FDA Executive Summary

Prepared for the
April 20, 2023, meeting of the
Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee
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NUsurface Meniscus Implant
Active Implants, LLC

Contents

LIST OF TABLES

LIST OF FIGURES

1. Introduction

This document is the FDA Executive Summary for the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee meeting on the NUsurface Meniscus Implant from Active Implants, LLC. The sponsor has submitted an original De Novo request to obtain marketing authorization for the NUsurface Meniscus Implant. The NUsurface Meniscus Implant is a sterile, single use polymeric disc-shaped device intended for use in the medial compartment of the knee to distribute load between the distal femur and proximal tibia. The implant is not intended to be fixed in place by sutures or bone cement.

The De Novo request is under review by the Division of Restorative, Repair, and Trauma Devices, Office of Health Technology 6: Office of Orthopedic Devices (OHT6), Office of Product Evaluation and Quality (OPEQ), within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) (also referred to as the Agency). This document will provide background on the NUsurface Meniscus Implant, describe the evidence, including clinical study data submitted in support of this new device, and summarize the areas for which FDA seeks expert input from the Panel. In particular, FDA seeks input on whether the clinical study data demonstrates that the probable benefits of the device outweigh its probable risks to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected.

1.1 Rationale for Presentation to the Panel

The NUsurface Meniscus Implant is a first-of-a-kind polymeric meniscal implant device, and the Agency is presenting this De Novo request to the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee based on the reasons listed below. In response to feedback from the Agency about the clinical datasets and FDA's ability to evaluate the benefit-risk profile and understand effectiveness risk mitigations, the sponsor has provided a subgroup analysis to identify a population that has fewer secondary surgical interventions (SSIs). The following cited issues impact FDA's ability to analyze and interpret the study results for the purpose of assessing safety and effectiveness, as well as the benefits and risks of the NUsurface Meniscus Implant. Please consider the following:

- The patient population that would benefit from this device, in consideration of available alternative non-surgical and surgical treatments;
- The adequacy of the overall clinical success criteria and the clinical significance of the SSIs related to the device;
- The overall success rate of the modified MERCURY dataset and its impact on the benefit-risk determination;
- The contribution of the Patient Preference Information (PPI) studies on the benefit-risk determination;
- The impact of the proposed risk mitigation strategies on the clinical reproducibility, particularly accurate identification of the target patient population; and
- Whether a favorable benefit-risk profile has been demonstrated for the subject device for its proposed intended use.

The Panel will be asked to discuss these as part of the voting and non-voting questions.

2. Background

2.1 Regulatory Background

The regulatory submission that is the topic of discussion at this meeting is a De Novo Classification Request. De Novo requests are appropriate for novel devices of low-to-moderate risk that are not of a type of device that is already reviewed through the 510(k) or premarket approval (PMA) review pathways. Per section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act, a device is eligible for the De Novo pathway if there is no legally marketed predicate device and if general controls alone, or general and special controls, would provide reasonable assurance of the safety and effectiveness of the device. FDA determined that the NUsurface Meniscus Implant device met the criteria to be considered. If the NUsurface Meniscus Implant is granted marketing authorization through the De Novo pathway, the resulting new device regulation places the device type in class I (general controls) or class II (general and special controls). Special controls (if classified as class II) can include specialized bench testing, animal testing, and clinical testing requirements that are specific to the device's intended use and technological characteristics, Future devices that are of the same type as the De Novo device can then receive marketing authorization from FDA through the 510(k) review process, which requires that a device be found to be as safe and effective ("substantially equivalent") to another legally marketed device in the new regulation.

The data which CDRH considers for review is identified as valid scientific evidence. Per 21 CFR 860.7(c)(2), "valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use." De Novo requests must adhere to this standard.

In order to be granted, the evidence in the submission must demonstrate a reasonable assurance of safety and effectiveness as defined in 21 CFR 860.7(d)(1) and (e)(1), respectively. Summarized, the evidence must show that when using the device properly, the probable benefits to health outweigh any probable risks and there is an absence of unreasonable risk (safety), and that there are clinically significant results in a significant portion of the target population (effectiveness).

The FDA guidance document entitled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications"[1] is applicable to this submission. More information regarding the FDA's views regarding the NUsurface Meniscus Implant benefit-risk profile is included in Section 10.

In addition, since the FDA Modernization Act of 1997 (FDAMA), Congress has directed FDA to take a least burdensome approach to medical device premarket evaluation in a manner that eliminates unnecessary burdens that may delay marketing of beneficial new products, while maintaining the statutory requirements for clearance and approval.

2.2 Clinical Context

The normal meniscus is a smooth, crescent-shaped structure composed of fibrocartilage. The menisci enhance the articulation between the rounded femoral condyles and flat tibial plateaus. To serve this purpose, they are

[1] *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications,* available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de.

triangular shaped in cross-section. The medial and lateral menisci are anchored to the tibia via anterior and posterior roots of the meniscus as well as peripheral attachments of the coronary ligaments.

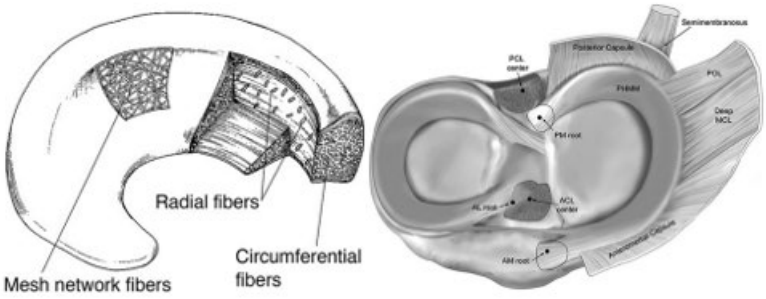


Figure 1. Diagram of the interior structure of the meniscus and its positioning on the tibial plateau[2]

The menisci serve to maintain the long-term health of the knee joint by protecting the tibiofemoral joint cartilage through four important roles: alteration of load transmission, shock absorption, stabilization, and lubrication of the knee joint.[3] They fill the void created by the mismatch in the curvature between the femoral condyles and tibial plateaus, transmitting forces more evenly across the joint space.

The menisci may be subject to damage from acute trauma or degeneration due to chronic wear. Overall, the loss of function of the meniscus can result in an increase in pressure and can lead to chondral damage.[4] The unique structures of the menisci make treatment and repair challenging, and long-term damage to the meniscus leads to degenerative changes in the knee joint,[5] including osteoarthritis. Knee osteoarthritis is one of the most common causes of pain and a leading cause of work disability. There is a high risk (45%) of developing symptomatic knee osteoarthritis over a lifetime.[6] As the U.S. population is becoming increasingly older on average, the AAOS predicts that the rate of total knee arthroplasty (TKA) procedure will double by the year 2030.[7] Nearly 60% of Americans with arthritis are currently younger than 64 years old.[8] Patients who had a meniscectomy are much more likely to have an arthroplasty than those whose menisci are intact[9] and are more likely to have a knee replacement at an earlier age.[10]

Arthroscopic partial meniscectomy is a common treatment for symptomatic meniscal damage and is one of the most common orthopedic surgical procedures; however, evidence suggests that it may not provide meaningful benefit to patients. Research suggests that the partial meniscectomies are not statistically better than non-surgical therapy after two years. After meniscectomy, the contact area of the tibiofemoral joint is decreased. Because of the protective nature of the menisci, there is a strong correlation between meniscal absence and arthritic disease

[2] DePhillipo NN, Moatshe G, Chahla J, Aman ZS, Storaci HW, Morris ER, Robbins CM, Engebretsen L, LaPrade RF. Quantitative and Qualitative Assessment of the Posterior Medial Meniscus Anatomy: Defining Meniscal Ramp Lesions. Am J Sports Med. 2019 Feb;47(2):372-378. doi: 10.1177/0363546518814258. Epub 2018 Dec 7. PMID: 30525875.

[3] Gee SM, Posner M. Meniscus Anatomy and Basic Science. Sports Med Arthrosc Rev. 2021 Sep 1;29(3):e18-e23. doi: 10.1097/JSA.0000000000000327. PMID: 34398117.

[4] Rath E, Richmond JC. The menisci: basic science and advances in treatment. Br J Sports Med. 2000 Aug;34(4):252-7. doi: 10.1136/bjsm.34.4.252. PMID: 10953895; PMCID: PMC1724227.

[5] Markes AR, Hodax JD, Ma CB. Meniscus Form and Function. Clin Sports Med. 2020 Jan;39(1):1-12. doi: 10.1016/j.csm.2019.08.007. PMID: 31767101.

[6] Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Kock G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM. (2008) Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum;59(9):1207-1213.

[7] Projected volume of primary and revision total joint replacement in the U.S. 2030 to 2060. AAOS March 6, 2018.

[8] Abram SGF, Judge A, Beard DJ, Carr AJ, Price AJ. (2019) Long-term rates of knee arthroplasty in a cohort of 834,393 patients with a history of arthroscopic partial meniscectomy. Bone Joint J;101-B(9): 1071-1080.

[9] Pengas LP et al. (2012) Total meniscectomy in adolescents. A 40-year follow-up. J Bone Jt Surg;94B(12):1649-1654.

[10] Brophy et al. (2014) total knee arthroplasty after previous knee surgery. J Bone Jt Surg.96A(10):801-805.

progression, and partial meniscectomies are currently recommended for patients who have mechanical problems in addition to pain.

2.3 Current Treatment Options

Treatment options for patients with persistent knee pain after meniscectomy are dependent on the degree of symptoms and level of function in conjunction with radiographic evaluation. Both non-surgical and surgical treatments are available.

- **Non-Surgical Treatments.** Conservative management of knee pain is typically the first line of treatment for patients and include pharmacological pain relief (e.g., non-steroidal anti-inflammatory drugs (NSAIDs); steroids, intra-articular hyaluronic acid injections, physical therapy, and weight loss.
- **Surgical Treatments.** Surgical treatments are dependent on factors that contribute to pain[11] and other symptoms/signs, and may include:
    - Meniscal allograft transplantation
    - Use of resorbable scaffold devices for meniscal repair
    - Unloading Osteotomy

The NUsurface Meniscus Implant was evaluated as a potential alternative surgical treatment in patients for whom mild or greater pain exists in the medial compartment of the knee when the medial meniscus has been previously resected. The sponsor includes language that the patient population should not be indicated for any of the above alternative treatments. Additionally, the target population would not be candidates for any type of knee arthroplasty, which represents the end-stage surgical intervention for patients with advanced osteoarthritis.

2.4 Description of the NUsurface Meniscus Implant

The NUsurface Meniscus Implant is a sterile, single use polymeric disc-shaped device for use in the medial compartment of the knee to distribute load between the distal femur and proximal tibia. *Poly-carbonate urethane (PCU) Bionate I 80A* makes up the bulk material of the implant and is reinforced with Ultra-High Molecular Weight Polyethylene (UHMWPE) fibers (Dyneema Purity) that are embedded around the periphery. These fibers are purported to help resist radial deformation. The device in this submission is identified as NUsurface 2.0 and represents the third-generation design iteration. It is offered in 7 sizes - 40-30-2, 42-31-3, 44-32-3, 46-33-3, 48-34-3, 50-35-3, 52-36-3. The numbers denote the length – width – thickness in millimeters and each size is available in a left or a right configuration.

[11] Drobnič M, Ercin E, Gamelas J, Papacostas ET, Slynarski K, Zdanowicz U, Spalding T, Verdonk P. Treatment options for the symptomatic post-meniscectomy knee. Knee Surg Sports Traumatol Arthrosc. 2019 Jun;27(6):1817-1824. doi: 10.1007/s00167-019-05424-3. Epub 2019 Mar 11. PMID: 30859265.

Figure 2. NUSurface Meniscus Implant.

Figure 3. The NUsurface Meniscus Implant in the medial compartment of the knee.

The implant **is a free-floating, interpositional spacer and is not intended to be fixed in place by sutures or bone cement.** Instead, the device is inserted between the tibia and femur using the provided instruments (Figure 3) which include a Universal Insertion Instrument, Meniscus Probe, Bone Rasp (right and left configurations) and Extraction Instrument, each of which are housed in a case. Each of these instruments are Class I exempt under 21 CFR 888.4540.

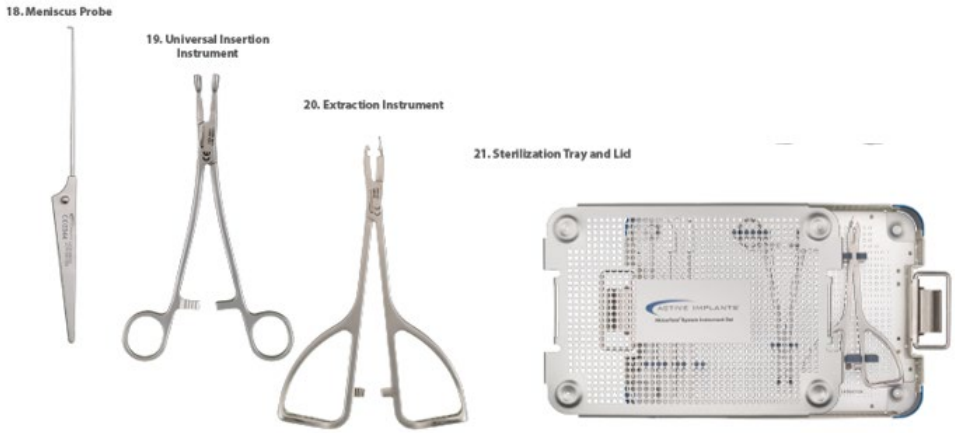


Figure 4. Instrumentation -- Meniscus Probe, Universal insertion instrument, Extraction instrument, Instrument Tray (Active Implants figure)

The stated principles of the NUsurface Meniscus Implant are 1) to mimic the physical and mechanical properties of a normal meniscus, 2) more evenly distribute stress, and 3) absorb strain that would otherwise be transferred to the cartilage in the absence of a normally functioning meniscus.

2.5 Comparison to Alternatives

The sponsor compared their NUsurface Meniscus Implant to 510(k)-cleared free floating interpositional metal spacer devices such as the Unicondylar Interpositional Spacer, Sulzer Orthopedics, Inc. (K003269; Figure 4, left) and Tri-Compartmental Resurfacing (tCR) Device, ConforMIS, Inc. (K052687; Figure 4, right).

Figure 5. Previous unfixed interpositional devices, Unispacer (left) and iForma (right) (figure from Active Implants)

These metallic spacer devices are no longer clinically used as longer-term clinical performance demonstrated high secondary surgery failure rates. The American Academy of Orthopaedic Surgery (AAOS) has printed an evidence based clinical guideline of non-arthroplasty treatment recommendations including the statement that**, "*In the absence of reliable or new evidence, it is the opinion of the work group not to use free-floating (un-fixed) interpositional devices in patients with symptomatic medial compartment osteoarthritis of the knee*."**

3. Proposed Indications for Use

When evaluating the device's benefit-risk profile, it is important to consider the device's stated indications for use and labeling information, including contraindications, warnings, and surgical technique. In response to the Agency's feedback, the sponsor proposed modifications to the contraindications and warnings to improve the likelihood that the device is used in patients with a positive benefit-risk profile where the risks can be adequately mitigated. These labeling changes are intended to reflect the subgroup analysis where the sponsor asserts there is an improved benefit-risk. Please refer to Appendix A for a complete list of the proposed contraindications, warnings, and precautions.

3.1 Indications for Use

The following Indications for Use are proposed by the sponsor in the De Novo request:

> *"The intended for 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 osteoarthritis,*
>
> *--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."*

4. Regulatory History

4.1 Regulatory History – United States (US)

There are currently no FDA-cleared or approved polymer devices indicated for the improvement of pain and function in the medial compartment of a knee in which the medial meniscus has been resected.

- 2008: An initial 510(k) application was determined to be "*not substantially equivalent (NSE)*" because the polymer device raised different questions of safety and effectiveness compared to the metallic predicate devices that were proposed.

- 2012: First Investigational Device Exemption (IDE) Study (VENUS) was approved with conditions. See Section 4.3 for clinical study history.
- 2013: A second 510(k) application was also determined to be NSE due to different questions of safety and effectiveness between the polymeric device and the metallic proposed predicate devices.
- 2014: An initial De Novo request was denied because there was no clinical data provided and as a result, we were unable to determine if the benefits outweighed the risks.
- 2015: Second IDE Study (SUN) was approved. See Section 4.3 for clinical study history.
- 2019: FDA granted Breakthrough Device Designation.[12]
- 2020-2021: A second De Novo request was denied due to the large number of device failures and unmitigated risks that raised uncertainty about the benefit-risk profile as well as the clinical safety of the device.
- 2022: The current De Novo request was submitted with a modified target population proposed following a modified subgroup analysis of the existing dataset. See Section 4.3 for clinical study history.

4.2 Regulatory History – Outside United States (OUS)

The sponsor received the CE Mark and marketing authorization in the European Union in March 2008. The NUsurface Meniscus Implant has been used in Europe under CE Mark since 2008 and Israel since 2011. There is a post-market study, the MCT study, that was conducted in Europe and Israel.

4.3 Clinical Study History

The safety and effectiveness of the NUsurface Meniscus Implant was evaluated under four clinical studies and two datasets as follows:

Table 1. Overview of clinical study history for the NUsurface Meniscus Implant

Study Name	Date	Site	Device Version	Overview
Feasibility Study	2008	OUS	NUsurface Meniscus Implant 0.0	Results from this study were not provided as part of the De Novo request but used in support of the original IDE submissions.
MCT	2011	OUS	NUsurface Meniscus Implant 1.0	Although it uses an older version of the device, the MCT was included in the De Novo application request as a supplementary dataset to support the sponsor's proposed labeling mitigations and sub-group analysis,
VENUS	2012	US	NUsurface Meniscus Implant 2.0	This is a prospective, randomized controlled study with 127 subjects: 61 subjects receiving the device and 66 subjects in the non-surgical control arm. The study was reviewed and approved by the Agency.
SUN	2015	US	NUsurface Meniscus Implant 2.0	This is a single arm, prospective, non-randomized, observational study with 115 subjects receiving the NUsurface device. This study was reviewed and approved by the Agency.

[12] The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products. Devices are eligible for breakthrough device designation if both of the following criteria are met: (1) the device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and (2) the device also meets at least one of the following: (a) Represents breakthrough technology, (b) No approved or cleared alternatives exist, (c) Offers significant advantages over existing approved or cleared alternatives or (d) Device availability is in the best interest of patients. The guidance is available here: https://www.fda.gov/media/108135/download.

Note: The feasibility study was used on an older version of the NUsurface Meniscus Implant as proof of concept.

Table 2 Overview of datasets presented in the De Novo request.

Name	Date	Clinical data source	Overview
MERCURY Dataset*	2019	VENUS and SUN	The MERCURY dataset consists of pooled data from the VENUS and SUN studies and included a total of 242 subjects (176 NUsurface and 66 non-surgical controls[13]).
Modified MERCURY Dataset*	2021	MERCURY Dataset	The modified MERCURY dataset excludes subjects with meniscus extrusion ≥5mm and tibial spine height <11mm from the MERCURY Dataset and included a total of 109 subjects (74 NUsurface and 35 non-surgical controls[14]).

*The sponsor refers to the MERCURY Study, whereas FDA has chosen to identify this as the MERCURY dataset to better reflect that this is the result of pooling two datasets from two different studies.

5. Non-Clinical Evaluation of the NUsurface Meniscus Implant

5.1 Bench Performance Testing

The sponsor conducted fatigue, shear, and viscoelastic property testing to characterize the physicochemical and mechanical properties of the NUsurface Meniscus Implant. No significant concerns were identified in any of these non-clinical tests, and there are no non-clinical concerns being brought to the Panel.

5.2 Biocompatibility and Animal Testing

In accordance with the Agency's Biocompatibility Guidance, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"*,[15] this meniscal implant is in contact with bone and or/tissue, with a permanent duration of contact (> 30 days). For this type of product, FDA recommends the following biocompatibility tests be considered: cytotoxicity, sensitization, irritation (or intracutaneous reactivity), material mediated pyrogenicity, acute systemic toxicity, subchronic toxicity, implantation, chronic toxicity, genotoxicity (mutagenic and clastogenic testing) and carcinogenicity. Additionally, the sponsor provided data from a functional sheep total meniscectomy model that was also used to evaluate biocompatibility implantation endpoints; however, the device was sutured in place in this study (i.e., a different implantation and fixation technique). The biocompatibility data was reviewed as part of the sponsor's original IDE applications. However, additional biocompatibility guidelines were established with the publication of FDA's Biocompatibility Guidance,[16] issued on September 4, 2020. Therefore, there are several, outstanding concerns about the biocompatibility evaluation that are under review. These concerns are not being brought to the Panel.

6. Clinical Study Methodology Overview

The sponsor relies upon the modified MERCURY dataset as the pivotal dataset to support a reasonable assurance of safety and effectiveness of the NUsurface Meniscus Implant. This modified dataset was created though a

[13] There were 4 NUsurface and 14 control subjects who were lost to follow-up or withdrew consent during the original VENUS and SUN studies leaving 172 NUsurface and 52 non-surgical control subjects.

[14] There were 2 NUsurface and 4 control subjects who were lost to follow-up or withdrew consent during the original VENUS and SUN studies leaving 72 NUsurface and 31 non-surgical control subjects.

[15] Available at https://www.fda.gov/media/85865/download.

[16] Guidance for Industry and FDA Staff - *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"* (available at: https://www.fda.gov/media/85865/download

retrospective analysis of the MERCURY dataset. The original MERCURY dataset is pooled from two studies, VENUS and SUN, for a total of 242 subjects (176 NUsurface subjects and 66 control subjects). Both VENUS and SUN have nearly identical inclusion/exclusion criteria and similar follow-up; however, VENUS was a randomized controlled study and SUN was a single-arm observational study. There are additional differences discussed in-depth below. Additional exclusion criteria - meniscus extrusion and tibial spine height - were identified and correlated by the sponsor to impact the rate of SSI in the MERCURY dataset. After modifying this dataset for the identified exclusion criteria, a total of 109 subjects (74 NUsurface subjects and 35 control subjects) were included in the modified MERCURY dataset. The modified MERCURY dataset was analyzed for superiority at 24 months and compared the non-surgical control subjects to the NUsurface Meniscus Implant subjects. The sponsor applied these same exclusion criteria to the MCT study. However, the MCT study was not intended to serve as pivotal data for the NUsurface Meniscus Implant.

6.1 Investigational Plan Overview

The clinical data methodology presented in this section is for the VENUS and SUN studies. Where applicable, the differences between the two studies will be noted.

6.2 Study Objectives

The MERCURY dataset used for the De Novo request is combined from the VENUS and SUN studies; however, these two studies originally had different study objectives.

- The VENUS study was intended to compare the safety and effectiveness of the NUsurface Meniscus Implant with a non-surgical control group in subjects with previous meniscectomy and pain. Success was designed to be evaluated based on superiority of the investigational device over the control by comparing the ratio of subjects who were successful in multiple assessments ("Overall Success"). That is, success based on a composite endpoint including pain, function, and absence of an SSI as follows:

  "*Safety. To demonstrate peri- and post-operative safety of the NUsurface device up to and including 24 months along with an interim analysis at 12 months on a subgroup of NUsurface patients defined in the Statistical Analysis Plan (SAP).*

  Performance. To demonstrate probable clinical benefit up to 24 months post implantation by means of Patient Reported Outcome (PRO) measurements.

  - *To evaluate the changes in the patient perceived pain compared to Baseline up to 24 months post-implantation with the $KOOS^{pain}$ sub-scale*
  - *To evaluate the changes in the patient perceived pain compared to Baseline up to 24 months post implantation with $KOOS_5$ sub-scale.*
  - *To evaluate the changes in Patient Related Outcomes and all other measured outcome data relative to baseline at all post-operative evaluation time points.*
  - *To evaluate the changes in the patient Quality of Life (QOL) relative to Baseline at present time points."*

- The SUN study was intended to increase the sample size of subjects treated with the NUsurface Meniscus Implant to better understand the safety outcomes. As part of the objective, the sponsor focused on malfunction rate and identified that, "*The most crucial study hypothesis is that the NUsurface Meniscus Implant treated subjects have a safety rate ≤ 10%. The null hypothesis is that the NUsurface Meniscus Implant treatment is not safe and has a malfunction rate > 10%.*" However, this objective was modified for the analysis of the MERCURY dataset given the larger reported adverse safety event rates than the sponsor's originally identified 10% rate.

6.3 Subject Enrollment (Inclusion/Exclusion Criteria)

The inclusion/exclusion criteria for the VENUS study are outlined below. Please note that the SUN and VENUS study inclusion/exclusion criteria are identical except for use of MRI, where MRI is listed as an inclusion criterion for VENUS (i.e., the subject needs to be able to undergo MRI) and is an exclusion criterion for SUN (i.e., patients who are contraindicated for MRI). Additionally, the VENUS study requires that subjects be willing to be entered into either arm of the study, reflecting the randomized, controlled design. For SUN, which ran concurrent to the VENUS study, there was no such requirement. Finally, the SUN study had an additional exclusion criterion about patient populations that are at high risk for poor healing or outcomes such as patients who have a co-morbidity that reduces life expectancy to less than 36 months.

For the VENUS study, both investigational and non-surgical control arms had the same inclusion/exclusion criteria. However, the investigators would have been able to directly confirm that subjects in the investigational arm met the inclusion/exclusion criteria during the surgery (e.g., directly visualizing the cartilage rather than relying upon imaging (e.g., MRI), which is prone to error). Inclusion/exclusion criteria for the VENUS study are presented below.

The inclusion/exclusion criteria detailed in sections 6.3.1 and 6.3.2 were proposed for the actual clinical studies (VENUS and SUN); however, the sponsor has included additional inclusion/exclusion criteria in the sub-group analysis which created the Modified MERCURY dataset. This sub-group population excluded patients with medial meniscus extrusion of 5mm or greater and medial tibial spine heights less than 11 mm as measured by MRI. The sponsor had proposed corresponding changes in labeling to reflect the need to consider tibial spine height (warning) and meniscus extrusion (contraindication) when selecting patients. Please refer to Appendix A for a detailed listing of the revised warnings, contraindications, and precautions that are proposed by the sponsor.

