Sponsor's Executive Summary

NUsurface® Meniscus Implant

DEN (b) (4)

Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee

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1 Introduction

This Executive Summary outlines the clinical study data submitted in support of a de novo application for the NUsurface Meniscus Implant, DEN(b) (4), a breakthrough designated device. The NUsurface is a discoid shaped device, designed to improve pain and function in the medial compartment of a knee in which the medial meniscus has been resected. The device replicates the function of the normal meniscus and evenly distributes the load in the medial compartment of the knee joint.

The Sponsor conducted a prospective, randomized, multi-center superiority clinical trial named MERCURY to compare the NUsurface to non-surgical treatment, the standard of care for the population enrolled in the trial. The trial was conducted under FDA oversight under an Investigational Device Exemption. 176 subjects were treated with the NUsurface implant, and 66 patients were treated with non-surgical care. Non-surgical care included multimodal therapies such as injections with corticosteroids or hyaluronic acid (HA), Prescription or Non-Prescriptions NSAIDs, physical therapy, or bracing.

Study success required a statistically greater success rate measured by the primary composite endpoint in the NUsurface arm compared to the control arm. The primary endpoint was a composite endpoint that included the following components:

1. ≥20-point improvement in the KOOS Overall score, the average of the 5 KOOS domains, which includes the Pain domain
2. ≥20-point improvement in KOOS Pain considered independently
3. Confirmation of the position and condition of the NUsurface device on MRI
4. Absence of a protocol-defined secondary surgical intervention that qualified as an automatic failure of study, defined as:
    a. NUsurface subjects who had surgery to remove the device, with or without replacement, for any reason
    b. Control group subjects who underwent any surgical procedure on the medial compartment of the index knee

The primary endpoint was evaluated at 24-months and outcomes of a subpopulation of the MERCURY study were submitted to FDA in de novo application DEN(b) (4). The subpopulation identified subjects with a more favorable benefit/risk profile compared to the total MERCURY population; subjects with improved outcomes and a lower incidence of second surgeries. Two MRI criteria were used to identify the subpopulation. Following discussions with FDA's review team, the Sponsor submitted an analysis of 109 subjects.

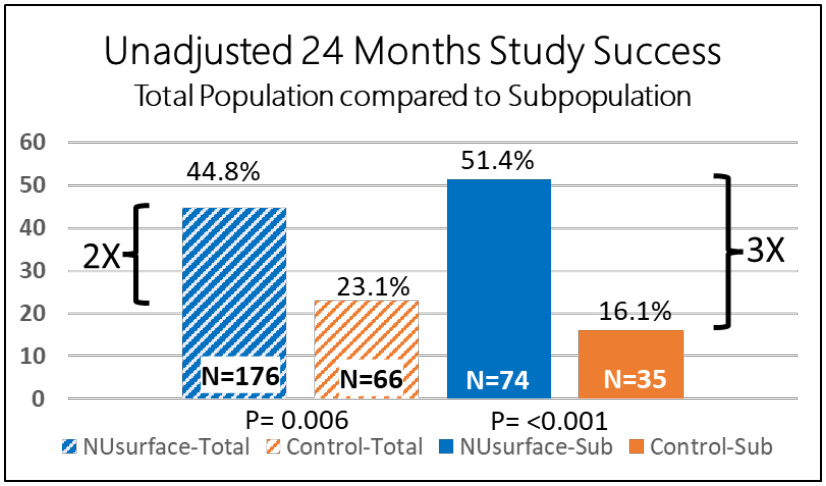
The clinical data demonstrated that the NUsurface implant was statistically superior to the non-surgical control in the primary composite endpoint that combines both safety and effectiveness outcomes (p=0.011). In addition to the primary composite endpoint, the NUsurface implant was superior to controls in the first 3 secondary endpoints (Table 1) of the pre-specified, hierarchical rank order. The rank order controlled for Type I error in all secondary analyses. A detailed discussion of the MERCURY study design, including the primary and secondary outcomes, is provided in Sections 9 and 10 below.

Table 1 Primary and Secondary Endpoint Measurements for the MERCURY Subpopulation.

Number	Hierarchical Rank Order	Calculated p Value
1	**Overall Success at 24 Months**	0.011
2	24 Month VAS vs Baseline	0.036
3	24 Month MRI vs. Baseline of Cartilage Condition in Medial Compartment	0.006
4	24 Month IKDC SKEF Score vs Baseline	0.003

The clinical data demonstrate that the NUsurface implant is statistically superior to the non-surgical control in the primary composite endpoint in the subpopulation. This was also the outcome in the total MERCURY population. However, the NUsurface subpopulation had 50% fewer secondary surgical interventions compared to the total MERCURY NUsurface population and the overall study success rate increased, from 44.8% to 51.4%, as illustrated in Figure 1. The indications for use proposed in the current submission are limited to the subpopulation.

Figure 1: NUsurface Subpopulation Success Rate Compared to the Total Population.



In addition to outcomes data from the MERCURY trial, this Summary includes the results of radiographic observations and confirmation of the subpopulation in a multicenter clinical trial conducted in Europe and Israel prior to the start of the MERCURY trial. The findings in this separate study support the two radiographic criteria that are used to define the eligible population. Non-clinical data in support of the device is also summarized.

This summary concludes with a benefit/risk analysis of the NUsurface implant in the treatment of pain and function in the medial compartment of a knee in which the medial meniscus has been resected.

