De Novo Request for the NUsurface Meniscus Implant From Active Implants, LLC

Meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee

FDA Presenters:

Travis Prest, Ph.D.

Marc DeHart, M.D.

Cynthia Liu, M.S.

David Gebben, Ph.D.

Overview of NUsurface De Novo Request

Travis Prest, PhD
Lead Reviewer, Biomedical Engineer
Restorative, Repair, and Fracture Fixation Devices Team
Division of Restorative, Repair and Trauma Devices (DHT6C)
Office of Orthopedic Devices (OHT6)
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Review Team

Lead Reviewer	Travis Prest, PhD
Reviewer	Melissa Ramcharan, PhD
Clinical	Marc DeHart, MD
Statistics	Cynthia Liu, MS Alvin Van Orden, MS
Patient Preference Information	David Gebben, PhD
Veterinary	Sara Thompson, DVM
Sterility	Diane Smith, PhD
Biocompatibility	Aprajita Garg, PhD
Chemical Characterization	Anne Talley, PhD
Toxicological Risk Assessment	Caroline Pinto, PhD Tromondae Feaster, PhD
Project Manager	CDR Randoshia Miller, MS

Outline of FDA Presentations

- **Background Information:** Travis Prest, Ph.D.
  - Regulatory Background
- **Clinical Evidence:** Marc DeHart, M.D.
  - Overview of Meniscus and Knee Pain
  - Device Description
  - Indications for Use
  - Clinical Background
  - Clinical Studies and Datasets
- **Statistical Considerations:** Cynthia Liu, M.S.
- **Social Science and Patient Preference:** David Gebben, Ph.D.
- **Benefit and Risk Considerations:** Marc DeHart, M.D.

Regulatory Background

- De Novo eligibility – NUsurface is eligible for evaluation in a De Novo because it:
  - Does not fit into any existing regulation (any device class)
  - Does not have a previously approved Premarket Approval (PMA)
  - Presents a low to moderate risk profile

- During review of a De Novo, FDA:
  - Assesses whether the probable benefits of the device outweigh the probable risks
  - Takes into account risk mitigations
  - Considers clinical and/or non-clinical testing

- If granted, FDA would likely place NUsurface in Class II and it may serve as a predicate for future devices which can be appropriately regulated through the 510(k) pathway.

- De Novo request, including non-clinical and clinical data, currently under review
  - **Focus of today's meeting is limited to discussion of clinical data**

Topics of Discussion at Panel Meeting

- 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 device-related Secondary Surgical Interventions (SSI)
- 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) 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
- Whether a favorable benefit-risk profile has been demonstrated for the subject device for its proposed intended use

Clinical Background and NUsurface Clinical Studies

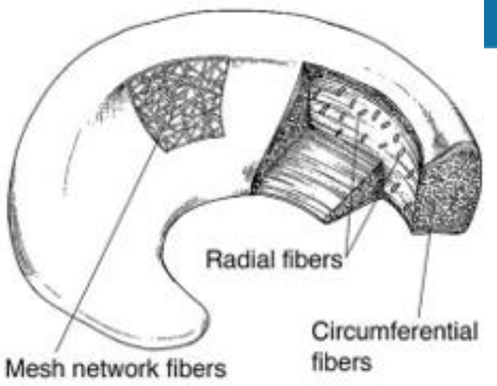
Marc DeHart, MD
Orthopedic Surgeon
Adult Hip and Knee Reconstructive Surgery
Sports Medicine, Certificate of Added Qualification

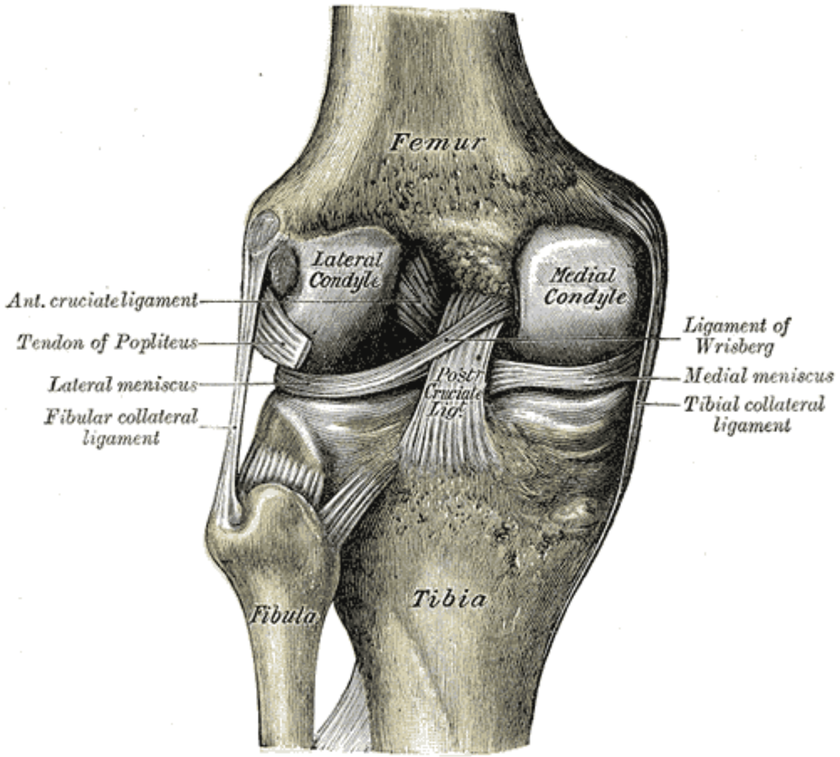
Medical Officer
Hip Arthroplasty Devices Team
Division of Joint Arthroplasty Devices (DHT6A)
Office of Orthopedic Devices (OHT6)
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Knee Meniscus

- Menisci maintain health of the knee joint by protecting joint cartilage via:
  - Load transmission, shock absorption, stabilization, and lubrication
- Medial Meniscus is fixed to tibia by the

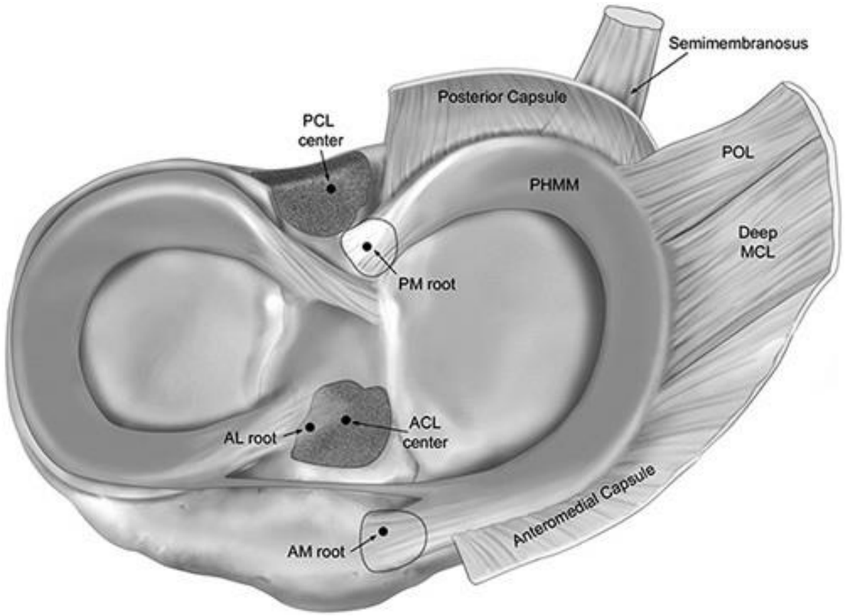
  Tibial (medial) collateral ligament
- Loss of function of the menisci can increase pressure on cartilage and lead to chondral damage
- Long-term damage to the meniscus can lead to degenerative changes in the knee joint, including osteoarthritis





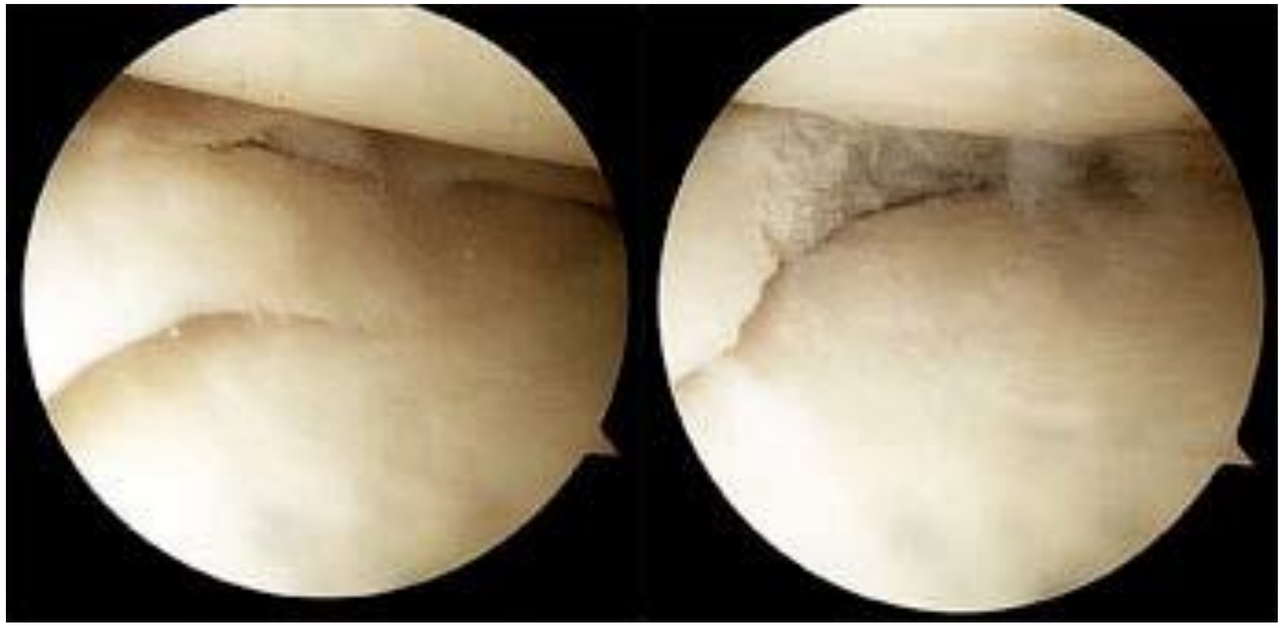
Medial Meniscus and Knee Pain

- Multicenter randomized controlled trials (RCTs) have failed to identify substantial benefits of arthroscopic partial meniscectomy over nonoperative treatment or placebo surgery. (Avila et al., 2022)
- Asymptomatic meniscus tears are common on MRI. (Feeley et al., 2018)
- Amount of meniscus removed is correlated to later arthritis. (Englund et al., 2008)
- Meniscus pathology and arthritis are commonly associated. (Avila et al., 2022)
- Greater association of “meniscus symptoms” with arthritis than meniscus pathology (Farina et al., 2021)



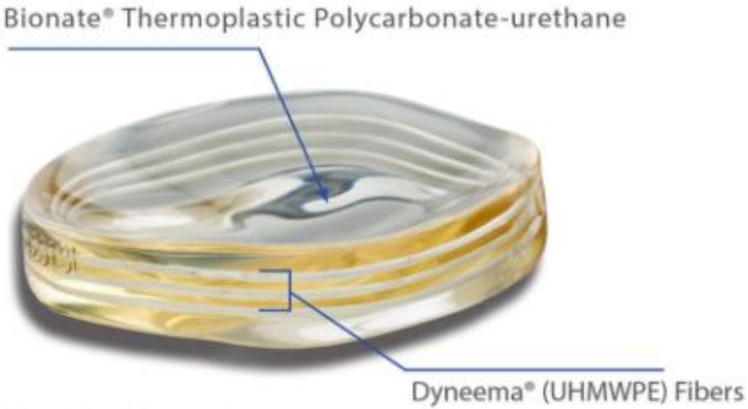
Surgical Options for Symptoms Related to Meniscus Pathology

- Meniscus Repair
- Meniscectomy
- Meniscus Augmentation
- Meniscus Allograft



NUsurface Meniscus Implant

- The NUsurface Meniscus Implant is a polymeric disc-shaped device intended to be inserted into the medial compartment of the knee to distribute load between the distal femur and proximal tibia and restore function of a damaged meniscus.
- The implant is a non-anchored, interpositional spacer and is not intended to be fixed in place by sutures or bone cement.
- Device composition:
  - Polycarbonate urethane (PCU)(Bionate I 80A) reinforced with UHMWPE fibers (Dyneema Purity),
  - Dyneema Purity fibers embedded around the periphery.



