitable subpopulation by disqualifying those with more than one previous meniscectomy. 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. Thus, exclusion of 28 subjects with meniscus extrusion greater than 5 millimeters significantly reduced the rate of permanent removals and exchanges. Exclusion of those with lower-than-average tibial spine height similarly reduced the rate of removals and exchanges. With both of these exclusion parameters applied, total surgical failures reduced from 33% to 16% in the subpopulation.

These exclusion principles were applied to data from the European multi-center trial data, and found that failures were also significantly reduced in that population, and all analyses had similar results with primary and secondary endpoints met by improved KOOS outcomes. **Dr. Hershman** stressed that for those with milder arthritic changes in the knee, arthroplasty can be avoided with use of NUsurface. He urged the Panel to understand the unique patient population that does not have other treatment options, for whom NUsurface is appropriate. He concluded by emphasizing that he has seen success with this device in his clinical practice.

Dr. Nogah Shabshin discussed the MRI findings of the Mercury study. Images of NUsurface are well-delineated with sharp margins surrounding the dark signal. The device does not create any artifacts and therefore does not interfere with the evaluation of the joint structures. Studies were consistent in technology and machines used at all time points, and the protocol was consistent with ICRS recommendations. 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.

She described images of MRIs from the study. Ultimately, in terms of full thickness cartilage defects in the medial compartment, the implanted patients dominated the positive outcomes, and 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. Although at baseline both groups were similar, at the finish line, the NUsurface was superior. Thus, the NUsurface implant may delay the need for arthroplasty. Additionally, 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.

Dr. Shabshin concluded by stating that her experience as a radiologist supports a hope that NUsurface will improve quality of life for eligible patients by providing an alternative to arthroplasty.

Dr. Deryk Jones presented on the benefits and risks of the device. In NUsurface patients, improvement occurs by six months, and the results last. Three-quarters of the patients improved

by at least the MCID and KOOS overall score. Additionally, NUsurface acts to preserve the cartilage. A vast majority of patients in a simulation study preferred NUsurface to other treatments, and real-world patients who required re-implantation elected to undergo the surgery again because of the favorable results. Re-implantation conferred similar benefits to the initial implant. Surgeon training is essential to mitigate the risk of re-operation. Heavy wear and tear on the implant is the other high risk factor leading to re-operation. Replacement procedures have a lower risk of adverse events. Preoperative risk of NUsurface were comparable to risk reported from meniscectomies, and the rate of second surgeries is comparable to or lower than the rate of commonly performed joint preservation procedures.

Q & A

In question and answer, **Dr. Kirkpatrick** requested clarification on the sponsor's definition and determination of "full thickness." **Mr. Belaney** and **Dr. Shabshin** clarified that the parameter was set during early clinical arthroscopies, it was determined that a threshold of 8 millimeters was acceptable to prevent implant-bone contact. This parameter was set to avoid tearing.

Dr. Manner inquired how many patients were approached for participation versus how many enrolled in the Venus study. **Mr. Belaney** answered that the study was advertised, and an initial 12,000 subjects came to Active Implants seeking enrollment. Bone on bone contact and eligibility criteria were evaluated, narrowing the pool to over 200 patients. Then, radiographic and physical clinical assessments were performed, ultimately reducing the eligible study participants to 66 and 61 participants in the two arms of the Venus trial.

Dr. Cizik asked for more information on the age range in the study and whether indications for use have an age range. **Dr. Hershman** responded that patients' ages ranged from 30s to 70s and that participants were selected based on challenges in their clinical situation.

Dr. Banerjee wondered if his observation that propensity score adjustments were performed for the Mercury dataset; **Mr. Belaney** responded affirmatively. **Dr. Banerjee** asked what constitutes 'low propensity' versus 'high propensity' in the categorizations. **Dr. Fred Haler,** a biostatistician consultant to Active Implants, responded that the propensity score was divided based on the median, creating the high and low categories used for adjustment.

Dr. Barber scrutinized the BMI criteria, stating that he found the average BMI to be very low compared to his population of patients, and probed whether the sponsor agreed that the BMI is low. He also wondered whether there is a contraindication towards higher BMI patients or if that was just a study choice. **Mr. Belaney** answered that a BMI over 32.5 is indeed contraindicated.