2 Summary

The NUsurface has been developed for the treatment of a patient population that suffers from pain and loss of function of the knee joint caused by degeneration of the cartilage in the medial compartment. Patients enrolled in clinical trials to evaluate the NUsurface are a salvage population who have already undergone one or more failed meniscectomies, have undergone non-operative therapy and have remained symptomatic for at least 6 months. These patients already failed knee surgery and thus it is anticipated they are at increased risk for failure and complications in any subsequent surgical procedures. Operative treatments such as meniscal allograft, which is indicated in a younger population, are no longer an option for these patients[1] due to their age >35 years. Results from 12 randomized trials confirm that meniscectomies are not statistically more effective than non-operative therapy after 2 years. [2] Patients indicated for NUsurface are not considered good candidates for arthroplasty[3] because their articular cartilage remained in good condition. Thus, the current standard of care is non-surgical therapy. This leaves many patients in a treatment gap where continued non-surgical therapy is their best option. These are some of the most challenging patients that knee surgeons treat today and there is a need for a new treatment option that is able to address their pain and symptoms. These were the patients enrolled in the MERCURY Trial, and it is in this context that the results of the MERCURY Trial should be considered.

The NUsurface device is a discoid shaped device designed for use in the medial compartment (Figure 2). The device is made of two commonly used biomaterials, Bionate® polycarbonate-urethane (PCU) and Dyneema Purity® fibers of Ultra-High Molecular Weight Polyethylene (UHMWPE) embedded inside the periphery of the device. The procedure to implant the device is outpatient with limited blood loss. After arthroscopically preparing the rim of the remaining meniscus, a 5cm incision is made to place the implant into the medial compartment. The NUsurface device is not physically anchored, and its range of motion replicates the anterior-posterior translation of the natural meniscus. Patients can begin weight-bearing, as tolerated, immediately after surgery.

[1] American Academy of Orthopaedic Surgeons (AAOS) Meniscus transplantation: indications, techniques, clinical outcomes. Instruction Course Lecture 54:341-353, Feb 2005.

[2] Section 23.10, page 3991 of DEN (b) (4) contains all 24 citations associated with these 12 clinical studies.

[3] AAOS "What are the AAOS guidelines for total knee arthroplasty in the treatment of osteoarthritis (OA)? October 12, 2020.

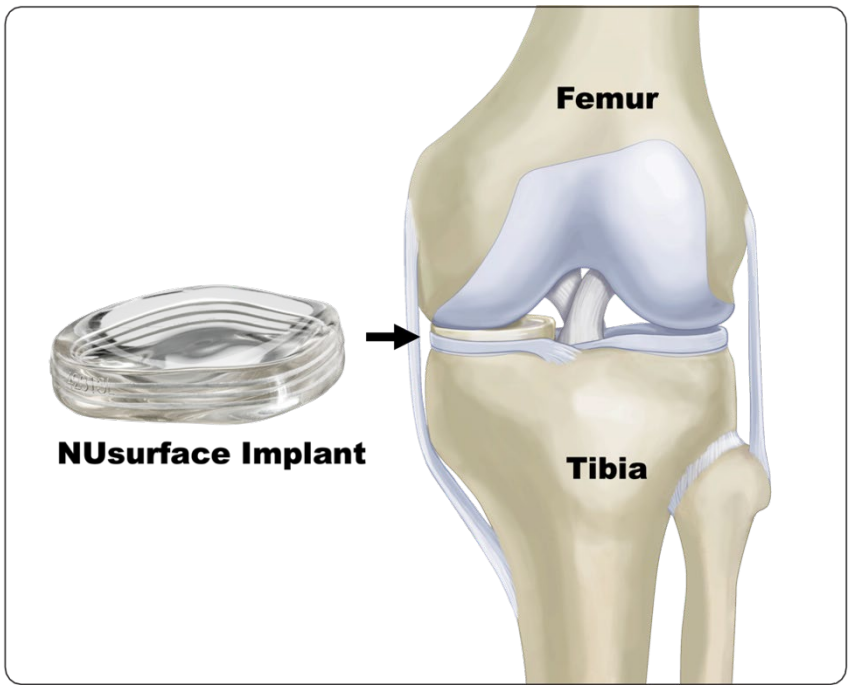


Figure 2. View of knee implanted with a NUsurface.

The NUsurface device was CE-marked for commercial distribution in the European Union in 2008. In 2015, following 8 years of extensive interaction with FDA, the Sponsor initiated an IDE trial to evaluate the safety and effectiveness of the NUsurface device. The IDE trial was a randomized, multi-center trial with a control arm treated with non-operative therapy. The trial, called VENUS (b) (4) enrolled 127 subjects: 61 in the treatment arm and 66 in the control group. A single arm IDE trial was also initiated in 2016 with the same major inclusion and exclusion criteria as the randomized trial, called SUN ((b) (4)) which enrolled 115 subjects. The SUN study was undertaken to provide additional data on safety of the device. The outcomes of these two trials were subsequently combined in consultation with FDA, following the Agency's review of the statistical analysis plan ((b) (4)). The de novo petition summarizes the outcomes of these combined studies, called MERCURY.

In September 2019, FDA granted the NUsurface device breakthrough designation in recognition of a treatment for an irreversibly debilitating condition and the potential to be a more effective treatment compared to available options.

The study primary endpoint was a composite endpoint that included all of the following components. Study success required a statistically greater success rate on the primary composite endpoint in the NUsurface device at 24 months as compared to the control arm.

1. ≥20-point improvement in the KOOS Overall score, the average of the 5 KOOS domains, which includes the Pain domain.
2. ≥20-point improvement in KOOS Pain considered independently.
3. Confirmation of the position and condition of the NUsurface device on MRI
4. Absence of protocol-defined secondary surgical interventions that qualified as an automatic failure of study, defined as:

a. NUsurface subjects who had surgery to remove the device, with or without replacement, for any reason.
b. Control group subjects who underwent any surgical procedure on the medial compartment of the index knee.

The total population of the MERCURY study met:

- primary endpoint of superiority over controls (p=0.013)
- secondary endpoints of superiority in the total population.