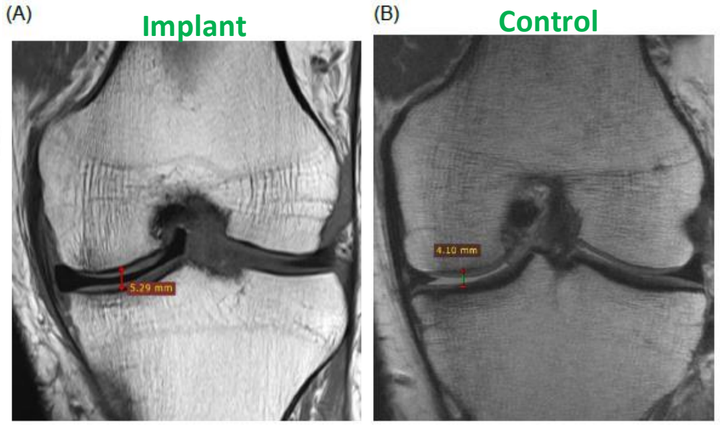


***Figure 3**. Representative MR-image of joint space measurement for an A) Implanted patient with NUsurface device and B) Control patient*

Indications for Use

"The intended use of the NUsurface Meniscus Implant is to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected. The indication for use is in patients with:

--mild-to-moderate 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."

Clinical Study History

- 2008: Feasibility Study (OUS) - NUsurface Meniscus Implant
- 2011: Multi-Center Trial (MCT) (OUS)
  - Pilot study with NUsurface Meniscus Implant 1.0
  - 7 sites in Europe and Israel
  - Used for validation of Modified MERCURY dataset criteria
- 2012: VENUS (US) - **V**erifying the **E**ffectiveness of the **NU**surface **S**ystem
  - NUsurface Meniscus Implant 2.0
  - Study was reviewed and approved by the Agency
- 2015: SUN (US) - **S**afety **U**tilizing **N**Usurface® Meniscus Implant
  - NUSurface Meniscus Implant 2.0
  - Study was reviewed and approved by the Agency

VENUS Study

Verifying the **E**ffectiveness of the **NU**surface **S**ystem

- Prospective, randomized (1:1), 2-parallel-arm, non-surgical-controlled, multi-center, interventional, superiority trial
  - 61 NUsurface and 66 Control
- Limitations: 30% (20/66) of control subjects lost to follow-up or withdrew by 12 months
- Overall Success based on a composite endpoint including improvement in pain and function, and absence of a device-related SSI (NUsurface group) or any SSI (control group).

SUN Study
(**S**afety **U**tilizing **N**Usurface® Meniscus Implant)

- SUN study was added to provide for more robust numbers for safety analysis.
- Prospective, non-randomized, multi-center, single-arm, 24-month observational study (optional 60 month), 115 NUsurface subjects
- Safety hypothesis proposed by the sponsor:

  "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%."

Overview of the Datasets

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).
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).

*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.

Key Inclusion Criteria

- Had >6 months ago a previous medial meniscectomy as confirmed by diagnostic MRI and patient history at least 6 months prior to the start of study treatment
- Has a pain score of 75 or less on the KOOS (Knee injury Osteoarthritis Outcome Score) pain scale
- Has ≥ 2 mm intact meniscal rim and is capable of receiving a NUsurface device, if used
- Is between age 30 and 75 years at the time of the start of study
- Is willing to be entered into either arm of the study: implanted with the NUsurface device OR treated with the recommended control arm therapies

Key Exclusion Criteria

- Has evidence of a Grade IV (Outerbridge) articular cartilage loss on the medial tibial plateau or femoral condyle that could contact the NUsurface implant (e.g., a focal lesion >0.5 cm^2)
- Has lateral compartment pain and Grade III or Grade IV Outerbridge cartilage score in the lateral compartment
- Has patellar compartment pain and/or patellar articular cartilage damage greater than Grade II
- Has an ACL reconstruction performed less than 9 months before implanting the NUsurface implant
- Has a BMI > 32.5
- Has a varus/valgus knee deformity > 5 degrees
- Has a knee laxity level of more than II (ICRS), secondary to previous 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)

Investigational Treatment

Key steps to the placement of the device:

(1) Meniscectomy and arthroscopic confirmation of lack of arthritis

(2) Osteophyte removal and notchplasty

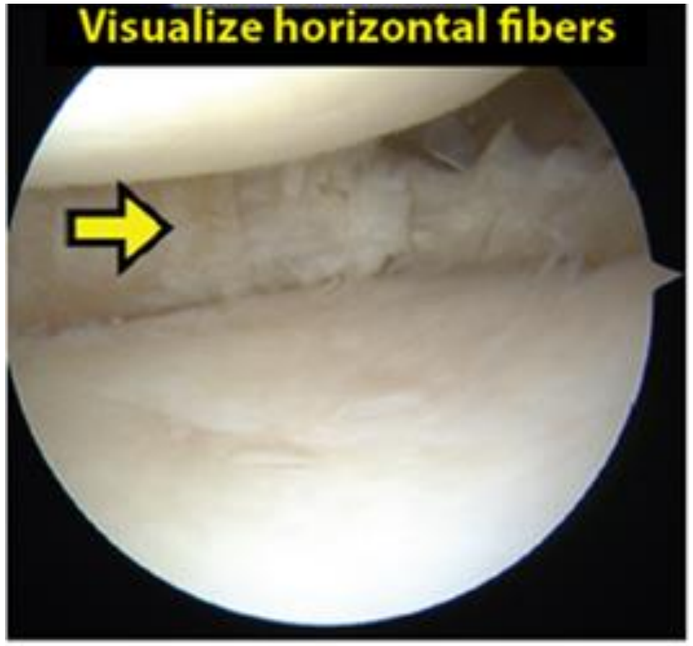
(3) Trial insertion

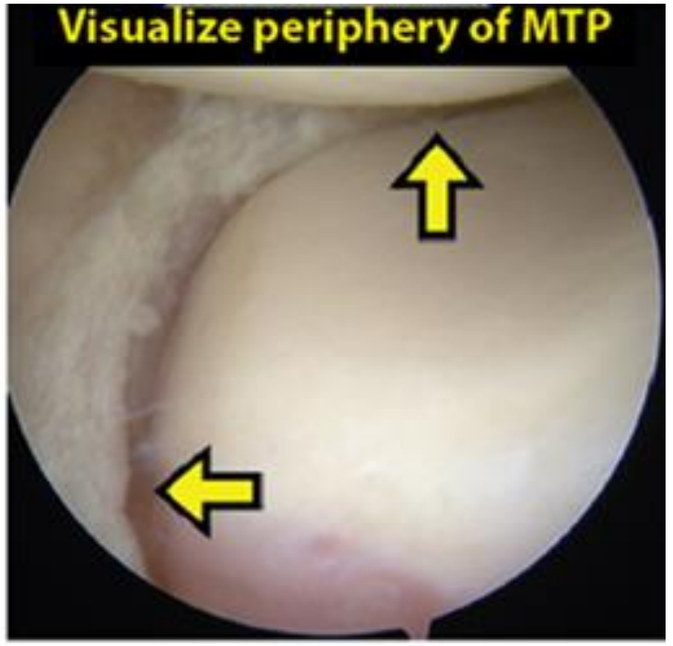
(4) Trial assessment

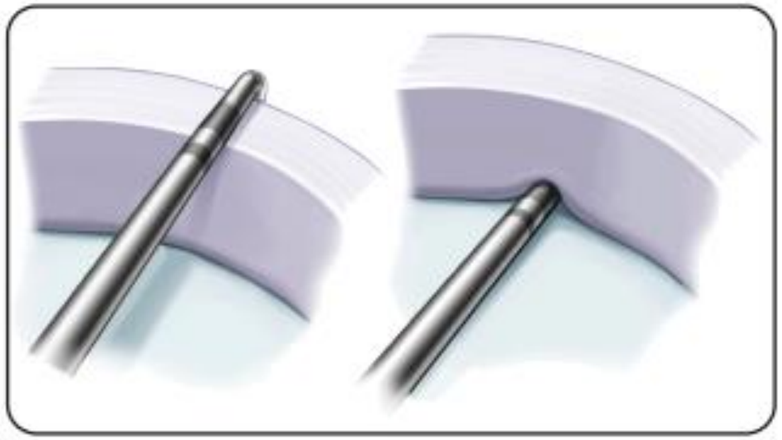
(5) Final placement of the device

1. Meniscectomy

- To prepare the medial compartment the technique notes, “Unlike a typical partial meniscectomy, it is important to remove as much of the meniscus as possible leaving no more than a 2mm margin around its periphery.”