6.3.1 Inclusion Criteria

"*In the opinion of the investigator, if ALL of the following 9 conditions are applicable for the index knee, then the patient is included if he/she:*

1) *Had > 6 months ago a medial partial meniscectomy as confirmed by patient history and MRI*
2) *Has a KOOS Pain of ≤ 75 (100 being the highest attainable and no pain)*
3) *Is between age 30 and 75 years (inclusive) at the time of study treatment*
4) *Has neutral alignment ±5° of the mechanical axis, as measured from the angle formed by a line drawn from the center of the femoral head to the medial tibial spine and a line drawn from the medial tibial spine and the center of the ankle joint*
5) *Has ≥ 2 mm intact medial meniscal rim capable of being fitted with a NUsurface device AND is also recommended for the baseline non-surgical (and, if likely to receive benefit, any injection) therapies to be administered in the study.*
6) *Is willing to be entered into either arm of the study: implanted with the NUsurface device OR treated with the recommended control arm therapies.*
7) *Is able to do the study required follow-up visits, questionnaires, X-rays and MRI's*
8) *Is able to read and understand the English language*
9) *Is able and willing to understand and sign the Informed Consent Form*"

6.3.2 Exclusion Criteria

"*In the opinion of the investigator, if ANY of the following 35 conditions are applicable for the index knee, then the patient is excluded if he/she:*

1) *Has a symptomatic knee because of a tear that could be addressed by a repeat partial meniscectomy leaving > 4 mm of medial meniscus rim*

2) *Has evidence of a Outerbridge Grade IV cartilage loss on the medial tibial plateau or femoral condyle that potentially could contact a NUsurface implant (e.g., a focal lesion > 0.5 cm^2 correlating to a circular defect of > 8 mm in diameter)*
3) *Has complete disruption of the posterior root attachment of the meniscus*
4) *Has lateral compartment pain and Grade III or Grade IV Outerbridge cartilage score in the lateral compartment*
5) *Has a varus or valgus knee deformity > 5° requiring a tibial or femoral osteotomy*
6) *Has a laxity level of more than Grade II (IKDC), primary or secondary to an injury of the anterior cruciate ligament (ACL) and/or posterior cruciate ligament (PCL) and/or lateral collateral ligament (LCL) and/or medial collateral ligament (MCL)*
7) *Has significant trochlear dysplasia, patellar instability or symptomatic patellar misalignment*
8) *Has patellar compartment pain and Grade III or Grade IV Outerbridge cartilage score in the patellar compartment.*
9) *Compared to a normal knee, has obvious radiological evidence of medial femoral squaring, anatomical variance in the medial tibial plateau, or irregularly shaped cartilage surface*
10) *Had an ACL reconstruction performed < 9 months prior to study treatment*
11) *Has a BMI > 32.5 at the start of study treatment*
12) *Decides to receive (if eligible and an option) allograft medial meniscus transplantation*
13) *Received any type of prosthetic knee implant made of artificial non-resorbable plastic, metal or ceramic, not including the NUsurface® Meniscus Implant*
14) *Has a knee flexion contracture > 10º*
15) *Has flexion < 90º*
16) *Had a previous medial femoral condyle surgery (not including microfracture) or High Tibial Osteotomy (HTO)*
17) *Has insufficiency fractures or avascular necrosis of the medial compartment*
18) *Has an active infection or tumor (local or systemic)*
19) *Has any type of knee joint inflammatory disease including Sjogren's syndrome*
20) *Has neuropathic knee osteoarthropathy, also known as Charcot joint*
21) *Has any medical condition that does not allow possible arthroscopy of the knee*
22) *Has neurological deficit (sensory, motor, or reflex)*
23) *Is currently involved in another investigation of the lower extremity*
24) *Anticipates having another lower extremity surgery during the study period*
25) *Is contraindicated for hyaluronic acid injections (i.e., patients with known hypersensitivity [allergy] to hyaluronan [sodium hyaluoronate] preparations); patients having knee joint infections or skin diseases or infections in the site of possible injections*
26) *Is contraindicated for corticosteroid injections (i.e., patients with allergy to any of the components or with idiopathic thrombocytopenic purpura)*
27) *Has received any corticosteroid knee injections ≤ 3 months prior to study treatment*
28) *Has chondrocalcinosis*
29) *Is on immunostimulating or immunosuppressing agents*
30) *Has ipsilateral or contralateral lower limb joint conditions that may affect ambulation or KOOS (e.g., have a leg length discrepancy > 2.5 cm [1 inch], causing a noticeable limp)*
31) *Is a female who is lactating, expecting, or is intending to become pregnant during the study period*
32) *Is an active smoker*
33) *Is mentally incapacitated (incapable of appraising or controlling conduct) or have mental disability (e.g., dementia or Alzheimer's)*
34) *Is a prisoner*
35) *Is a patient who has economic incentive not to improve*."

6.3.3 Control Treatment

The control arm for the VENUS study was a non-surgical control. There was no formal protocol for order of treatment or required treatment; instead, the Investigator was given the "*flexibility to start and/or stop these acceptable treatments at his/her discretion (as long as there is a minimum of 3 months of documented Baseline Treatment during the course of the study).*" The allowable pharmacological and non-surgical options are:

- "*Non-prescription drugs, creams, vitamins, and supplements*
- *Prescription or Non-Prescriptions NSAIDs*
- *Non-weight bearing and/or open chain physical therapy or self-administered exercise*
- *The following weight bearing exercises: cycling, elliptical, and/or leg presses or other*
- *physical therapy directed closed chain exercises*
- *Ice or heat therapy*
- *Compression sleeves, braces, crutches, and/or canes for the index knee*
- *Body weight reductions*
- *Limitations in activities*
- *Shoe inserts or other types of orthotic devices*
- *The following are also options that may be repeated every 2 months, but are excluded within 6 months of 24-month trial ending measurements:*
    - *Intra-Articular Injections with Corticosteroids*
    - *Intra-Articular Injections with Hyaluronic Acid (HA)"*

The only limitations regarding treatments not permitted in the non-surgical control arm in the VENUS study were:

- "*Platelet Rich Plasma (PRP) Injections*
- *Acupuncture*
- *Any other treatment device that does not have regulatory approval for use*
- *Any surgical treatment requiring operative intervention to the index Knee*"

6.4 Investigational Treatment

Subjects in the investigational arm were treated with the NUsurface Meniscus Implant. There are two key considerations for subjects in this group: correctly implanting the device following a detailed surgical technique and post-activity restrictions.

6.4.1 Surgical Technique

The surgical technique for the clinical study describes the importance of a physical exam and imaging to appropriately enroll subjects. The description of the diagnostic arthroscopy includes a technical note that, "*careful attention should be directed to any chondral lesions identified on the preoperative MRI. Measure all focal Grade 4 chondral lesions*" and to "*evaluate for cartilage coverage any osteophytes identified on MRI for potential contact with the NUsurface Meniscus Implant. Rough and unstable cartilage lesion margins should be debrided to a stable base. Great care should be taken not to damage healthy cartilage or to expose bone on the femur or tibia. Cartilage lesions may be treated based on the surgeon preference*."

The role of the surgical technique and implantation of the device have been prominent in the Agency's discussions with the sponsor about the device's benefit-risk. In the surgical technique for the clinical study, the investigator is warned that "*Not having adequate space for the anterior-lateral wall of the NUsurface Meniscus Implant may damage the device and cause it to be removed or exchanged."* The role of surgical technique and the ability to successfully identify the appropriate device size and implant the device are key considerations in risk mitigation.

After evaluating the gross state of the joint, there are four key parts to the placement of the device: (1) meniscectomy, (2) fossa assessment and notchplasty, (3) trial insertion, and (4) trial assessment.

Table 3. Surgical Technique for NUsurface Meniscus Implant placement (FDA Table)

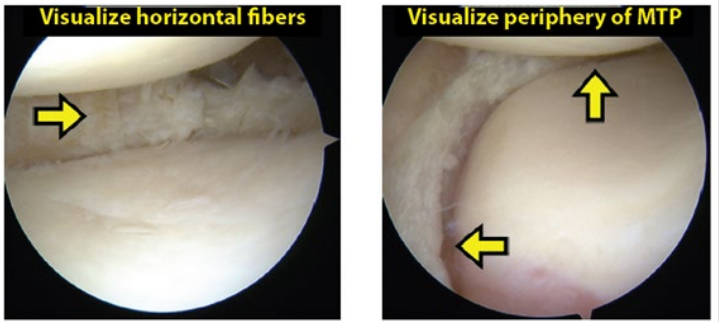
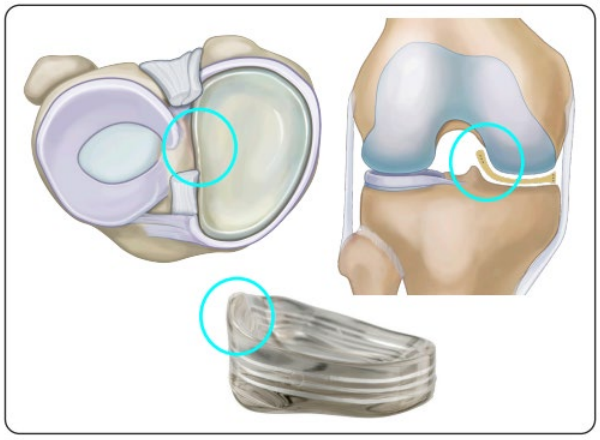
<table>
<tr><th colspan="2">Step 1: Meniscectomy</th></tr>
<tr><td><u>Meniscectomy</u>. The surgeon is directed to "remove as much of the meniscus as possible leaving no more than a 2mm margin around its periphery" to allow room for the NUsurface Meniscus Implant.</td><td> 

Figure 6. Inspection and diagram of the near total meniscectomy leaving no more than a 2mm margin around the periphery (Active Implants figure)</td></tr>
<tr><th colspan="2">Step 2: Preparation of the Intercondylar Fossa</th></tr>
<tr><td><u>Preparation of the Intercondylar Fossa:</u>
"The NUsurface Meniscus Implant is non-anchored and its design includes a raised area around its circumference with a prominent lateral 'bridge' for placement between the tibial eminence and the femoral notch."

The surgical technique also notes that "During deep flexion activities there is a potential for the device to become impinged, preventing it from moving as designed. Ensure adequate removal of osteophytes along the posterior lateral corner of medial femoral condyle to reduce the potential for impingement during deep flexion activities."

<u>Notchplasty/Roofplasty Recommendations:</u>
The surgical technique cautions that "the notch must always be checked for osteophytes and stenosis." The sponsor also includes recommendations for roofplasty and warns against over-resection leading to implant instability and articular cartilage damage.</td><td> 
Figure 7. Placement of the discus shaped implant into the medial space showing the prominent lateral "bridge" placed between the tibial eminence and femoral notch. (Active Implants figure)

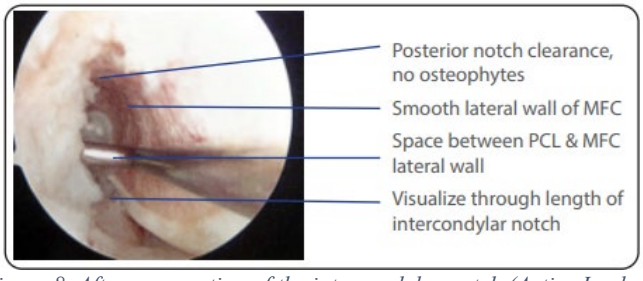
 

Figure 8. After preparation of the intercondylar notch (Active Implants Figure)</td></tr>
<tr><th colspan="2">Step 3: Trial Insertion</th></tr>
</table>

Trial Selection: Select trial and confirm size based on sizing chart (right). The surgical technique requires that the surgeon "*position the NUsurface insertion instrument parallel to the medial femoral condyle. The posterior edge of the Trial must engage inferior to the MFC*" and "*extend the knee while placing a strong posterior force on the insertion instrument.*"

Table 4. Device dimensions present in the clinical study (Active Implants Table)

Size Embedded on Trial and Implant Five Digits Give the Length (LL), Width (WW) and Thickness (T) in mm [LLWWT]	Approximate Minimum Medial-to-Lateral Width of the Proximal Tibia (mm)	Approximate Maximum Medial-to-Lateral Width of the Proximal Tibia (mm)
40302	65	69
42313	69	72
44323	72	75
46333	75	78
48343	78	82
50353	82	85
52363	85	89

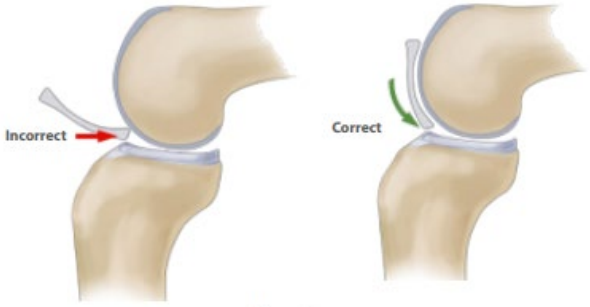


Figure 9. Insertion of the NUsurface® Meniscus Implant requires the correct angle of knee flexion. (Active Implants figure)

Step 4: Trial Assesment

Trial Assessment: to ensure the trial is the appropriate size, the sponsor has provided an algorithm (right) to assess the trial's fit. The assessment includes additional notes about the following:

- "*Reinsert scope and confirm implant placement*
- *Confirm the Trial is seated on the tibial plateau up to 1 mm lateral of the medial tibial plateau and no more than 4 mm overhang on the medial tibial plateau peripheral margin and < 2 mm posterior of the anterior tibial plateau periphery.*
- *Complete one final cycle of the full ROM, from hyper-flexion to full extension. At 90˚ flexion, check for anterior lift-off as performed previously.*
- *As the knee moves into full extension, check for deformation/contact of the anterior-lateral wall of the device against the roof of the notch. In cases where this occurs, contact could lead to*

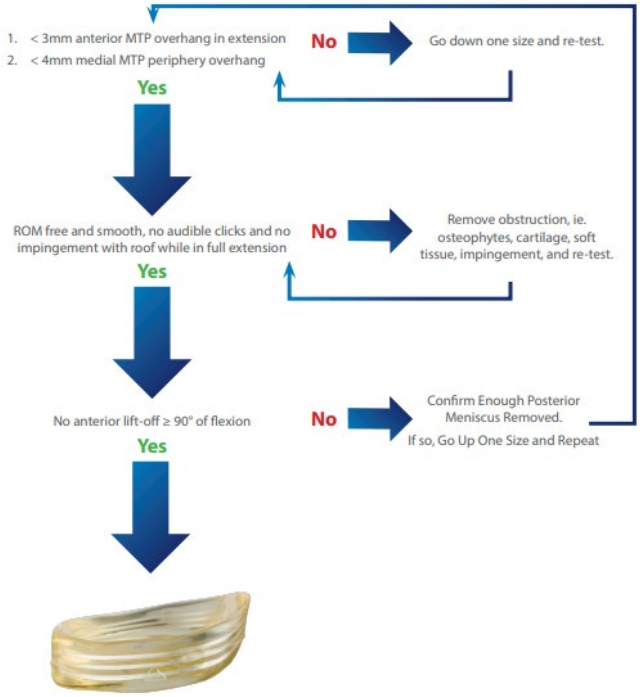
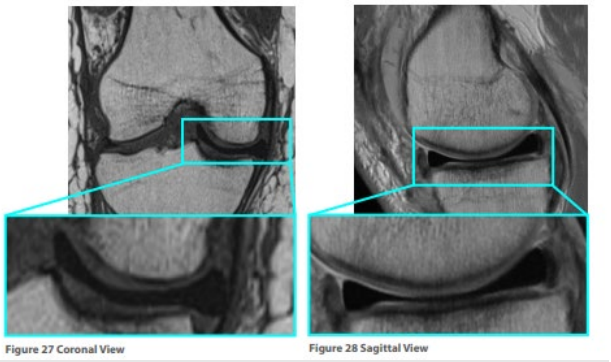


Figure 10. NUsurface Meniscus Implant Sizing Algorithm (Active Implants figure)

impingement and loss of motion and an anterior zone notchplasty/roofplasty may be necessary."	 *Figure 11. Ideal sizing and placement of the NUsurface Implant in the coronal view and the sagittal view (Active Implants Figure)*

6.4.2. Post-Procedure Activity Restrictions

Following implantation, there are additional activity restrictions to minimize the risk of dislocation or other device-related adverse events that would require an SSI. These are described below:

Table 5. Recommended post-operative activity guide. (Active Implants Table)

Recommended	Recommended Only with Prior Experience	Not Recommended
Walking	Cycling	Raquetball/Squash
Low-Impact Aerobics	Hiking	Contact Sports (Football, Rugby, Hockey, Soccer)
Bowling	Rowing	Rock Climbing
Golf	Cross-Country Skiing	Jogging/Running
Dancing	Speed Walking	Singles Tennis
Swimming	Doubles Tennis	Water-Skiing
Yoga	Ice Skating	Baseball/Softball
Boating/Canoeing		Handball
		Martial Arts
		High-Impact Aerobics
		Basketball

6.5 Study Follow-up Schedule

Subjects in both the VENUS and SUN studies made regular, recurring, in-person assessments. These included pain and function evaluations as well as imaging (MRI) to assess device tearing and position. A key difference in the follow-up was that the VENUS study ended at 24 months (2 years), whereas the SUN extended to 60 months (5 years). The MERCURY dataset pooled the data collected during the initial 24-month period.

The primary endpoint was assessed at 24 months (2 years). Some follow-up data were collected out to 5 years for approximately 20% (35/172) of the NUsurface group but no data related to these additional timepoints have been provided as part of the De Novo request. While the primary endpoint was defined at 24 months, the additional follow-up could have been valuable to assess the long-term safety and effectiveness of the device. Additionally, given that a high percentage of subjects needed an SSI to either replace or reposition the device, long-term data on

the outcomes of these subjects would help to understand the benefit-risk profile for patients who need a device replacement or reposition.

Table 6. Combined follow up schedule for the VENUS and SUN studies presented for the pooled MERCURY dataset (Active Implants Table)

Evaluation Method	Baseline	Surgery	1.5 Mo	3 Mo**	6 Mo	12 & 24 Mo	36 Mo	60 Mo
Range	n.a.	n.a.	± 2 w	± 2 w	± 1 mo	± 2 mo	± 3 mo	± 6 mo
Assessments								
Screening	✓							
Treatment		✓						
3 Mo Questionnaire **				✓				
Patient Reported Outcomes								
KOOS	✓		✓		✓	✓	✓	✓
IKDC ^	✓				✓	✓	✓	✓
Pain VAS	✓		✓		✓	✓	✓	✓
WOMET	✓		✓		✓	✓	✓	✓
EQ-5D	✓		✓		✓	✓	✓	✓
Clinician Assessment								
Physical Examination	✓	✓	✓		✓	✓	✓	✓
Imaging								
Weight bearing (standing) A/P & Lat radiography	✓							
45° Weight-bearing A/P knee x-ray (Rosenberg)	✓							
Merchant view knee x-ray	✓							
MRI index knee	✓		✓			✓		✓
Fluoroscopy index knee		✓						

6.5.1 Primary Endpoint and Study Success

When evaluating the study success, the sponsor used a composite primary endpoint to categorize subjects as Overall Success or Overall Failure. While there are some differences in evaluating Overall Success or Failure in the NUsurface and control groups, both of these generally focused on patient reported outcomes (PRO) and absence of SSI, as described in Figure 12. Subjects needed to be successful on both PRO and imaging/SSI to be considered successful for the purpose of the sponsor's analysis.

	Investigational Group	Control Group
Overall Success	Provisional PRO **AND** Positive MRI **AND** No device removal	Provisional PRO **AND** No surgical intervention to index knee for 24 months
Overall Failure	Negative PRO KOOS **OR** Negative MRI **OR** Device removed/replaced for any reason	Negative PRO KOOS **OR** Any surgical intervention to index knee during 24 months of study

Figure 12. Patient Overall Success / Overall Failure (Active Implants Figure)

The key PRO for effectiveness was symptom and pain improvement using the Knee Injury and Osteoarthritis Outcome Score (KOOS) instrument, which is a validated outcome measurement commonly used for assessing knee related injuries and treatments. These scores were used to measure pre-treatment and post-treatment condition including activity levels, pain, swelling, locking, stability, support, sports activity, and quality of life assessment. Subjects needed to show a minimum improvement from baseline, as described below.

$KOOS_{pain} \geq 86.1$ **AND** $KOOS_{Overall} \geq 86.2$ at 24 Months

OR

$KOOS_{pain}$ Δ (improvement from Baseline) $\geq$ 20 points at 24 Months
AND
$KOOS_{Overall}$ $\Delta \geq 20$ points at 24 Months
AND
$KOOS_{pain} \geq 40$ points at 24 Months

Figure 13. Definition of Provisional PRO (Active Implants Figure)

For NUsurface subjects to be considered an Overall Success, there should be no device problems identified by MRI (i.e., a positive MRI) and absence of device-related SSI (removal, replacement, reposition). A positive MRI was defined as an image with the device in one piece and not subluxed more than 50% of the device length, whereas a negative MRI was an image showing the device fractured in two or more pieces and/or subluxed more than 50% the length of the device. For non-surgical control cases, there should be no interventional surgery on the index knee. Notably, for the SUN trial, the sponsor also identified that "*The most crucial study hypothesis is that the NUsurface Meniscus Implant treated subjects have a safety rate ≤ 10%. The null hypothesis is that the NUsurface Meniscus Implant treatment is not safe and has a malfunction rate > 10%.*" As discussed above, this is a key consideration for the Panel in evaluating benefit-risk.

6.5.2 Secondary Endpoints

The sponsor proposed a hierarchical evaluation of secondary endpoints. These included pain (visual analogue scale, VAS), MRI cartilage assessment, International Knee Documentation Committee (IKDC), and quality-adjusted life year (QALY; EQ-5D). The secondary endpoints included cartilage assessment performed by a single, musculoskeletal-trained radiologist reviewer who could not be blinded to device treatment; however, no pre-specified protocol was provided.

Table 7. Hierarchical rank order for superiority tests (Active Implants Table)

Number	Hierarchical Rank Order
1	**Overall Success at 24 Months**
2	24 Month VAS vs Baseline
3	24 Month MRI vs. Baseline of Cartilage Condition in Medial Compartment
4	24 Month IKDC SKEF Score vs Baseline
5	24 Month QALY Score (using EQ-5D)
6	24 Month KOOS Pain
7	24 Month KOOS Overall
8	12 Month KOOS Pain
9	12 Month KOOS Pain vs Baseline
10	12 Month VAS vs Baseline
11	12 Month KOOS Overall vs Baseline
12	12 Month MRI vs Baseline Cartilage Thickness at Center of Medial Tibial Plateau
13	12 Month IKDC SKEF Score vs Baseline
14	12 Month QALY Score (using EQ-5D)
15	24 Month Return to Work
16	6 Month KOOS Pain
17	6 Month VAS vs Baseline
18	6 Month IKDC SKEF Score vs Baseline
19	6 Month KOOS Overall
20	6 Month QALY Score (using EQ-5D)

6.6 Generation of the MERCURY and Modified MERCURY datasets

The sponsor generated two datasets from the clinical data from the VENUS and SUN studies. First, the MERCURY dataset was created by combining the VENUS and SUN datasets. In response to the rates of adverse events and the rate of SSI in the MERCURY dataset (38%, 66/172), the sponsor proposed identifying a sub-population from the MERCURY dataset based on tibial spine height measurements and meniscus extrusion to reduce the rate of SSI. This analysis population is identified as the "Modified MERCURY Dataset." This population excluded patients with medial meniscus extrusion of 5mm or greater and medial tibial spine heights less than 11 mm as measured by MRI. The sponsor had proposed corresponding changes in labeling to reflect the need to consider tibial spine height (warning) and meniscus extrusion (contraindication) when selecting patients. In response to a request for validation of these risk mitigation factors, the sponsor applied them to the MCT dataset, which is a 2008 study that uses an older version of the device

6.6.1 Proposed Risk Mitigations

The sponsor proposed several different mitigation strategies that might address the root cause of the device failures and thereby reduce the rate of SSI or otherwise improve the overall success of the device listed below. The last of which is pursued in the current De Novo request.:

- "*A much more detailed surgical technique*" to address "*surgeon error*";
- Adequate osteophyte removal with new instruments (a rasp);
- Better evaluation of patient notch anatomy and notchplasty as needed;
- Stricter avoidance of arthritis;
- Patient education to avoid "*uncontrolled traumatic events*";
- Restriction of patient postoperative activity level;
- Better instruction on sizing implant;
- Increased choices for implant sizing ;
- A change in material properties of the device;
- Limitations to the patient population for single vs multiple previous meniscectomies; and

- Anatomical differences (femoral condylar thickness, **tibial spine height**, notch differences, **meniscus extrusion**).

The risk mitigation strategies have not been independently evaluated. The Agency requested data showing that the risk mitigations are effective in reducing the rate of SSI or otherwise identifying a population with a better benefit-risk profile.

6.6.2 Rationale for Meniscus and Tibial Spine Height Exclusions

The sponsor correlated a meniscus extrusion ≥5mm with increased failures of the NUsurface Meniscus Implant. Similarly, the sponsor asserted that shorter medial tibial spines were associated with higher device failures. The sponsor notes that the lateral edge of the NUsurface device has an "*arch or lateral bridge*" that provides stability.

The sponsor's rationale for the ≥5 mm meniscus extrusion links meniscal integrity and arthritis. Because meniscal extrusion correlates with disease progression of arthritis, one consideration is that this exclusion criterion may indirectly select for subjects with less severe disease. While the SSI rate is reduced in the selected population with <5 mm of meniscal extrusion, it is unclear if the selection criteria significantly impact the benefit-risk profile by selecting for a healthier population. Extrusion of 5 mm or more was found in a relatively small number of subjects (17.0%, 30/176), and the automatic study failures were evenly distributed throughout the rest of the population. Results presented in Figure 14.

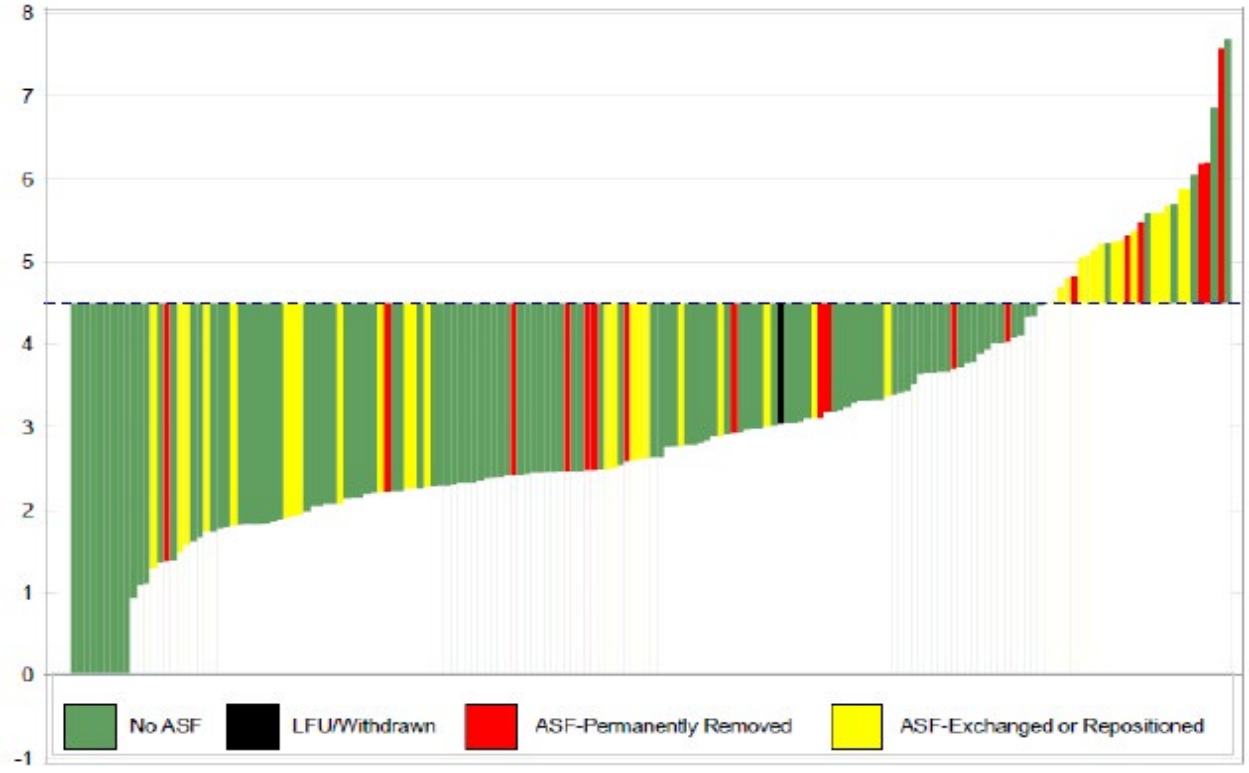


Figure 14. Waterfall chart showing SSI occurrences (X-axis) in correlation with the degree of meniscal extrusion. Y-axis shows degree of meniscal extrusion in mm (Active Implants figure)

The sponsor hypothesizes that a taller medial tibial spine prevents movement of the non-anchored device. The sponsor's scientific rationale is that the device has a "lateral bridge" that provides stability against tibial spine, and a lower tibial spine height was associated with more failure. The Agency notes that the 11 mm height selected as the cut-off is near the average for the population as shown in Figure 15. Additional discussion on the difficulty

in reproducibly measuring tibial spine height is included below in Section 6.6.4. Effect of Inter-Rater Disagreements.