One of the secondary endpoints provided evidence that validated the mechanism of action of the implant through MRI analysis, by documenting preservation of cartilage in the medial compartment in the NUsurface arm and progressive deterioration of the cartilage in the control group. These radiological findings correlated with the clinical outcomes. Adverse events in the NUsurface arm were statistically different compared to the control in only one clinical finding, the rate of transient post-op effusion. There were no statistically significant differences in the rates of adverse events between the two groups after 6 months follow-up. Effusion rates in the MERCURY trial were comparable to rates reported for other commonly performed orthopedic surgeries such as meniscectomy, ACL reconstruction, arthroplasty, and even ipsilateral hip surgery[4,5,6,7,8,9]. In the total population, the NUsurface was permanently removed in 10.3% of subjects in the MERCURY trial. It was repositioned or replaced in 22.9%. The rates of adverse events recorded in replacement surgeries were lower than rates recorded in the primary surgeries. 67% of subjects had >20- point improvement in KOOS overall following replacement surgery.

To address FDA's concerns following review of the initial de novo submission and after subsequent guidance from FDA regarding its benefit/risk assessment of outcomes in the MERCURY Trial, the Sponsor analyzed the study population to assess whether there was a group that could be identified that was more likely to benefit from the device and less likely to undergo a secondary surgical operation. This review identified 2 radiographic variables that correlated with greater risk and poorer outcomes in NUsurface patients: extrusion of the medial meniscus and the height of the medial tibial spine. Significant extrusion is indicative of severe degenerative changes in the meniscus. A reduced height of the tibial spine in the medial compartment may affect the stability of the implant and could result in an increased incidence of replacements.

[4] Fabricant PD, Rosenberger PH, Jokl P, Ickovics JR. Predictors of short-term recovery differ from those of long-term outcome after arthroscopic partial meniscectomy. *Arthroscopy*. 2008;24(7):769-778. doi:10.1016/j.arthro.2008.02.015

[5] Pakuts, A. and Martin, L. (2019) Knee Effusion after Arthroscopic Partial Meniscectomy: Prospective Study Comparing Preventing Methods. *Open Journal of Orthopedics*, **9**, 152-158. doi: 10.4236/ojo.2019.98016.

[6] Alkan K, Unay K, Berkem L, Güven M, Poyanlı O. Suction drainage influence on knee effusion following partial meniscectomy with partial fat pad or synovium resection. *Acta Orthop Traumatol Turc*. 2011;45(4):221-224. doi:10.3944/AOTT.2011.2545

[7] Jawish, R., Najdi, H., Abi Safi, C., & Chameseddine, A. (2015). The effect of intra-articular Tenoxicam on knee effusion after arthroscopy. International Orthopaedics, 39(7), 1423–1426. doi:10.1007/s00264-014-2640-3

[8] Shahid MS, Murphy D, O'Donnell T, et al. A prospective study for evaluation of knee effusion after hip surgery. Irish Medical Journal. 2002 May;95(5):140-141. PMID: 12092694

[9] Christodoulou A, Givissis P, Antonarakos P, Petsatodis G, Hatzokos I, Pournaras J. Knee Joint Effusion following Ipsilateral Hip Surgery. *Journal of Orthopaedic Surgery*. 2010;18(3):309-311. doi:10.1177/230949901001800310

In the indicated population of 109 subjects, NUsurface was successful in 37 of 72 subjects, compared to 5 of 31 controls. After propensity adjustment, the success rate was statistically superior at 48.1% for NUsurface Arm compared to 18.2% for the Control Arm (p=0.011). The NUsurface Arm was also statistically superior in 10 secondary outcome variables. The NUsurface was removed in 6.9% (5/72) of subjects in the subpopulation. It was repositioned or replaced in 9.7% (7/72). 83% (5 of 6) NUsurface subjects had >20-point improvement in KOOS Overall following replacement surgery. One of the 7 subjects did not report 24-month KOOS scores.

The Sponsor also conducted a prospective, Multicenter, OUS trial from 2011-2015 that enrolled 128 patients in Europe and Israel who were followed for 24-months. Subjects in this trial were a similar baseline age and KOOS scores. Subjects followed a similar treatment schedule and were analyzed using the same criteria to identify the subpopulation in the MERCURY study. This retrospective analysis of data from this trial provided confirmatory evidence of improved outcomes and a reduced rate of second surgeries when patients with significant meniscus extrusion and low medial tibial spine heights are excluded. Thus, the criteria used to identify the subgroup have been validated in an independent population.

Active Implants conducted seven surveys or focus groups of over 700 US individuals with knee pain. Participants who matched the IDE study demographics were directly asked whether the rate of secondary surgery was acceptable to them, considering the potential benefits of the device along with a question of potential benefit versus potential risk. The results of all seven surveys or focus groups reached similar conclusions: the risk of second surgery was acceptable to this population.

Active Implants believes that the subpopulation data demonstrate the probable benefits of NUsurface outweigh its probable risks:

- NUsurface is 3 times more efficacious compared to controls measured by the primary outcomes variable of 51.4% success vs 16.1% success.
- Superiority in 10 secondary variables in the subpopulation confirm the benefit of NUsurface compared to controls.
- Surgical risks are mild to moderate and comparable to the risk of similar knee preservation procedures including meniscectomy surgery, one of the most commonly performed surgical procedures in the U.S.[10,11,12,13,14,15].

[10] Abram SGF, Hopewell S, Monk AP, Bayliss LE, Beard DJ, Price AJ. Arthroscopic partial meniscectomy for meniscal tears of the knee: a systematic review and meta-analysis. *Br J Sports Med*. 2020;54(11):652-663. doi:10.1136/bjsports-2018-100223

[11] Sihvonen R, Paavola M, Malmivaara A, et al. 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;77(2):188-195.

[12] Yim JH, Seon JK, Song EK, et al. A comparative study of meniscectomy and nonoperative treatment for degenerative horizontal tears of the medial meniscus. Am J Sports Med. 2013;41(7):1565-1570.