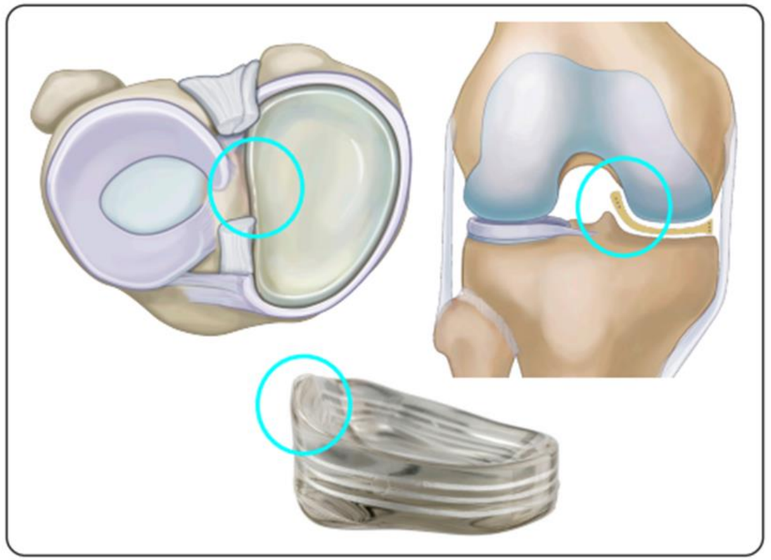


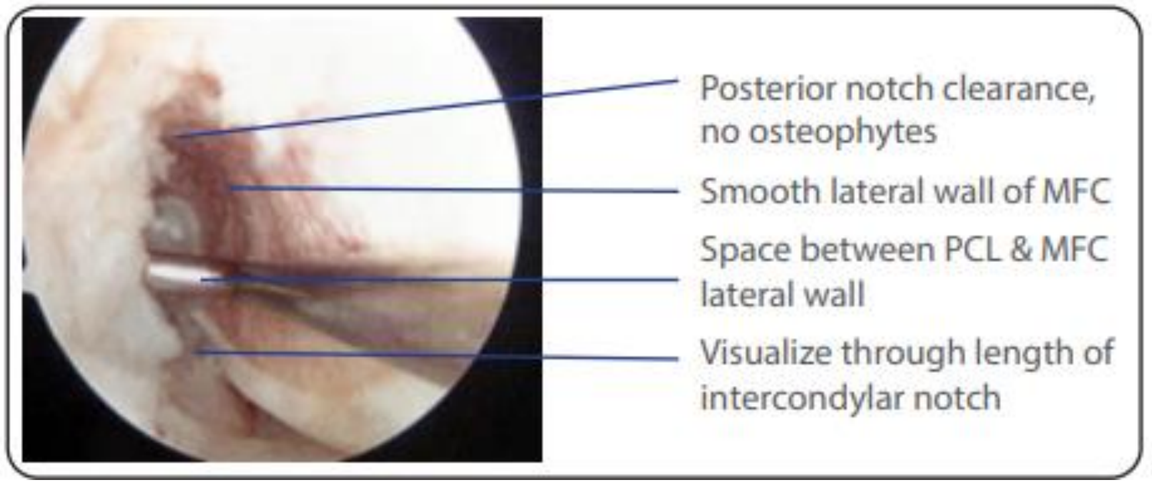




2. Prepare Intercondylar Fossa

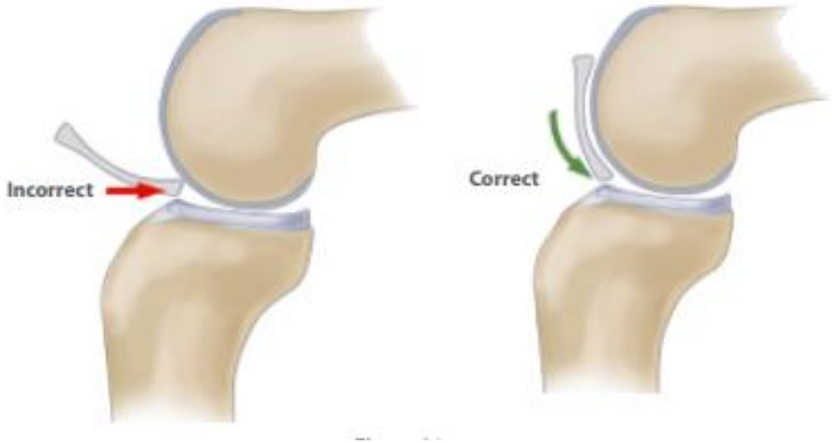
- “The NUsurface® Meniscus Implant is non-anchored and its design includes a raised area around its circumference with a prominent lateral “bridge” for placement between the tibial eminence and the femoral notch.”
- To avoid impingement during deep flexion activities: "Ensure adequate removal of osteophytes along the posterior lateral corner of medial femoral condyle to reduce the potential for impingement during deep flexion activities.”

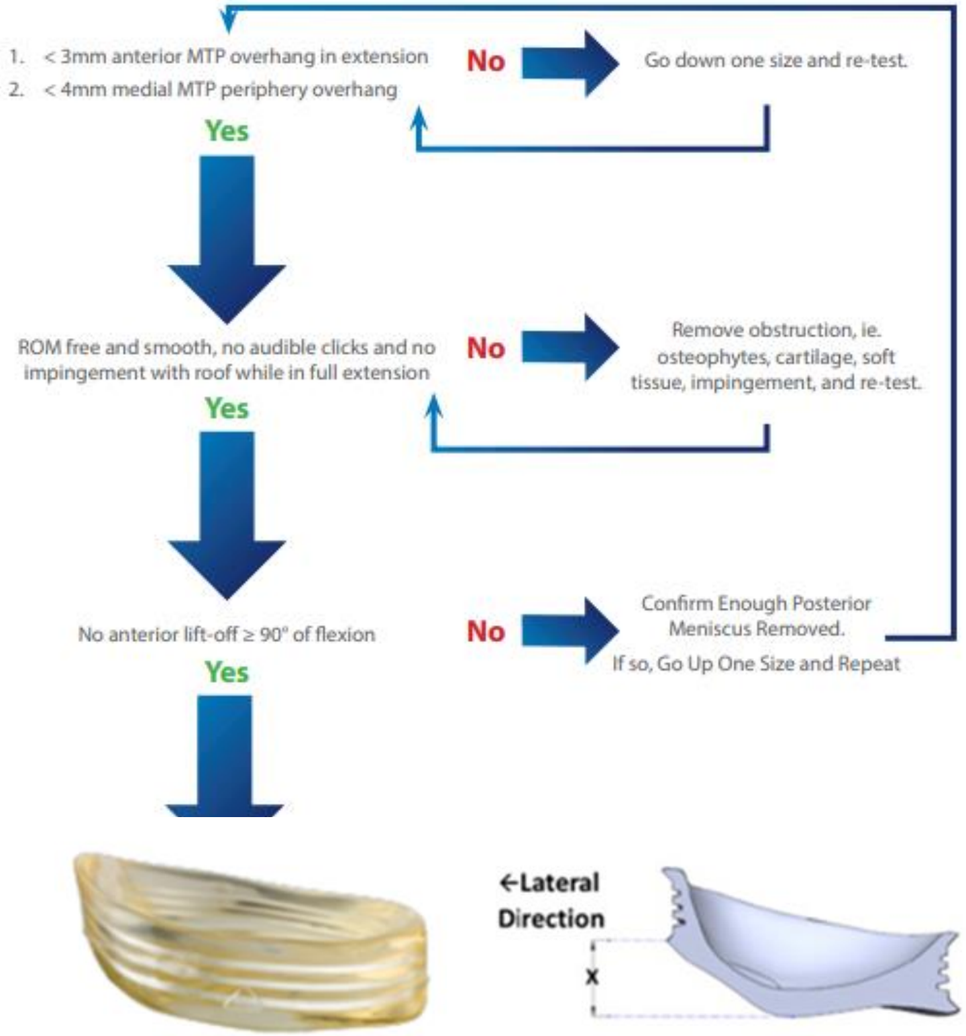




3. Trial Insertion and Assessment

- Make a 4-8 cm para patellar arthrotomy
- Insert and test position and ROM
- “Important: 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.”





4. Remove Trial and Place Final Implant

- Ideal sizing and placement of the NUsurface Implant in the coronal view and the sagittal view

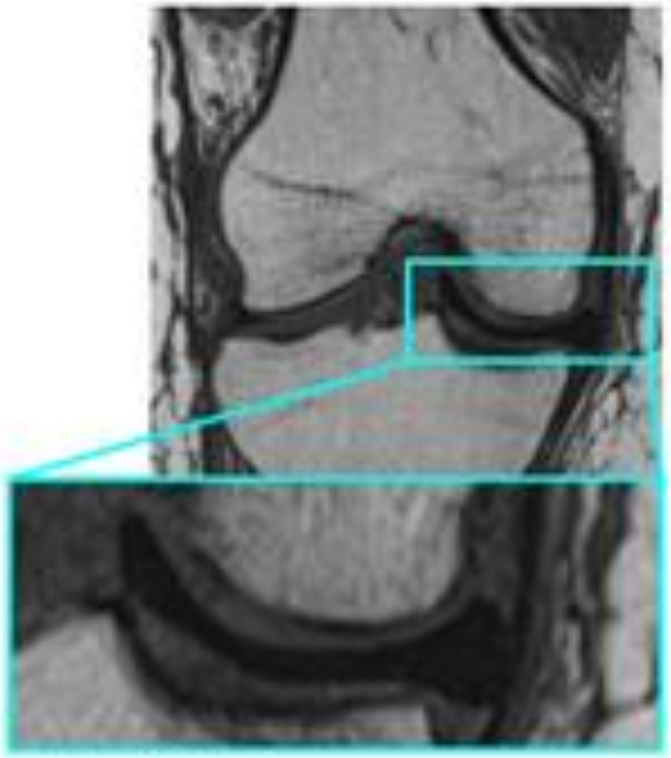


Figure 27 Coronal View

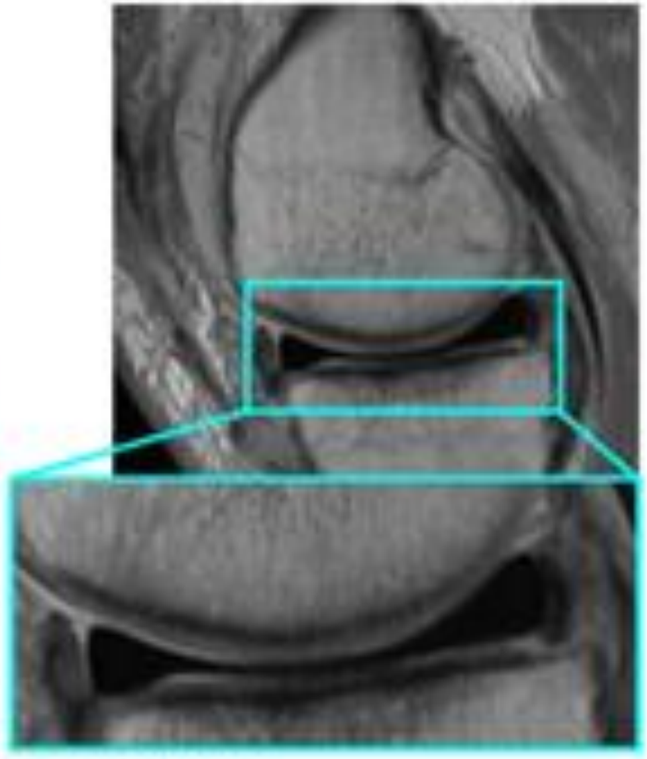
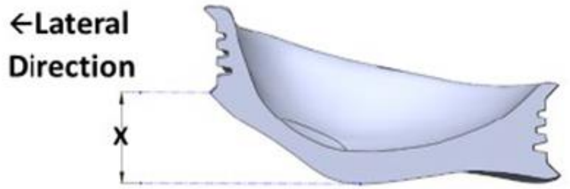


Figure 28 Sagittal View



Control: Non-Operative Treatment Options

- Non-prescription drugs, creams, vitamins, and supplements
- Prescription or Non-Prescriptions NSAIDs
- Self-administered exercise: cycling, elliptical, and/or leg presses or other
- Physical therapy
- 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)

Patient Assessment Schedule

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		✓						

Study Endpoints: Composite of 3 Endpoints

- Patient Reported Outcome Score endpoints included improvement in $KOOS_{pain}$ and $KOOS_{overall}$

- Positive MRIs: Device not torn / displaced on MRI
  - NUsurface only

- Absence of Automatic Study Failures (ASF)
  - NUsurface ASF: Limited to device-related SSI
  - Control: Any SSI to index knee

	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

Study Endpoints: KOOS Scores

- Knee Injury and Osteoarthritis Outcome Score (KOOS) instrument is a validated outcome measurement commonly used for assessing knee related injuries and treatments.