Dr. Reed asked: how were patients identified and selected for the patient preference study? Additionally, when were the subgroup eligibility criteria determined, and were sensitivity analyses conducted to vary the criteria that defined that subgroup? **Mr. Belaney** answered the subgroup questions: the Mercury study subpopulation selection occurred after the total population analyses as a response to Agency feedback. He reminded that the Venus study alone

(total population) did meet the threshold of superiority. He further clarified that the measurements for tibial spine height, for example, were taken even during the initial De Novo submission, so the creation of the subgroup did not require any additional data collection.

Mr. Belaney introduced **Dr. Treharne** to answer Dr. Reed's patient preference question: individuals in the general population who experience knee pain were selected by an outside agency to respond to preference questions. **Dr. Reed** clarified that these were not people who had previous meniscal surgery, and this was confirmed by **Dr. Treharne**.

Dr. Subhawong asked if there was data on analgesic use between the two arms and viscosupplementation and steroid use in the control arm. **Mr. Belaney** answered that corticosteroid and hyaluronic acid injections were used in the control arm, and he requested time to prepare a more complete answer on analgesic use between the two arms.

Colonel Helgeson wrapped up question and answer, wondering whether effusion data was based on clinical exam or MRI, and how quantitative the data on effusion was. **Mr. Belaney** answered that it was measured radiographically, and **Dr. Shabshin** clarified that at six months, an increased number of implanted patients experienced effusion, but by 24 months, there was no difference between the control and implant groups. **Mr. Belaney** added that there was not an increase in one-year and two-year pain rates in subjects that experienced effusion.

FDA PRESENTATION: OVERVIEW OF NUSURFACE DE NOVO REQUEST

Next, FDA presented their perspective on the NUsurface request. **Dr. Travis Prest**, lead reviewer for the Restorative, Repair, and Fracture Fixation Devices Team, introduced some of his team members and provided an introduction and regulatory background. He reiterated that the NUsurface meniscus implant was deemed eligible for the De Novo classification, does not fit into any existing regulations, does not have a previously approved pre-market approval, and that it presents a low to moderate risk profile. He also summarized FDA's requests for Panel contributions on clinical data.

Dr. Marc DeHart provided an overview of the meniscus in knee pain and stated that 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 basis for the inclusion of a non-surgical control group. Surgical options for meniscus-related symptoms include meniscus repair, meniscectomy, meniscus augmentation, and meniscus allograft.

Dr. DeHart introduced the device design: 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 is made of polycarbonate urethane called Bionate and requires a near total meniscectomy as part of implantation. He recapped the intended use: to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected. He restated the indication for use in patients with mild to moderate arthritis, mild or greater knee pain, and cartilage present on the load-bearing articular surfaces.

Dr. DeHart continued with a walkthrough of the clinical background studies and data sets. In 2011, the device underwent a feasibility study outside the US, coined the Multi-Center Trial (MCT) at seven sites in Europe and Israel. This was a single arm trial using a prior version of the implant, but the sponsor uses this data to validate current anatomic selection criteria. Then, the Venus trial, dated 2012, was a prospective, randomized, one-to-one, parallel arm, multi-centered interventional superiority trial. The Sun trial was a prospective, single arm, non-randomized trial to evaluate safety over 24 months. The Mercury dataset is the data pooled from both the Venus and Sun trials. The modified Mercury dataset excluded subjects with meniscus extrusions of five millimeters or more and those who had tibial spines that were shorter than 11 millimeters. This modified group is the basis for the current De Novo request, and it had 74 subjects who received the device and 35 non-surgical control subject.

Dr. DeHart recapped the surgical procedure and provided further information on the non-operative control group, noting especially the lack of official treatment protocol in the control group that may have created outcome differences between the experimental and control groups. He summarized the three study endpoints, which were subjective panel reported outcomes using KOOS survey instruments, where higher-than-average acceptable patient scores were deemed appropriate as endpoints, MRIs that look for structural failure of the device, and the absence of secondary surgical interventions. Automatic study failure was classified as a device-related surgical event, and this rate hit 34% as compared to the projected 10%. In the control group, any surgical intervention was counted as a failure. Together with inconsistent exclusion criteria, this forced problematic comparisons.

In addition, semi-quantitative approaches to whole knee arthritis assessments were neglected, preventing claims for joint preservation. Further, the assessment of being device-related was not made on an individual basis, but instead employed categorization techniques, creating considerable uncertainty. The sponsor suggested a set of extensive mitigation strategies to address the 34% failure rate, including the two selected for the subpopulation: meniscus extrusion and tibial spine height. Selecting by meniscus extrusion excludes patients with more extensive arthritis that demonstrated less favorable study results. Notably, the sponsor selects for a spine height greater than the average population's. **Dr. DeHart** outlined more issues with data selection, including rater uncertainty.