[13] Fabricant PD, Rosenberger PH, Jokl P, Ickovics JR. Predictors of short-term recovery differ from those of long-term outcome after arthroscopic partial meniscectomy. *Arthroscopy*. 2008;24(7):769-778. doi:10.1016/j.arthro.2008.02.015

[14] Salzler MJ, Lin A, Miller CD, Herold S, Irrgang JJ, Harner CD. Complications after arthroscopic knee surgery. *Am J Sports Med*. 2014;42(2):292-296. doi:10.1177/0363546513510677

[15] Katz JN, Brophy RH, Chaisson CE, et al. Surgery versus physical therapy for a meniscal tear and osteoarthritis. N Engl J Med. 2013;368(18):1675-1684.

- The rate of second surgeries is comparable to the rates of second surgery in other procedures intended to preserve the joint, including meniscectomy surgeries, meniscal allograft and cartilage repair[16,17,18,19,20].
- Radiographic data from the MERCURY study supports the conclusion that NUsurface does not introduce new safety concerns as a result of the materials from which the implant is made, when compared to safety data reported for predicate meniscus replacements manufactured from metal. NUsurface does not harm the cartilage and data confirm a positive benefit, cartilage condition preserved or potentially improved in some cases, when compared to the progressive degeneration measured in patients undergoing non-operative therapy.

Sufficient information has been submitted to establish special controls that, with general controls, provide a reasonable assurance of the safety and effectiveness of NUsurface for its intended use.

3 Background Information

3.1 Applicants Name and Address

Active Implants, LLC.

6060 Primacy Parkway, Suite 460

Memphis, TN 38111

3.2 Device Description

3.2.1 Implant Materials

The NUsurface Meniscus Implant is a discoid shaped device for use in the medial compartment. Seven sizes were available during the MERCURY TRIAL for the left and right knees (Figure 3). The

[16] Cole, B. J., Dennis, M. G., Lee, S. J., Nho, S. J., Kalsi, R. S., Hayden, J. K., & Verma, N. N. (2006). *Prospective Evaluation of Allograft Meniscus Transplantation. The American Journal of Sports Medicine, 34(6), 919–927.* doi:10.1177/0363546505284235

[17] Kempshall, P. J., Parkinson, B., Thomas, M., Robb, C., Standell, H., Getgood, A., & Spalding, T. (2014). *Outcome of meniscal allograft transplantation related to articular cartilage status: advanced chondral damage should not be a contraindication. Knee Surgery, Sports Traumatology, Arthroscopy, 23(1), 280–289.* doi:10.1007/s00167-014-3431-5

[18] Saltzman, B. M., Meyer, M. A., Weber, A. E., Poland, S. G., Yanke, A. B., & Cole, B. J. (2016). Prospective Clinical and Radiographic Outcomes After Concomitant Anterior Cruciate Ligament Reconstruction and Meniscal Allograft Transplantation at a Mean 5-Year Follow-up. The American Journal of Sports Medicine, 45(3), 550–562. doi:10.1177/0363546516669934

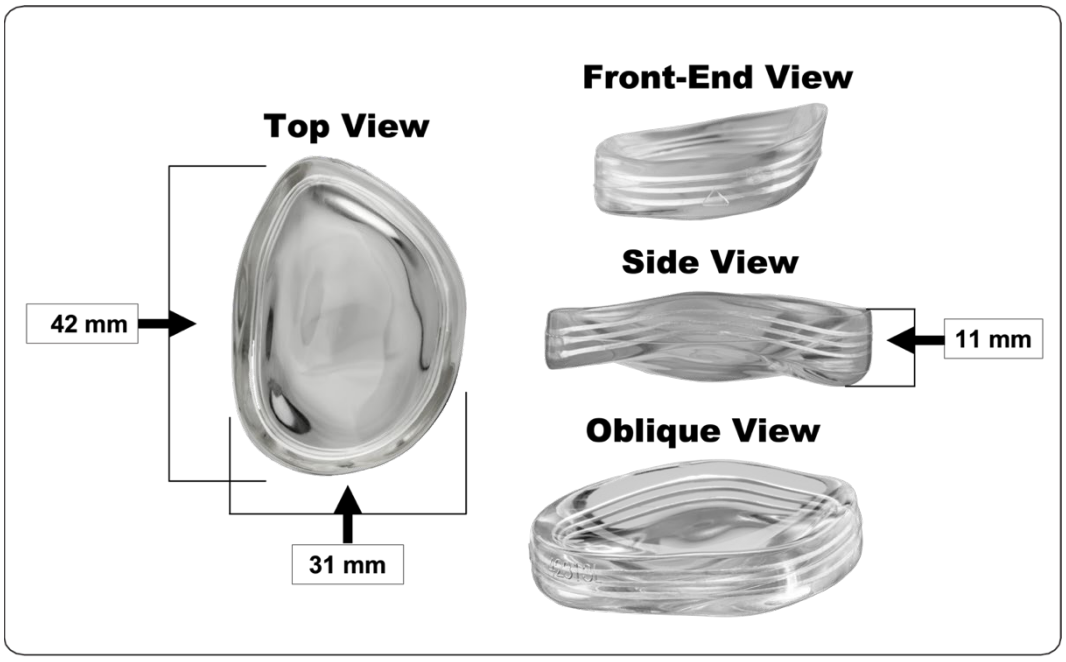
[19] Frank RM, McCormick F, Rosas S, et al. Reoperation Rates After Cartilage Restoration Procedures in the Knee: Analysis of a Large US Commercial Database. *Am J Orthop (Belle Mead NJ)*. 2018;47(6):10.12788/ajo.2018.0040. doi:10.12788/ajo.2018.0040

[20] Saltzman BM, Meyer MA, Weber AE, Poland SG, Yanke AB, Cole BJ. Prospective Clinical and Radiographic Outcomes After Concomitant Anterior Cruciate Ligament Reconstruction and Meniscal Allograft Transplantation at a Mean 5-Year Follow-up. *Am J Sports Med*. 2017;45(3):550-562. doi:10.1177/0363546516669934

two materials used to construct the NUsurface® Meniscus Implant are Bionate® polycarbonate-urethane (PCU) and Dyneema Purity® fibers of Ultra-High Molecular Weight Polyethylene (UHMWPE) embedded around the periphery (Figure 4).