$KOOS_{pain} \geq 86.1$ **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

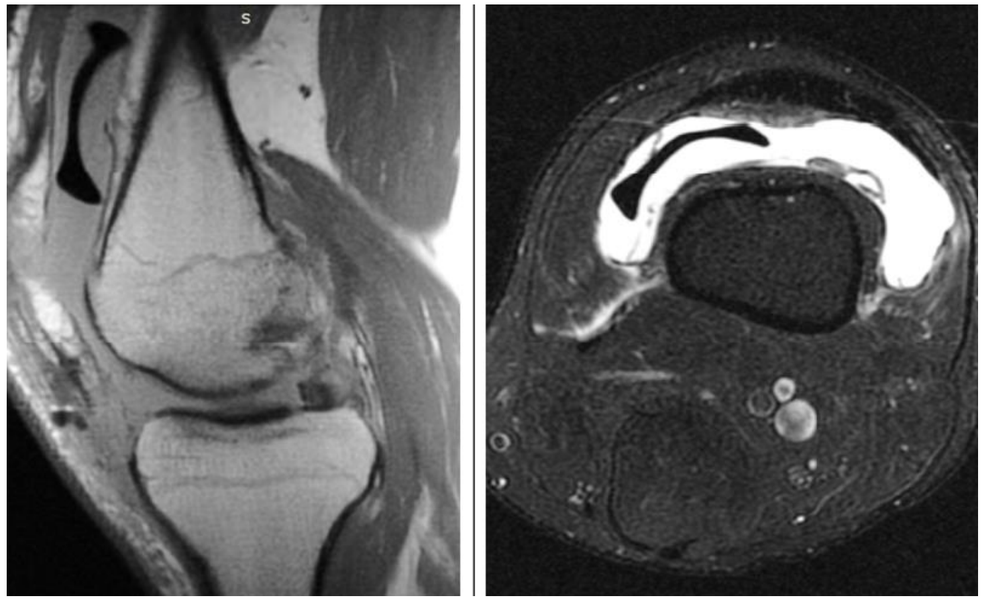
AND

$KOOS_{pain} \geq$ 40 points at 24 Months

Study Endpoints: MRI (NUsurface arm only)

Negative MRI is defined as MRI images taken at 12 OR 24 Months that show the device fractured in two (or more) pieces and/or subluxed more than 50% of the device length (dislocated)

Dislocation



Device fracture

Study Endpoints: Automatic Study Failures (ASFs)

Different definitions between NUsurface and Control

- **NUsurface Device -** Removed, Replaced, Exchanged, Repositioned
  - SSI not considered device-related were excluded from the ASF rates, such as:
    - Adhesions
    - Infections
    - New traumatic meniscus tears

- **Control –** any SSI on the index knee
  - Not limited by type of surgery (arthroscopic washout, high tibial osteotomy, unicompartmental knee arthroplasty, total knee arthroplasty)

Secondary Endpoints

- PROs
- MRI Cartilage Condition

Hierarchical Rank Order	Endpoint Description* in the Statistical Analysis Plan
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 vs Baseline (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 vs Baseline (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 vs Baseline (using EQ-5D)

MERCURY Dataset Results
NUsurface Group

Results (limited to 24 months)	MERCURY
Overall Success Rate	45% (77/172)
ASF Rate (Device-Related SSI)	**34% (58/172)**
PRO Failure Rate (excluding device-related SSI)	23.5% (36/153)
Overall Failure Rate	54% (95/172)

MERCURY Dataset: Root Causes of ASF

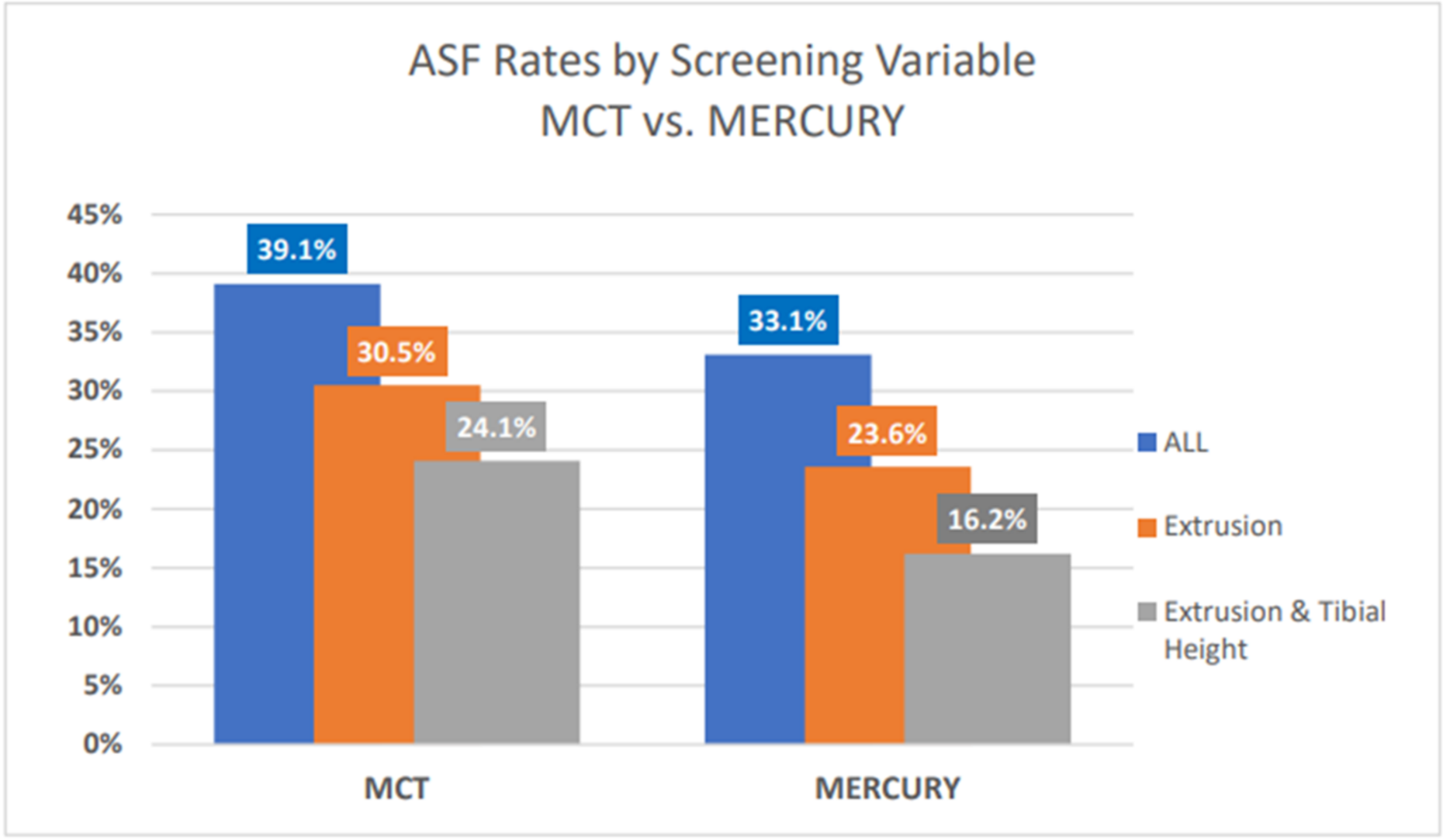
- Classification:
  - Fatigue (n=11 events)
  - Surgical technique (n=14 events)
  - OA progression (n=3 events)
  - Implant stability
    - Rotation (n=4 events)
    - Dislocation (n=2 events)
  - Trauma (n=1 event)
  - Infection (n=1 event)
  - Fibrous adhesions (n=2 events)

- The sponsor hypothesized the ASF rate could be lowered with mitigation strategies.

Proposed Mitigation Strategies

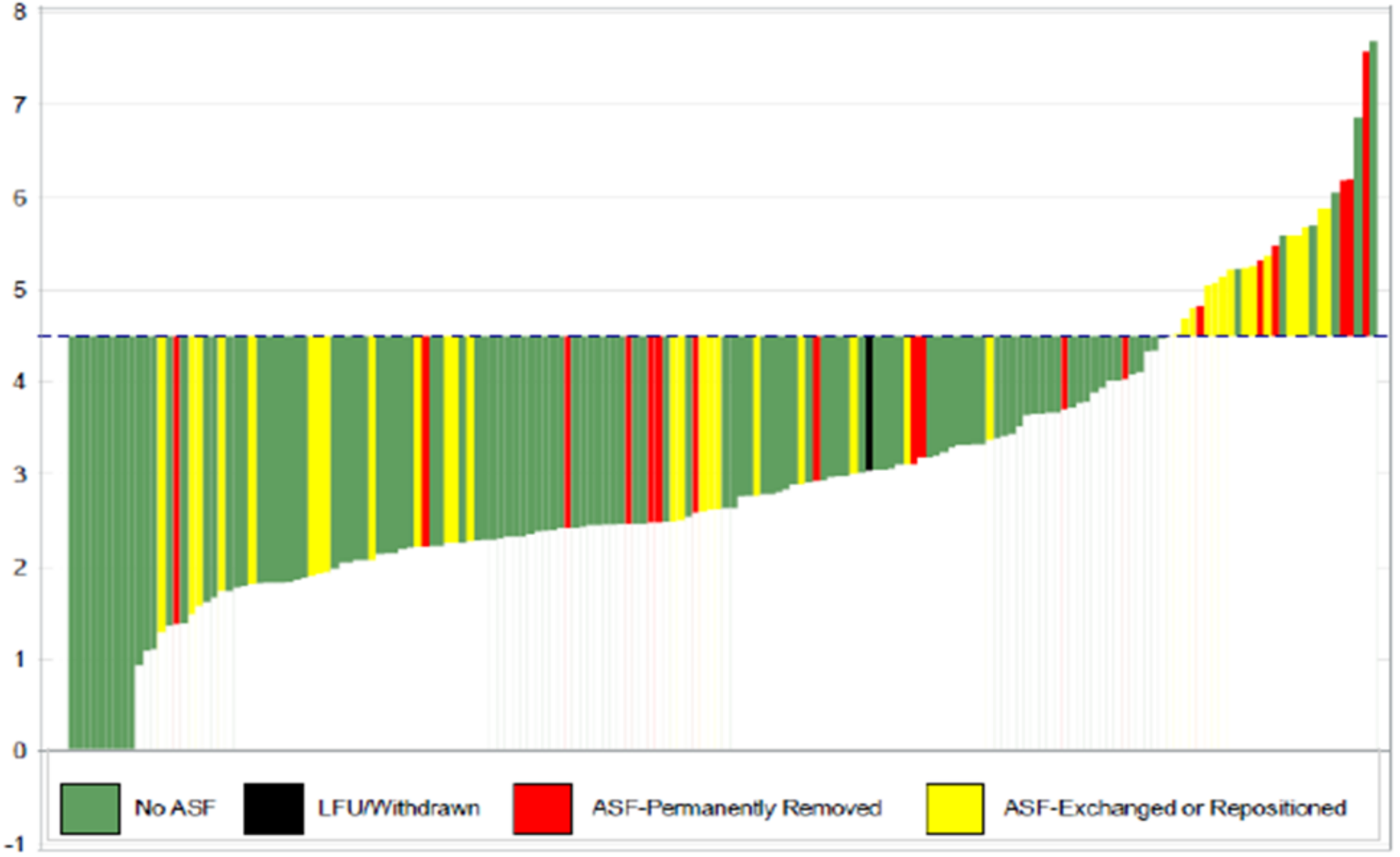
- “A much more detailed surgical technique” to address “surgeon error”;
- Adequate osteophyte removal with new instruments (a rasp);
- Better evaluation of patient notch anatomy and notchplasty as needed;
- Stricter avoidance of arthritis;
- Patient education to avoid “uncontrolled traumatic events”;
- 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, notch differences)
  - **Meniscus Extrusion**
  - **Tibial Spine Height**