Dr. DeHart continued to detail issues with the safety data in Mercury datasets. Adverse events classification was questionable and created data uncertainty. Few adverse events were found in the control groups. The modified dataset lowered automatic surgical failure rates from 34% to 17%. Retrieval analyses showed a consistent pattern of device abrasion and fracture/tearing in the lateral section of the device which is required for fixation. Also, device implantation requires near complete meniscectomy in each subject which creates uncertainty for knee joint health in all patients, with special concern for those who need device removal.

For the surgical success data, **Dr. DeHart** noted that neither control nor experimental groups could be blinded, resulting in a biased assessment of the outcomes. Also problematic is that only full thickness cartilage lesions were evaluated for cartilage preservation, some MRI

data was missing, and last evaluation carried forward data is inappropriate for arthritis evaluations over time.

Statistical reviewer **Ms. Cynthia Liu** presented on statistical considerations. She expressed concerns regarding bias, missing data, and nominal P values. It is unclear whether last observation carried forward and imputation techniques were suitable for the data. She reiterated concerns about patient exclusion due to reader uncertainty, as readers disagreed nearly 20% of the time in both groups, and the inclusion of the uncertain results could sway the data in either direction.

She noted that the Mercury subpopulation included only 45% of the total Mercury subjects and was concerningly small. Further, 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. 122 baseline variables reported for the Mercury dataset, while only 55 baseline variables were reported for the modified Mercury dataset. Implementation of the propensity score analysis is unclear. Ms. Liu wondered whether the selection of baselines may have been influenced by a knowledge of the observed outcome.

The propensity score model for the modified Mercury dataset is questionable. 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. In conclusion, she stated that it is challenging to draw a sound conclusion based on any statistical inference.

Dr. David Gebben presented on the patient preference information. He first provided background on what makes a patient preference study interpretable and well-conducted. He noted the sponsor's continual inability to address FDA concerns by implementing a more thorough study design for patient preference, falling short in areas such as inadequate presentation of the risks, biased presentation of benefits and risks, and unclear educational materials. 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, which likely biased the responses.

Data analysis was not performed through interval regression as per published literature on acceptable approaches. Informed consent was not obtained, nor was IRB approval. PPI guidance was not followed, and **Dr. Gebben** found it challenging to interpret these patient preference results as valid.

Finally, **Dr. Marc DeHart** summarized the benefits and risks of the NUsurface implant. For benefits: 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. 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.

For 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.

Further, the NUsurface implant and the near-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 by 24 months due to disease progression versus 1 out of the 31 nonsurgical control group who received no arthroscopic screening prior to inclusion in the study. 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.

Dr. DeHart finished with additional considerations regarding uncertainty. There's 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. 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 lesions and other excluding pathology led to “bailouts” from the study in the NUsurface group, but the control group was not arthroscopically screened. This study was not designed to evaluate cartilage preservation, regrowth or whole knee arthritic changes. 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.

Q & A

In question and answer, **Dr. Cizik** began by requesting clarification on why the KOOS overall score was calculated and whether or not the preference study was population-based and

did not need informed consent as a result. **Dr. DeHart** responded that the KOOS overall score is accepted in sports medicine. **Dr. Price** recommended making the sub-scores available. **Dr. Fraser Bocell** confirmed that a KOOS overall score is not typically calculated from sub-scores as the manufacturer did, and that the sub-scores should be relied upon more heavily than the calculated overall. **Dr. Gebben** responded to the patient preference part of the question, stating that informed consent is a standard part of the process even in population-based social science studies.

Dr. Price expressed concerns regarding the joining of data between a non-randomized and a randomized trial and asked how that came to pass. **Dr. DeHart** responded that prior reviewers might have suggested the combination as a way to obtain more safety data in a larger population, and **Ms. Liu** confirmed that the merged data seems questionable to FDA, as well.

Dr. Smith wondered about lack of clarity in radiographic parameters, such as varied field strengths, angles, and other technical details, and he requested comment towards this. **Dr. DeHart** responded that this point is well taken, and there are concerns about the ability to look at cartilage and MRI data in a meaningful way. **Dr. Coyne** prompted the Panel to consider this as a degree of uncertainty and comment on how it altered the benefit risk profile.