Figure 3. Photograph of a NUsurface Implant, a natural meniscus and an illustrated view from the top of the right knee, showing the orientation of the NUsurface® meniscal implant.

Figure 4. Photographs of one of the seven NUsurface Implant sizes from top, front, side, and oblique views.



3.2.2 Design Principles

The NUsurface Meniscus Implant was designed to replicate the function of the normal meniscus by evenly distributing the load in the medial compartment of the knee joint. The figures below illustrate the pressure distribution of a normally functioning meniscus (5A), the painful pressure distribution in a knee where the meniscus has been damaged or partially removed (5B), and normal pressure distribution after implantation of the NUsurface (5C).

Figure 5A: A healthy meniscus distributes loads from the upper body through the lower extremities.

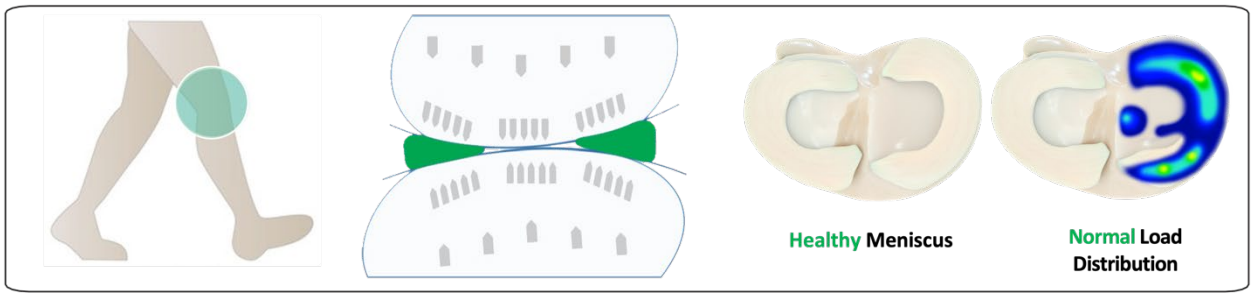


Figure 5B: After a meniscectomy, the load is concentrated in a smaller area and the pressure increases, which over time can lead to damage to the underlying bone and cartilage, causing a persistent, dull, aching type of pain.

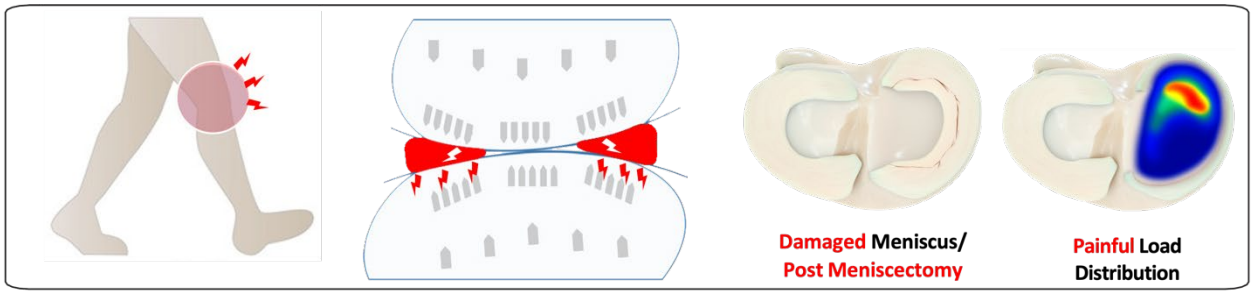
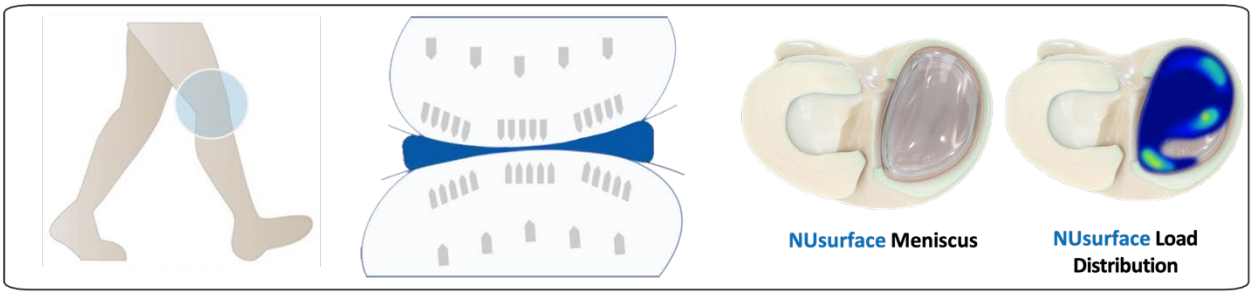


Figure 5C: The NUsurface implant restores normal load distribution, reducing painful pressure.