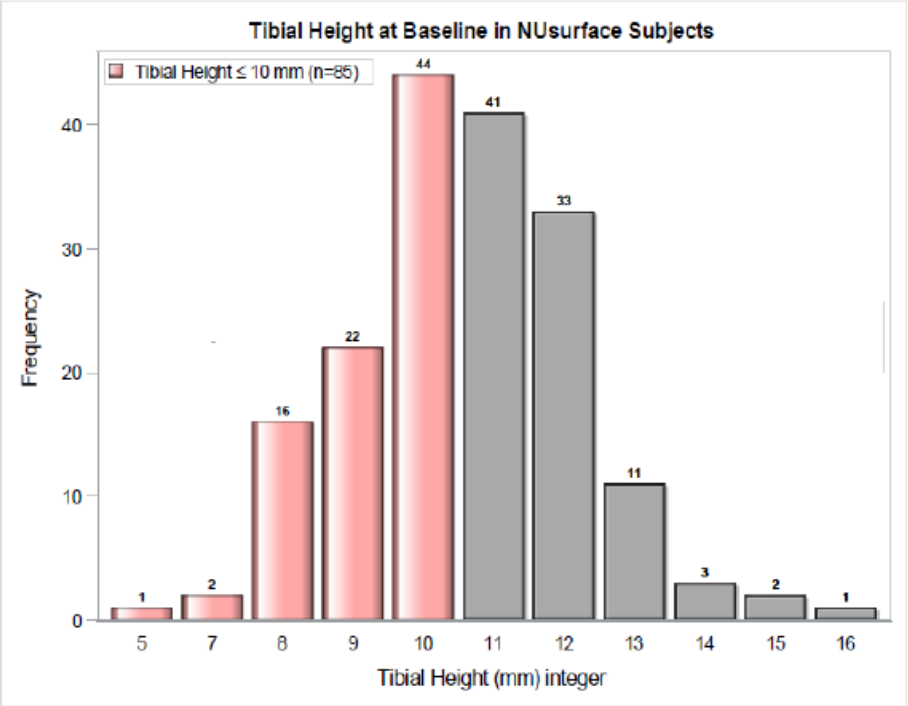


Figure 15. Tibial Spine Height histogram showing the selected population (Active Implants figure)

6.6.3 Meniscus Extrusion and Tibial Spine Height Methodology

The meniscal extrusion and tibial spine height measurements were conducted on baseline MR-scans for both NUsurface Meniscus Implant and non-surgical control subjects. Both the tibial spine height and meniscal extrusion are measured using the same radiographic imaging. Images are in the mid-coronal plane with an image slice that contains the largest tibial spine. Two independent orthopedic surgeons read all MERCURY baseline MRIs for meniscus extrusion. A single independent orthopedic surgeon and single independent radiologist served as reviewer and read the MRIs to measure tibial spine height. Examples of the measurements are provided below in Figure 16 and 17.

Because a third rater was not included to resolve disagreements, the current subgroup may not be representative of the intended clinical population. The cause of the reviewer disagreement with the tibial spine height measurement is unclear and may impact the reproducibility in a clinical setting which may subsequently impact the clinician's ability to identify patients that would benefit from the device.

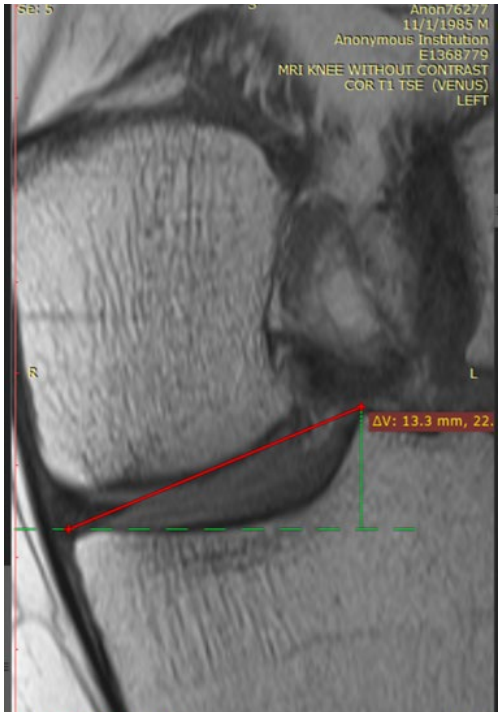


Figure 16. Tibial Spine Height - A triangle is formed starting at the tip of the cortex of the medial spine. A tangent line is drawn with the flattest region of the cortex of the medial tibial plateau. A right-angle is formed, and the vertical distance is measured. (Active Implants figure)

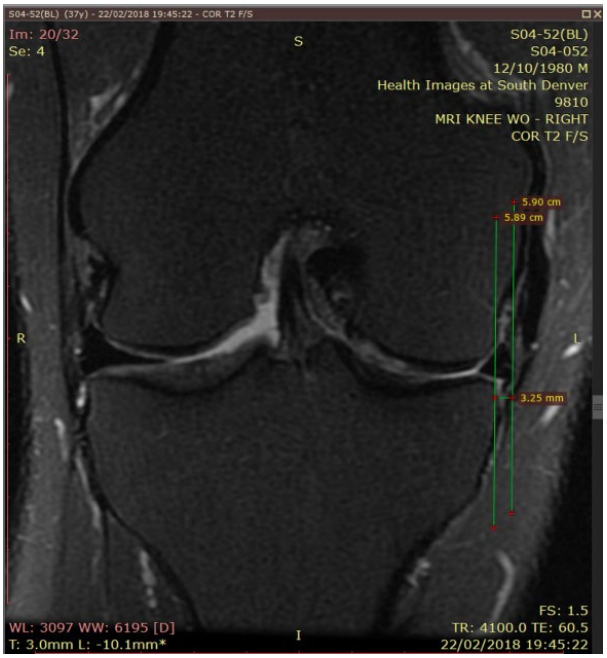


Figure 17. Meniscal Extrusion - The lateral distance between the corner of the medial tibial plateau and the outer most edge of the medial meniscus. (Active Implants figure)

6.6.4 Effect of Inter-Rater Disagreements

An analysis was performed for subjects that required an SSI (which were determined to be automatic study failures; ASF) that also considered the disagreement between the clinical raters for meniscal extrusion and tibial spine height (Table 8). As compared to the SSI rate in the original MERCURY dataset (33.7%, 58/172), the addition of meniscus extrusion exclusion criterion alone contributed to about a 10%-point decrease in SSI rate and adding the tibial spine height exclusion criterion alone contributed to about a 6%-point decrease in SSI rate. Meniscus extrusion contributed more to the reduction of SSI rate and had high rater agreement. Tibial spine height had nearly 20% inter-rater disagreement. The NUsurface subjects who were excluded because of disagreement over tibial spine height had a higher rate of surgical failure (39.4%, 13/33) than the included tibial spine height group (27.6%, 24/87). When considering the ASFs of tibial spine height alone if disagreements were included, the rate would increase from 27.6% (24/87) to 30.8% (37/120). Considering the disagreement amongst this measurement, the impact of tibial spine height on SSI rate may be as small as 3%. The high rate of disagreements between raters when defining the sub-group for the Modified MERCURY dataset contribute to the overall uncertainty about the data analysis of the modified dataset.

Table 8. Automatic Study Failure (Surgical Failure) at 24 Months based on Rater's Findings (FDA Table)

Risk Factors	Raters	N	Observed N	NUsurface	Control

Both Criteria	Both Include	110	103	12/72 (16.7%)	3/31 (9.7%)
	Disagree	46	37	**12/32 (37.5%)**	**1/5 (20.0%)**
	Both Exclude	86	83	33/67 (49.3%)	5/16 (31.3%)
Meniscus Extrusion	Both Include	210	192	34/142 (23.9%)	8/50 (16.0%)
	Disagree	7	6	**5/6 (83.3%)**	**0/0**
	Both Exclude	25	25	18/23 (78.3%)	1/2 (50.0%)
Tibial Spine Height	Both Include	128	120	24/87 (27.6%)	4/33 (12.1%)
	Disagree	46	38	**13/33 (39.4%)**	**1/5 (20.0%)**
	Both Exclude	68	65	20/51 (39.2%)	4/14 (28.6%)

Panel Non-Voting Question
Risk Mitigation:
The sponsor has identified several key considerations in risk mitigation, including the appropriate selection of patients (e.g., exclusion of meniscal extrusion ≥5mm and tibial spine height <11mm), 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 criterion.

- How might these factors impact the clinical reproducibility, particularly the clinician's ability to identify patients that would benefit from the device?

7. Clinical Data Results

The sponsor provided a sub-group analysis of a population obtained after applying additional exclusion criteria related to meniscal extrusion and tibial spine height to obtain the modified MERCURY dataset. The sponsor also provided a summary of the MCT data before and after applying these same exclusion criteria to validate the exclusion criteria for defining the sub-group. The Agency is providing a summary of the combined clinical data report emphasizing the clinical safety and effectiveness evaluations that are most relevant for the benefit risk assessment. The overall success of the study relies on reducing the rate of device-related adverse events (e.g., replacement, removal, repositioning requiring SSI) and improving the patient-reported outcomes (e.g., KOOS). These are the drivers for the benefit-risk evaluations and are key considerations for the Panel discussion.

7.1 Subject Demographics and Baseline Characteristics of modified MERCURY Dataset

A summary and comparisons of selected demographic variables and patient presurgical characteristics between the NUsurface Meniscus Implant and control groups for the modified MERCURY dataset is provided in Table 9 below. Please note that the values in Table 9 are not the observed values; the values are estimated from models by the sponsor.

Table 9. Subject Demographics for the Modified MERCURY Dataset (Active Implants Table)

Major Baseline Demographics and KOOS Values of the Modified Patient Population Study Subjects, Adjusted for Covariance. Data Presented are Numbers, Means, or Percentages.

	NUsurface Arm	Control Arm	Statistically Different?
Number of Subjects	74	35	-
Age (Years)	50.9	50.8	No, p = 0.95
% Male	82.2%	80.8	No, p = 0.87
% Right Knee	47.0%	58.1%	No, p = 0.30
BMI (Body Mass Index)	26.8	27.2	No, p = 0.50
KOOS Pain	53.7	56.3	No, p = 0.38
KOOS Overall	48.5	52.4	No, p = 0.19

Among the many baseline variables measured, some were balanced between the NUsurface group and the Control group and some were not balanced between the two groups. For the MERCURY dataset, among the 122 baseline variables the sponsor reported in their initial De Novo submission, 14 showed a relatively small p-value with magnitude of < 0.05 based on the observed data (Table B2). For the modified MERCURY dataset, among the 55 baseline variables the sponsor reported in their current De Novo submission, 3 showed a relatively small p-value with magnitude of < 0.05 based on the observed data (see table below). In each submission, the sponsor used a different analysis model with different baseline covariates included for the final outcome analyses of the primary endpoint. The source of their propensity score model for analyzing the primary endpoint in the modified MERCURY dataset is not stated. Given the small sample size in the modified MERCURY dataset, there is considerable uncertainty in the sponsor's propensity score analysis strategy to address the unbalanced baseline characteristics.

7.2 Study Success and Failure Criteria

Success criteria were different between subjects implanted with the NUsurface Meniscus Implant and the non-surgical control group. The major difference was that, for NUsurface Meniscus Implant, only surgeries that the sponsor attributed to device failures were considered ASFs. In the non-surgical control group, any surgery on the index knee was considered an ASF. Therefore, identical surgical procedures (e.g., arthroscopic meniscectomy) were not considered an ASF for the investigational group whereas they were considered an ASF for the control group.

The observed study success rate of the NUsurface Meniscus Implant group was 51.4% (37/72) which was greater than the non-surgical control group whose study success rate was 16.1% (5/31). The sponsor used a propensity score analysis to adjust for baseline differences in the outcome analysis. Therefore, their reported study success rates were 48.1% for the NUsurface Meniscus Implant group and 18.2% for the non-surgical control group when adjusted for baseline differences. MRI failure, also known as a negative MRI, is attributed to one study failure indicating either a damaged or dislocated device. The details in Table 10 below include only surgical procedures used to manage dislocated, displaced/subluxed, rotated or torn NUsurface Meniscus Implants. Table 10 does not include all secondary surgical procedures of the NUsurface Meniscus Implant population. However, it does include all surgeries performed on the Control population.

The three success criteria for the NUsurface device included (refer to Figure 12; Section 6.5.1)

- No device removals/replacements
- No radiologic failures
- Adequate KOOS pain and overall scores

Of the 74 patients in the NUsurface group, 2 were lost or withdrew their consent leaving 72 study patients. Of those subjects implanted with the NUsurface Meniscus Implant, 51.4% (37/72) met the study success criteria and 48.6% (35/72) were categorized as study failures. Of those study failures, 34.3% (12/35) resulted from secondary

surgery to manage dislocations, displaced/subluxation, rotated or torn devices or MRI 2.9% (1/35) that identified a dislocated, displaced/subluxated, rotated or torn device. Of those study failures, 71.4% (25/35) resulted from PRO criteria including inadequate pain relief 60% (21/35) despite having the device remaining implanted in the knee.

The two success criteria for the non-surgical control group included (refer to Figure 12; Section 6.5.1):

- No secondary surgery on the index knee
- Adequate KOOS pain & overall scores

Of the 35 patients randomized to the non-surgical control group, 4 were lost or withdrew their consent leaving 31 study patients. Of the remaining non-surgical control group, 16.1% (5/31) were overall study successes and 83.9% (26/31) were categorized as study failures. Of the study failures in the control group, 11.5% (3/26) failed by having surgery and 88.5% (23/26) failed by PRO criteria including inadequate pain relief 69.2% (18/26) from non-surgical treatment.

Table 10. Breakdown of the overall success criteria in the Modified MERCURY dataset (observed/unadjusted rates). (FDA Table)

	Device related SSI	**MRI failure**	**PRO failure[17]**	**Overall failure rate**	**Overall Success rate**
NUsurface	16.7% (12/72)	1.4% (1/70)	37.9% (25/66)	48.6% (35/72)	**51.4% (37/72)**
	Any SSI		**PRO failure**		
Control	9.7% (3/31)		82.1% (23/28)	83.9% (26/31)	**16.1% (5/31)**

As discussed in Section 7.1 above, the overall success rates with propensity score adjustments to account for baseline differences were 48.1% and 18.2% for the NUsurface group and the non-surgical control group, respectively. Due to the small sample size, it is unclear whether the propensity score method is applicable as the propensity model may not adequately accommodate the covariates.

7.2.1 Interpreting SSI and PRO results

The primary endpoint is a composite that features both safety (presence of SSI, MRI status) and PROs. Although the PROs generally showed good results for the NUsurface subjects, it is challenging for the Agency to interpret the PRO results in conjunction with the SSIs because the MERCURY dataset included a non-surgical control that lacks the context of care of previous non-surgical controlled studies. This makes it challenging for us to interpret the data and understand the true impact of the effect from the device.

Improvement in KOOS scores associated with non-surgical treatment from the literature range from 22.8 points to 24.3 points compared to the non-surgical control group in this study of 16.6 points. The average improvement in the KOOS scores for the surgical treatment with meniscectomy are reported as 31.6[18] points and 26.8[19] points, compared to the NUsurface surgical treatment which improved by 27.2.

When considering the results from these prior studies, it is not clear whether there is a substantial difference between the NUsurface arm PROs compared to effects of sham surgery. The magnitudes of the NUsurface

[17] PRO measures at 24 months for 6 NUsurface and 3 controls were missing or not collected

[18] Van der Graaff SJA, Eijgenraam SM, Meuffels DE, et al. Arthroscopic partial meniscectomy versus physical therapy for traumatic meniscal tears in a young study population: a randomised controlled trial. British Journal of Sports Medicine 2022;56:870-876.

[19] Katz JN, Brophy RH, Chaisson CE, de Chaves L, Cole BJ, Dahm DL, Donnell-Fink LA, Guermazi A, Haas AK, Jones MH, Levy BA, Mandl LA, Martin SD, Marx RG, Miniaci A, Matava MJ, Palmisano J, Reinke EK, Richardson BE, Rome BN, Safran-Norton CE, Skoniecki DJ, Solomon DH, Smith MV, Spindler KP, Stuart MJ, Wright J, Wright RW, Losina E. Surgery versus physical therapy for a meniscal tear and osteoarthritis. N Engl J Med. 2013 May 2;368(18):1675-84. doi:10.1056/NEJMoa1301408. Epub 2013 Mar 18. Erratum in: N Engl J Med. 2013 Aug 15;369(7):683. PMID: 23506518; PMCID: PMC3690119.

datasets closely mirror the historical more dedicated physical therapy protocols and arthroscopic partial meniscectomy. The similarity of the magnitude of these scores raises uncertainty as to whether the results are partially due to the placebo effect or pain relief due to the partial meniscectomy required to implant the device. The outlying values of the KOOS and WOMET non-operative control scores from the MERCURY and modified MERCURY datasets also may reflect the low expectation of the control patients who had no new treatment. Because it was impossible to blind these groups, there may be responder bias and expectancy bias inherent in the PROs. These low values of the controls and the "in line" values of the experimental cohorts create uncertainty regarding comparisons between control and experimental arms.

Table 11. Changes in PROM scores after treatment in the modified MERCURY dataset compared to literature from Van der graft et al.[20], Katz et al.[21], and Silhoven et al.[22].

	Change in PROM Scores after RX	
	KOOS Pain	WOMET
MCT*	29.9	
MCT* Modified	27.4	
MERCURY NUsurface	27.7	36.3
MERCURY Control	16.6	18.3
Modified NUsurface	24.3	30.4
Modified Control	11.8	12.9
Partial Meniscectomy#	31.6	33.8
Physical Therapy#	24.3	33
Partial Meniscectomy^	26.8	
Physical Therapy^	27.3	
Partial Meniscectomy&		26.6
SHAM Surgery&		31.8

* Multi-center trial cohort (used for CE)
# 18-45 years old without OA (Van der graft 2022)
^ >45 years old with mild-moderate OA (Katz 2013)
& 35-65 years old with mild OA (Silhoven 2018)

Panel Non-Voting Question
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 (ASF). The Statistical Analysis Plan for the modified MERCURY dataset predefined Automatic Study Failures (ASF) as Secondary Surgical Interventions (SSI) to permanently remove the device and revisions to reposition or replace the device.

[20] Van der Graaff SJA, Eijgenraam SM, Meuffels DE, et al. Arthroscopic partial meniscectomy versus physical therapy for traumatic meniscal tears in a young study population: a randomised controlled trial. British Journal of Sports Medicine 2022;56:870-876.
[21] Katz JN, Brophy RH, Chaisson CE, de Chaves L, Cole BJ, Dahm DL, Donnell-Fink LA, Guermazi A, Haas AK, Jones MH, Levy BA, Mandl LA, Martin SD, Marx RG, Miniaci A, Matava MJ, Palmisano J, Reinke EK, Richardson BE, Rome BN, Safran-Norton CE, Skoniecki DJ, Solomon DH, Smith MV, Spindler KP, Stuart MJ, Wright J, Wright RW, Losina E. Surgery versus physical therapy for a meniscal tear and osteoarthritis. N Engl J Med. 2013 May 2;368(18):1675-84. doi: 10.1056/NEJMoa1301408. Epub 2013 Mar 18. Erratum in: N Engl J Med. 2013 Aug 15;369(7):683. PMID: 23506518; PMCID: PMC3690119.
[22] Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Kalske J, Ikonen A, Järvelä T, Järvinen TAH, Kanto K, Karhunen J, Knifsund J, Kröger H, Kääriäinen T, Lehtinen J, Nyrhinen J, Paloneva J, Päiväniemi O, Raivio M, Sahlman J, Sarvilinna R, Tukiainen S, Välimäki VV, Äärimaa V, Toivonen P, Järvinen TLN; FIDELITY (Finnish Degenerative Meniscal Lesion Study) Investigators. Arthroscopic partial meniscectomy versus placebo surgery for a degenerative meniscus tear: a 2-year follow-up of the randomised controlled trial. Ann Rheum Dis. 2018 Feb;77(2):188-195. doi: 10.1136/annrheumdis-2017-211172. Epub 2017 May 18. PMID: 28522452; PMCID: PMC5867417.

17% (12/72) of NUsurface subjects experienced a device-related SSI and 25% (3/12) of those subjects had more than one SSI.

- Please discuss the adequacy of the overall clinical success criteria and the clinical significance of the SSIs related to the device.
- Please comment on the classification of these SSIs as ASFs.

7.3 Clinical Safety Evaluation

The safety evaluations for the NUsurface Meniscus Implant consisted of adverse event (AE) collection and MRI. In addition to planned visits and imaging, safety information was also captured during unscheduled visits (e.g., if a device suddenly dislocated, needing immediate clinical evaluation and SSI).

AEs were recorded peri-operatively or at baseline and annually thereafter until the last subject reached 2 years follow-up. Additional follow-ups were scheduled for 36 and 60 months (SUN only); however, as previously discussed, a full set of long-term data has not been made available for the De Novo request. All AEs were either serious device/procedure-related, serious non-device-related, non-serious device/procedure-related, or non-serious non-device-related. AEs may require an unscheduled visit or have been captured at the next follow-up.

The sub-group population was also assessed for safety based on MRI imaging. MRIs were scheduled to be taken at baseline, and at 1.5, 12, and 24 months after surgery. These images are used to evaluate changes to device integrity and positioning, and may identify problems before they become symptomatic.

A summary of safety information followed by in-depth discussions of the AEs and imaging for each study group is outlined below.

7.3.1 Overview of Clinical Safety Results

The NUsurface group had a total of 124 adverse events in 69.4% (50/72) NUsurface subjects[23], compared to the non-surgical control group which had a total of 14 adverse events in 35.5% (11/31) subjects.

[23] The study started with N=35 controls and N=74 NUsurface subjects but 2 NUsurface and 4 control subjects were lost to follow-up or withdrew consent by 24 months. Only a subset of NUsurface subjects originally enrolled in the SUN study were followed out to 60 months.

Table 12 Adverse Events at Index Knee or Possibly Related to Treatment from 0-60 months (Active Implants Table) (page 1 of 2)

	Control (N=35) 33199 patient-days			NUsurface (N=74) 74982 patient-days			
Body System / Preferred Term	n*	n**	%	n*	n**	%	p
Any Adverse Event							
All	**14**	**11**	**31.4%**	**124**	**50**	**67.6%**	**<0.001**
UNCORRECTABLE DEV. FAILURE							
All	.	.	-	10	10	13.5%	-
DAMAGE	.	.	-	3	3	4.1%	-
DISLOCATION	.	.	-	1	1	1.4%	-
DISLOCATION AND DAMAGE	.	.	-	2	2	2.7%	-
KNEE GENERALIZED OSTEOARTHRITIS	.	.	-	1	1	1.4%	-
LIMITED ROM	.	.	-	1	1	1.4%	-
NON-SPECIFIC KNEE PAIN	.	.	-	1	1	1.4%	-
ROTATION	.	.	-	1	1	1.4%	-
CORRECTABLE DEVICE FAILURE							
All	.	.	-	29	24	32.4%	-
DAMAGE	.	.	-	18	16	21.6%	-
DISLOCATION	.	.	-	4	4	5.4%	-
DISLOCATION AND DAMAGE	.	.	-	4	4	5.4%	-
FAT PAD SYNDROME / PLICA	.	.	-	1	1	1.4%	-
ROTATION	.	.	-	2	1	1.4%	-
EXPECTED DEVICE EFFECTS							
All	.	.	-	12	9	12.2%	-
NOISE	.	.	-	12	9	12.2%	-
CARDIOVASCULAR							
All	0	0	0.0%	3	3	4.1%	0.550
DEEP VEIN THROMBOSIS	0	0	0.0%	3	3	4.1%	0.550
GASTROINTESTINAL							
All	0	0	0.0%	1	1	1.4%	1.000
OTHER GASTROINTESTINAL ILLNESS / DISORDER	0	0	0.0%	1	1	1.4%	1.000
KNEE							
All	14	11	31.4%	69	37	50.0%	0.098
ADHESIONS	0	0	0.0%	4	4	5.4%	0.303
ARTHROFIBROSIS	0	0	0.0%	1	1	1.4%	1.000
BAKER'S CYST	0	0	0.0%	2	2	2.7%	1.000

p values determined using the Fisher exact test. n*=Total number of reported events. n**=number of patients with a reported event.

Table 13. Adverse Events at Index Knee or Possibly Related to Treatment from 0-60 months (Active Implants Table) (page 2 of 2)

	Control (N=35) 33199 patient-days			NUsurface (N=74) 74982 patient-days			
Body System / Preferred Term	n*	n**	%	n*	n**	%	p
KNEE							
DAMAGE	0	0	0.0%	1	1	1.4%	1.000
DEHISCENCE	0	0	0.0%	1	1	1.4%	1.000
DISLOCATION	0	0	0.0%	2	2	2.7%	1.000
EFFUSION (*)	**1**	**1**	**2.9%**	**27**	**20**	**27.0%**	**0.002**
FEMORAL OSTEONECROSIS	0	0	0.0%	1	1	1.4%	1.000
INFECTION	0	0	0.0%	1	1	1.4%	1.000
KNEE GENERALIZED OSTEOARTHRITIS	1	1	2.9%	2	1	1.4%	0.541
KNEE SYNOVITIS	1	1	2.9%	2	2	2.7%	1.000
LIMITED ROM	0	0	0.0%	3	3	4.1%	0.550
MECHANICAL SYMPTOMS	0	0	0.0%	4	3	4.1%	0.550
NON-SPECIFIC KNEE PAIN	7	7	20.0%	10	9	12.2%	0.384
OTHER KNEE INJURY	3	3	8.6%	4	4	5.4%	0.678
PATELLOFEMORAL PAIN SYNDROME	1	1	2.9%	1	1	1.4%	0.541
POST-TRAUMATIC PATELLOFEMORAL PAIN	0	0	0.0%	2	2	2.7%	1.000
SAPHENOUS NEUROMA	0	0	0.0%	1	1	1.4%	1.000

p values determined using the Fisher exact test. n*=Total number of reported events. n**=number of patients with a reported event.