Sponsor's Assessment of Applicability of Exclusion Criteria



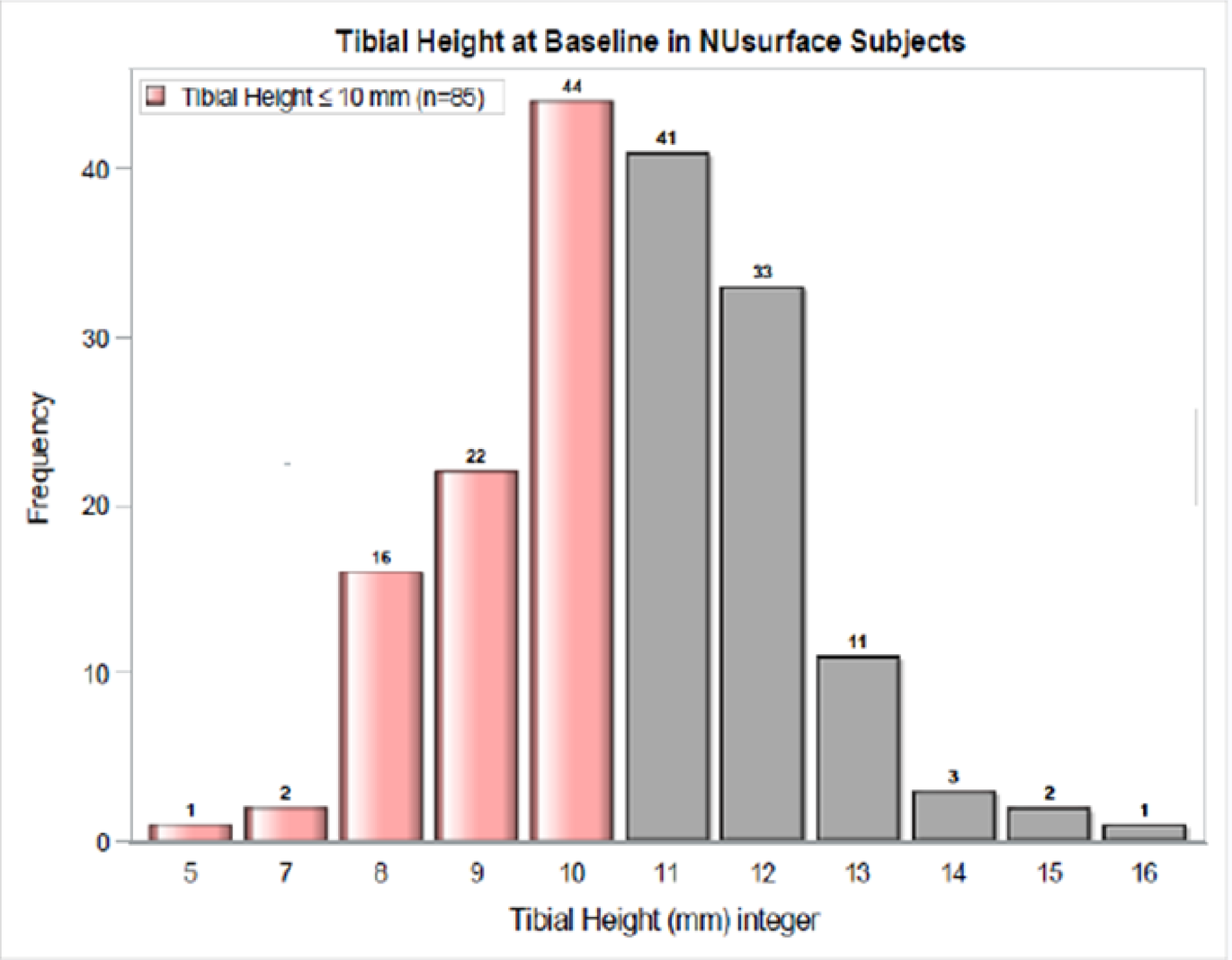
Rationale for Meniscus Extrusion

- Excluding the population with meniscus extrusion ≥ 5 (or greater than 4.5 as depicted in this waterfall graph) selects out a population with fewer ASF (device-related SSI)
- Excluded 17% of the population
- ASF (device related SSI) are evenly distributed throughout the rest
- Contributed to a 9.8% decrease in ASF rate (device-related SSI)



Rationale for Taller Medial Tibial Spine

- Device's "lateral bridge" is required for stability. A shorter spine was associated with more ASF (device-related SSI).
- 11 mm is close to the population average.
- Reproducibility of the measurement of tibial spine height was challenging.
- Contributed to a 6.1% decrease in ASF (device related SSI) rate.



Tibial Spine Height Measurement

- Two raters were utilized, and disagreements were automatically excluded.
- Measuring tibial spine height (19% disagreement) was more challenging than meniscus extrusion (4% disagreement).
- Population with uncertainty for tibial spine height had higher ASF (device related SSI) rates (39%) than the included spine group (28%).

Nusurface Subjects	Disagree
Tibial Spine Height	**18.8% (33/171)**
Meniscus Extrusion	4% (7/171)
Both Criteria	18.8% (33/171)

Risk Factor	Rater agreement	ASF Rate (device related SSI)
Tibial Spine Height	Both Include	24/87 (27.6%)
	Disagree	13/33 (39.4%)
	Both Exclude	20/51 (39.2%)

Modified MERCURY Dataset

- Safety Assessments
- Effectiveness Assessments

Modified MERCURY Dataset: Safety Assessments

- Adverse Events
  - Device-Related Adverse Events
  - Device-Related Secondary Surgical Interventions
- Retrieval Analysis
  - Implant Analysis

Safety: Adverse Events

"at Index Knee or Possibly Related to Treatment"

- Subjects with adverse events
  - 69.4% (50/72) of NUsurface subjects
  - 35.5% (11/31) of control subjects

- Total Adverse Events:
  - NUsurface: n=124
  - Control: n=14

Safety: Adverse Events

	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.

	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.

Safety: Adverse Events

"at Index Knee or Possibly Related to Treatment"

- Noise **16%** (12/72) NUsurface vs **0%** in Control
  - Mechanical symptoms including clicking, popping, and squeaks

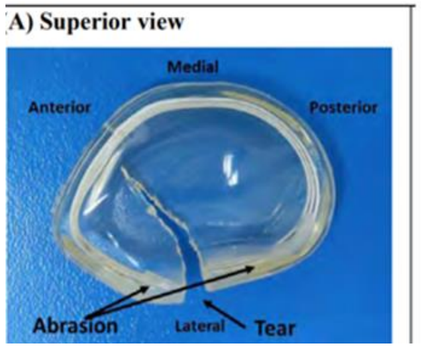
- The following Adverse Events may be device-related but were not consistently attributed to the device (some led to SSI):
  - Effusion **27%** (20/72) NUsurface vs **2.9%** (1/35) in Control
  - Adhesions **5.4%** (4/72) NUsurface vs **0%** Control
  - Arthrofibrosis **1.4%** (1/72) NUsurface vs **0%** Control
  - Limited range of motion **5.4%** (4/72) NUsurface vs **0%** Control

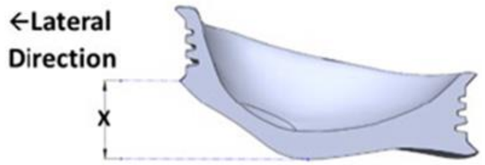
Safety: Serious Adverse Events (SAE)
NUsurface group

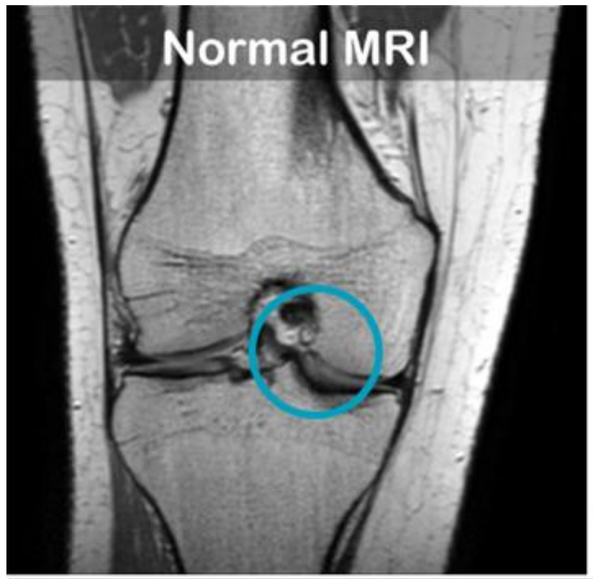
- Largest category of SAE: device issues resulting in ASF (device-related SSI)
- In the first 24 months, 17% (12/72) had at least one device-related SSI.
  - Damage to device 29.2% (21/72)
  - Dislocations 15.3% (11/72)
  - Rotations 2.7% (2/72)
  - Some subjects experienced more than 1 category (e.g. damage and dislocation), and some subjects experienced device-related SSI after the subsequent device replacement.
- In the first 24 months, 25% (3/12) of the NUsurface subjects with ASF (device-related SSI) subsequently underwent arthroplasty.
  - 2 Unicompartmental arthroplasty
  - 1 Total knee arthroplasty

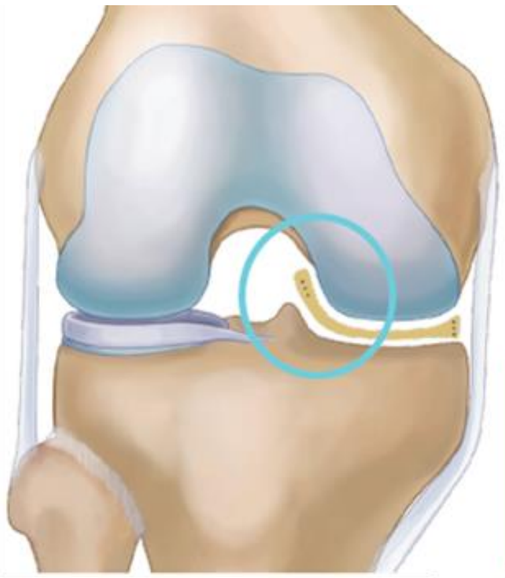
Safety: Retrieval Analysis

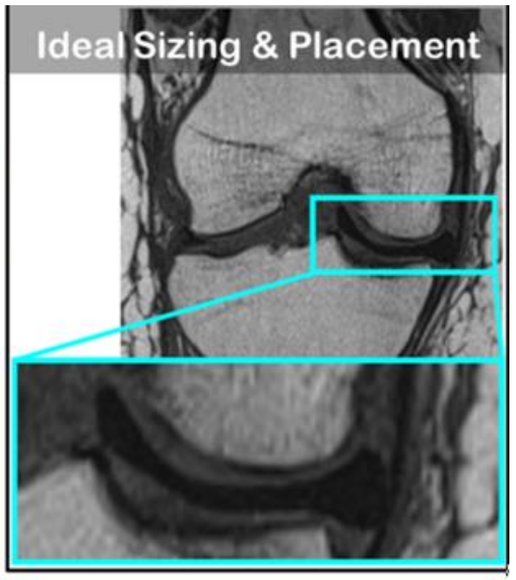
- Consistent pattern of abrasion and tear.
- Lateral device sits in anatomic location where no tissue normally exists.
- Lateral overload may cause the device to tear by fatigue or by trauma loading.