The implant was designed to mimic the physical characteristics of the native meniscus[21]. The thickness of the implant is similar to the normal meniscus to replicate its strain displacement and

[21] Elsner JJ, Portnoy S, Guilak F, Shterling A, Linder-Ganz E. MRI-based characterization of bone anatomy in the human knee for size matching of a medial meniscal implant. J Biomech Eng. 2010 Oct;132(10):101008. (https://doi.org/10.1115/1.4002490)

physical properties[22,23]. On a microscopic level the NUsurface Meniscus Implant reduces the strain on the medial cartilage by acting as a strain absorber to help protect the chondrocytes and prevent cartilage degeneration. The NUsurface has similar properties to the natural meniscus because the PCU from which it is made is a hydrophilic polymer, resulting in an implant coefficient of friction against cartilage that is as low as the natural cartilage-meniscus interface [24,25,26,27,28,29,30,31]. The NUsurface device replicates the anterior-posterior translation of a functioning meniscus since it is not physically anchored, relying on the remaining medial meniscus and capsule for stability. Standing MRIs of NUsurface patients confirm that the implant moves in the anterior-posterior direction approximately the same amount as the contralateral medial meniscus in patients.[32]

Orthopaedic prostheses typically replace a joint with two separate articulating surfaces made of medical grade materials designed to wear against one other. Only two Class II orthopaedic implants in the U.S. describe devices for use adjacent to native cartilage. These are FDA's product classifications for hip endoprostheses (21 CFR 888.3360) and knee joint metallic tibial resurfacing devices (21 CFR 888.3590). Cartilage erosion caused by a high modulus metal device next to, and wearing against soft cartilage, is a well-recognized complication of these devices[33,34,35,36]. A 2019 review of hip endoprosthesis articles found acetabular cartilage erosion or chondrolysis, occurs in up to 66% of cases, usually months or years after surgery. It can occur as early as weeks[37] after

[22] Elsner JJ, Portnoy S, Zur G, Guilak F, Shterling A, Linder-Ganz E. Design of a free-floating polycarbonate-urethane meniscal implant using finite element modeling and experimental validation. J Biomech Eng. 2010 Sep;132(9):095001. (https://doi.org/10.1115/1.4001892)

[23] Shemesh, M., Shefy-Peleg, A., Levy, A. *et al.* Effects of a novel medial meniscus implant on the knee compartments: imaging and biomechanical aspects. *Biomech Model Mechanobiol* **19**, 2049–2059 (2020).

[24] Shriram, D., Praveen Kumar, G., Cui, F. *et al.* Evaluating the effects of material properties of artificial meniscal implant in the human knee joint using finite element analysis. *Sci Rep* **7**, 6011 (2017). https://doi.org/10.1038/s41598-017-06271-3

[25] Zur G, Linder-Ganz E, Elsner JJ, et al. Chondroprotective effects of a polycarbonate-urethane meniscal implant: histopathological results in a sheep model. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(2):255-263. doi:10.1007/s00167-010-1210-5

[26] Kanca Y, Milner P, Dini D, Amis AA. Tribological evaluation of biomedical polycarbonate urethanes against articular cartilage. *J Mech Behav Biomed Mater*. 2018;82:394-402. doi:10.1016/j.jmbbm.2018.04.001

[27] Almhdie-Imjabbar, A., Toumi, H., Harrar, K. *et al.* Subchondral tibial bone texture of conventional X-rays predicts total knee arthroplasty. *Sci Rep* **12**, 8327 (2022). https://doi.org/10.1038/s41598-022-12083-x

[28] Felson D T, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum 2007; 56(9): 2986-92. Fu K, Robbins

[29] Inyang AO, Vaughan CL. Functional Characteristics and Mechanical Performance of PCU Composites for Knee Meniscus Replacement. Materials. 2020; 13(8):1886. https://doi.org/10.3390/ma13081886

[30] Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. *Med Clin North Am*. 2009;93(1):1-xv. doi:10.1016/j.mcna.2008.08.009

[31] Majd SE, Rizqy AI, Kaper HJ, Schmidt TA, Kuijer R, Sharma PK. An in vitro study of cartilage-meniscus tribology to understand the changes caused by a meniscus implant. Colloids Surf B Biointerfaces. 2017;155:294-303. doi:10.1016/j.colsurfb.2017.04.034

[32] De Coninck T, Elsner JJ, Linder-Ganz E, Cromheecke M, Shemesh M, Huysse W, Verdonk R, Verstraete K, Verdonk P. (2014) In-vivo evaluation of the kinematic behavior of an artificial medial meniscus implant: A pilot study using open-MRI. Clin Biomech (Bristol, Avon);29(8):898-905.

[33] McCann L, Ingham E, Jin Z, Fisher J. Influence of the meniscus on friction and degradation of cartilage in the natural knee joint. Osteoarthritis Cartilage. 2009;17(8):995-1000.

[34] McCann L, Ingham E, Jin Z, Fisher J. An investigation of the effect of conformity of knee hemiarthroplasty designs on contact stress, friction and degeneration of articular cartilage: a tribological study. J Biomech. 2009;42(9):1326-1331.

[35] McCann, L., Udofia, I., Graindorge, S., Ingham, E., Jin, Z., Fisher, J., 2008. Tribological testing of articular cartilage of the medial compartment of the knee using a friction simulator. Tribol Internat 41:1126-1133.

[36] Pöllänen R, Tikkanen A-M, Lammi MJ, Lappalainen R. (2011) The effect of loading and material on the biomechanical properties and vitality of bovine cartilage in vitro. J Appl Biomater Biomech;9(1):47-53.

[37] Adenikkinju A, Slover JD, Egol KA. (2019) Rapid acetabular chondrolysis following hemiarthroplasty of the hip: A poor prognostic sign. Case Reports in Orthopedics;2019:1-8. https://doi.org/10.1155/2019/7328526

surgery. For metal tibial resurfacing devices, the revision surgery for cartilage erosion is knee reconstruction. One registry[38] found the cumulative revision rate for metal resurfacing knee devices was 62% by 3 years. The modulus of metal is approximately 10,000 times higher than the modulus of elasticity of soft tissue and this difference has been identified as the cause of this rapid onset of chondrolysis[9].