7.3.2 Investigational Group Safety Information

The largest category of SAE reflected physical or positional changes to the device resulting in an SSI. These changes included rotations (2.7%, 2/72), dislocations (15.3%, 11/72), and device damage (e.g., tears; 29.2%, 21/72). For some SAE categories, individual subjects experienced more than one SAE necessitating an SSI, and some subjects experienced more than one occurrence of the same SAE and required an additional SSI. For example, 23 device damage SAEs were reported for 21 subjects and 3 rotations were reported in 2 subjects. In some subjects, a device was noted as dislocated or was replaced or relocated in an SSI, and subsequently dislocated a second time.

During the 24-month time frame reported for this study, 17% (12/72) of implant subjects had at least one SSI for rotations, dislocations, exchanges, removals and lysis of adhesions. The goal of the modified MERCURY dataset was to reduce the rate of SSI when compared to the MERCURY dataset (34%, 58/172). The Modified MERCURY Population has approximately twice the surgical failure rate as compared with the non-surgical control group (7.2%, 3/31). Table 13 reports the surgical failures alone.

Table 14. Adjusted Surgical Failure for the modified target population (extrusion and tibial height) (Active Implants Table)

	Control		NUsurface		
Variable	n/N	Percent	n/N	Percent	p
6 Weeks	0/35	0%	0/74	0%	.
6 Months	1/34	2.9% (0.0%)	0/74	0%	.
12 Months	3/32	9.4% (8.9%)	6/74	8.1% (8.2%)	0.911
24 Months	3/31	9.7% (7.2%)	12/72	16.7% (17.0%)	0.173

p values calculated using logistic regression adjusted for propensity score strata.

The 17% (12/72) SSI rate does not capture subjects that had multiple revision procedures. Of the subjects with SSI, 25% (3/12) had multiple SSI to reposition or replace the device. An additional subject had a procedure to lyse adhesions and resect scar tissue before a subsequent procedure to replace the device.

In addition to the 17% (12/72) SSI rate specifically related to the NUsurface device, 25% (3/12) of the patients who experienced failures of their NUsurface Meniscus Implant required treatment with permanent arthroplasty replacements. The additional surgeries needed by subjects whose device failed included the following during the 24 month follow-up:

- 2 subjects required unicompartmental knee arthroplasties;
- 1 subject required total knee arthroplasty;

The SAE rates were higher in the investigational group compared to control and were reported to be statistically different (p=0.002) for effusion (27%, 20/72 NUsurface vs 3%, 1/31 control) primarily occurring at early timepoints. Additionally, the following categories were unique to the investigational group: noise (12.2%, 9/72), device damage (29.2%, 21/72 NUsurface), device dislocation (15.3%, 11/72 NUsurface), and device rotation (2.7%, 2/72 NUsurface).

Although the specific SAE (e.g., dislocation, rotation, damage) is varied, there is consistency to the failure mode of the device. Images are included below in Figures 19-20 and Table 14 for illustration. Dislocations could occur both anterior or posterior, and some were displaced into the suprapatellar pouch. The fracture or tearing of the device was consistently found in the lateral bridge area of the device which is the portion of the device that sits between the tibial spine and the femoral condyle.

When considering the sponsor's retrieval analysis (full images in Appendix B), we considered the pattern of damage and device wear, which is almost exclusively lateral abrasion and tearing on the lateral wall. The NUsurface implant is a "non-anchored" (un-fixed) interpositional device and the 2 mm of remaining meniscal tissue along the periphery does not integrate into the device. One hypothesis is that the lateral wall of the "cup design" sits in an anatomic location where no normal tissue usually exists. When the pinching load between the femoral condyle and the medial tibial spine wall exceeds the material properties of the implant, abrasion and tearing occurs. A typical case example from the retrieval set demonstrates what is described as a device "showing a good match of the implant to the joint" on the 6 week image and the implant with an observable tear that is wider close to the high load area on the 12 month image (Figure 19).

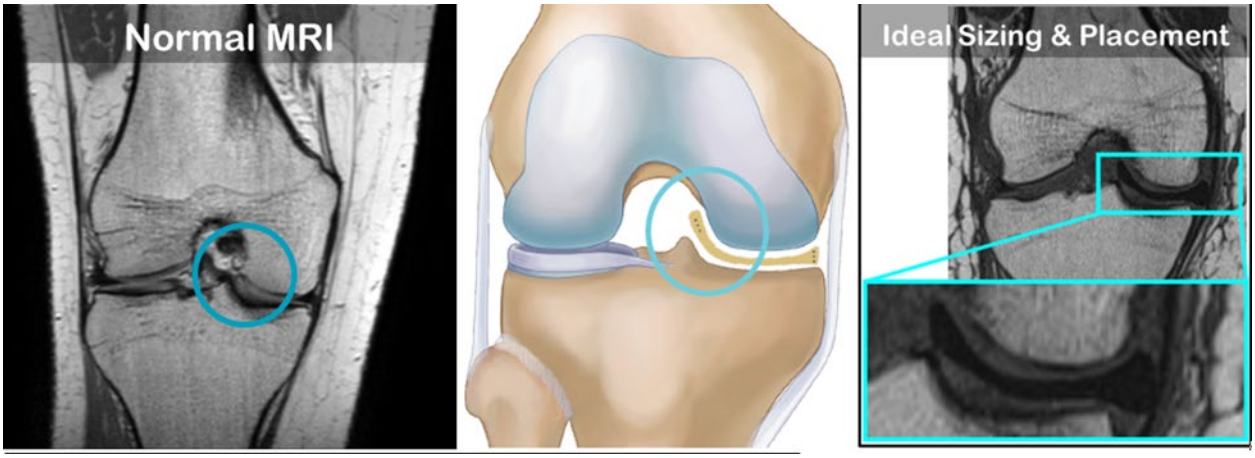


Figure 18. Normal MRI without natural tissue between femoral condyle and tibial spine (Left, FDA Image), Cartoon of NUsurface Meniscus Implant in position (Center, Active Implants image), MRI image of ideal sizing and placement (Right, Active Implants image)

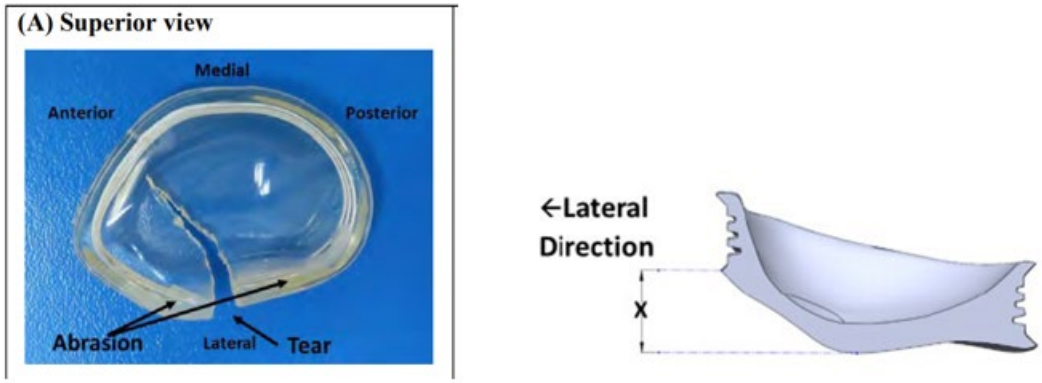


Figure 19. (A) Superior view of lateral tear in a NUsurface Meniscus Implant (Left, Active Implants image) (B) Diagram of meniscal cup pinpointing the lateral wear pattern (Right, FDA image)

Further evidence to support the lateral overload hypothesis is seen in the case below. The MRI that shows white (T2 MRI signal) bone edema where fluid from pathology is seen where the lateral device contacts the medial tibial spine (Figure 20, below left). At arthroscopy when the device was removed, a new full thickness (grade IV) cartilage lesion is seen in this location (Figure 20, below center). This location also corresponds to the lateral failure of the implant which is also seen (Figure 20, below right).

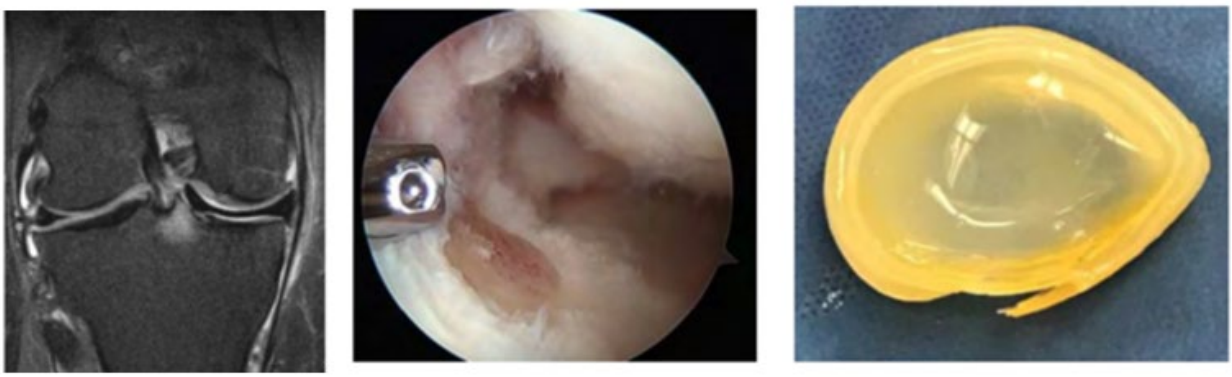
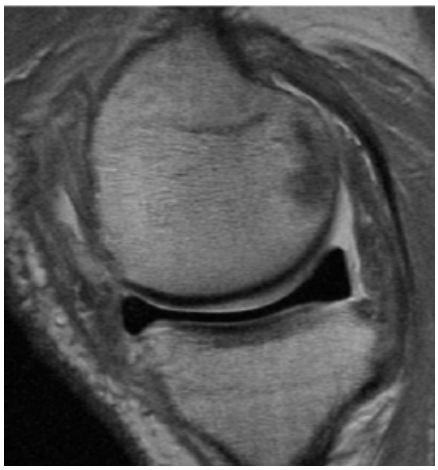
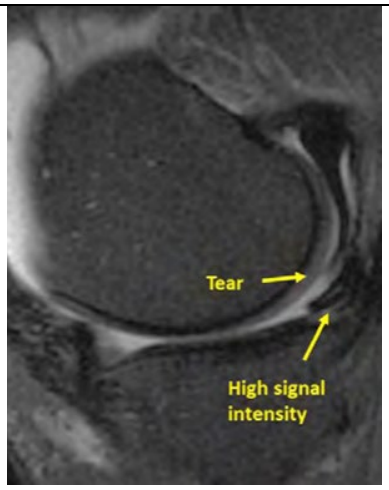
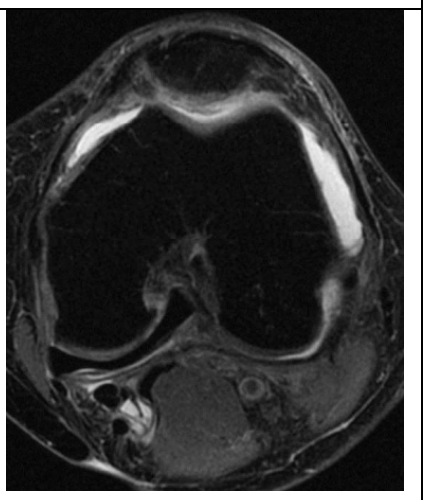
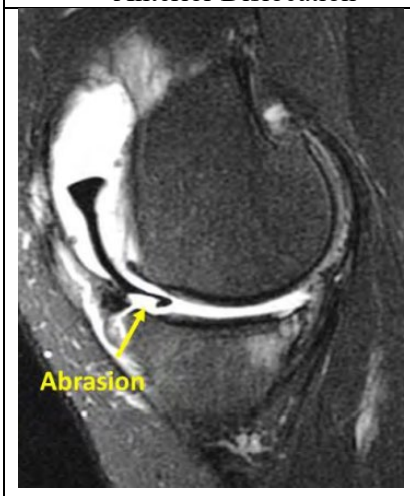
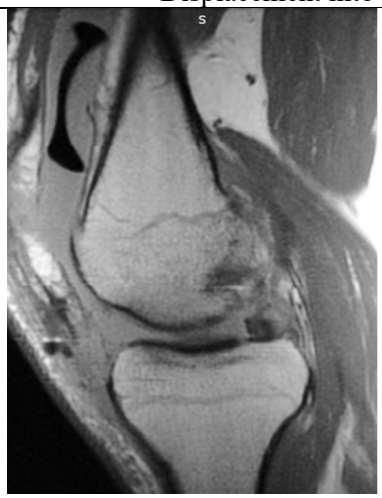
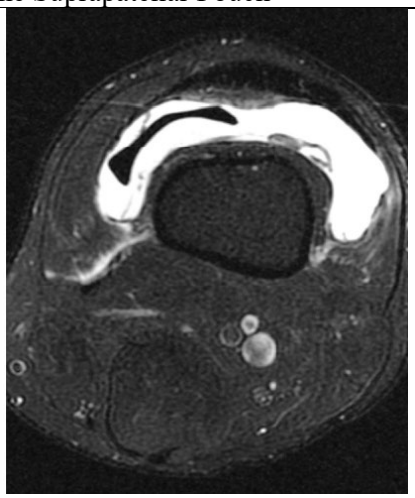
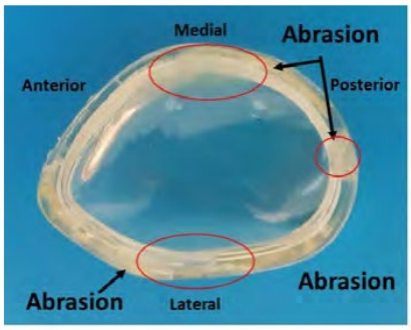
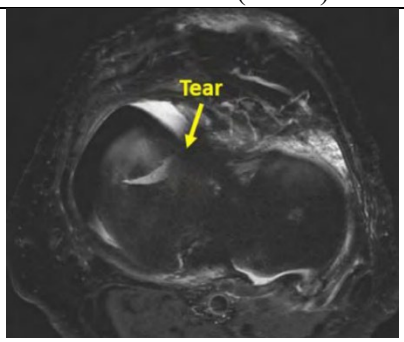


Figure 20. MRI demonstrating bone edema where the lateral device contacts the medial tibial spine (left), New full thickness (grade IV) cartilage lesion on tibia identified following implant removal (center), Tear to the lateral aspect of the NUsurface Meniscus Implant (right) (Active Implants figure)

We note that the shape of the device is closely associated with a discoid meniscus pathophysiology, which is an anatomic variant that may occur on lateral or medial compartments of the knee. The clinical symptoms of a discoid meniscus can include mechanical noises (clunks and clicks) as well as effusions with bending and squatting. Tearing of a discoid meniscus occurs in the high load portions of the knee between the femur and the tibia and can be a source of symptoms. A variation of discoid meniscus that is unfixed to the posterior capsule (Wrisberg variant) causes more mechanical symptoms when the discoid meniscus translates from the normal position in the knee. Given the similarities between the device AE/SAE profile and a discoid meniscus, this raises the possibility that the difficulties maintaining the device in position are due to the device's design itself.

Table 15. MRI and Device Images from Device-Related Failures (Active Implants Figures, FDA compilation)

<table>
<tr><th colspan="2" rowspan="2">Normal Device Placement</th><th colspan="2">Dislocations</th></tr>
<tr><td colspan="2">Posterior Dislocation</td></tr>
<tr><td colspan="2">  </td><td> 
</td><td>  </td></tr>
<tr><td colspan="4">Dislocations (continued)</td></tr>
<tr><td colspan="2">Anterior Dislocation</td><td colspan="2">Displacement into the Suprapatellar Pouch</td></tr>
<tr><td colspan="2"> 
</td><td>  </td><td>  </td></tr>
<tr><td colspan="4">Device Damage</td></tr>
<tr><td>Abrasions</td><td>Lateral Tear</td><td colspan="2">Lateral Tear (In situ)</td></tr>
<tr><td> 
</td><td>  </td><td colspan="2"> 
</td></tr>
</table>

In face of the numbers of mechanical failures reported as device damage, dislocation, and rotation, the Agency also considered AEs that potentially suggest joint irritation similar to an unstable discoid meniscus. The following AEs are ones that may be device-related but, because of uncertainty, the sponsor did not attribute to the device:

- Effusion (27.0%, 20/72 investigational vs 2.9%, 1/35 control)
- Adhesions (5.4%, 4/72 investigational vs 0% control);
- Arthrofibrosis (1.4%, 1/72 investigational vs 0% control);
- Limited range of motion (5.4%, 4/72 investigational vs 0% control); and

In addition, there were many subjects who reported noise events (mechanical symptoms including clicking, popping, and squeaks) (16%, 12/72 investigational vs 0% control).

There was no information provided about SSIs performed outside of the 24-month study window for the modified MERCURY dataset. In the MERCURY dataset, an additional 31 SSIs were performed outside of the 24-month study window but before the closure of the study, including an additional 15 subjects that had not had an SSI during the initial 24 month window.

MRI (T1 weighted with fat suppression, T2 weighted fluid sensitive) was also used to evaluate the knee joint with respect to the integrity and position of the device. The information was used for the primary endpoint (i.e., MRI positive or negative). The sponsor also performed an analysis of the cartilage to support secondary endpoints, but this evaluation was determined to be subject to considerable uncertainty.

7.3.3 Non-Surgical Control Group Safety Information

A total of 35 subjects were identified in the modified MERCURY dataset, and 31 subjects completed 24 months follow-up. The following 3 surgeries were reported in this group:

- Unicondylar knee arthroplasty 2.9% (1/35);
- High tibial osteotomy (HTO) 2.9% (1/35); and
- Arthroscopic Debridement and Meniscectomy 2.9% (1/35).

These 3 procedures, which the sponsor considers failures, raise uncertainty about whether the subjects were eligible for enrollment in the study. In many cases, the indications for these surgical procedures correspond to exclusion criteria. In addition, each of these three surgeries happened within an unexpectedly short amount of time. The investigational and non-surgical controls underwent a different level of screening of patients because the NUsurface Meniscus Implant group was arthroscopically screened as part of the surgical procedure to implant the device. This difference introduces additional uncertainty into the subjects enrolled in the study and by extension the results of the study. The sponsor provided narrative for each of the SSI/failed subjects in the non-surgical control group. The details of each surgery, and the potential exclusion criteria, are:

- **Unicondylar arthroplasty.** A subject received a unicondylar arthroplasty within 5 months of the study start date. The progression to arthritis severe enough for implantation of a unicondylar arthroplasty device within a relatively short time raises uncertainty about whether the patient should have met the exclusion criterion "*2. Has evidence of an Outerbridge Grade IV cartilage loss on the medial tibial plateau or femoral condyle that potentially could contact a NUsurface implant (e.g., a focal lesion > 0.5 cm^2 correlating to a circular defect of > 8 mm in diameter).*"
- **HTO.** A subject received an HTO 7 months after study start date. The level of varus deformity to support surgical intervention with an HTO would meet exclusion criterion "*5. Has a varus or valgus knee deformity > 5° requiring a tibial or femoral osteotomy*".
- **Arthroscopic Debridement and Meniscectomy**. Less than 3 months after inclusion in the study as a control patient, a patient with multicompartment degenerative changes received arthroscopy with "chondroplasty" of the medial femoral condylar cartilage for diffuse grade III and areas of grade IV

changes with a degenerative meniscus tear. Described as "left knee arthroscopy, minor synovectomy in the patellofemoral joint, chondroplasty in the medial compartment of diffuse grade III with some minor superimposed grade IV changes on the femoral condyle, and significant medial meniscectomy for a complex flap tear."

7.4 Clinical Effectiveness Evaluation

The primary endpoint included PRO measures (KOOS scores) as part of the composite assessment. The sponsor also included individual PRO measures as secondary endpoints. In addition, the sponsor also provided an MRI-based cartilage assessment on a limited number of subjects. Together, these assessments provide information on the device's effectiveness.

7.4.1 KOOS Patient Reported Outcomes

There were 9 subjects (6 NUsurface and 3 Control) with SSI that were not assessed for PROs, leaving only 66 NUsurface and 28 control subjects with PROs at 24-months. The sponsor originally planned to perform a sensitivity analysis using last observation carried forward (LOCF). At 24-months, 37.9% (25/66) of NUsurface subjects with PRO data within the modified MERCURY dataset did not meet success criteria for PROs. 82.1% (23/28) of control subjects also did not meet the success criteria for PROs. The PROs were the major contributor to the overall failure for both NUsurface (71.4%, 25/35) and Control (88.5%, 23/26) subjects.

The exclusion of the PROs from 6 surgical failure patients represents a deviation from the study protocol and may have impacted PRO analysis and the end of study outcome results. The study protocol notes that, "*Patients in the Investigational Group that had the device removed will continue to be studied because those patients would have been exposed to the investigational device. Patients in the Control Group who fail by receiving surgery (with the type of surgery being captured) will be followed so as to gather adverse event information to aid in the interpretation of the adverse event data in the Investigational Group*." The missing data from these 6 device failure patients represent 50% (6/12) of the surgical failure group, 17.1% (6/35) of the total NUsurface failure group, and 8.3% (6/72) of the total population who received the NUsurface device.

Table 16. Breakdown of the overall clinical success criteria for NUsurface subjects. (FDA Table)

NUsurface Subjects	Device related SSI	PRO failure[24]	PRO failure w/o SSI	Overall failure rate
MERCURY Dataset[25]	34% (58/172)	35% (53/153)	24% (36/153)	**55% (95/172)**
Modified MERCURY Dataset[26]	17% (12/72)	38% (25/66)	35% (23/66)	**49% (35/72)**

The sponsor's initial rationale for the modified MERCURY dataset was to identify a subpopulation with a reduced SSI rate compared to the original MERCURY dataset. The original dataset is described in Appendix A and a summary of the primary endpoint is summarized in Table 16. The summary results demonstrate the selection of patients based on less meniscus extrusion and higher medial tibial spines height appears to select a group who fail less by surgery (17% vs 34%) but have a higher failure rate by PRO scores in subjects that did not fail from device related SSI (35% vs 24%). Overall failure rates are nearly identical between the MERCURY and modified MERCURY database based on the subgroup analysis (55% vs 49%).

[24] PRO failures are not mutually exclusive from device related SSI. There were 17 subjects in the MERCURY and 2 in the Modified MERCURY Datasets that were both Device related SSI and PRO failures. Subjects that did not have a device failure leading to SSI but still did not reach PRO success criteria are shown in "PRO failure w/o SSI."

[25] The total number of subjects that had PRO measures at 24 months was 153 because 19/172 NUsurface subjects in the MERCURY dataset did not have PRO collected or were missing.

[26] PRO measures at 24 months for 6/72 NUsurface in the Modified MERCURY dataset were missing or not collected

Panel Non-Voting Question
Sub-group Analysis:

The sponsor provided a subgroup analysis intended to identify a modified target population with a reduced rate of SSIs from the unmodified MERCURY dataset. The modified MERCURY dataset involves the exclusion of meniscal extrusion ≥5mm and tibial spine height <11mm.

- Please comment on the overall success rate of the modified MERCURY dataset.
- Please comment on whether the modified MERCURY dataset provide sufficient information to understand whether the device improves pain and function in the medial compartment of a knee in which the medial meniscus has been resected.
- Please comment on the study design characteristics as different datasets were utilized compared to a non-surgical control for the MERCURY trial, modified MERCURY dataset, and MCT study.
- 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?

7.4.2 Secondary Endpoints

The sponsor planned to assess 19 secondary endpoints following the primary endpoint. The results of the statistical analysis are provided in Table 17.

Table 17. Overview of endpoints in the modified MERCURY study and significance outcomes for each. (Active Implants Table)

Number	Hierarchical Rank Order	Calculated p Value	Superior?
1	**Overall Success at 24 Months**	0.011	Yes
2	24 Month VAS vs Baseline	0.036	Yes
3	24 Month MRI vs. Baseline of Cartilage Condition in Medial Compartment	0.006	Yes
4	24 Month IKDC SKEF Score vs Baseline	0.003	Yes
5	24 Month QALY Score (using EQ-5D)	0.810	No
6	24 Month KOOS Pain	0.101	No
7	24 Month KOOS Overall	0.273	No
8	12 Month KOOS Pain	0.107	No
9	12 Month KOOS Pain vs Baseline	0.019	Yes
10	12 Month VAS vs Baseline	0.002	Yes
11	12 Month KOOS Overall vs Baseline	0.004	Yes
12	12 Month MRI vs Baseline Cartilage Thickness at Center of Medial Tibial Plateau	-	NA*
13	12 Month IKDC SKEF Score vs Baseline	0.039	Yes
14	12 Month QALY Score (using EQ-5D)	0.850	No
15	24 Month Return to Work	-	NA*
16	6 Month KOOS Pain	0.054	No
17	6 Month VAS vs Baseline	<0.001	Yes
18	6 Month IKDC SKEF Score vs Baseline	0.003	Yes
19	6 Month KOOS Overall	0.034	Yes
20	6 Month QALY Score (using EQ-5D)	0.155	No

The sponsor's data presentation shows that all the secondary endpoints, except two that could not be evaluated, were statistically significant. However, it is necessary to consider the SAP and whether the ultimate results

adequately control for multiplicity. It is noteworthy that the SAP called for a hierarchical rank order analysis where a test was conducted for each individual secondary endpoint until the test is not successful (e.g., a p-value >0.05), which controls for multiplicity. However, there were two endpoints that could not be evaluated, and the sponsor continued the assessment. Additionally, there was considerable uncertainty in the MRI assessments, which featured in two of the secondary endpoints including the second ranked endpoint.

7.4.3 Other Assessments

The sponsor included an additional assessment of cartilage thickness. This was originally proposed as a secondary endpoint. However, there was no pre-specified protocol for the assessments. The following major limitations were identified in the presented data:

- **Inability to measure tibial cartilage**. The sponsor found that evaluating the tibial cartilage thickness was "*technically beyond the capability of MRI scans to provide reliable data and no measurements were possible*."
- **Single reviewer not blinded to treatment**. Although blinded to subject information, it was not possible to blind the reviewer to the presence of the device, which was visible on the MRI.
- **Lack of confirmatory data**. MRI-based imaging has error associated with cartilage measurements, and there was no direct confirmation (e.g., arthroscopic evaluation).

Cumulatively, these uncertainties make it challenging for the Agency to rely upon the cartilage assessment with any degree of certainty as an evaluation of the device's effectiveness.