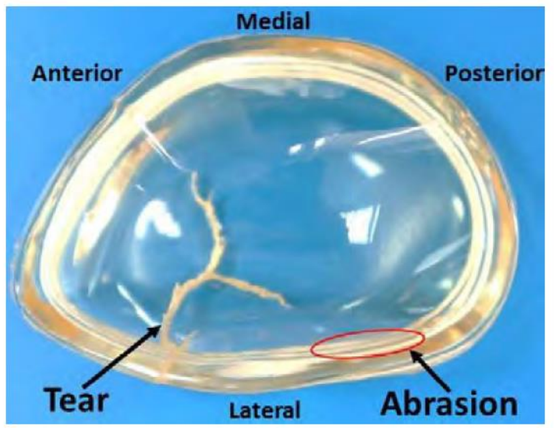








Safety: Retrieval Analysis



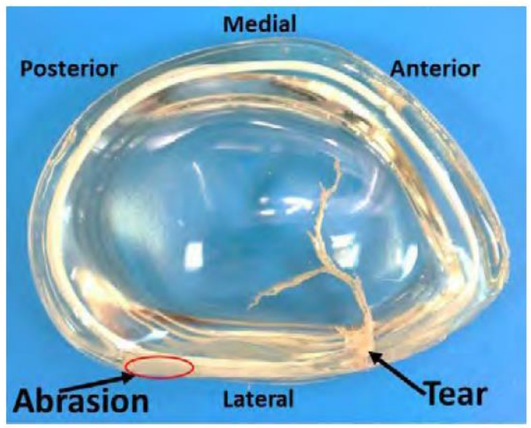
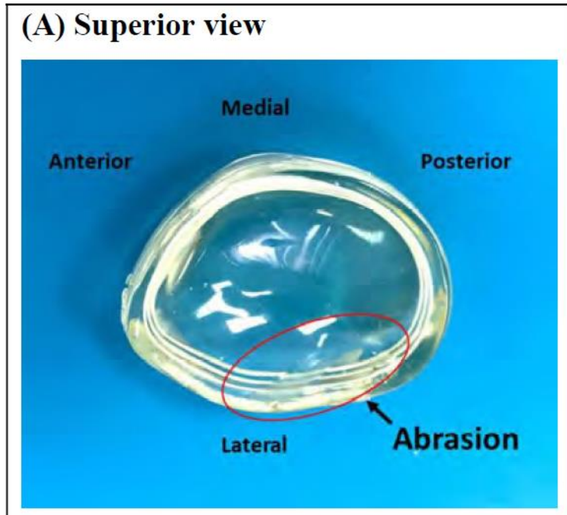


Figure 5. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*



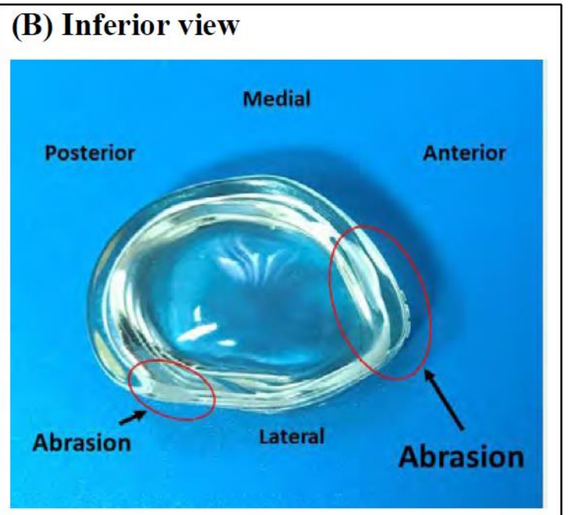
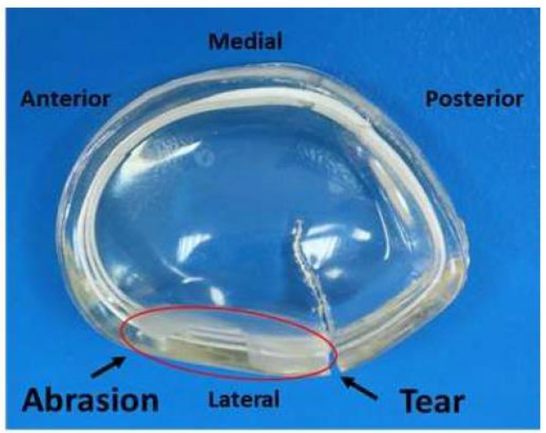


Figure 3. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*



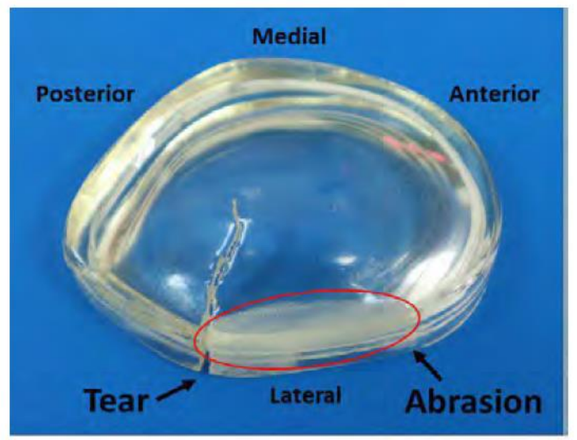
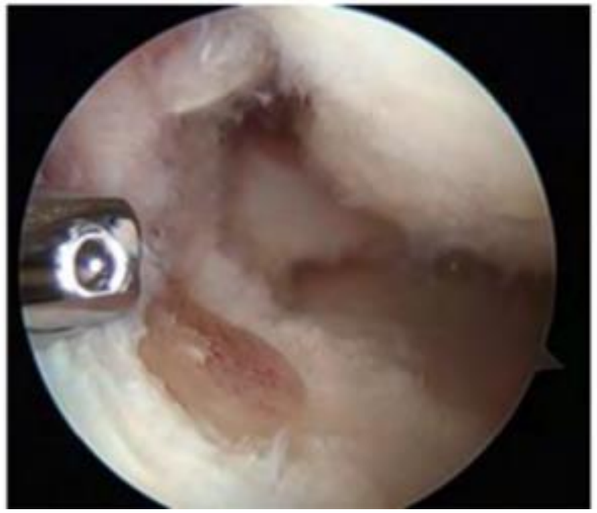


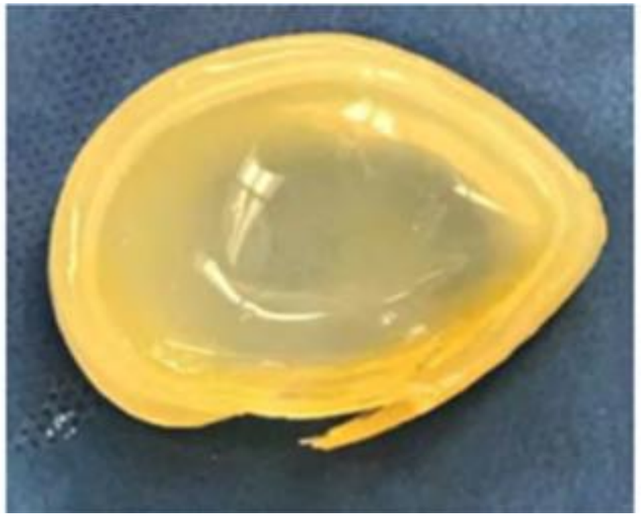
Figure 6. *Marked areas of the device showing the tear damage of the device from (A) Superior and (B) Inferior views.*

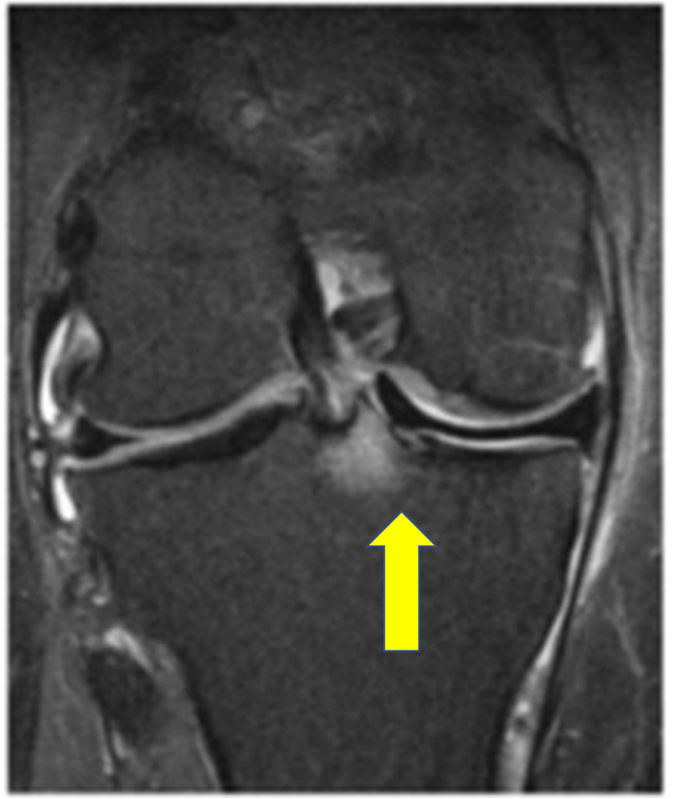
Figure ##. *The torn device from (A) arthroscopic view before removal and from (B) superior view after removal.*

Safety: Retrieval Analysis

- MRI - T2 signal shows bone edema (white area).
- Arthroscopy - Full thickness cartilage lesion
- Lateral wall of device is mostly intact.







Summary - Safety

- ASF due to device-related SSI was lowered by half, from 34% (MERCURY dataset) to 17% (Modified MERCURY dataset).
- Adverse Events and Serious Adverse Events were higher in the NUsurface group compared to the control group.
- Retrieval analysis showed a consistent pattern of device abrasion and fracture/tearing in the lateral section of the device required for fixation (“lateral bridge”).
- Device use requires near total meniscectomy for insertion.

Modified MERCURY Dataset: Effectiveness Assessments

- Patient Reported Outcomes (PRO)
- Absence of ASF
  - NUsurface – Device-Related SSI
  - Control – Any SSI
- Absence of MRI Failure
- Overall Success Rate

Patient-Reported Outcomes

- NUsurface: 62.1% (41/66) subjects met the primary endpoint for KOOS improvement.
- Control: 17.9% (5/28) subjects met the primary endpoint for KOOS improvement.

$KOOS_{pain} \geq 86.1$ **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

Absence of ASF

- NUsurface: 83.3% (60/72) of subjects did not require any device-related SSI (ASF).
- Control: 90.3% (28/31) of subjects did not require any SSI (ASF).
- Note: ASF was evaluated differently in the NUsurface and control groups.

Absence of MRI Failure

- One subject in the NUsurface group was classified as an MRI failure because a damaged or dislocated device was noted on MRI, but did not undergo a device-related SSI.
- In the control group, MRIs were not consistently obtained.

Overall Study Success

- NUsurface: 51.4% (37/72) of subjects met the study success criteria for safety and effectiveness.
- Control: 16.1% (5/31) of subjects met the study success criteria for safety and effectiveness.

Other Assessments – Cartilage Preservation

Limitations of the cartilage preservation assessments introduced uncertainty.

- **Incomplete MRIs at 24 months in both groups**

  34.8% (23/66) missing MRI data from control group

  17.1% (30/176) missing MRI data from NUsurface group

- **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 was 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).

Summary - Study Success

	Absence of ASF (Device Related SSI)	Absence of MRI Failure	PRO Success Rate*	Overall Success Rate
NUsurface	83.3% (60/72)	98.6% (69/70)	62.1% (41/66)	51.4% (37/72)
	Absence of ASF (any SSI)		PRO Success	Overall Success
Control	90.3% (28/31)		17.9% (5/28)	16.1% (5/31)

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

Statistical Considerations

Cynthia Liu, MS
Mathematical Statistician
Biostatistics Team 1
Division of Clinical Evidence & Analysis (DCEA2)
Office of Clinical Evidence & Analysis (OCEA)
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Statistical Background of MERCURY Dataset

- Consisting of data from VENUS and SUN studies
  - VENUS Study
    - Prospective, **randomized** (1:1), **2-parallel-arm**, non-surgical-controlled
    - 61 NUsurface and 66 Control enrolled from 1/21/2015 to 6/12/2018
  - SUN Study
    - Prospective, **non-randomized**, **single-arm**
    - 115 NUsurface enrolled from 5/19/2016 to 6/14/2018
- Idea of combining the 2 data sources proposed in 2017
- Statistical Analysis Plan (SAP) for the combined dataset approved on 3/7/2019; database lock on 6/30/2020
- 242 subjects from 20 different sites (176 NUsurface, 66 Control)

Baseline Comparability in MERCURY Dataset

- Among the 122 baseline variables reported, the following had a nominal p value of less than 5%.