Dr. Banerjee requested more details on the procedure for the multiple imputation analyses. He also questioned the inter-rater disagreement and the statistical significance of those failure rates. **Ms. Liu** responded that perhaps the sponsor can provide more information on the multiple imputation procedures. She quoted some statistical measures regarding tibial spine height as it related to study failures from uncertainty, noting that the failure rate dropped to 23% if the disagreements re-entered the dataset. **Dr. DeHart** added that it was unclear to FDA how the parameters for tibial spine height was chosen from the data provided.

Concluding the question and answer session, **Dr. Barber** asked if bone lysis was analyzed from the MRI data. **Dr. DeHart** responded that some histopathology evaluations were performed, but not across the entire population. Bone spurs and increased size of arthritis lesions were found, along with some evidence of residual Bionate particles. He reiterated that the most serious adverse events were dislocation or fracture of the device itself, which makes it a risky call when every recipient needs removing the meniscus for implantation.

OPEN PUBLIC HEARING

Dr. Smith broke for lunch and reconvened the Panel at 2:00 p.m. **Dr. Awojope** read the Open Public Hearing (OPH) disclosure process statement. 18 speakers registered for the OPH, and 17 spoke.

Rene Verdonk, M.D. spoke on how NUsurface is safe and easy to revise.
Elizaveta Kon, M.D. stated it provides patients with a reasonable alternative and helps to address the significant unmet clinical need.
Christian Lattermann, M.D. compared NUsurface to the allograft meniscus transplants, stating it compares favorably, that none of his patients were worse off as a result of the NUsurface implant, and all significantly improved.

Kenneth Zaslav, M.D. asserted that this treatment fills a void in the options currently available to treat middle-aged patients who are, at the moment, stuck to just having NSAIDs.
Christopher Kaeding, M.D. stated that NUsurface fills a void in our knee care, and without it, a large segment of patients with knee pain have few treatment options and no other good alternative.
Seth Sherman, M.D. positioned NUsurface as a bridging procedure for a challenging and growing population and described the procedure as technically straightforward for surgeons of differing skill levels with relatively easy rehabilitation and recovery timeline. He supported NUsurface approval.
Lori Stogner Anderson, John Foerster, Debra Tongue, Caman Lilley, Laura Wood, Steve Kistler, Don Bennett, Rebecca Robinson, and **Mike Smith** are all NUsurface implant recipients and spoke favorably on their experience with the implant, citing improved knee function, mood, lifestyle, pain levels, and overall quality of life. This concluded the OPH session.

PANEL DELIBERATIONS

In Panel deliberations, the Panel asked questions to the sponsor and FDA. **Dr. Kirkpatrick** began by asking whether the implant is appropriate for injured patients with a partial meniscus tear that is resected, or if that patient must wait until they begin to develop arthritis to be a candidate for implant. **Dr. Jones** answered on behalf of Active Implants that ideal use is 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, ligamental structures, and patella frontal compartment, and that it is not appropriate to wait for further arthritis to develop.

Dr. Cizik requested transparency of the KOOS subscale scores for her interpretation of the data. **Mr. Belaney** provided previously requested information on how the KOOS overall scores were calculated as an average of the five KOOS subcategories.

Col. Helgeson asked if informed consent concerns were conveyed to the sponsor back in the 2012-2014 timeframe, and if the sponsor changed their approach as a result of expressed concerns. In response, **Mr. Belaney** answered a prior question and mentioned that previous FDA reviewers condoned the initiation of Venus and Sun data merging in 2017 on the basis of shared inclusion/exclusion criteria, and he also mentioned that the IDEs for Venus and Sun were previously discussed with and approved by FDA. **Rick Trejan** of NUsurface answered that according to 45 CFR 46.104, informed consent and IRB approval are not required for surveys of the general public when they are not identified, are not young, and are not put at liability. **Dr. Gebben** refuted, stating that IRB approval is needed to determine exempt status from informed consent. **Captain Peat** reminded that guidance documents are available for patient preference matters.

Dr. Prest further commented that there have been difficulties as a result of reviewer alterations.

Mr. Belaney took the opportunity to clarify a few points on statistical uncertainty, correlative values, and the missing data points in the implant group.

Dr. Coyne stated that when the sponsor received IDE supplementation, feedback was provided to them about insufficiencies in their study designs through that process, and **Dr. Gebben** clarified that an IRB board must designate an exception for patient preference surveys and the investigator cannot declare the study exempt from informed consent matters.