8. Patient Preference Information (PPI)

FDA relies on valid scientific evidence[27] when making benefit and risk determinations and values patients' perspectives. Patient preference information (PPI) is one specific type of patient perspective information. PPI is defined as 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. PPI may be submitted for consideration as valid scientific evidence as part of FDA's benefit-risk assessment during its review of PMAs, HDE applications, and De Novo requests. Submission of PPI to FDA is voluntary. PPI may not be relevant or appropriate for all device types. However, it may be useful for sponsors to collect and submit such information for certain PMAs, HDE applications, and De Novo requests, particularly for those product types and diseases or conditions where usage decisions by patients are preference sensitive.[28] In FDA's Guidance on PPI[29] , PPI study qualities are outlined that are considered, among other things, when deciding whether PPI constitutes valid scientific evidence.

The sponsor has submitted information from a PPI study in the current De Novo request to support the benefit-risk assessment. This is the 7th PPI study conducted by the Sponsor as related to this device.

8.1 Current PPI Study

The purpose of the study was to determine how much additional risk of reconstructive knee surgery patients would be willing to accept in exchange for a certain amount of pain reduction (also referred to as maximum acceptable risk). The study intended to collect PPI using the techniques described in the Hauber and Colter

[27] See 21 CFR 860.7(c)(2).

[28] Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian *Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications (page 3).

[29] *Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.

publication.[30] The study was intended to indicate at what point the risk outweighed the benefit from the treatment. This "threshold technique" indicates when the tipping point would occur. Appendix D contains information regarding this 7th PPI study.

The study was conducted by creation of a survey that asked 207 respondents about options for surgical treatment for knee pain. The Sponsor did not seek IRB approval and study participants did not provide informed consent. The survey was created using a structure that is not in alignment with most published health preference literature The analysis (an ANOVA) and linear probability model (LPM) are not consistent with published literature approaches for analyzing threshold technique data, which is typically done using a biprobit or an interval regression analysis (see Appendix D5). Therefore, the results presented by the sponsor are challenging to interpret and needed estimates of patient preferences to inform the benefit-risk assessment were not provided.

The survey was created in a way that may have presented the information in a biased format (see Appendix D2 and D4, Questions on pages 96 and 97), impacting the interpretability of the resulting information. Since the analysis was not conducted in a way consistent with published literature, the results are challenging to interpret. In the sponsor's survey, the presentation of the benefits and risks appear to overstate the positive benefits and minimize the risks (see examples on pages 87 & 89 of the survey in Appendix D2). The result of this presentation approach can lead to an overestimation of the willingness of a respondent to accept risks associated with the device intervention. The review team raised concerns that the risks and benefits of the presented options were not accurately conveyed in an unbiased format. As stated in the CDRH PPI Guidance (Page 12), "*the study quality can be established if it follows guidelines for good research practices established by a recognized professional organization. For example, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published a set of good research practices for preference-based methods*."

Because the elements of the current PPI study do not align with accepted preference-based, good research methods, the Agency has concerns with relying on the results of the study. For example, the conduct of the threshold technique was not in alignment with other threshold technique studies in published literature, nor was the analysis done in a way that was consistent with other published literature using the threshold technique. The statistical model did not provide a clear evaluation of the tradeoff, and the resulting analysis did not provide a useful measure of the value of treatment relative to the alternative. (See Appendix D.2, D.4, and D.5).

The concerns identified in the 7th PPI survey are similar to those identified for each of the previous PPI studies. The sponsor intended to leverage the PPI study to support the benefit-risk assessment for the current De Novo request; however, the current survey instrument did not adequately resolve the issues present in previous iterations. Given the major issues present, the Agency is concerned that the current PPI study does not provide valid, scientific evidence that would contribute significantly to the benefit-risk determination.

Panel Non-Voting Question
Patient Preference Information (PPI):

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 7).
- Please discuss the contribution of the PPI studies to the final benefit-risk determination.

9. Clinical Data and Discussion

In general, the NUsurface subjects appeared more likely to be considered Overall Successes compared to the non-surgical control arm, and experienced improvements in several PROs for pain and function. However, there are

[30] Hauber B, Coulter J. Using the Threshold Technique to Elicit Patient Preferences: An Introduction to the Method and an Overview of Existing Empirical Applications. Appl Health Econ Health Policy. 2020 Feb;18(1):31-46. doi: 10.1007/s40258-019-00521-3. PMID: 31541362.

several findings that make it challenging to understand the device's benefit-risk profile - most notably, the rate of SSIs and SAEs in the NUsurface arm, and the root cause of the device failures, including device damage, dislocation, and rotation, that led to the SSI. Additionally, it is difficult to interpret the PRO improvement in the context of the high SSI rate, and the risks (short- and long-term) associated with the NUsurface Meniscus Implant.

9.1 Challenges in Data Interpretation and Confounding Factors

On the surface, the modified MERCURY dataset presented support that the device offers benefit. However, there are also considerable risks and confounding factors that complicate FDA's ability to draw conclusions. Our key data interpretation challenges and confounding factors are:

- **Rate of SAEs and SSI-related SAEs that exceed sponsor's initial safety goal**. Although many subjects experienced improvements in PROs for pain and function, a large percentage also experienced an SAE, which required surgical intervention. The sponsor pre-defined a safety hypothesis for the SUN study that device-related SAE would be less than 10%. NUsurface Meniscus Implant subjects had more than twice as many AEs and five times as many SAEs as compared to the non-surgical control subjects, and the modified MERCURY dataset reported a 17% (12/72) SSI rate for rotations/dislocations/removals at 24 months. This SSI rate exceeds the predefined safety hypothesis. The high rate of SSI presents risk to the subject, and it is unclear how to interpret the risk associated with the SSI in light of the improvements in PRO pain and function. In the absence of longer-term data, it is not clear what sort of risks are presented by SSI, particularly for subjects that received a new device or had their device re-positioned.
- **Root cause of SSI**. A better understanding of the root cause for the SSI would help better identify a patient population at lower risk of SAE or SSI, or a population that otherwise has a clearer benefit-risk profile. While the sponsor has presented a number of hypotheses for the root cause, it is not clear why the device may become damaged or move out of position. The sponsor's current proposal to identify a more favorable population focuses on selecting patients based on tibial spine height and meniscus extrusion; however, there is considerable uncertainty in this analysis. It is possible that replacing a damaged device will result in a similar failure, since the root cause is unclear. The Agency notes there were 3 "*secondary device procedures*" where the first device was re-implanted and then failed a second time within the 24 month study duration. In the absence of long-term data following subjects whose device has been replaced or repositioned, it is difficult for the Agency to understand the root cause of the device failures and whether a simple replacement or repositioning is a reasonable approach for subjects, especially in light of unknown long-term risks (below).
- **Root cause of higher KOOS pain scores in NUsurface subjects who kept the device**. Increased KOOS pain scores and decreased function were observed in NUsurface subjects who kept the device and resulted in increased failures based on PRO criteria. Reasons for this finding are unclear. One potential mechanism for this finding is that subjects who kept the NUsurface Meniscus Implant may experience increased forces on the bone in the region of the tibial spine. Although the NUsurface Meniscus Implant remained in place, the presence of this device in an anatomical location where no tissue normally exists creates forces on the bone in the region of tibial spine or femoral condylar that may cause bone edema, cartilage failure and increased pain (see figure 20 in Section 7.3.2).
- **High rate of conversion to arthroplasty in NUsurface subjects**. Of the subjects experiencing an SSI, 25% (3/12) of the subjects were converted to arthroplasty at 24 months. The overall rate of arthroplasty procedures in NUsurface subjects (4.1%, 3/74) was greater than the control arm (2.9%, 1/35). Since arthroplasty surgical treatment is only for end-stage osteoarthritis, conversion of NUsurface subjects to arthroplasty raises concerns about whether the NUsurface Meniscus Implant may wear on the cartilage and therefore accelerate degeneration and osteoarthritis progression. This is an established failure mode for metallic interpositional spacers (Section 2.4). Additionally, the surgical procedure needed to implant the NUsurface Meniscus Implant requires a sub-total meniscectomy, which is also expected to contribute to further disease progression.
- **Longer term risks**. There are limited long-term data for the device, and especially limited data on subjects who needed their device to be replaced or repositioned. Subjects who receive the device require

surgery, but in many cases required more than one SSI in a short time frame. For example, subjects in the study whose device failed or did not remain in position had at least two independent SSI in less than 24 months prior to arthroplasty. This would increase the risk of infection associated with subsequent arthroplasty. Even for subjects who receive benefit from the NUsurface Meniscus Implant, it is uncertain how to balance the benefits in improvement in pain and function PROs compared to the risks of disease progression due to the need for a sub-total meniscectomy and cumulative risks of multiple surgeries.

- **Broad and non-specific patient population**. The current indication for use identifies patients with medial compartment knee pain and meniscus resection for mild-to-moderate osteoarthritis, mild or greater knee pain, and with cartilage present on the load bearing articular surfaces. The indication for the NUsurface Meniscus Implant focuses on pain and imaging criteria, and does not include mechanical criteria. Current literature acknowledges that clinicians may have difficulty distinguishing between the various causes of medial knee pain and that patient reported knee symptoms more reliably indicates arthritic symptoms than meniscus related symptoms.[31]

10. Benefit/Risk Assessment

When making a determination of a device's benefit-risk profile, the Agency considers the following:[32]

- **Benefits**: type of benefits, magnitude of benefits, probability of the patient experiencing one or more benefits, and duration of effect;
- **Risks**: types, number, and rates of harmful events associated with the use of the device (device-related serious, device-related non-serious, and procedure-related adverse events), probability of a harmful event, and duration of harmful events; and
- **Additional factors (if applicable)**: uncertainty, characterization of the disease, patient tolerance for risk and perspective on benefit, availability of alternate treatments, risk mitigation, post-market data, and novel technology addressing unmet needs.

We present a summary of benefits and a summary of risks, followed by additional considerations. Both the benefit and risk sections should be interpreted in the context of the additional benefit-risk considerations, especially those of data uncertainty. Any assessment of benefit-risk profile would need to consider the totality of evidence, including the uncertainty.

10.1 Summary of Benefits

The following benefits were considered with use of the NUsurface Meniscus Implant:

- Patients may experience an improvement in pain, function, and quality of life PROs, including $KOOS^{pain}$, $KOOS^{overall}$, VAS, IKDC (SKEF), WOMET, and EQ-5D, at 24 months.
    - Improvements compared to the non-surgical control;
    - Improvements over time; and
    - Magnitude of improvement is clinically meaningful.
- Patient may experience an improvement in pain and function and keep their device in place or need a surgery to replace or reposition the device.
- 51% (37/72) of NUsurface subjects within the modified MERCURY dataset met PRO improvement goals and had no SSI or by MRIs at 24 months. Success for individual components of the composite endpoint are as follows:
    - PRO endpoint success: 62% (41/66) NUsurface vs 18% (5/28) control.

[31] Farina EM, Lowenstein NA, Chang Y, Arant KR, Katz JN, Matzkin EG. Meniscal and Mechanical Symptoms Are Associated with Cartilage Damage, Not Meniscal Pathology. J Bone Joint Surg Am. Mar 3 2021;103(5):381-388. doi:10.2106/jbjs.20.01193

[32] *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications,* available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de.

- No SSI: 83% (60/72) of NUsurface subjects within the modified MERCURY dataset were able to retain their device for 24 months and did not require SSI vs 90% (28/31) of subjects in the non-surgical control that did not require surgical intervention.

10.2 Summary of Risks

The following risks were considered with use of the NUsurface Meniscus Implant:

- There is a risk that patients will not experience any improvement in pain and function
  - 38% (25/66) of subjects did not experience study defined success for PRO improvement.
- The NUsurface Meniscus Implant may become damaged or become dislocated/rotated, which would necessitate an SSI.
  - 49% (35/72) subjects did not meet PROs goals for pain and function **or** needed an SSI.
  - 17% (12/72) of NUsurface subjects needed an SSI by 24 months.
  - 12.5% (9/72) of NUsurface subjects experienced noises including clicking, popping, and squeaks, which may portend device-related mechanical integrity or positioning issues.
- The NUsurface Meniscus Implant and the sub-total meniscectomy required to implant this device may accelerate osteoarthritis disease progression.
  - 4.2% (3/72) of NUsurface subjects in the modified MERCURY dataset needed a joint replacement (TKA or UKA) by 24 months due to disease progression versus 3.2% (1/31) in the non-surgical control group.
- NUsurface subjects experienced more AEs and SAEs compared to the non-surgical control group.
  - 41.6% (30/72) of NUsurface subjects had an SAE, versus 12.9% (4/31) of the non-surgical control
- NUsurface subjects may experience restricted mobility.
  - 13% (9/72) of NUsurface subjects experienced restricted motion, adhesions, arthrofibrosis, stiffness, and limited range of motion, versus 0% of the non-surgical control group.

10.3 Additional Considerations for the Benefit-Risk Assessment

There is considerable uncertainty in our understanding of the benefits of the NUsurface Meniscus Implant compared to the non-surgical control. These sources include:

- Lack of understanding about the root cause of SSI associated with the NUsurface Meniscus Implant, and which subjects are at increased risk of an SSI;
- There is a large percentage of missing data in the non-surgical control arm;
- The types of surgeries required by subjects in the non-surgical control arm suggests there may be differences in screening between the study arms due to the nature of direct visualization of the cartilage in the NUsurface control arm;
- The design and conduct of the PPI studies used to support patient preference for the NUsurface Meniscus Implant over no surgical intervention and whether the patients were willing to undergo SSI were not in alignment with most accepted practices described in published health preference literature and did not follow fundamental principles for this kind of research, rendering the results challenging to interpret; The study was not designed to evaluate cartilage condition, there was a high percentage of missing data, and the cartilage data was only provided for the femoral condyle.

To address the risks and support an improved benefit-risk profile for the NUsurface Meniscus Implant, the sponsor proposes modifications to the labeling related to meniscal extrusion (contraindication) and tibial spine height (warning) to select patients with an improved benefit-risk profile. However, the MCT dataset used to support the validity of these modifications employed a different device, and there are no prospective data using the current version of the device to validate that these are effective.

10.4 Benefit-Risk Conclusions

The benefits for the NUsurface Meniscus Implant are improved pain and function PRO scores, with improvements greater than the non-surgical control arm. However, a high percentage of NUsurface subjects needed an SSI because of device damage, dislocation, or rotation. Additionally, the increase seen in PROs for the NUsurface subjects is comparable to the increase observed with partial meniscectomy as reported in literature, and it is challenging to separate the short-term effect from the partial meniscectomy from the surgical technique for implanting the NUsurface Meniscus Implant. Finally, both the NUsurface Meniscus Implant and near complete meniscectomy present long-term risks of accelerating osteoarthritis, and there are no available long-term data to understand these risks. The sponsor's proposed mitigations do not appear to change the overall failure rate, but instead reduce the number of SSI failures while increasing the rate of subjects who fail because of inadequate PROs. This high rate of SSIs confounds our interpretation of the benefit as measured by the PRO. Given the uncertainty associated with the study population, nonoperative control group, study endpoints / assessment timepoints, proposed mitigation strategies, retrieval analyses, radiographic outcomes, and adverse events; it is difficult to determine the relative weight of the benefits and risks of this device.

Non-Voting Panel Question

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 ≥5mm and tibial spine height <11mm.

- Please comment on what patient population(s) 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.

Panel Voting Question

The following Indications for Use are proposed by the sponsor in the De Novo request:
"The intended for 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 osteoarthritis,
--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."

- Contraindication*: "Patients with extrusion of the medial meniscus 5mm or greater are contraindicated for the device.*"
- Warning*: "Patients in which the height of the tibial spine is below 11mm are at greater risk of device related adverse events."*

Based on a consideration of the clinical information provided, do the probable benefits to health of the NUsurface Meniscus Implant outweigh the probable risks when used in patients in accordance with the proposed indications for use?

11. Panel Discussion and Questions

The Agency has prepared a selection of non-voting and voting questions. These are designed to seek feedback on interpretation of the data that will inform our understanding of benefit-risk.

11.1 Panel Non-Voting Questions

1. 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 ≥5mm and tibial spine height <11mm.
   - Please comment on what patient population(s) 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.

2. 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 (ASF). The Statistical Analysis Plan for the modified MERCURY dataset predefined Automatic Study Failures (ASF) as secondary surgical interventions (SSI) to permanently remove the device and revisions to reposition or replace the device. 17% (12/72) of NUsurface subjects experienced a device-related SSI and 25% (3/12) of those subjects had more than one SSI.
   - Please discuss the adequacy of the overall clinical success criteria and the clinical significance of the SSIs related to the device.
   - Please comment on the classification of these SSIs as ASFs.

3. Sub-group Analysis:
   The sponsor provided a subgroup analysis intended to identify a modified target population with a reduced rate of SSIs from the unmodified MERCURY dataset. The modified MERCURY dataset involves the exclusion of meniscal extrusion ≥5mm and tibial spine height <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 a knee in which the medial meniscus has been resected.
   - Please comment on the study design characteristics as different datasets were utilized compared to a non-surgical control for the MERCURY trial, modified MERCURY dataset, and MCT study.
   - 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?

4. 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 7).

- Please discuss the contribution of the PPI studies to the final benefit-risk determination.

5. Risk Mitigation:
   The sponsor has identified several key considerations in risk mitigation, including the appropriate selection of patients (e.g., exclusion of meniscal extrusion >5mm and tibial spine height <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 criterion.
   - How might these factors impact the clinical reproducibility, particularly the clinician's ability to identify patients that would benefit from the device?

11.2 Panel Voting Question

The following Indications for Use are proposed by the sponsor in the De Novo request:
"The intended for 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 osteoarthritis,
--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."

- Contraindication*: "Patients with extrusion of the medial meniscus 5mm or greater are contraindicated for the device."*
- Warning*: "Patients in which the height of the tibial spine is below 11mm are at greater risk of device related adverse events."*

Based on a consideration of the clinical information provided, do the probable benefits to health of the NUsurface Meniscus Implant outweigh the probable risks when used in patients in accordance with the proposed indications for use?

Appendix A: Contraindications, Warnings, Precautions

A1. Summary

As part of their proposed risk mitigation strategy, the sponsor proposed additional contraindications and warnings to address the meniscal extrusion and tibial spine height which were identified as potential risks associated with increased device failures. Based on the subgroup analysis, the sponsor has expressly narrowed the intended population by the adding a contraindication for "*patients with extrusion of the medial meniscus 5mm or greater*," and a warning related to use of the device in patients with a tibial spine height below 11 mm are at greater risk. This is intended to better identify patients who are expected to have a more favorable benefit-risk profile.

The complete proposed labeling is included below with the important contraindication and warning in bolded and underlined text.

A2. Contraindications

The sponsor's full set of proposed contraindications for the NUsurface Meniscus Implant are as follows:

- "*Full thickness cartilage lesion (exposed bone) in the medial compartment that would be in direct contact with either the femoral or tibial side of the device, as determined using diagnostic imaging prior to surgery or observed intraoperatively; e.g.,>0.5cm^2 diameter bony lesion in the weightbearing area of the medial joint;*
- *Abnormal knee laxity secondary to acute ligament injury and/or chronic soft tissue laxity, such as loss of complete integrity of the MCL. Physical examination discloses a positive Lachman test and/or pivot shift sign; or a positive posterior drawer test 2 plus or greater; or asymmetric valgus or varus laxity greater than 3mm in full extension (0 degrees) or at 30 degrees of flexion. A history of patellofemoral instability and/or clinical signs of patella instability;*
- ***Patients with extrusion of the medial meniscus 5mm or greater****;*
- *>5º loss of extension and >15º loss of flexion difference between index and contralateral knee; greater than ±5º of varus/valgus femoral/tibial alignment.*
- *Irregularly shaped cartilage surfaces or squared femoral condyle or Grade 4 Kellgren-Lawrence Grading Scale indicating large osteophytes, marked narrowing of joint space, and definite deformity of bone contour;*
- *Grossly distorted anatomy or neuropathic joint such as Charcot joint;*
- *Knee joint bone resorption, avascular necrosis, or rapid joint destruction;*
- *Skeletally immature;*
- *Severely deformed bones in the knee or cases with a significant loss of musculature, poor bone stock, or poor skin coverage around the knee joint;*
- *Morbid obesity;*
- *Patients with inflammatory or systemic disease such as psoriatic arthritis or rheumatoid arthritis;*
- *Patients with an allergy to any of the materials used to construct the implant;*
- *Patients with insufficient quantities of synovial fluid to allow for proper lubrication of the knee, such as occurs with Sjogren's Syndrome;*
- *Active Infection, sepsis, or osteomyelitis;*
- *Medial compartment anatomy requiring a NUsurface device size larger or smaller than available;*
- *Use of the NUsurface device in the lateral compartment of the knee or in any part of the body other than the medial knee;*
- *Patients incapable of following instructions, such as having certain types of mental illnesses, or unwilling or unable to be compliant with directions."*

A3. Warnings
The sponsor's full set of proposed warnings for the NUsurface Meniscus Implant are as follows:

- ***"Patients in which the height of the tibial spine is below 11mm are at a greater risk of device- related adverse events.***
- *Warn patients of an elevated risk of having device-related adverse events when they perform strenuous activities. If patients insist on performing these activities, consider prescribing a functional brace for them to wear while performing those activities.*
- *The pivotal clinical study did not evaluate effectiveness in patients with a complete disruption of the medial posterior meniscal root, or with less than a 2 mm medial meniscal rim.*
- *The pivotal clinical study did not evaluate device effectiveness in patients who are pregnant, smoke, or younger than age 30, had a BMI > 32.5, have cancer, had previous knee surgery removing bone, or did not have at least one previous medial meniscectomy*."

A4. Precautions
The sponsor's full set of proposed precautions for the NUsurface Meniscus Implant are as follows:

- "*Caution: Federal law restricts this device to sale by or on the order of a physician. For use only by physicians specially trained on the surgical procedure.*
- *Biologic, biomechanical, and other factors may affect the useful life of the NUsurface Meniscus Implant device. Strict adherence to the indications, contraindications, warnings, and precautions for this Implant are essential to maximize its useful service life;*
- *To reduce the risk of infection, use total joint replacement sterile surgical techniques at the start of surgery. Use antibiotic prophylaxis perioperatively when performing a NUsurface surgery and any subsequent surgical procedures such as dental operations, especially in high risk patients;*
- *Surgeons must receive training and understand all aspects of the surgical procedure. Implant the NUsurface Meniscus Implant following the latest version of the operative technique and Instructions for Use that describe device limitations and life expectancy of the Implant. Physicians must instruct the patient on all the limitations of the Implant, including, but not limited to, the impact of excessive loading and rotation of the operated knee. If the patient performs an occupation requiring substantial walking, running, lifting, or muscle strain, the resultant forces may compromise the results of the surgery, the device, or both. Patients with too much exposed bone (Grade 4) are not good candidates for this procedure;*
- *The surgical technique used to implant the NUsurface Meniscus Implant device will affect its useful life. Follow the implantation procedure and recommendations provided in a separate operative technique, available upon request, that describes how to insert, reposition, remove, or exchange the device, as well as address potential device complications such as dislocation. Although the details of the technique are too lengthy for this document, here are a few key precautions: Remove all osteophytes that could contact or impinge the device or could enlarge and do so in the future. Improperly preparing the meniscal rim, selecting the Implant size, or positioning of the Implant in the knee space may cause displacement of the Implant. During insertion of Trial and Implant, care must be taken not to damage the cartilage or underlying bone.*
- *Carefully select the size of the NUsurface Meniscus Implant. The Implant is available in left and right versions of the medial compartment, be sure to implant the correct left/right component on the correct left/right medial side using the correct superior/inferior and anterior/posterior orientation of the device. As a final check of correct device orientation and left/right before closing, when viewed through the incision the surgeon should see on the anterior-medial end of the device an "up arrow" triangle pointing cephalad. If the device edge appears white it is a Trial; if amber, it is an Implant. The NUsurface trial should not be left in the patient after the surgery.*

- *After implantation of the NUsurface Meniscus Implant device and before closing, it is important to check the knee range of motion and confirm the Implant remains in proper place. Make several flexion/extension motions to assure the Implant has no tendency to move out of position. Less than ideal Implant sizing and/or joint preparation could cause excessive wear, dislocation, or other complications. Prior to closing, if the implant surface appears dry, lubricate with fluid. Prior to closing, again perform a full range of motion to confirm proper positioning of the device and leg length restoration. Confirm the Implant is stable, and the device does not have any impingement in motion or contact with exposed bone.*
- *Prior to final insertion and closing of the incision, remove all loose debris by using copious irrigation of the surgical site. Any surgical debris left may damage the Implant or cause damage to tissue. Before closing the incision re-confirm the Trial is not inside the patient.*
- *If needed, use the Extraction Instrument to remove the NUsurface Meniscus Implant from the knee. Since the tips of the Extraction Instrument might cause damage any NUsurface Implant extracted with the Extraction Instrument should not be reused. Never reuse an Implant or Trial removed from a patient. Although the product may appear undamaged, previous use may create small imperfections that could reduce the service life of the product or act as an infection carrier.*
- *To reduce the risk of venous thromboembolism (VTE) prescribe anticoagulation medication prophylactically after surgery*
- *To achieve the best results, the patient must comply with all postoperative instructions. Instruct patients to follow physician orders regarding permissible post-operative activities. Advise patients to exercise extreme caution when getting in and out of tight areas such as cars, walking up or down steps or ladders (especially taking more than one step at a time), performing deep knee bends, or applying extreme rotary motions to the operated knee especially while flexing the knee.*
- *The surgeon is the learned intermediary with the patient and must convey the patient-related information in this document to them*."

Appendix B: MERCURY DATASET

B1. Clinical Study Overview

The sub-group analysis referred to as the Modified MERCURY Database was detailed in the main body of the Executive Summary. The original MERCURY dataset is presented here to provide some additional context to the review and discussion of the Modified MERCURY dataset.

B2. Clinical Study Results

B2.1. Subject Demographics and Baseline Characteristics of MERCURY Dataset

Table A1 provides a summary and comparisons of selected demographic variables and patient presurgical characteristics between the NUsurface Meniscus Implant and non-surgical control arm in the MERCURY dataset.

Table B1: Major baseline demographics and KOOS values of the MERCURY Dataset. (Active Implants Table)

	NUsurface Arm	Control Arm	Statistically Different?
Number of Subjects	176	66	-
Age (Years)	49.8	49.9	No, p = 0.92
% Male	74.6%	71.9%	No, p = 0.68
% Right Knee	49.4%	53.2%	No, p = 0.60
BMI (Body Mass Index)	27.0	26.9	No, p = 0.71
KOOS Pain	53.5	52.5	No, p = 0.57
KOOS Overall	47.6	48.2	No, p = 0.70

The MERCURY dataset, from which the modified MERCURY dataset was created via non-random sampling, had the following variables at baseline which were significantly different between the NUsurface group and the non-surgical control group at a nominal significance level of 5%. among variables reported by the sponsor.