The Sponsor supported an ex vivo knee cartilage study to investigate the effect of implant modulus on articular cartilage chondrolysis[9]. To our knowledge, this is the first ever attempt to measure this effect. Cylindrical samples of either metal or polycarbonate-urethane were loaded in compression against freshly removed living bovine cartilage. Metal compressed against living cartilage killed virtually all the chondrocyte cells while polycarbonate-urethane cylinders loaded by the same amount and for the same amount of time resulted in cell viability 13 times greater in comparison. These histological results were statistically different. The results indicate that a force exerted on cartilage can over-compress articular cartilage cells resulting in cell death. This study also indicates the modulus of the material contacting the cartilage is crucial to ensuring cell viability. Soft cartilage responds better to a soft, compliant material in which it is in contact compared to stiff metal. Radiographic outcomes of the MERCURY Trial confirm the NUsurface device helps protect condylar cartilage, especially femoral cartilage. The MRI analysis at 2-year follow-up confirms the NUsurface implant was statistically superior in slowing degradation of the distal medial femoral cartilage compared to non-surgical controls. These results validate the design criteria established for the NUsurface device and are included in Appendix B.

In summary, the principles of the NUsurface Meniscus Implant are:

1) mimic the physical and mechanical properties of a normal meniscus,

2) more evenly distribute stress, and

3) absorb some of the strain that would otherwise be transferred to the cartilage in the absence of a normally functioning meniscus.

The MERCURY Study indicates that a device with these qualities can lower pain and delay the progression of osteoarthritic degeneration in the medial compartment of the knee, confirming the findings of the ex vivo cartilage viability study previously discussed[6] and a sheep knee study[39] conducted by the Sponsor entitled Chondroprotective effect on a polycarbonate-urethane meniscal implant: histopathological results in a sheep model. More discussion of chondroprotective studies are included in Section 8 and Appendix B.

3.2.3 Surgical Technique

NUsurface Implant Clinical Vignette and Description of Procedure

Typical Patient

[38] Australian Registry Report on the UniSpacer Device 2004-2006.

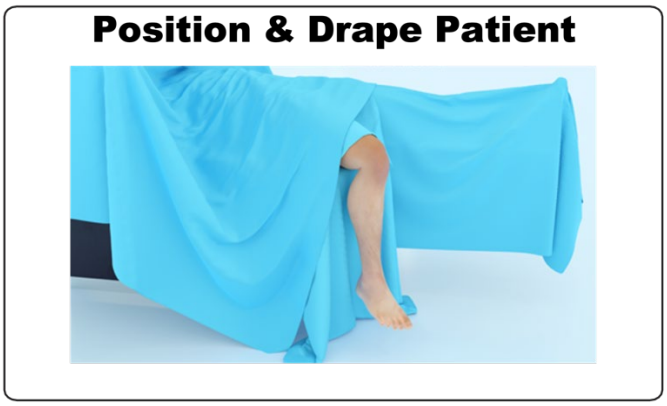
[39] Zur G, Linger-Ganz E, Elsner JJ, Shani J, Brenner O, Agar G, Hershman EB, Srnoczky SP, Guilak F, Shterling A. (2010) Chondroprotective effects of a polycarbonate-urethane meniscal implant: histopathological results in a sheep model. Knee Surg Sports Traumatol Arthrosc;19(2):255-263.

A 50-year-old man presents with pain and swelling of the left knee. The patient previously underwent arthroscopic partial medial meniscectomy for a tear of the meniscus. The patient has Kellgren-Lawrence Grade 2 osteoarthritis and a Grade III Outerbridge lesion in the center of the medial femoral condyle. An MRI confirms a substantial portion of meniscus had been previously removed and shows thinning of the articular cartilage surrounding the medial compartment. Despite medical management and physical therapy, the pain and disability persist, impacting activities of daily living. The affected medial meniscus is determined to be unsuitable for meniscal repair or further meniscectomy.

Description of Procedure

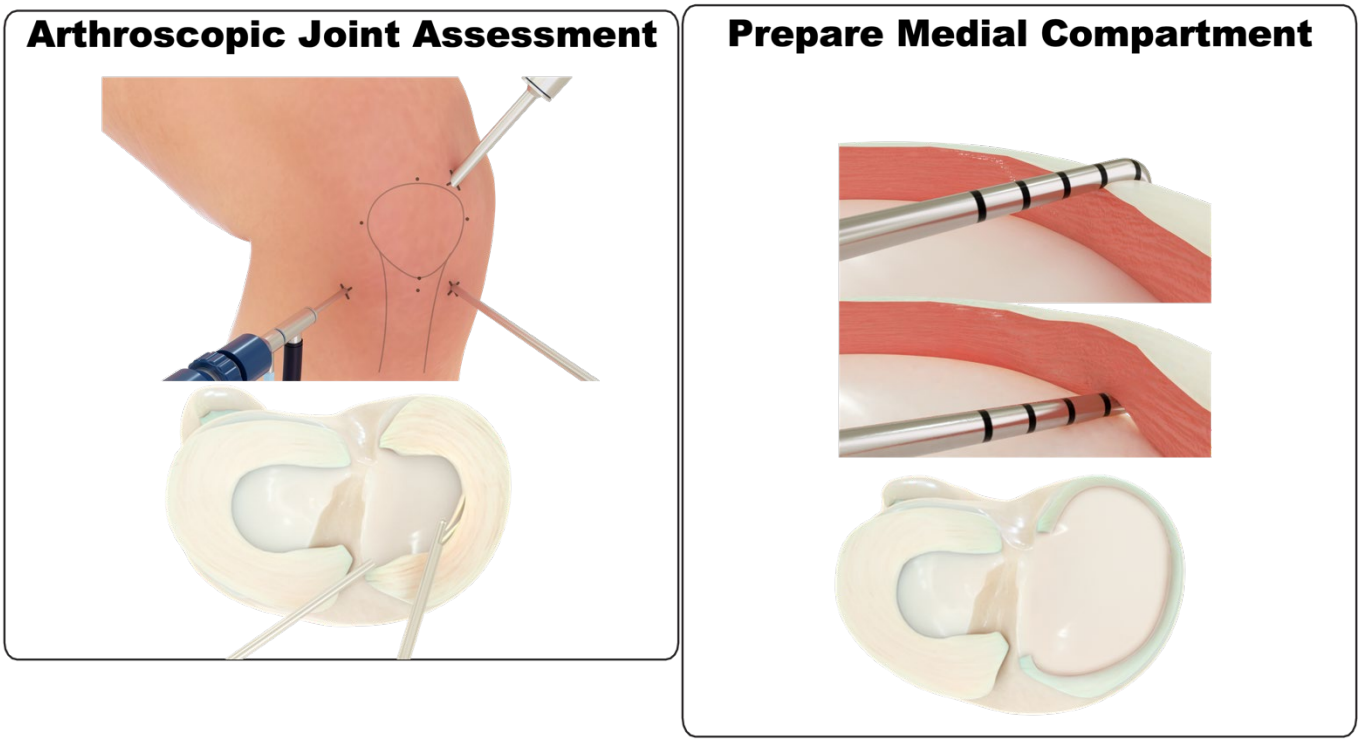
Under anesthesia, a tourniquet is applied above the knee; a bolster is placed under the buttock and at the end of the table to support the heel when the leg is bent during surgery. The leg is prepped, draped, and positioned for a knee arthroscopy (Figure 6).