Dr. Barber asked if there are functional differences in impact tolerance between patients with NUsurface implant and those with a total knee replacement; **Dr. Hershman** responded that high impact activity is not recommended for implant recipients, either. **Dr. Jones** amended that total knee replacements are much more difficult and involved procedures with higher risks if the device fails in a high impact activity. **Dr. Barber** continued: how can it be ensured that surgeons in the future are going to follow the recommendations for the very specific intended population? He identified concerns with patients over the age of 55 possibly not being able to receive insurance-covered MRIs. **Mr. Belaney** asserted that this is part of the training process, and **Dr. Shabshin** provided details on tibial spine height measurement. **Dr. Hershman** added that patients with severe osteoarthritis may not be indicated for MRI, but many patients are, and MR is obtainable for surgical planning in those cases.

Dr. Porter shared her perspective as the patient representative, noting that patient preference data from individuals with knee pain who have never undergone surgery is highly limiting, as those patients do not know what they are willing to tolerate. She also asked for specific data on how long the device lasts before it fails. In response to the data request, **Mr. Belaney** shared 60-month data from the Sun study and extrapolated removal data to the 60-month time point, as well.

Dr. Subhawong restated a need for information regarding analgesic use in the control arm. He asked if FDA had experts evaluate the sponsor's MRI findings and if the position of the implant is detectable on plain films. **Mr. Belaney** addressed analgesics by sharing a graph on pain control measures. **Dr. Shabshin** confirmed that the NUsurface implant is radio-opaque and its position is confirmed during surgery, with MRI necessary for complications post-surgery. **Dr. Shabshin** answered that no FDA staff reviewed the MRI data, which **Dr. Prest** confirmed. **Capt. Peat** noted that the key point is that even the sponsor's readers disagreed whether certain cases should be success or failure.

Dr. Bocell clarified for the Panel that the KOOS sub-scores were broken up into daily life activities and sport/recreation functions but provided no further data. He pointed out that the 60-month sample size was only 28, which is concerningly low to allow for data extrapolation. **Mr. Belaney** clarified that other secondary endpoints were met to show improved quality of life other than KOOS scores, such as VAS, IKDCSKEF, and EQ-5D.

Dr. Smith questioned whether if excluding data about failures prevented a complete picture of how the device compares to non-operative management and requested comment on patients who experienced a total failure and are now living without the device and without a meniscus as a result of the surgery. **Dr. Jones** provided his opinion that those who experienced

total failures often already had one or two meniscectomies with retained symptoms, and do not experience removal of a functioning meniscus. Their cartilage was preserved in the NUsurface procedure, so normal treatment options can continue if the implant fails. He stated that this option does not burn bridges like osteotomies or replacements. **Dr. Hershman** shared data from three patients who advanced to further surgery after NUsurface removal, one of whom elected against re-implantation as personal preference and two who no longer met eligibility criteria for implantation at the time of device failure.

Dr. DeHart weighed in, stating that it is problematic that the study excluded outcomes of failed devices and control group patients who elected for alternative surgery down the line. In the end, 50% of NUsurface study subjects failed as a result of this design. 25% of patients with the device failure and removal went on to receive arthroplasty despite the stringent eligibility criteria: arthroscopic prescreening for arthritis severity and selection of less meniscus extrusion which is a surrogate for higher levels of knee degeneration. He acknowledged the study is not powered to extrapolate that failure rate to the total eligible population.

Mr. Belaney refuted that the study does factor in failure of the surgical treatment. He argued that the data obtained on subjects who withdrew from the study reported low quality of life at the time of removal. He presented data on those who obtained additional surgery after device failure. He stressed that the NUsurface population is unique and not necessarily comparable to previous literature. **Dr. Hershman** added that sham studies and non-operative controls were discussed with FDA and decided against at the time of study design.

FDA QUESTIONS

After a short break, the Panel resumed with discussion of FDA questions.

QUESTION ONE

Dr. Smith read voting question one on 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.

In **Dr. Barber**'s opinion, it is difficult to apply these criteria to actual practice and surgeons will expand use beyond what is represented in the study.

Dr. Price was concerned with patient's weight increasing as they age and the resultant increased pressure and likelihood of slippage.

Ms. Bonnell suggested that the representative study population should drive the labeling and restrictions for use, as this is within FDA's control.

Dr. Smith asked **Dr. Subhawong** if he thinks the radiological findings are clinically significant. **Dr. Subhawong** affirmed; he found the suggested measurements reasonable.