Table B2: Baseline variables with nominal significance level of 5% extracted from Active Implants' Table (FDA Table)

Baseline Variable	NUsurface		Control		ANOVA/Logistic Regression p
	N	Mean/%	N	Mean/%	
Intervention: Physical Therapy	176	58.5%	66	81.8%	0.001
Intervention: Steroid Injection	176	33.0%	66	47.0%	0.045
Intervention: Analgesics	176	39.8%	66	25.8%	0.045
Intervention: Glucos/Chond	176	21.0%	66	9.1%	0.036
Current: Subacute Problem	176	2.3%	66	9.1%	0.028
Prior: Cartilage Surgery	176	8.0%	66	19.7%	0.012
Group Grade 4	176	1.24	66	1.48	0.005
Final Grade	176	1.57	66	1.85	0.006
Patella Centered	173	92.5%	65	70.8%	<0.001
IKDC Score	174	40.6	66	45.4	0.011
Other: Synovitis	176	8.0%	66	18.2%	0.026
KOOS Sports	176	32.2	66	39.3	0.023
EQ5D Scale	176	75.5	66	79.9	0.042
EQ5D Usual Activity Problems	176	26.7%	66	43.9%	0.011

Extracted from Active Implants' Table 23.16.1

B2.2. Overall Success and Failure Rates

The three success criteria for the NUsurface device included:

- No device removals/replacements
- No radiologic failures
- Adequate KOOS pain and overall scores

Table B3: Breakdown of overall clinical success criteria for the MERCURY Dataset. The three success/failure criteria are not mutually exclusive. (FDA Table)

	Device related SSI Rate	MRI Failure Rate	PRO Failure Rate	Overall Failure Rate	Overall Success Rate
NUsurface	34% (58/172)	3% (5/159)	(35%) 53/153	55% (95/172)	45% (77/172)
	Any SSI		**PRO Failure**		
Control	17% (9/52)		72% (31/43)	77% (40/52)	23% (12/52)

Of the 176 subjects randomized to the NUsurface group, 172 subjects received an implant, and 45% (77/172) of the implanted subjects met the study success criteria and 55% (95/172) of those subjects were categorized as study failures. Of those study failures, 61% (58/95) resulted from secondary surgery to manage dislocations, displaced/subluxation, rotated or torn devices or MRI (5/95) that identified a dislocated, displaced/subluxated, rotated or torn device. Of those study failures, 42% (40/95) resulted from inadequate pain relief despite having the device remaining implanted in the knee.

The two success criteria for the non-surgical control group included:

- No secondary surgery on the index knee
- Adequate KOOS pain & overall scores

Of the 66 patients randomized to the non-surgical control group, 14 were lost or withdrew their consent leaving 52 study patients. Of those remaining, 23% (12/52) control subjects were overall study successes, and 77% (40/52) control subjects were categorized as study failures. Of the study failures, 22.5% (9/40) control subjects failed by having surgery and 60% (24/40) control subjects failed by inadequate pain relief from non-surgical treatment.

B2.3. Clinical Safety Evaluation

B2.3.1 Overview of Clinical Safety Results

The NUsurface Meniscus Implant group had a total of 296 adverse events in 72.7% (128/176) NUsurface subjects, compared to 23 adverse events in 30.3% (20/66) non-surgical control subjects. Additionally, 12.5% (22/176) NUsurface subjects had at least one unscheduled visit. There were 1.5% (1/66) subjects from the non-surgical control group with one unscheduled visit.

Table B4: Accounting of Unscheduled Visits (Active Implants Table)

	NUsurface® Arm	Control Arm
Subjects Where Unscheduled Visits Were Not a Factor		
Lost or Withdrawn	2	14
KOOS Failure At 24 Mos	38	31
Surgical Failure	58	9
MRI Failure (not within KOOS Failure or Surgical Failure)	1	
No Unscheduled Visits (Success Subjects)	55	11
	154	**65**
Subjects Where Unscheduled Visits Could Have Biased Success		
One Unscheduled Visit	20	1
Two Unscheduled Visits	2	
	22	**1**
	176	**66**

Unscheduled Visit Timeframe	NUsurface® Subjects	AE Complaint
Before 1.5 Month Visit	*2*	*Knee Abrasion; Rash*
Before 1.5 Month Visit & Before 3 Month Visit	*1*	*Noise; Dislocation*
Before 3 Month Visit	*4*	*Effusion; Noise; DVT*
Before 6 Month Visit	*7*	*DVT; Common peroneal nerve*
Before 12 Month Visit	*5*	*Effusion; Sprain; Pain; ROM; Clicking*
After 12 Month Visit	***3***	***Trauma; No Reason Given (2)***
	22	

Table *B5*: All adverse events at Index Knee or Possibly Related to treatment (*Active* Implants Table, FDA highlights):

	Control (N=66)			NUsurface (N=176)		
Body System / Preferred Term	# of events	# of subjects	%	# of events	# of subjects	%
Knee						
All	23	20	30.30%	296	128	72.70%
ADHESIONS	0	0	0.00%	6	6	3.40%
ARTHROFIBROSIS	0	0	0.00%	3	2	1.10%
BAKER'S CYST	0	0	0.00%	4	4	2.30%
DAMAGE	0	0	0.00%	57	50	28.40%
DEHISCENCE	0	0	0.00%	4	4	2.30%
DISLOCATION	0	0	0.00%	23	19	10.80%
DISLOCATION AND DAMAGE	0	0	0.00%	18	18	10.20%
EFFUSION	2	2	3.00%	47	37	21.00%
FAT PAD SYNDROME / PLICA	0	0	0.00%	2	2	1.10%
FEMORAL OSTEONECROSIS	0	0	0.00%	2	2	1.10%
INFECTION	0	0	0.00%	2	2	1.10%
KNEE ABRASION	0	0	0.00%	1	1	0.60%
KNEE GENERALIZED OSTEOARTHRITIS	2	2	3.00%	1	1	0.60%
KNEE SYNOVITIS	1	1	1.50%	4	4	2.30%
LATERAL COLLATERAL LIGAMENT	0	0	0.00%	1	1	0.60%

LATERAL MENISCAL TEAR	1	1	1.50%	2	2	1.10%
LIMITED ROM	0	0	0.00%	8	7	4.00%
MECHANICAL SYMPTOMS	0	0	0.00%	10	9	5.10%
MEDIAL MENISCAL TEAR	2	2	3.00%	0	0	0.00%
NOISE	0	0	0.00%	26	22	12.50%
NON-SPECIFIC KNEE PAIN	9	9	13.60%	33	28	15.90%
OTHER KNEE INJURY	3	3	4.50%	14	13	7.40%
PATELLAR TENDINOPATHY	1	1	1.50%	0	0	0.00%
PATELLAR TENDON TEAR/RUPTURE	0	0	0.00%	1	1	0.60%
PATELLOFEMORAL PAIN SYNDROME	1	1	1.50%	3	2	1.10%
POST-TRAUMATIC PATELLOFEMORAL PAIN	0	0	0.00%	2	2	1.10%
RASH	0	0	0.00%	2	2	1.10%
ROTATION	0	0	0.00%	15	10	5.70%
ROTATION AND DAMAGE	0	0	0.00%	1	1	0.60%
SAPHENOUS NEUROMA	0	0	0.00%	1	1	0.60%
STIFFNESS	0	0	0.00%	2	2	1.10%
SUBLUXATION	0	0	0.00%	1	1	0.60%
TIBIAL-FEMORAL FUNCTIONAL INSTABILITY	1	1	1.50%	0	0	0.00%

B2.3.2. NUsurface Meniscus Implant Safety Information

The largest category of SAE was physical or positional changes to the device that led to an SSI. The rates were higher in the NUsurface Meniscus Implant group compared to the non-surgical control group and were reported to be statistically different in the following categories:

- Effusion: NUsurface 21% (37/176) vs control 3% (2/66),
- Noise: NUsurface 12.5% (22/176) vs control 0%,
- Restriction in motion: NUsurface 4% (7/176) vs control 0%,
- Device damage (e.g., tears): NUsurface 28.4% (50/176) vs control 0%,
- Device dislocation: NUsurface 10.8% (19/176) vs control 0%, and
- Device rotation: NUsurface 5.7% (10/176) vs control vs 0%.

For some SAE categories, individual subjects experienced more than one SAE necessitating an SSI, and some subjects experienced more than one occurrence of the same SAE and required an additional SSI. For example, there were 57 SAE reports related to device damage, yet only 50 subjects reported device damage; therefore, 7 of those events were second occurrences of device damage in that pool of 50 NUsurface subjects. Similarly, there were 21 dislocation SAEs reported for only 17 total subjects, and 15 rotation SAEs were reported in only 10 total subjects. In those subjects, a device was noted as dislocated or was replaced or relocated in an SSI, and subsequently dislocated a second time.

Of the 176 subjects enrolled into the NUsurface Meniscus Implants group, 4 were lost to follow up or withdrawn, leaving 172 subjects. During the 24-month time frame reported for this study, 38% (66/172) of NUsurface subjects had at least one surgery for rotations, dislocation, exchanges, removals and lysis of adhesions. The 38% SSI rate does not capture subjects that had multiple revision procedures. The SSIs included:

- Lysis of adhesions: 2.9% (5/172) subjects

- Device exchanged at least once but completed the study: 21.5% (37/172) subjects
- Device exchanged twice but completed the study: 5.4% (2/37) subjects
- Device exchanged twice but removed after a third procedure: 13.5% (5/37) subjects
- Removal of the device: 10.5% (18/172) subjects
- Reposition of the device following dislocation or rotation: 4% (7/172) subjects

The mechanisms of these device-related SAE are varied, and images of the damaged devices following removal are included in Appendix B. Of the subjects that had the devices replaced, 38.5% (15/39) received devices of a different size. It is uncertain if improper sizing was a contributing factor to the device failure.

In addition, 13.6% (9/66) of the subjects who experienced failures of their NUsurface Meniscus Implant required treatment with permanent arthroplasty replacements. The additional surgeries needed by subjects whose device failed included the following during the 24-month follow-up:

- Unicompartmental knee arthroplasties: 10.6% (7/66) subjects;
- Total knee arthroplasties: 3% (2/66) subjects; and
- Meniscus allograft transplant 1.5% (1/66) subjects.*

*Please note that meniscal allograft transplants were covered as part of the enrollment eligibility. The exclusion criteria for the study specifically addressed the meniscus allograft population as follows: "*12. Decides to receive (if eligible and an option) allograft medial meniscus transplantation.*"

An additional 2.9% (5/172) subjects underwent SSIs for other reasons that are not included in the 38% SSI rate. The reasons for these other SSI are as follows:

- Exploratory surgery related to knee trauma 1.2% (2/172);
- Baker's cyst 0.6% (1/172);
- Osteoarthritis 0.6% (1/172); and
- Synovitis 0.6% (1/172).

In face of the numbers of mechanical failures reported as device damage, dislocation, and rotation, and the SSI rates in the experimental arm, the Agency also considered AEs that potentially suggest joint reactivity or risk of device mechanical failures. The following AEs are ones that may be device-related but, because of uncertainty, were not included in the 38% SSI rate:

- Adhesions 3.4% (6/172);
- Arthrofibrosis 1.1% (2/172);
- Limited range of motion 4% (7/172);
- Stiffness 1.1% (2/172); and
- Noises (included clicking, popping, and squeaks) 12.5% (22/172).

An additional 31 SSIs were performed outside of the 24-month study window but before the closure of the study, including an additional 15 subjects that had not had an SSI during the initial 24 month window.

MRI (T1 weighted with fat suppression, T2 weighted fluid sensitive) was also used to evaluate the knee joint with respect to the integrity and position of the device. The information was used for the primary endpoint (i.e., MRI positive or negative). The sponsor also performed an analysis of the cartilage to support secondary endpoints, but this evaluation was subject to considerable uncertainty. The results of the device position evaluation are provided in Table A5. Notably, the implant was dislocated in 4 scans (2.48%) and not visualized in 15 scans (9.32%). Finally, 15 subjects (9.32%) did not have MRI imaging performed.

Table B6: Summary of MRI Findings (FDA Table)

	Number of MRIs	% of total number of MRIs read (161)
Implant in Place	**142**	**88.2%**
Implant Dislocated	**4**	**2.48%**
No implant visualized	**15**	**9.32%**
MRI Images Missing	**15**	

B2.3.3. Non-Surgical Control Group Safety Information

A total of 66 subjects were enrolled in the non-surgical control group (VENUS), and 43 subjects completed 24 months follow-up. The following 9 surgeries were reported in this group:

- Arthroscopic surgeries 6% (4/66);
- Unicondylar knee arthroplasty 1.5% (1/66);
- High tibial osteotomy 1.5% (1/66);
- Trochlear chondral allograft 1.5% (1/66);
- Lateral corner reconstruction 1.5% (1/66); and
- Meniscus allograft transplant 1.5% (1/66).*

*As noted for the investigational arm, meniscal allograft transplants were covered as part of the enrollment eligibility.

These 9 procedures, which the sponsor considers failures, raise uncertainty about whether the subjects were eligible for enrollment in the study. In many cases, the indications for these surgical procedures correspond to exclusion criteria. The investigational and non-surgical controls underwent a different level of screening of patients because the NUsurface Meniscus Implant group was arthroscopically screened as part of the surgical procedure to implant the device. This difference raises uncertainty about the study subject enrollment and by extension the study results. The sponsor provided narrative for each of the SSI/failed subjects in the non-surgical control group. The details of each surgery, and the potential exclusion criteria, are as follows:

- **Arthroscopic surgeries (4 subjects)**.
  - Arthroscopic debridement and meniscectomy at less than 3 months due to diffuse grade III and areas of grade IV change with a degenerative meniscus tear;
  - Medial meniscectomy and synovectomy in the patellofemoral medial compartment with extensive chondroplasty at 20 months after a twisting injury;
  - Medial and lateral meniscectomy at 6.5 months following multicompartment degenerative changes, severe loss of cartilage, and new medial meniscus tear; and
  - Exploratory knee arthroscopy at 8 months following continued pain.
- **Unicondylar arthroplasty (1 subject).** A subject received a unicondylar arthroplasty within 5 months of the study start date.
  - The progression to arthritis severe enough for implantation of a unicondylar arthroplasty device within a relatively short time raises uncertainty about whether the patient should have met the exclusion criterion *2.*
  - *"Has evidence of an Outerbridge Grade IV cartilage loss on the medial tibial plateau or femoral condyle that potentially could contact a NUsurface implant (e.g., a focal lesion > 0.5 cm^2 correlating to a circular defect of > 8 mm in diameter).*"
- **HTO (1 subject).** A subject received an HTO 7 months after study start date.
  - The level of varus deformity to support surgical intervention with an HTO would meet exclusion criterion *5.*
    "Has a varus or valgus knee deformity > 5° requiring a tibial or femoral osteotomy".

- **Chondral allograft (1 subject).** A subject received a trochlear cartilage transplant at 1.5 months after starting the study and had an MRI that identified trochlear cartilage delamination.
    - This surgical procedure is indicated for patellofemoral chondral loss, which would meet exclusion criteria *8.*
    - *"Has patellar compartment pain and Grade III or Grade IV Outerbridge cartilage score in the patellar compartment and/or exclusion criterion* and *7. Has significant trochlear dysplasia, patellar instability or symptomatic patellar malalignment*."
- **Ligament reconstruction (1 subject).** A subject received a ligament reconstruction with hamstring tendon 7 months after beginning study without history of new trauma.
    - This reconstructive procedure is indicated for treatment of a knee ligamentous laxity and would meet exclusion criterion *6.*
    - *"Has a laxity level of more than Grade II (IKDC), primary or secondary to an injury of the anterior cruciate ligament (ACL) and/or posterior cruciate ligament (PCL) and/or lateral collateral ligament (LCL) and/or medial collateral ligament (MCL)*".

B2.4. Clinical Effectiveness Evaluation

B2.4.1. KOOS Patient Reported Outcomes

KOOS scores were available at 24 months for 86.9% (153/176) NUsurface subjects. Scores were not available for 4 subjects who were either lost or withdrawn and 19 subjects who were early surgical failures and have no further post-device follow up. Only 65% (43/66) control subjects had available scores at 24 months. Scores were not available for 14 who withdrew consent or were lost to follow up and no scores were reported for 9 patients who underwent further surgery.

In general, both NUsurface and non-surgical control arms showed improvement in scores with the NUsurface appearing to out-perform the non-surgical control for these PROs at 6, 12, and 24 months. The average improvement in $KOOS^{pain}$ score at 24 months was 27.2 points for the NUsurface arm (153 subjects) vs 16.6 for the non-surgical control arm (43 subjects). Graphs in Figure A1 and A2 show the trends in $KOOS^{pain}$ and $KOOS^{Overall}$.

However, the exclusion of the PROs from these 19 surgical failure subjects represents a deviation from the study protocol and may have impacted PRO analysis and the overall study results. The study protocol notes that, "*Patients in the Investigational Group that had the device removed will continue to be studied because those patients would have been exposed to the investigational device. Patients in the Control Group who fail by receiving surgery (with the type of surgery being captured) will be followed so as to gather adverse event information to aid in the interpretation of the adverse event data in the Investigational Group*." The missing data from these 19 device failure subjects represents 33% (19/58) of the surgical failure group, 20% (19/95) of the total NUsurface failure group and 11% (19/172) of the total population who received the NUsurface Meniscus Implant.

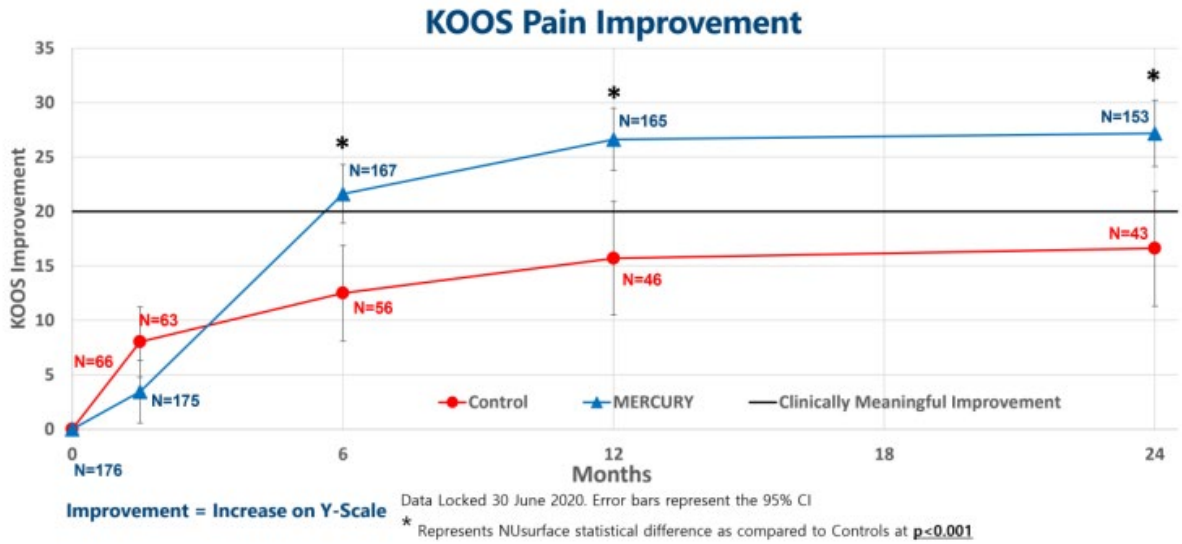


Figure B1: Average improvement of KOOS Pain score in the MERCURY dataset for NUsurface (Blue) and control (red) (Active Implants Figure)

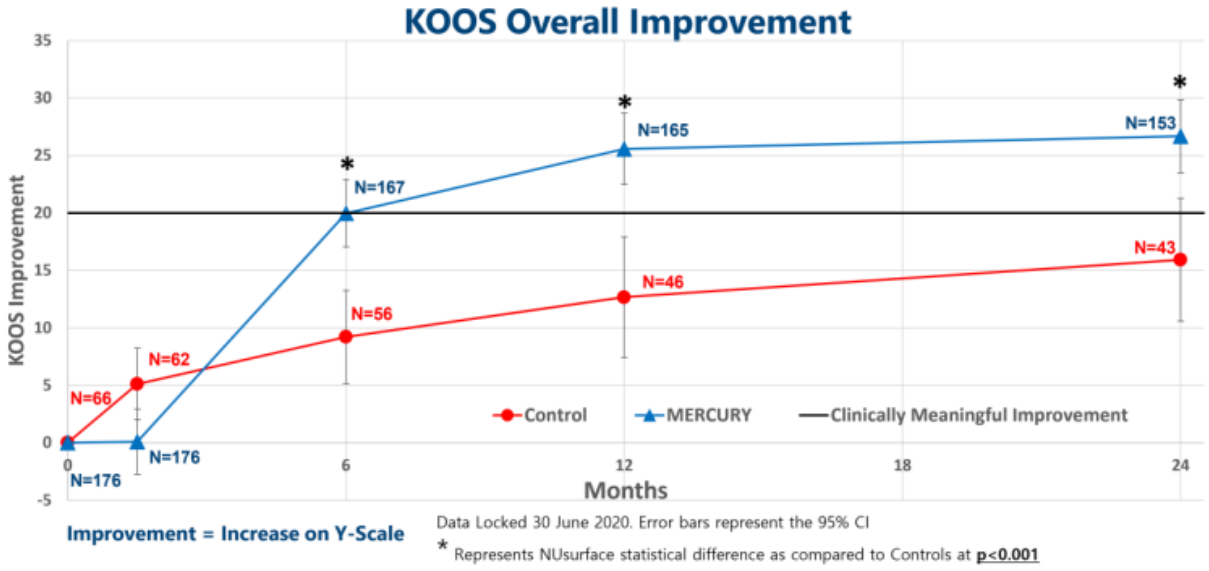


Figure B2: Average improvement of KOOS Overall score in the MERCURY dataset for NUsurface (Blue) and control (red) (Active Implants Figure)

B2.4.2 Comparison to historic results of metal free-floating implants

The sponsor provided Table A4 below to highlight a comparison between historic results of metal free-floating (unfixed) device in the literature and the results of the current unfixed polymeric NUsurface device. Given that these types of metallic spacer devices are no longer used clinically, consideration should be given to the similarities of the NUsurface device to these metallic spacer devices. Of note, the NUsurface secondary surgical failure rate is similar to the historic failure rates seen with free floating interpositional metal spacer devices.

Table B7: Comparison of SSI Rates of the metallic meniscal spacer, "Unispacer" and the NUsurface Meniscus Implant (Active Implants table)

	Hallock & Fell 2003	Hallock 2005	Friedman 2003	Bailie et al. 2008	Sisto and Mitchell 2005	Australian National Joint Registry 2005		Catier 2011	NUsurface MERCURY
Number of Devices	71	157	23	18	37	40		17	**175**
Mean Age	54			49	55	54.7		58	**47.8**
SSI Rate (%)	45%	14%	34%	56 %	32%	38.7%	58.1%	41%	**37.7%**
TKA/UKA Rate (%)	7%	9%	13%	33%	32%	33.7%*	50.6%*	35%	**4.6%**
Mean follow-up in months	12	12	12	19	26	12	36	40	**24**

* Calculated from 2015 Australian Orthopedic Association National Joint Replacement Registry.

In the absence of longer-term data for the NUsurface implant, it is not clear whether this device will present a similarly concerning clinical profile as the metallic spacers. A better understanding of long-term performance (and risks of SSI and osteoarthritis progression) would also help understand the trade-offs patients may be willing to accept for the improvement in PRO.

B2.5. Summary of MERCURY Dataset

- KOOS Score Success at 24 months:
  - 65% (100/153) of the NUsurface subjects met the KOOS score success criteria by 24 months; however, of those 23% (23/100) subjects were ultimately deemed Overall Failures because of SSIs (22) and/or MRI failure (1).
  - 50% (77/153) of the NUsurface subjects met the KOOS score success criteria and also had no failure due to additional surgery or MRI failure. These 77 subjects who retained their device had average $KOOS^{pain}$ score improvements of 36.4 points.
  - 67.2% (39/58) of NUsurface subjects that failed by SSI had average $KOOS^{pain}$ score improvements of 27.9.
  - 32.8% (19 /58) of NUsurface subjects that failed by secondary surgery did not have any 24-month KOOS scores recorded.
  - 27.9% (12/43) of the non-surgical control subjects met the KOOS score success criteria by 24 months.
- KOOS Score Failures at 24 months
  - Of the 35% (53/153) of NUsurface subjects that did not meet the KOOS score success criteria by 24 months, 32% (17/53) of these also failed by secondary surgery.
  - There were 23.5% (36/153) NUsurface patients with KOOS scores that did not require a secondary surgery but failed by lack of adequate pain relief ("Painful Keepers").
- The Control group that failed by surgery (9/66) did not have KOOS scores to report so their final outcome cannot be assessed.

Appendix C: RETRIEVAL IMAGES

The sponsor provided a Retrieval Analysis Summary that includes 62 implants removed from 55 patients.

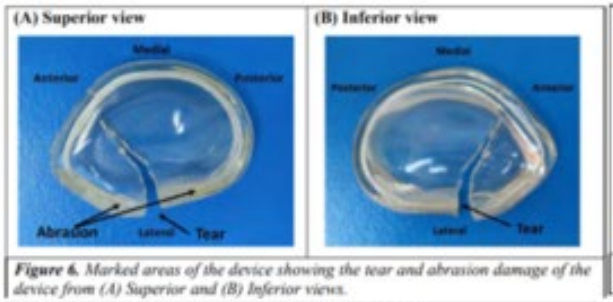


Figure 6. Marked areas of the device showing the tear and abrasion damage of the device from (A) Superior and (B) Inferior views.