MERCURY 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

Table extracted from Table 23.16.1 provided by sponsor in DENXXXXXX

Missing Data in MERCURY Dataset

- High missing data rate especially in the Control group

	MERCURY	
	NUsurface	Control
Lost to follow-up or withdrawn	4/176 (2%)	14/66 (21%)
Primary endpoint missing	4/176 (2%)	14/66 (21%)
KOOS missing at 24 months	23/176 (13%)	23/66 (35%)
MRI missing at 24 months	17/176 (10%)	14/66 (21%)
SSI missing at 24 months	4/176 (2%)	14/66 (21%)

Compiled based on success.xpt in DENXXXXXX

- Assumption for missing data handling method may not hold
  - Last observation carried forward done (assuming missing completely at random)
  - Multiple imputation done (assuming missing at random)
  - Missing may be due to different reasons between groups

Modified Patient Population

- Respective threshold values, 5 mm of meniscus extrusion and 11 mm tibial spine height, determined based on analyses of raters' MRI measurements
- MERCURY subjects with meniscus extrusion < 5 mm and tibial spine height ≥ 11 mm at baseline included
- Subjects with disagreements between the raters excluded

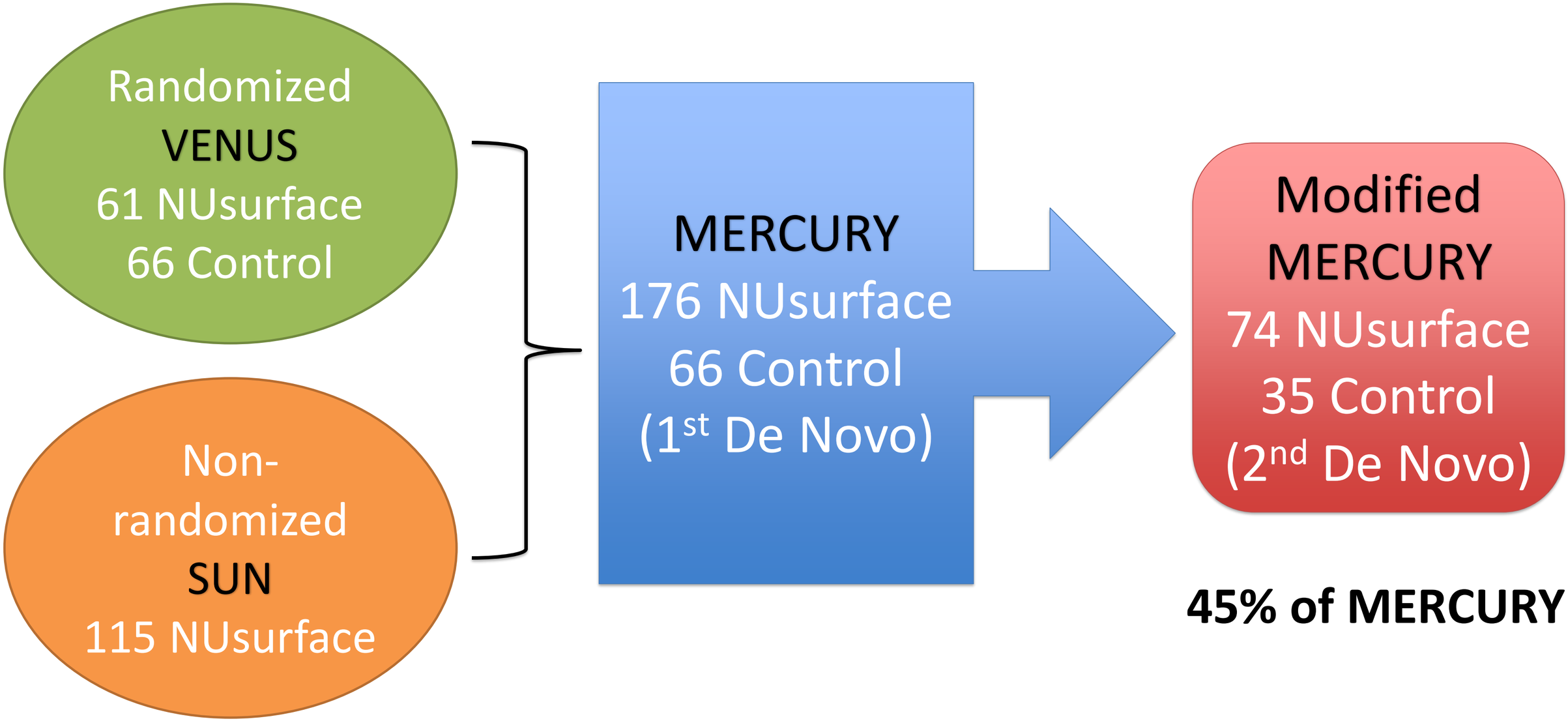
MERCURY	Rater	NUsurface (N = 176)		Control (N = 66)	
		#1 - Exclude	#1 - Include	#1 - Exclude	#1 - Include
Both Criteria	#2 - Exclude	68	19	18	11
	#2 - Include	14	75[a]	2	35

Green color for disagreements; gold color for agreements to include

[a] Including SN1 subject who had an infection

Extracted from Active Implants Report

Data Source and Datasets



45% of MERCURY

Baseline Comparability in Modified MERCURY Dataset

- Among the 55 baseline variables reported, the following had a nominal p value of less than 5%.

Modified MERCURY Baseline Variable	NUsurface		Control		Fisher Exact p
	n/N	%	n/N	%	
Prior: Cartilage Surgery	6/74	8.1%	9/35	25.7%	0.018
Intervention: Physical Therapy	48/74	64.9%	30/35	85.7%	0.025
Intervention: Steroid Injection	26/74	35.1%	20/35	57.1%	0.038

Extracted from Active Implants' Appendix in Clinical Report in DENXXXXXX

Outcome Analyses in Modified MERCURY Dataset

- No analysis methods pre-specified
- Propensity score method used to account for baseline differences
  - Propensity score adjustments created from baseline comparisons of NUsurface to Control
  - Logistic regression model appears to include prior cartilage surgery and steroid injection intervention via model selection process
- Outcome analyses adjusted for 2 propensity score strata

Sponsor Propensity Score Adjustments

Basis of Propensity Score Adjustments

	All Patients	Evaluability - Extrusion	Evaluability - Extrusion+Tibial height
Variables used in Propensity Score (Control vs NUsurface) Logistic Regression (with p values)			
Intervention: Physical therapy	<0.001	0.013	.
Intervention: Glucos/Chond	0.002	.	.
Current: Chronic problem	0.002	0.028	.
Prior: Cartilage surgery	0.007	.	0.019
Intervention: Analgesics	0.017	.	.
Usual activities	0.097	0.041	.
Sports/Recreation baseline category	.	0.112	.
Intervention: Steroid injection	.	0.152	0.034
Current: Subacute problem	.	0.261	.

Binary Propensity Score Category

	Control	NUsurface	Control	NUsurface	Control	NUsurface
Low propensity score	15	105	20	93	11	44
High propensity score	51	71	44	52	24	30

Patient SN1_____(infection) was dropped from all Evaluability groups.

Initially, all variables with statistically significant p values ($p<0.05$) in the Table 2.1, 2.4 and 2.5 series were included in the propensity score logistic regression models.

If additional variables became statistically significant ($p<0.05$) in the adjusted analyses, they were added to the models.

If no variables were statistically significant ($p<0.05$) in the adjusted models, the variables with the worst p values were removed as long as no statistically significant ($p<0.05$) effects reappeared.

Missing Data in Modified MERCURY Dataset

- Similar missing data pattern observed as in MERCURY dataset

	Modified MERCURY	
	NUsurface	Control
Lost to follow-up or withdrawn	2/74 (3%)	4/35 (11%)
Primary endpoint missing	2/74 (3%)	4/35 (11%)
KOOS missing at 24 months	8/74 (11%)	7/35 (20%)
MRI missing at 24 months	4/74 (5%)	4/35 (11%)
SSI missing at 24 months	2/74 (3%)	4/35 (11%)

Compiled based on success.xpt in DENXXXXXXX

- Similar missing data handling method used as in MERCURY dataset
  - Assumption for missing data handling method may not hold
  - Missing may be due to different reasons between groups

Statistical Limitations for Modified MERCURY Dataset

- Modified MERCURY dataset defined based on observed data
- Neither analysis plan pre-specified nor SAP of MERCURY dataset followed
- Uncertainty of results
  - Validity of propensity score model
    - Possible clinically relevant baselines not included
    - Unclear if selection of baseline variables influenced by observed outcome
    - Unclear if all clinically relevant baselines balanced
    - Small sample size
  - Missing outcome data
    - Missingness may not be at random

Patient Preference Information

David Gebben, PhD
Health Economist
Patient Science & Engagement (PSE) Team
Division of All Hazards Response, Science, and Strategic Partnerships (DARSS)
Office of Strategic Partnerships & Technology Innovation (OST)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Patient Preference Information (PPI)
CDRH Guidance

Guidance Document: *Patient Preference Information – Voluntary Submission, Review in PMAs, HDE Applications, and De Novo Requests and Inclusion in Decision Summaries and Device Labeling. August 2016*

- PPI Definition:

  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

  - Not a patient-reported outcome (PRO) or other clinical trial endpoint or outcome

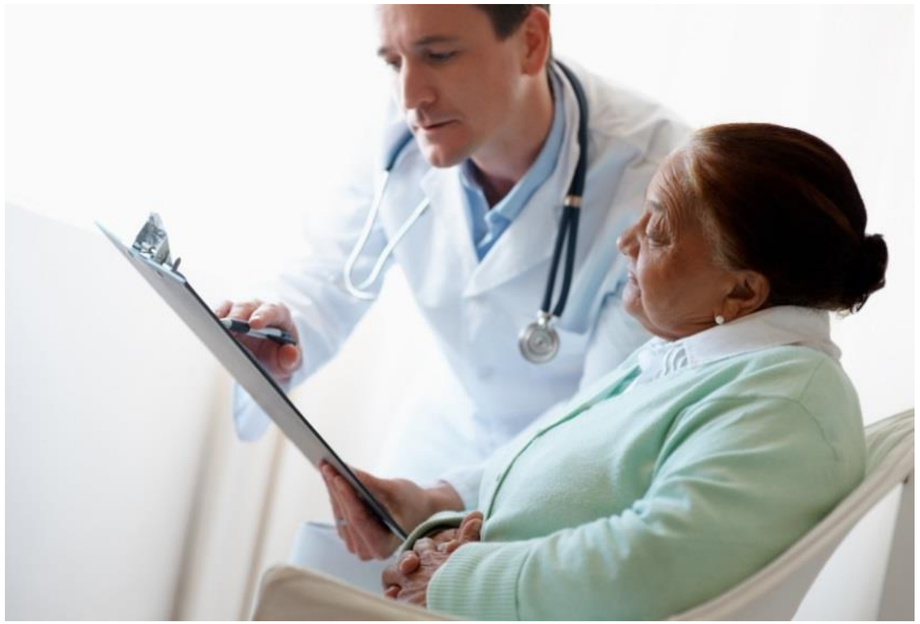
Recommended Qualities of Patient Preference Studies

Well-designed and conducted patient preference studies can provide valid scientific evidence regarding patients' risk tolerance and perspective on benefit. This may inform FDA's evaluation of a device's benefit-risk profile during the PMA, HDE application, and De Novo request review processes.