Col. Helgeson agreed with previous concerns and expressed that tibial spine height seemed to be chosen arbitrarily and highlighted that patients with more than one prior meniscectomy experienced better results than those with multiple, and this should be considered.

Dr. Kirkpatrick noted that the indications will need to be tight in order to fit the study.

Dr. Smith asked **Dr. Banerjee** and **Dr. Evans** if they felt there is a good handle on the target population and the statistics presented. **Dr. Banerjee** expressed doubts, especially regarding the low BMI threshold. **Dr. Evans** noted a failure to identify hypotheses without confirmation bias.

Dr. Manner added that the number of patients that qualify for the device with all these specifications is alarmingly small, especially excluding women, whose average tibial spine height is only 2 mm less than the indicated use. **Dr. Manner** also expressed concerns regarding the yield strength of the polycarbonate urethane and lack of data regarding that.

Dr. Cizik echoed previous sentiments on population specificity and practical use.

Dr. Subhawong noted, in the sponsor's defense, that patients do not have many options in this realm and that some weakness in the data must be tolerated. He finds the KOOS pain scores promising.

Dr. Smith summarized the contributions: 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. The panel voiced some concerns regarding the ultimate biomechanical strength and risk of deterioration of the device that perhaps has not been fully elucidated in the discussions.

Question Two

Dr. Smith read question two: 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.

Col. Helgeson critiqued that he finds it problematic that the long-term outcomes are not sufficiently tracked beyond 24 months, as the long-term outcome should be the ability to avoid a knee replacement at a specific age.

Dr. Barber commented that device-related complications like adhesions/infection create difficulty for future possible total knee replacements. He also expressed concern that patients are not saying they have greater function than with a total knee replacement.

Dr. Kirkpatrick thought the success criteria were well-defined but inadequate and worried about the high rate of future revisions.

Dr. Subhawong noted that the cartilage data is limited but can give an idea of chondroprotective outcomes of the device. He questioned FDA whether they would exclude those effects due to limited data, which **Capt. Peat** said will be answered later.

Dr. Cizik said she would have liked to see more sports criteria and functionality criteria specifically incorporated into outcomes rather than just overall KOOS and KOOS pain scores.

Dr. Manner put forth that any reoperation for an investigational device should be considered a failure. He stated concerns about the cherry-picked patient and surgeon base. If these groups have every possible advantage, the real-world population will see worse outcomes.

Dr. Barber agreed about automatic study failure of reoperations, and **Dr. Banerjee** agreed that this endpoint cannot be changed post hoc. **Dr. Barber** also asked why uni-compartmental knees are not being considered in the indicated population with mild to moderate osteoarthritis.

Dr. Smith summarized the Panel's contributions to question two: 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 are appropriately classified as automatic study failures.

Question Three

Dr. Smith read question three: please comment on the overall success rate of the modified Mercury dataset, including whether this 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?

Dr. Kirkpatrick found the improvements in pain to be promising but it is questionable whether it was enough of an improvement. He asserted it is tricky to pin down the appropriate population with an acceptable benefit risk profile and did not find it appropriate to speak on whether other groups might find benefit.

Dr. Reed questioned whether there was a differential treatment effect among people with higher or lower baseline levels of pain, as the testimonials given were all from people whose lives were significantly impaired at baseline. **Dr. Cizik** did not see that information. **Dr. Cizik** commented that the 20 point KOOS improvement is above MCID and detectable.

Col. Helgeson wished for more information on how the tibial spine height was determined and expressed concern that the parameter was chosen to produce favorable results, which creates clinical uncertainties. He did not find data to be sufficient to determine favorable profiles for other populations. **Dr. Barber** seconded this and restated doubts about the practicality of stringent parameters.

Dr. Price voiced that caution is necessary because this device, if approved, would pave the way for future devices with similar uncertainties. **Dr. Price** also observed problems with the control group receiving no specialized treatment and perhaps experiencing a placebo effect.

Dr. Porter agreed with the comments thus far and emphasized that the study should not have been ended at two years. As a replacement patient who experienced benefits, she found it inappropriate that total knee replacement is thought of as singularly something to avoid.

Dr. Subhawong asserted that the modified dataset provides good data about pain relief but is worried about flawed comparator groups. He further noted that it may be acceptable to tolerate higher risk levels of reoperation for a procedure where nothing is anchored into the bone.