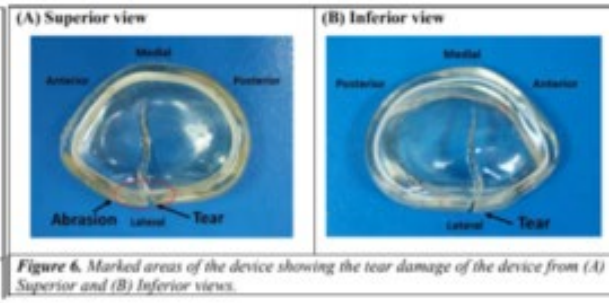


Figure 6. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

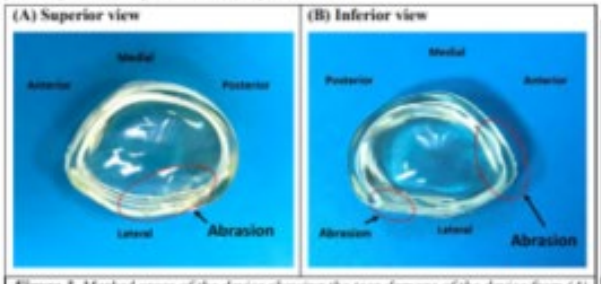


Figure 3. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

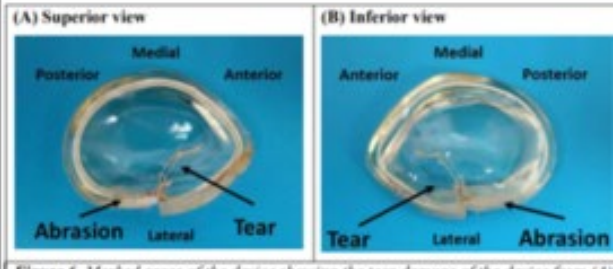


Figure 6. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

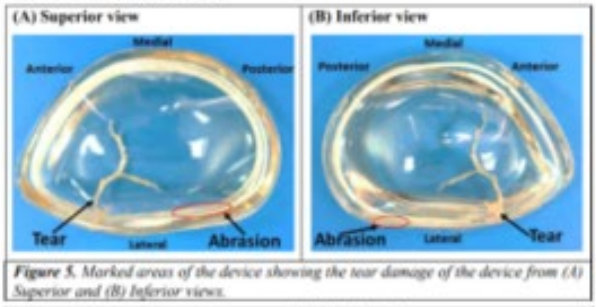


Figure 5. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

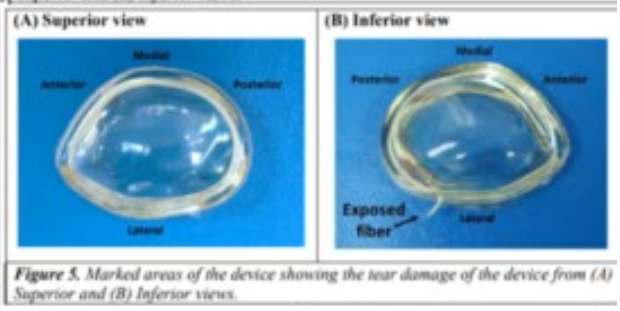


Figure 5. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

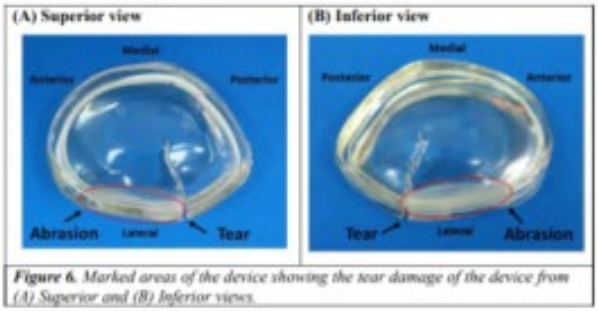


Figure 6. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

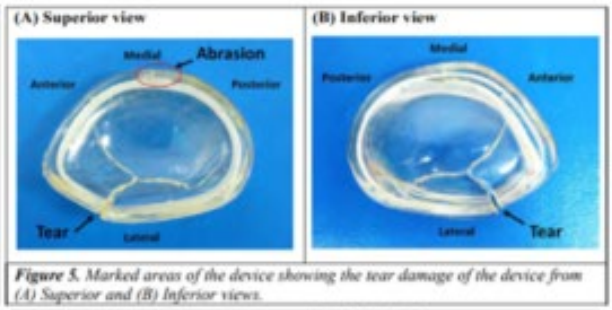


Figure 5. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

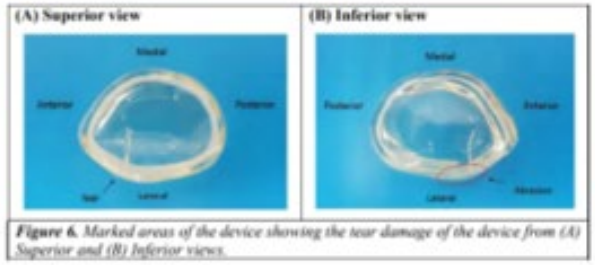


Figure 6. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

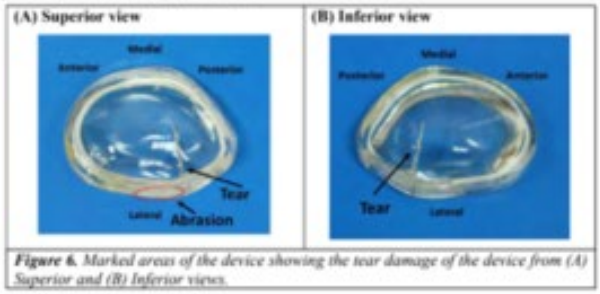


Figure 6. Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.

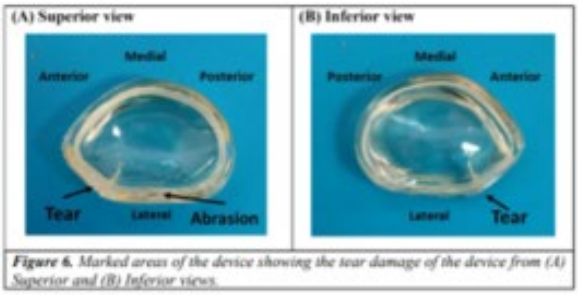


Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

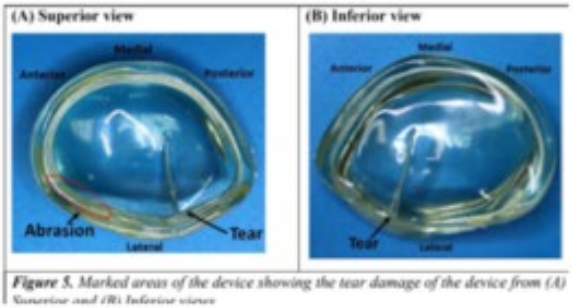


Figure 5. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

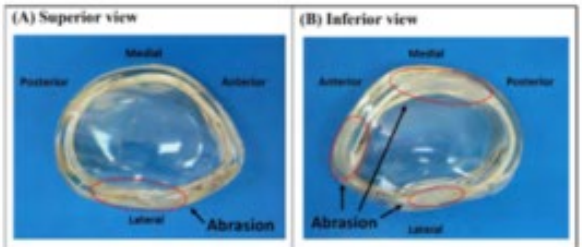


Figure 5. *Marked areas of the device showing the damage of the device from (A) Superior and (B) Inferior views.*

Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

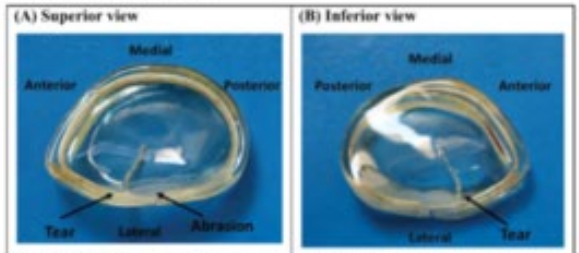


Figure 6. *Marked areas of the device showing the damage of the device from (A) Superior and (B) Inferior views.*

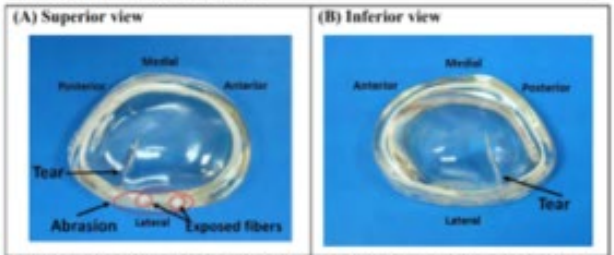


Figure 7. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

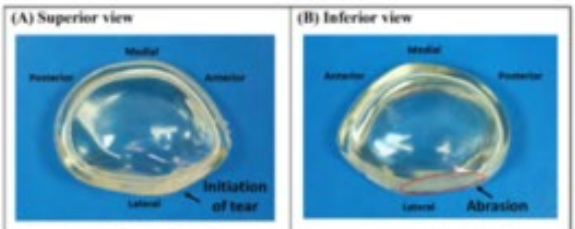


Figure 4. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

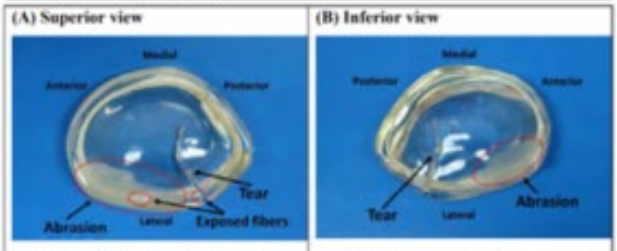


Figure 7. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

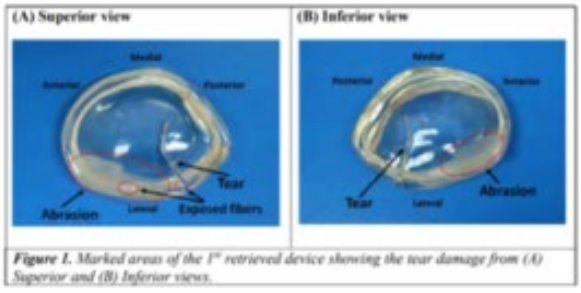


Figure 1. *Marked areas of the 1st retrieved device showing the tear damage from (A) Superior and (B) Inferior views.*

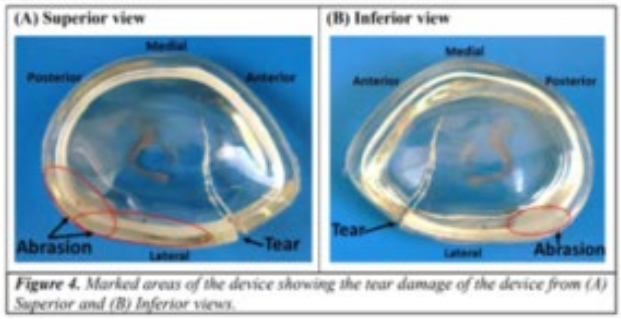


Figure 4. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

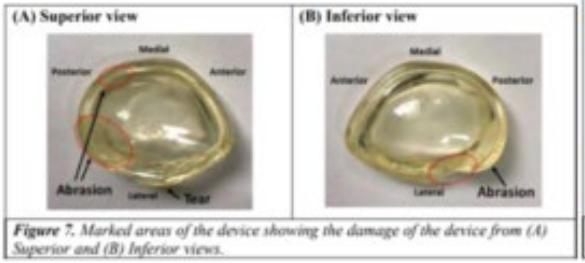


Figure 7. *Marked areas of the device showing the damage of the device from (A) Superior and (B) Inferior views.*

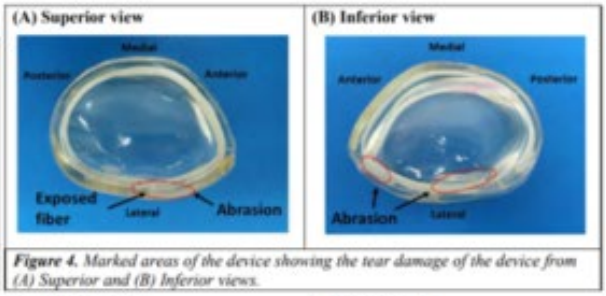


Figure 4. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

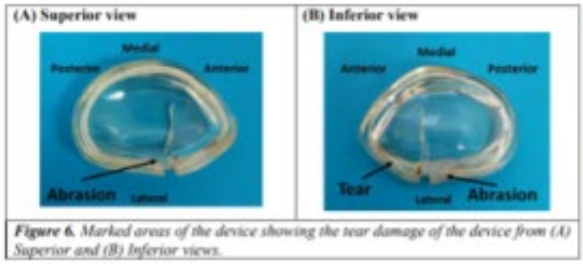


Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

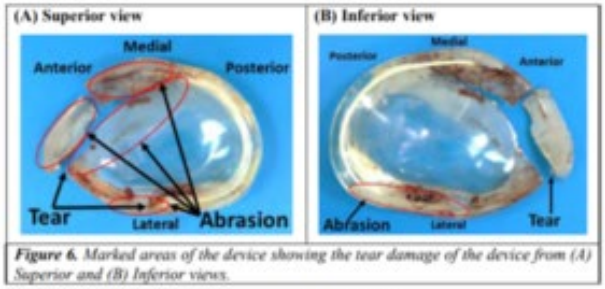


Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

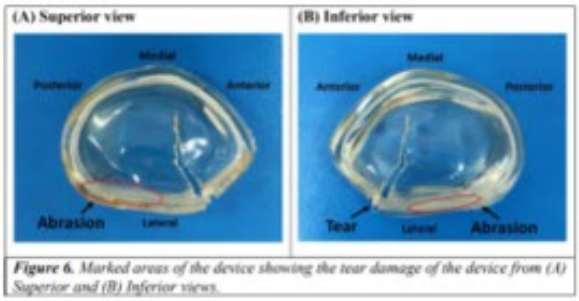


Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

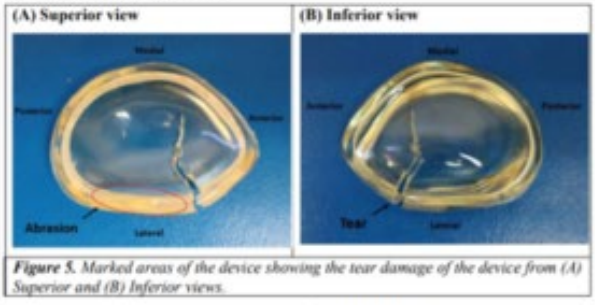


Figure 5. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

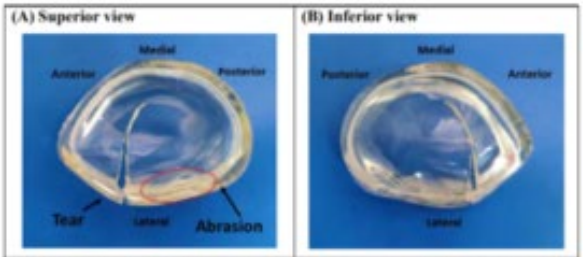


Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

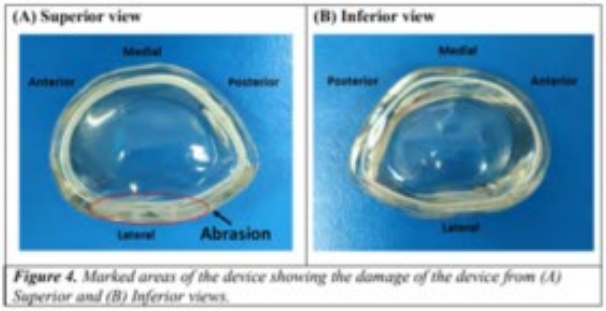


Figure 4. *Marked areas of the device showing the damage of the device from (A) Superior and (B) Inferior views.*

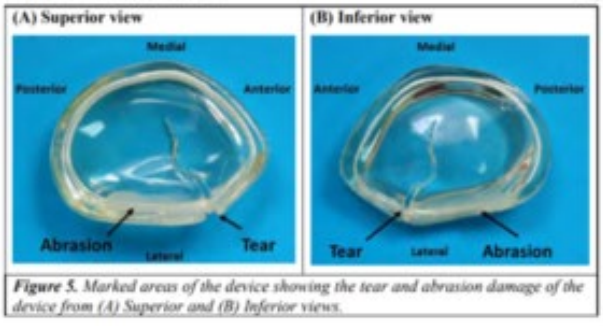


Figure 5. *Marked areas of the device showing the tear and abrasion damage of the device from (A) Superior and (B) Inferior views.*

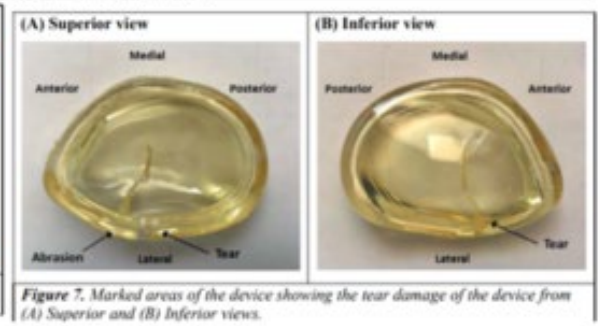


Figure 7. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

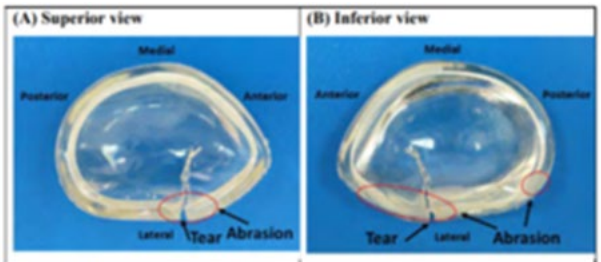


Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

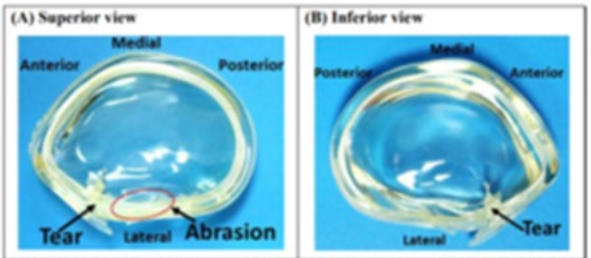


Figure 5. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

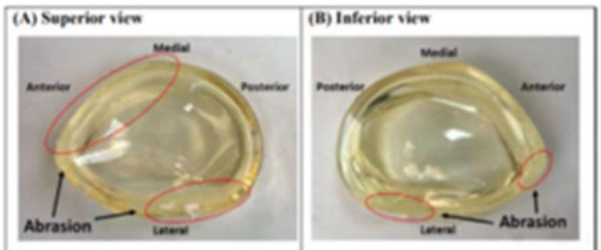


Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

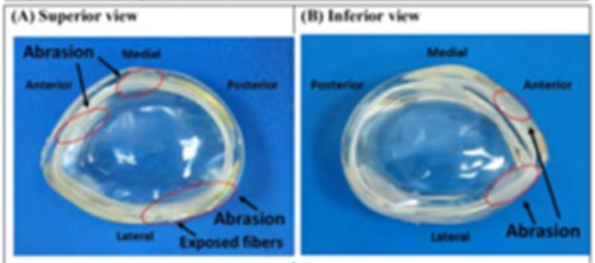


Figure 7. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

Appendix D: Patient Preference Information

D1. Sponsor's Discussion on Survey Administration from DENXXXXXX

The participants will watch a video presentation of clinical evidence-derived NO SURGERY data using visuals and graphs. (See attached script.) They will hear but not see a moderator reading a script. The moderator/speaker will first give a brief general introduction on the knee. During the entire presentation, the moderator will describe in sufficient detail the treatment options of NO SURGERY and SURGERY treatment options with enough information to allow the participant to make an informed Benefit/Risk determination. The presentation will be in a balanced, non-biased format and presented in such a simple manner that non-medical people can understand, yet knowing the goal was to match the IDE study population that 100% had a high school education.

The moderator will first describe the standard of care, which is non-surgical care, for treating knee pain--what it is, what are the Benefits, and what are the theoretical Risks. Then the moderator will explain the observed and theoretical Benefits and Risks found in the study when using NO SURGERY over 2 years.

The moderator will give general information about the surgical option. To keep it simple and non- descript as possible the moderator will not mention the meniscus, the tradename of the product, the company that makes it, or the FDA. The moderator will explain the theoretical Risks of SURGERY out to 2 years and mention the risks could continue after that point. To prevent any chance of cognitive bias, the moderator will give theoretical results for the surgical arm of the study and ask patients to choose between the actual NO SURGERY results and potential SURGERY results, by the manner discussed below.

Then the participants would be presented an option between two therapies for treating their knee pain using the non-surgical results with the actual % Benefits and % Risk measured in the study (the reference option). Next to those results would be theoretical results from a surgical option (the target option). As recommended in one of the PPI documents, the surgical option will start out showing theoretical identical Benefit and Risk rates and ask the participant "Which would you chose?" (NO SURGERY or SURGERY?). The participant would then choose between the two options starting with the same rates of the most important Benefit (pain reduction) and the most important Risk (SURGERY from increased pain after the start of treatment).

The following are the patient choice options. If the participant picks no surgery, then they will see the next line with an increased benefit. If the participant switches to surgery, then at what risk they will switch back to NO SURGERY?

The following outlines the choice options. If the participant picks NO SURGERY, then they will see the next line with an increased benefit. If the participant switches to SURGERY, then they will see increasing levels of risk to see at what risk they will switch back to NO SURGERY.)

Which would you choose? NO SURGERY if you knew you had a 25% chance of a minimum Benefit & a 10% chance of maximum Risk?

Or would you choose a SURGERY option if you knew by 2 years, you would have the following chances:

Choice 1: 25% minimum Benefit chance of benefit & 10% maximum Risk chance?

If they chose NO SURGERY at Choice 1, then they will see:

Choice 2: What if you had a 5 point[3] higher % chance—a 30% minimum Benefit chance & 10% maximum chance of risk? Which would you choose: NO SURGERY or SURGERY?

If they chose NO SURGERY at Choice 2, then they will see:

Choice 3: What if you had a 5 point[3] higher the chance—a 35% minimum Benefit chance & 10% maximum chance of risk? Which would you choose: NO SURGERY or SURGERY?

If they chose NO SURGERY at Choice 3, then they will see:

Choice 4: What if you had another 5 point improved chance—a 40% minimum Benefit chance of benefit & 10% maximum Risk chance? Which would you choose: NO SURGERY or SURGERY?

Choice 5: What if you had another 5 point improved chance—a 45% minimum Benefit chance & 10% maximum Risk chance? Which would you choose: NO SURGERY or SURGERY?

(And so on, with the minimum benefit increasing by the same amount of basis points with each choice. Whenever the participant chooses any of the SURGERY options, then they will start seeing questions about chances of maximum risk increasing by 5 points each time.)

What if the maximum chance of risk of additional surgery increased by 5 points to 15%, would that level of risk make you switch back to the NO SURGERY option? Which would you choose: NO SURGERY or SURGERY?

What if the maximum chance of risk of additional surgery another 5 points to 20%, would that level of risk make you switch back to the NO SURGERY option? Which would you choose: NO SURGERY or SURGERY?

What if the maximum chance of risk of additional surgery increased another 5 points would that level of risk make you switch back to the NO SURGERY option? Which would you choose: NO SURGERY or SURGERY?

(And so on with each risk level increasing by 5 points until the respondent switches back to NO SURGERY.)

However, if they chose SURGERY at Choice 1, they will see:

Choice 2: What if you had a 5 point less chance of Benefit—a 10% minimum Benefit chance & 10% maximum Risk chance? Which would you choose: NO SURGERY or SURGERY?

If they chose SURGERY again, then they will see:

Choice 3: What if you had a 5 point less the chance of Benefit—an 5% minimum Benefit chance & 10% maximum chance of risk? Which would you choose: NO SURGERY or SURGERY?

Since the minimum Benefit/maximum Risk rates will be identical for the first choice option, it would be understandable that most will pick the NO SURGERY option. When that happens, the participant will then be asked if an incremental increase in the % benefit would cause them to choose SURGERY? The participant will be asked again to choose between the NO SURGERY or SURGERY option. This process continues until the participant choses the SURGERY option. When that happens, the participant will see a series of questions that incrementally increase the % Risk of the SURGERY option until it causes them to choose NO SURGERY.

D2. Educational material for patient preference information study subjects: Script from video tutorial

Script for Active Implants Patient Preference Information Web-Based Survey

Date: May 22, 2022

Thank You for Participating in This Survey!

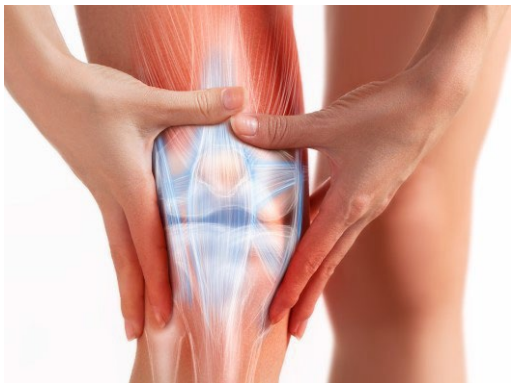
Thank you for participating today in this survey. You have been carefully selected to participate because you closely match a group of patients who participated in a clinical study. In today's survey we will compare the two different types of treatment they received. One treated the patients with no surgery and the other with surgery. The purpose of taking this survey today to find out your opinion about these two treatment options.

Why Are You Here?

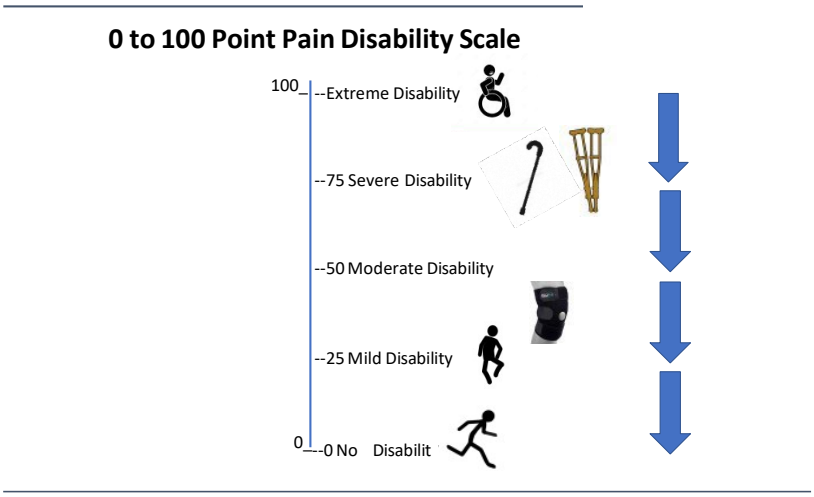
- **Good Thing (Benefit)**
- **Bad Thing (Risk)**
- **Compare Good to the Bad (Benefit vs. Risk)**
- **Compare Two Options**

Good things caused by treatment are benefits. Bad things that happen from a treatment are risks. We are going to talk about the benefits and risks of people who get treated with no surgery. Then we are going to tell you about a new surgical option. The reason you are here is because you will be asked to compare the good to the bad, the benefits to the risks, for these two treatment options and then we want you to tell us your honest opinion about which one you prefer.

Knee Pain



What is the medical condition we're talking about? We are talking about knee pain. One of the reasons for selecting you to take part in this survey is because you indicated you are familiar with knee pain. Knee pain is the most common reason people go to see a bone doctor. The knee is the most complicated joint of the body, easy to injure or damage, and often the source of a lot of pain that can interfere with your life.



Over the years doctors developed a very accurate scale to measure knee pain. We are going to explain this scale to you in a way that will be easy for you to understand—it goes from 0 to 100. Zero on the pain scale means you have no pain or disability at all. In other words, your knee is normal. You can do anything you want: Run, play golf, or do any other type of physical activity. If you have a score of 25 on this 100 point pain scale that means you have a <u>mild</u> disability. After certain

activities such as playing a round of golf or taking a hike, your knee starts to hurt, and it bothers you.

A score of 50 on this zero to 100 point scale indicates you have a <u>moderate</u>

disability. That means you might sometimes need to put a strap or brace around your knee or put some ice on it--or take some pain pills.

Anyone who scores a 75 on the scale means they have a <u>severe</u> disability. People

with this score may sometimes need a cane or crutches to get around. This level of pain significantly affects how you live your life.

And finally, anyone that scores 100 on this 100 point scale has the worst pain you can possibly imagine. These people are totally disabled. People who score 100 points on the scale have an <u>extreme</u> disability and are usually bed ridden or need

a wheelchair to get around. Their knee pain is so bad they cannot even put their foot on the ground, this is how much their knee hurts and how disabled they are.