A. All about Patients
   - Patient Centeredness
   - Sample Representativeness
   - Capturing Heterogeneous Patient Preferences
   - Comprehension by Study Participants

B. Good Study Design
   - Established Good Research Practices
   - Effective Benefit-Risk Communication
   - Minimal Cognitive Bias
   - Relevance

C. Good Study Conduct and Analysis
   - Study Conduct
   - Logical Soundness
   - Robustness of Analysis of Results



Overview of NUsurface PPI Studies

- Sponsor conducted 7 studies
  - Did not appear to follow standard accepted research practices for patient preference research, including addressing the potential for bias in structuring of survey
  - Each study asked different questions and collected data using different methods, and hence the poolability of the data is uncertain

PPI Study Quality:
Established Good Research Practices*

Informed Consent and IRB Approval

- GCP Guidelines (21 CFR Parts 50 and 56) and ethical principles of human research apply

- PPI studies are social science experiments and, as such, standard ethical principles and practices of human subject research apply

* CDRH PPI Guidance page 12

PPI Study Quality:
Established Good Research Practices?*

Informed Consent and IRB Approval

- Informed consent was not obtained for the PPI studies

- IRB approval was not sought

* CDRH PPI Guidance page 12

PPI Study Quality:
Effective Communication of Benefits and Risks?*

Communication of Risk to Patient

- Study Objective - Determination of how much additional risk of reconstructive knee surgery patients would accept in exchange for pain reduction relative to no surgical treatment

- Did not explain additional risks of other secondary surgical procedures with NUsurface (i.e., removal prior to total knee replacement) in the survey

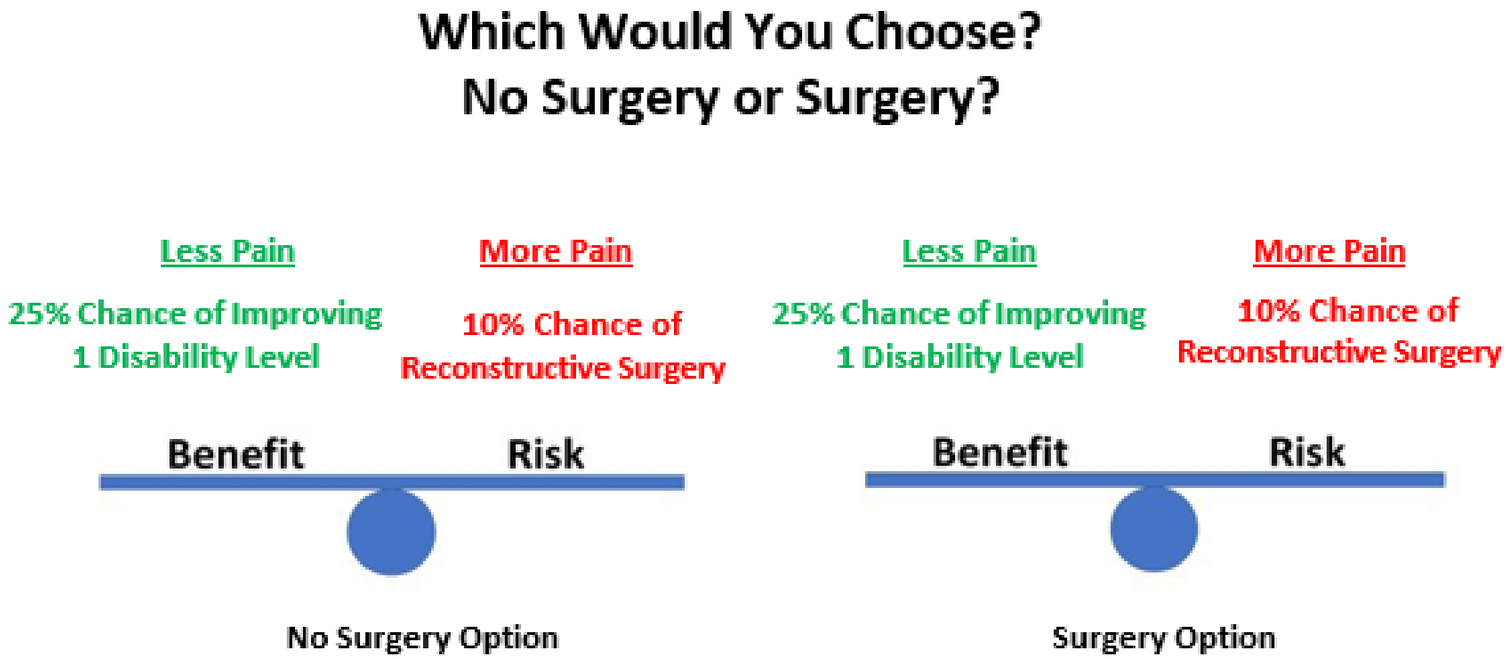
- Respondents may have overstated the risk they are willing to accept

*CDRH PPI Guidance page 13

PPI Study Quality:
Effective Communication of Benefits and Risks

Minimal Cognitive Bias?*

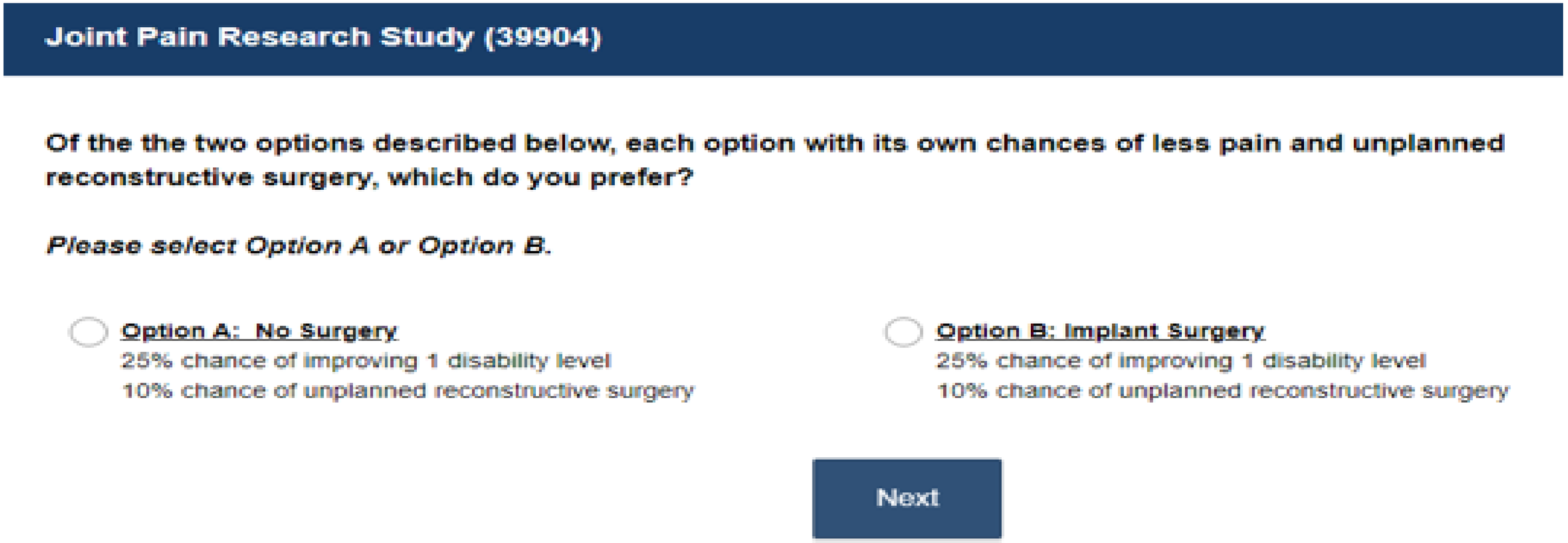
- **Risks may not have been presented in an easily understandable unbiased manner**



*CDRH PPI Guidance page 14

Threshold Technique

Identify point (“threshold”) at which the additional risk outweighs the benefit of NUsurface implant surgery vs. no surgery



Example Choice Question that the respondent would have seen.

PPI Study Quality: Robustness of Analysis and Results?*

May not have provided appropriate analysis of "threshold" or Maximum Acceptable Risk

PPI Study Number	Number of Respondents	Average Preference for NUsurface Device	95% Minimum Calculation
1	12	83%	61%
2	21	78.9% to 95.2%	60%
3	74	86.5%	78.7%
4	5	65% to 75%	-
5	205	75.6%	-
6	207	86.4%	65.5%
7	207	93%	88%
Total/Range	731	Range: 65% to 95.2%	Range: 60% to 88%

Results of 7 Patient Preference Studies (Table 22 from Sponsor's Executive Summary)

*CDRH PPI Guidance page 15 – Robustness Analysis of Results

Summary – Limitations of PPI Studies

- Risks may not have been clearly communicated in an unbiased manner
- Study may not have been appropriately designed to meet its objective
- Analyses may have been unclear, inappropriate or missing when necessary

Patient Preference Information (PPI) – Non-Voting Question

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.

SUMMARY OF BENEFITS AND RISKS

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Summary of Benefits

- Patients may experience an improvement in pain, function, and quality of life PROs, including $KOOS_{pain}$, $KOOS_{overall}$, and various secondary endpoint assessments at 24 months.
  - Numerical superiority was seen compared to the non-surgical control treatments used.
  - Improvements sustained through 24 months.
  - Magnitude of improvement is clinically meaningful

- Patients may experience an improvement in pain and function and keep their device in place or need a surgery to replace or reposition the device.

Summary of Benefits

- Overall Success: 51% (37/72) of NUsurface subjects within the modified MERCURY dataset met PRO improvement goals and had no device-related SSI (ASF) or failures assessed by MRI criteria at 24 months. Overall study success rate for nonsurgical control subjects was 16% (5/31).
- PRO endpoint success: 62.1% (41/66) NUsurface vs 17.9% (5/28) control.
- Absence of ASF: 83.3% (60/72) of NUsurface subjects retained their device for 24 months and did not require device-related SSI vs 90.3% (28/31) of nonsurgical control subjects who did not require an SSI.

Summary of Risks

- Patients may not experience any improvement in pain and function
  - 38% (25/66) of NUsurface subjects did not experience study defined success for PRO improvement.
- Implant may become damaged or become dislocated/rotated, which would necessitate an SSI.
  - 49% (35/72) of NUsurface subjects did not meet PRO goals for pain and function **or** needed an SSI.
  - 17% (12/72) of NUsurface subjects needed a device related 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.

Summary of Risks

- Implant and the sub-total meniscectomy required to implant the 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 subjects
- 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.

Additional Considerations: Uncertainty

- Lack of understanding about the root cause of ASF (device-related SSI), and which subjects are at increased risk of an SSI.
- Large percentage of missing data in the non-surgical control arm and MRI data from both groups.
- Types of surgeries required by subjects in the non-surgical control arm suggests there may be differences in screening between the study arms (i.e., direct visualization of the cartilage during implantation).
- Study was not designed to evaluate cartilage preservation. Arthritis progression analysis was not sufficiently robust.
- Design and conduct of the Patient Preference Information was not in alignment with accepted practices described in published health preference literature.

Additional Considerations: Proposed Risk Mitigation

- Modifications to the labeling related to meniscal extrusion (contraindication) and tibial spine height (warning) to select patients with an improved benefit-risk profile.
- Contraindication:
  - *Patients with extrusion of the medial meniscus 5mm or greater*
- Warning:
  - *Patients in which the height of the tibial spine is below 11mm are at a greater risk of device- related adverse events*

Thank you for your time and attention.

Panel Questions for reference

Panel Non-Voting Question 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.

Panel Non-Voting Question 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 ASFs as secondary surgical interventions (SSIs) 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.

Panel Non-Voting Question 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.

Panel Non-Voting Question 3 (cont.)

a) Please comment on the overall success rate of the modified MERCURY dataset.

b) 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.

c) Please comment on the strengths and limitations of the study design elements of the MERCURY dataset and modified MERCURY dataset.

d) Please comment on the benefit-risk profile for use of the NUsurface Meniscus Implant in alternative subgroups.

e) Are there any additional subgroups in which the NUsurface Meniscus Implant would have a favorable benefit-risk profile?

Panel Non-Voting Question 4

<u>Patient Preference Information:</u>

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 datasets to the final benefit-risk determination.

Panel Non-Voting Question 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?

Panel Voting Question

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

"The intended use of the NUsurface Meniscus Implant is to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected. The indication for use is in patients with:

--mild-to-moderate 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."*

Panel Voting Question

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?