Ms. Bonnell reoriented the Panel to remember this is a Class II moderate risk discussion, not Class III. Currently regulated Class II metallic resurfacing implants do not have a clinical special control. She finds the labeling discussion to be a salvage situation, She argued that the benefits for the population who does not have a reasonable alternative cannot be dismissed.

Dr. Smith recapped the Panel's sentiments on question three: there was data presented that did show there is an improvement in pain in the modified dataset, but the criteria and extrapolation to the larger population do not instill confidence. Some members of the panel felt that it was appropriate to have a non-operative control, while others felt that a sham surgery control may have been more beneficial. With respect to the benefit risk profile, the Panel agreed that the data presented was insufficient to reach a conclusion. Regarding additional benefits to other groups, the data presented was not adequate to reach a conclusion. Some members noted that there may well be a small segment of patients for whom this may be beneficial.

Question Four

Dr. Smith read the fourth question: please comment on the design and execution of the current patient preference information (PPI) study. Please discuss the contribution of the PPI datasets to the final benefit risk determination.

Dr. Reed outlined specific points of contention with the study, such as the way percentages were delivered, the way benefits were communicated, and the way pain was described. She found it impossible to relate the PPI to the clinical study.

Dr. Kirkpatrick agreed with FDA about the IRB oversight being necessary but neglected and found the survey to be overly complex.

Dr. Porter agreed with **Dr. Reed**'s comments and stated it is inappropriate that those surveyed had never received a knee surgery. **Dr. Reed** furthered that the variable pain baseline in the population surveyed likely impacted responses. **Dr. Porter** agreed that, yes, once you have experienced a chronic condition, you are willing to tolerate risks you would not have otherwise.

Dr. Cizik noted that it is understandable the sponsor did not know how to properly conduct a general population study as a device manufacturer. She advocated for the general design by saying that is the only way to determine a non-biased societal preference. However, she expressed discontentment with the methodology, such as the lack of discrete choice experiment and best worth scaling.

Dr. Manner asked what happened to the other six PPI studies, given that the one in question is the seventh. **Ms. Bonnell** clarified that those are on page 66 of the executive summary.

Dr. Price agreed with the other panelists and wondered how this can be considered a patient preference survey when it was not patients that were surveyed.

Ms. Bonnell reminded that the PPI surveys are supplementary evidence, not primary.

Dr. Smith summarized: the PPI data sets up significant methodological issues, which limited their applicability for drawing conclusions. He noted 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 rather than patient information.

Question Five

Dr. Smith read the fifth question: The sponsor has identified several key considerations in risk mitigation, including the appropriate selection of patients and a more detailed surgical technique. The sponsor also 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?

Dr. Helgeson stated he does not understand how these simple parameters of tibial spine height and meniscal extrusion were hard to measure. **Dr. Barber** furthered this by noting that adding orthopedic surgeons into the mix will decrease the reliability of interpretation even more. **Dr. Subhawong** seconded these points.

Dr. Cizik reiterated that the exclusionary tibial spine height in women is close to the average spine height.

Col. Helgeson asserted that if the measurement is easily uncertain, it will be up for manipulation to make patients eligible for the surgery.

Ms. Bonnell reiterated that it is the surgeon's responsibility to use as according to the label.

Dr. Subhawong a wondered whether the implant ever extruded in the direction of the medial tibia and asked if surgeons found the spine height clinically relevant.

Dr. Smith expressed doubts that tibial spine height can be measured accurately within a millimeter on a coronal MRI and worried that this selection was made just to obtain approval.

Dr. Smith summarized the contributions to question four: inter-rater disagreements over the measurements was a significant concern for reproducibility and clinical applicability. The radiologist expert on the panel noted that typically tibial spine height is not something that is measured. Medial extrusion will most likely need to be made by the surgeons in the office lacking radiology expertise.

FDA SUMMATION

Capt. Peat thanked the panel and summarized the FDA's requests for Panel contribution. She advised that the voting question to come will be on the benefit and risk profiles.

SPONSOR SUMMATION

Mr. Belaney asserted that Active Implants believes 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. He underscored the extensive interaction the sponsor has had with varied FDA reviewers over 17 years and argued that it is not appropriate to hold the manufacturer to standards that were not in place at the time of study approval. He noted that the two-year study duration is consistent with FDA guidance and numerous other orthopedic device approvals. Regarding uncertainty, he clarified that the 24-month outcome is known for over 90% of enrolled patients.