How much less knee pain would you and your doctor like to see? Both you and your doctor would like to see your pain improve by a minimum of one disability level, or 25 points. If you have a score of 100, you would like to get out of your wheelchair and become more mobile, which would mean you want to reach at least a target score of 75. If you need canes and crutches and have a score of 75, you hope to improve one more disability level and get down to at least a score of 50.

If you have a score of 50 and have a brace and are taking drugs for pain, you want to get to a score of 25. And if you are mildly disabled with a score of 25 point on the scale, your minimum benefit is to get to 0 where you would have no activity restrictions at all and are normal.

NO SURGERY TREATMENTS:

- **Lose Weight**
- **Limit Activities**
- **Exercise (Physical Therapy)**
- **Apply Heat and Cold**
- **Shots in Knee**
- **Braces, Wraps, Crutches**
- **Drugs**

And what type of treatment would patients with knee pain get if they get no surgery? The doctor could ask them to lose weight, limit their activities, do certain types of knee exercise called physical therapy to build up the muscles around their knee, or their doctor may have them apply heat or cold to their knee to try to lessen the pain.

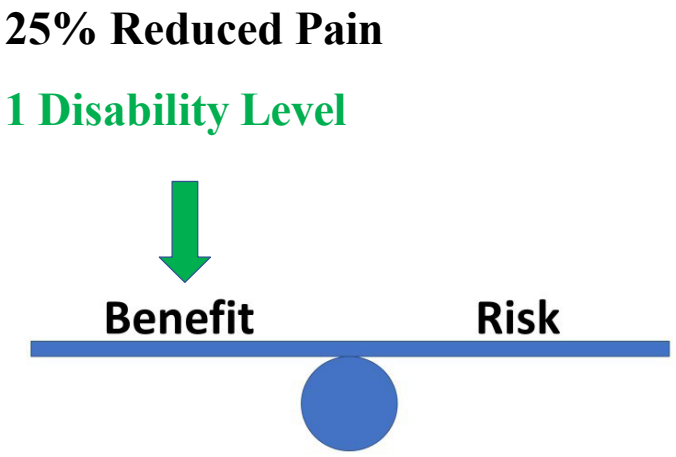
The doctor might give them some shots, or the doctor might ask them to use a brace or put a strap around their knee or give them crutches or canes to try to lower their knee pain. Doctors might also give their patients drugs to lower the pain.

All patients treated with no surgery in the clinical study came back at different times over a 2 year period and answered the same set of questions to find out and measure their pain and disability score. By comparing those results to how they were when they started the study, their doctors were able to figure out if their pain and disability were getting better, stayed the same, or got worse. For example, if your pain level remained the same, there would be no change in your pain and

disability over time. If your pain improved by one disability level, for example, you would have an improvement of 25 points.

And what happened in the study of knee pain patients treated with no surgery? We are now going to show you the results after 2 years of no surgery treatment of patients in knee pain. The following slide shows the results after 2 years of shots, drugs, exercise, and other treatments with no surgery.

Benefit Decision: No Surgery Option



On the slide is the percent of no surgery patients who had a 25 point pain improvement of one disability level by 2 years.

Now we are now going to describe the bad things or risks that happened or could happen to those patients who received no surgery.

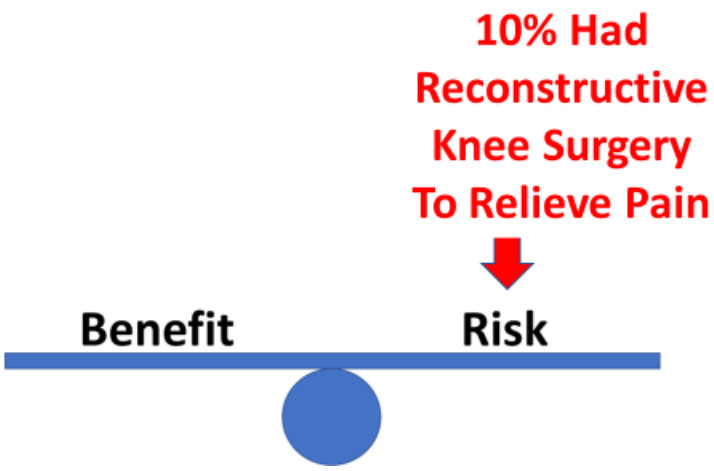
No Surgery
Does Not Mean No Risk

- **Shots**
- **Drugs**

We know what some of you maybe be thinking right now, which is if you had no knee surgery, there cannot be any bad thing that can happen, right? It turns out there are bad things that can happen even if you do not have surgery. Although it did not happen in the study, it is possible that shots in the knee could cause complications. Patients could have an infection or a reaction to the shots. Patients could also have reactions to any of the drugs taken, some of which could become addictive.

The maximum risk of all is even though the patient thought they were not getting surgery, their knee does not improve or may get worse, and they end up having surgery anyway. The worst risk of all is to need reconstructive knee surgery, meaning surgery that cuts bone to remove a wedge, or replace all or part of the joint, or remove or transfer or reconnect tissue such as ligaments. Those types of advanced knee surgery did happen in the patients treated in the study who started out being treated with no surgery. The following slide shows the results.

Risk Decision: No Surgery Option



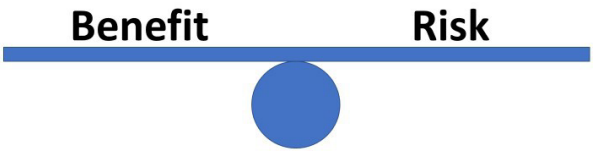
Keep in mind that the percent shown in the slide is just for the first two years. After 2 years, this rate of knee reconstructive surgery may increase even more.

The other thing to keep in mind is that patients not receiving surgery do not receive their no surgery treatment just once. Some part of the treatments they receive may need repeating. Patients may have to keep wearing a brace, keep taking medicine or drugs, keep doing exercise, keep losing weight, and/or keep getting shots in their knee—all of which could cause them to keep seeing their doctor.

Now we are going to ask you to compare the minimum benefit, which remember is a good thing that can happen, to the maximum risk, which some perceive is the worst thing that can happen to you. We do this all the time during our lives, whenever we narrow down choices to two different options, such as two different cars or housing or pieces of clothing.

Benefit/Risk Decision:

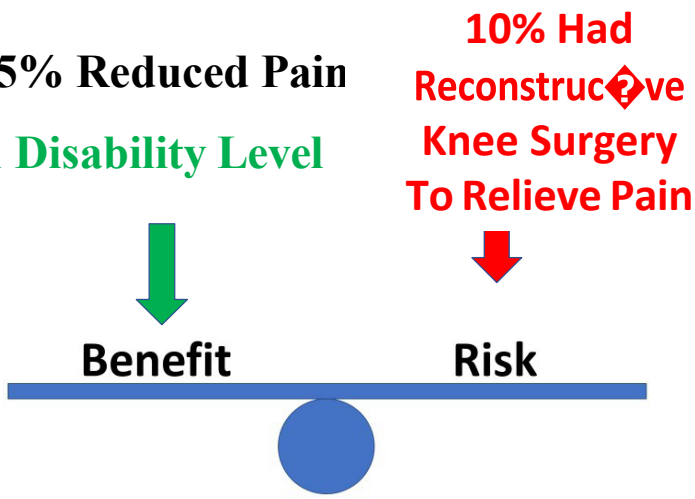
Weighing the Good vs. the Bad



We decide by weighing the good and the bad of each option and make a choice.

We want you to pretend you are visiting a doctor. The doctor is going to tell you what you can expect from no surgery treatment based on the results of patients who have knee pain just like yours who participated in the clinical trial.

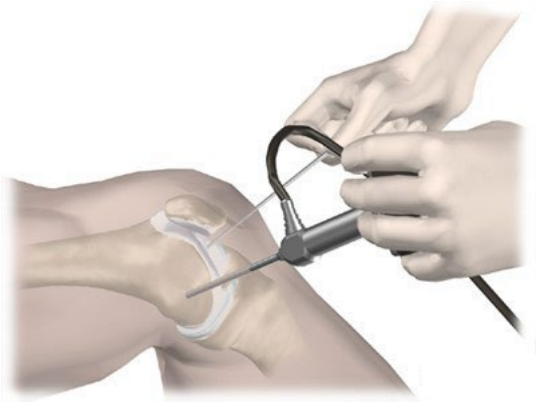
Benefit/Risk Decision: No Surgery Option



The doctor says you will have the percent chances shown on your screen of reducing your pain of one disability level after 2 years of no surgery treatment— that is the minimum benefit-- but also have the chance shown in the slide of having a reconstructive surgery anyway—that is the maximum risk.

After hearing these chances, you might ask your doctor, "Before I decide, is there another option?" The answer is, "Yes. There is a new treatment option that involves surgery."

Surgery Option:



What is this new type of surgery? Your doctor explains that you would need to go to what is called a minor surgery center that does not put you in a hospital. The doctor will put you to sleep with anesthesia, cut your skin, put a small camera inside your knee, and after using some small instruments to prepare your knee, insert a plastic device.

Perhaps the simplest way to describe what the plastic device does is that it is like an insert in your shoe. Just like the shoe insert absorbs the load on your foot, the

device the doctor puts into your knee absorbs the loads on your knee. The hope is the device will help reduce your knee pain.

Risks of Surgery

- **Put to Sleep (Anesthesia)**
- **Skin Cuts May Not Heal**
- **Infection**
- **Swelling**
- **Stiffness**
- **Pain from Surgery**
- **Scar**
- **Recovery from Surgery**
- **Device Inserted in Knee May Need Adjusted, Removed, or Replaced**

What are bad things or risks that could happen after a surgery? There are a number of possible bad things or risks that could happen. During surgery, you will be put to sleep--which has its own set of risks. Recovery from surgery may take longer than expected or have long term consequences.

It is very rare, but things can go wrong while you're asleep in surgery and while you are recovering from anesthesia. Although none of those happened in the study, those are possible risks for any type of surgery where the patient is put to sleep.

The doctor will explain that the surgery itself takes about 90 minutes and during the surgery your doctor will cut your skin around your knee joint. These cuts might get infected, or the cuts may not heal like they should, or they could create scars inside or outside your knee. These types of risks are the same for anyone who has any type of surgery that cuts the skin.

Everybody who has knee surgery has some type of swelling around where the doctor cuts your skin. How much swelling, and for how long, will vary from patient to patient. You will have some pain because the cuts made into the skin. After surgery, the doctors will put your leg in a brace to hold your knee straight for about a week. Your knee might also have some stiffness after surgery. You will go through six weeks of recovery, which will include various types of exercise, which could cause complications such as an increase in pain.

Another risk after surgery is you either will have no improvement in pain or it gets worse. One reason for an increase in pain is the device in your knee does not stay in place, causing the need for additional surgery. But just like for the option of "no surgery", the maximum worst case risk is you might need to have reconstructive knee surgery, meaning an additional surgery that cuts bone to remove a wedge, or replace all or part of the joint, or remove or transfer or reconnect major soft tissue such as knee ligaments. This risk of additional surgery caused by pain goes on for as long as you have the device in your knee.

Which Would You Choose?
No Surgery or Surgery?

No Surgery Option **Surgery Option**

As you can see, the no surgery and the surgery options each has benefits and risks. In this survey we are going to ask you to weigh the benefit and risk of each option—much like a seesaw or teeter-totter at a playground--and decide which side outweighs the other for each option. Then you decide which you prefer of the two options—no surgery or surgery.

We are now going to ask you to weigh the benefits and the risks for the two treatment options. You already saw the percent of patients who had benefit and risk after being treated with no surgery. But the way we are going to compare those results to the surgery treatment option is by asking you to choose based on different levels of percent benefit and risk for the new surgical technique. When presented with a choice, you need to pick one of the two options based on how you weigh the benefit and risk for each of the two options.

Always remember there are no wrong answers. We want you to tell us what you really think, not what you think someone else wants you to say. Please give us your honest answer because we want to know which choice you would prefer when comparing the chances of no surgery vs. different levels of benefits and risks of a new surgical option.

One more thing: do not be concerned about money or the cost of the two treatment options. Assume your insurance company covers both at no cost to you.

25% = 25 out of 100 = 1/4

Before we begin, we want to make sure you know how to compare one option to the other. A common way used to compare options is to use percentages. A percentage is a portion of 100. A 25% rate, for example, would be 25 out of 100, or one chance out of four. Another way to think about it is to look at a picture of a cake. 25% would be one fourth of the cake. A percentage is an easy and common way to compare the chances of something happening when trying to compare two different options.

You will now start choosing between the no surgery treatment option and the surgery treatment option. Initially, the percent chance of improving the pain level in your knee by one disability level and having reconstructive surgery will be the same for both the no surgery and surgery options.

Which Would You Choose?
No Surgery or Surgery?

Less Pain	More Pain
25% Chance of Improving	10% Chance of Reconstructive Surgery
1 Disability Level	

No Surgery Option

Less Pain	More Pain
25% Chance of Improving	10% Chance of Reconstructive Surgery
1 Disability Level	

Surgery Option

After your initial choice—no surgery or surgery-- you will see on your screen a second set of choices. The numbers on the left for the no surgery option will not change. But for the surgery option on the right, the percent chance of improving your knee by one disability level or the percent chance of reconstructive surgery risk will be change. The computer will continue changing the numbers for the surgery option on the right and you will continue choose one.

Time to Vote

Before you start voting, we need to tell you one other thing, which is you cannot go backwards on the computer. Once you choose between two options, you cannot change your mind and go back and change your previous answer.

Because it is so important that you understand what is being asked of you, we want to explain it one more time. In the first set of options where the benefit and the risk are the same for no surgery and surgery, you need to pick either no surgery or surgery. If you choose no surgery, for example, then you would be asked what would you say if the surgery option had a higher percent chance of pain improvement or benefit? Would you switch to surgery then? If not, you will see increasing percentages to see when you would you switch—if ever--from the no surgery option to the surgery option?

And after you switch to the surgery option--if you ever do--the percent chance of risk will start increasing to see how much higher percent chance of risk you would be willing to accept before until you switch back to the no surgery option.

Now we're going to start. We want to see which option you choose for different possible results.

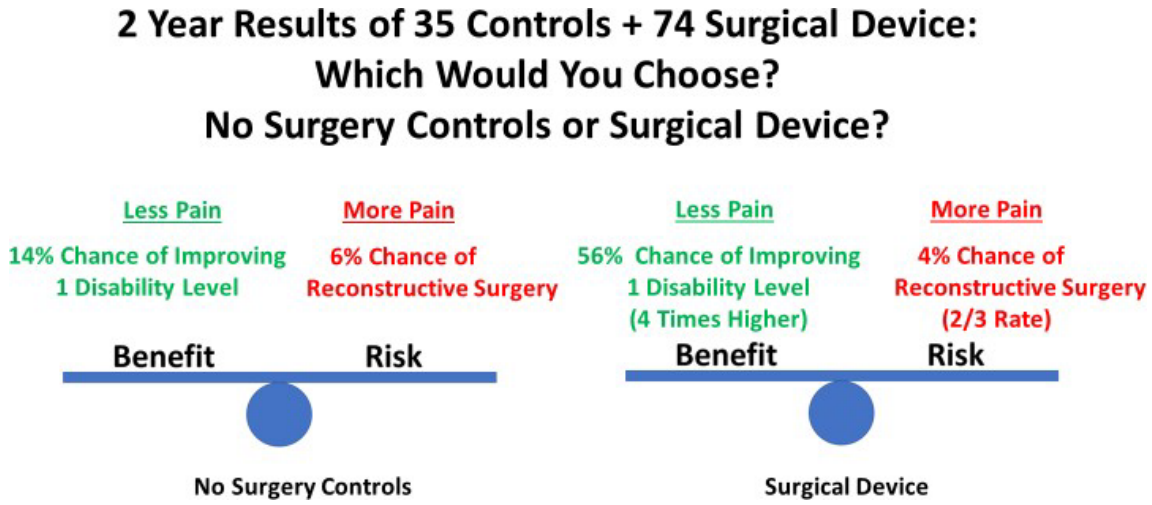
After your decision you will see a different set of numbers based upon your initial decision.

(pause)

This completes this portion of the survey. We have two simple questions we would like to ask you before we let you go.

Here is a question. Now that you are at the end of the survey, we want to show you the actual results from the clinical trial of no surgery vs. surgery.

Knowing these are the final results, if presented these numbers by a doctor, which option would you choose? No surgery or surgery?



From what you saw: Please check one of the following blanks on your screen:

Thank you very much for participating in this survey. We really appreciate your time and value your opinion.

D3. Survey Comprehension Questions

Copy of 8 Comprehension Questions for PPI study #7:

1. True* or false: Doctors can treat knee pain by using SURGERY or NO SURGERY?

2. What is a benefit?
   A. *The good things that can happen to you
   B. The bad things that can happen to you
   C. The cost of the procedure

3. What was the main benefit mentioned by the speaker?

   A. Chances of Improving mental health

   B. Chances of returning to sports

   C *Chances of lowering knee pain by more than 1 disability level

   D. Chances of less drug use

4. What is a risk?
   A. A good thing that can happen to you
   B. *A bad thing that can happen to you
   C. That you may improve too much

5. True* or false: If a doctor treats knee pain with no surgery, the knee pain might get worse over time and require surgery later.

6. What did the speaker say was the maximum risk?

   A. Chance of infection

   B.*Chance of having reconstructive knee surgery within 2 years

   C. Chance of knee swelling

   D. Chance of not returning to sports

7. How can anyone compare benefit and risk?

   A. They cannot be compared

   B. See which one costs less

   C. *Weigh the benefit and risk and decide if the benefit outweighs the risk

8. The speaker said he would ask you to:

   A.*Weigh the Benefit and Risk of two Options then choose one

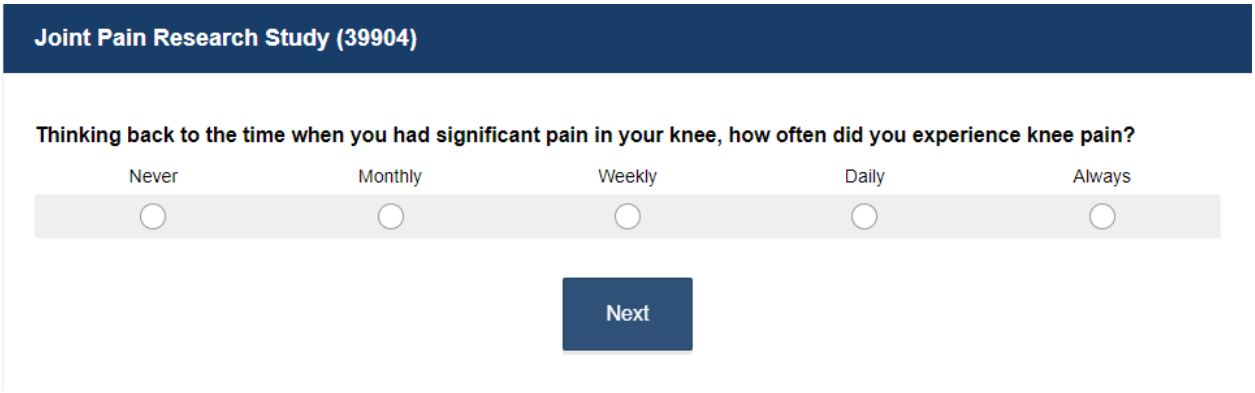
   B. Choose which option is easier

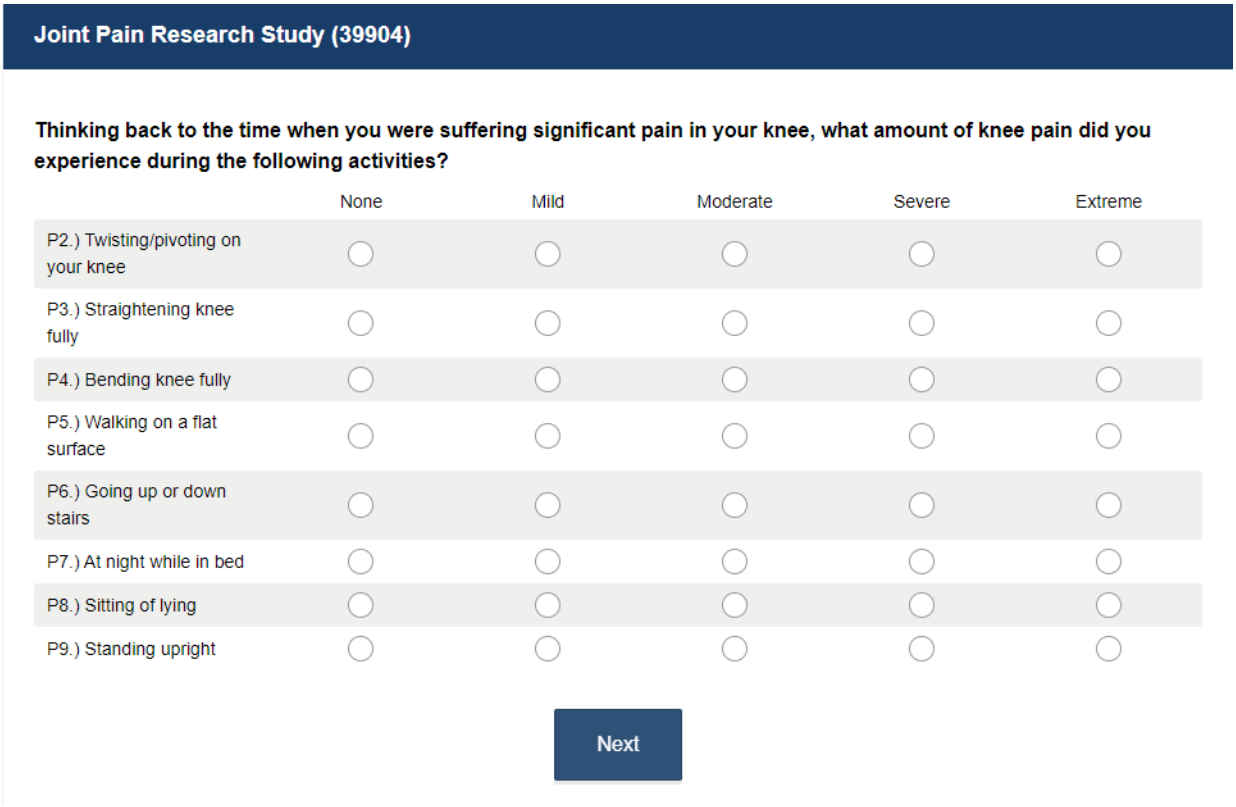
   C. Choose which option allows more sports activity

   D. Choose which of the two options costs less

The * denotes the correct answer.

D4. Example Threshold Questions
Representative Screen Shots of what the Respondents Saw During PPI study #7





Joint Pain Research Study (39904)

Doctors are able to treat knee pain with No Surgery or with Surgery?

- ◯ False
- ◯ True

Next

Joint Pain Research Study (39904)

What was the main benefit mentioned by the speaker?

- ◯ Chances of Improving mental health
- ◯ Chances of lowering knee pain by more than 1 disability level
- ◯ Chances of less drug use
- ◯ Chances of returning to sports

Next

Joint Pain Research Study (39904)

What is a benefit?

- ◯ Becoming addicted to drugs
- ◯ The bad things that can happen to you
- ◯ The cost of the procedure
- ◯ The good things that can happen to you

Next

Joint Pain Research Study (39904)

What is a risk?

- ◯ A bad thing that can happen to you
- ◯ That you may improve too much
- ◯ A good thing that can happen to you

Next

Joint Pain Research Study (39904)

"If a doctor treats knee pain with no surgery, the knee pain might get worse over time and require surgery later."

- ◯ True
- ◯ False

Next

Joint Pain Research Study (39904)

What did the speaker say was the maximum risk?

- ◯ Chance of having reconstructive knee surgery within 2 years
- ◯ Chance of not playing sports
- ◯ Chance of infection
- ◯ Chance of knee swelling

Next

Joint Pain Research Study (39904)

How Can Anyone Compare Benefits and Risk?

- ◯ Weigh the benefit and risk and decide if the benefit outweighs the risk
- ◯ They cannot be compared
- ◯ See which one costs less

Next

Joint Pain Research Study (39904)

The Speaker Said He Would Ask You To:

- ◯ Choose which option allows more sports activity
- ◯ Weigh the Benefit and Risk of two Options then choose one
- ◯ Choose which of the two options costs less
- ◯ Choose which option is easier

Next

Joint Pain Research Study (39904)

Of the the two options described below, each option with its own chances of less pain and unplanned reconstructive surgery, which do you prefer?

Please select Option A or Option B.

○ **Option A: No Surgery**
25% chance of improving 1 disability level
10% chance of unplanned reconstructive surgery

○ **Option B: Implant Surgery**
25% chance of improving 1 disability level
10% chance of unplanned reconstructive surgery

Next

12a

Joint Pain Research Study (39904)

(Please note: The probabilities under Option B have changed from the previous question.)

Of the the two options described below, each option with its own chances of less pain and unplanned reconstructive surgery, which do you prefer?

Please select Option A or Option B.

○ **Option A: No Surgery**
25% chance of improving 1 disability level
10% chance of unplanned reconstructive surgery

○ **Option B: Implant Surgery**
30% chance of improving 1 disability level
10% chance of unplanned reconstructive surgery

Next

12b

Joint Pain Research Study (39904)

(Please note: The probabilities under Option B have changed from the previous question.)

Of the the two options described below, each option with its own chances of less pain and unplanned reconstructive surgery, which do you prefer?

Please select Option A or Option B.

○ **Option A: No Surgery**
25% chance of improving 1 disability level
10% chance of unplanned reconstructive surgery

○ **Option B: Implant Surgery**
25% chance of improving 1 disability level
15% chance of unplanned reconstructive surgery

Next

D5. Patient preference study results

2. Linear Regression model with dummy variables for gender, ethnicity and education: $MAB = A_0 + B_1*BMI + B_2*KOOS + B_3*MALE + B_4*Age + B_5*CAUCASIAN + B_6*COLLGRAD$

where
MAB = minimal acceptable benefit
MALE = 1 if gender is male and =0 if gender is female
CAUCASIAN = 1 if caucasian and =0 if not
COLLGRAD = 1 if college degree or grad degree and =0 if high school grad or some college

Regression Statistics	
Multiple R	0.236
R Square	0.056
Adjusted R Square	0.028
Standard Error	0.210
Observations	207

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	6	0.522621	0.087104	1.971802	0.071304
Residual	200	8.834921	0.044175		
Total	206	9.357542			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.523	0.104	5.029	0.000	0.318	0.728
BMI	-0.002	0.002	-0.649	0.517	-0.006	0.003
KOOS	0.000	0.001	0.101	0.920	-0.002	0.002
Male=1	-0.063	0.030	-2.106	0.036	-0.123	-0.004
Age	0.002	0.001	2.036	0.043	0.000	0.004
Cauc=1	-0.032	0.041	-0.785	0.433	-0.113	0.049
CollGrad=1	-0.042	0.031	-1.389	0.166	-0.103	0.018