Mr. Belaney relayed that NUsurface was superior to controls in the original population and modified subpopulation used to seek clearance and met primary and multiple secondary endpoints. 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. The rate of re-operation is comparable to or lower than other devices that have been approved. He emphasized the importance of patient choice and the benefits of expanding the pool of available options.

He restated that training will be provided to mitigate risks and to help ensure proper patient selection. He noted the presence of 20 women in the subpopulation. He asserted that the company's commercial experience in Europe equips them to handle the transition to market. He concluded by thanking the panel and promising to incorporate their feedback.

Dr. Jones quickly wrapped up by reminding that not everyone is eligible for the device, but it is an important tool in the toolkit and that appropriate training is well within reach. He highlighted the importance of patient perspectives in determining whether this should be available and restated that NUsurface spares bone, soft tissue, and if complications arise, revision surgeries are quick and easy with rapid rehabilitation.

REPRESENTATIVE SUMMATIONS

Dr. Price, the consumer representative, thanked the panel and expressed her anticipation to see the results of whether they feel more years are needed to fine tune the studies, noting that 17 years is a long time.

Ms. Bonnell, the industry representative, highlighted the extensive collaboration between FDA and sponsor to ensure products are available in the US to advance patient care. She emphasized that one size does not fit all. She commended the sponsor for attempting to incorporate FDA feedback that spanned many years and different reviewers. She expressed a belief that the benefits outweigh the risks for a subset of patients.

Dr. Porter, the patient representative, asserted that the small subset for whom this is appropriate may see reasonable benefits. She expressed concerns that it will be used off-label if the labeling includes such specific requirements.

VOTE

Dr. Awojope reminded that 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 and read the definitions of safety and effectiveness before prompting the Panel for their votes on 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?

Ms. Bonnell requested to remind the Panel that the vote is for the on-label indications and that other considerations should be neglected during the vote. **Dr. Smith** acknowledged that this comment may be a result of a financial conflict of interest.

Dr. Smith announced a 15-minute timeframe for the vote to occur.

VOTE RESULTS

Dr. Awojope read the vote results: 2 yes, 6 no, and 1 abstain. **Dr. Smith** prompted explanations of the vote from the Panel members.

Dr. Barber voted no due to a high failure rate in an absolutely ideal population with a select group of surgeons. He did not feel labeling or other minor changes would make a difference. The implant does not provide the effectiveness and safety that he would like to see.

Dr. Cizik voted no and does not feel that a change in labeling would help. She did not think the data supported the conclusions drawn from the executive summary, and would have liked more functional data that was linked to the indications for use.

Col. Helgeson voted no and does not think label changes would help and found the data unclear and difficult to apply to the highly specific intended population.

Dr. Subhawong voted yes because of the demonstrated improvement in KOOS pain scores.

Dr. Evans voted no because of questionable quality of evidence, especially surrounding the selection of the subgroups, differences in criteria for the arms of the trial, and quality and conduct of the patient preference studies. He stated label change would not alter his vote.

Dr. Banerjee voted no due to issues with evidence quality and study design, seconding the prior comments in opposition. He does not think labeling changes would make a difference.

Dr. Manner voted no due to the highly selective nature of the patients and surgeons involved. He argued that effectiveness will be even lower in the real world and does not see an acceptable benefit to risk ratio.

Dr. Kirkpatrick voted yes. While in agreement with the critiques, he expressed that there is enough evidence to slightly tip the balance in favor of approval. He posed that post-market studies should be in consideration, such as tracking implants that need to be replaced. Overall, he found the device to fill a specific niche that does not have another good solution.

Dr. Reed abstained because she was equally torn. She would have liked to see greater benefit and better data and analyses, but she found the risks of a tolerable re-operation or advancing to inevitable arthroplasty to be minor. She found the labeling to be too broad and is concerned about scope creep.

CLOSING REMARKS

Dr. Smith thanked the Panel, FDA, sponsor, and Open Public Hearing participants. **Capt. Peat** echoed this, and **Dr. Smith** adjourned the meeting.

I approve the minutes of this meeting as recorded in this summary.

Harvey E. Smith, M.D.
Chairperson

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November 14, 2022

I certify that I attended this meeting on April 20, 2023 and that these minutes accurately reflect what transpired

Akinola A. Awojope -S Digitally signed by Akinola A. Awojope -S
Date: 2023.10.02 07:27:03 -04'00'

Akinola Awojope
Designated Federal Officer