Figure 6



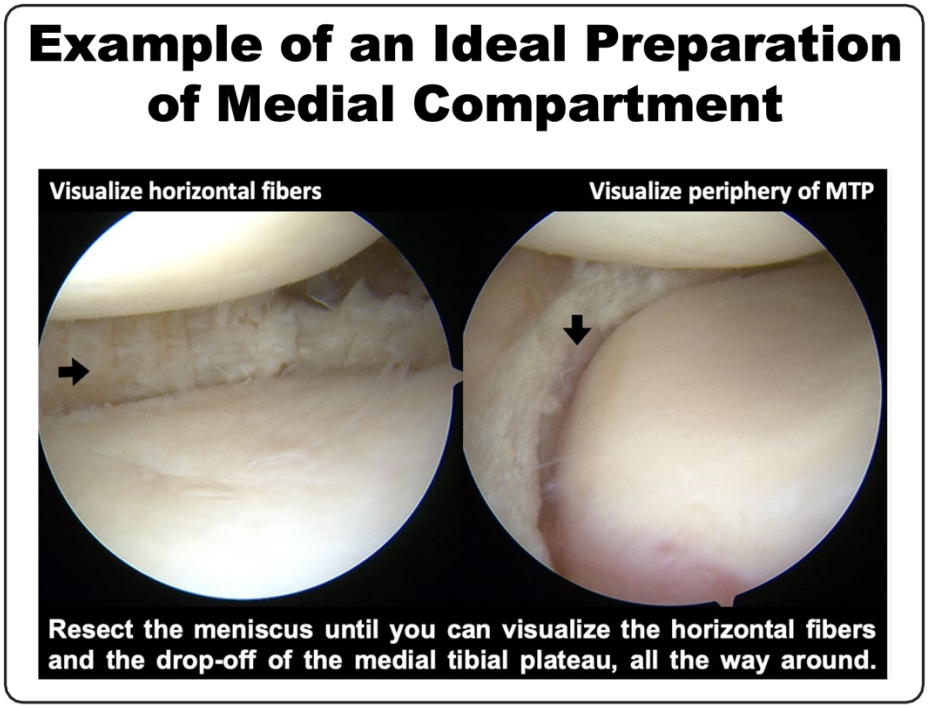
An arthroscopy is performed to evaluate joint condition, assess Outerbridge Grade and the size and position of any exposed bone. Using an arthroscopic approach, osteophytes are excised (Figure 7).

Figure 7



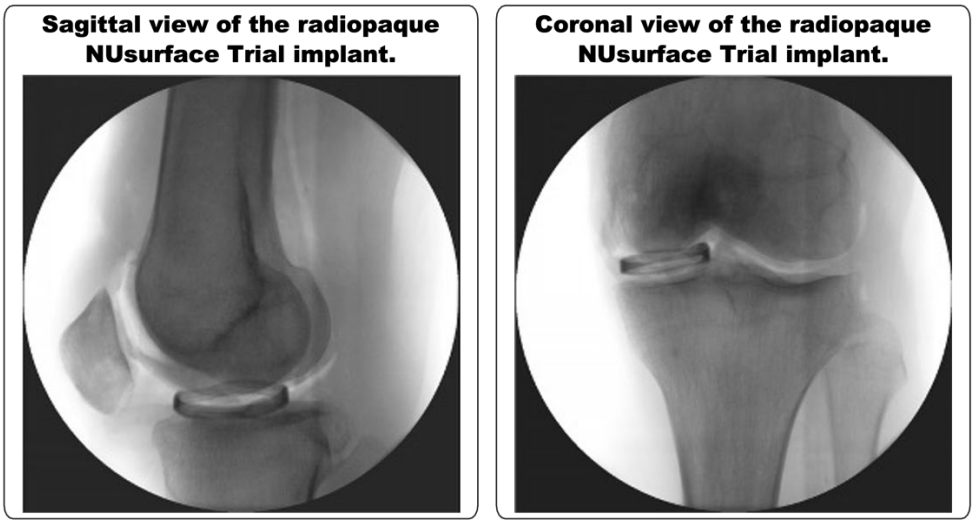
A circumferential meniscectomy in the avascular region of the medial meniscus is performed to create a 2mm vertical margin (rim) around the periphery. Preparation is complete after the remaining meniscus is stable and horizontal meniscus fibers are visible along with the drop-off of the MTP (Figure 8).

Figure 8



A 4-6cm medial parapatellar arthrotomy dissecting tissue to expose the medial compartment is performed. A sizing trial is used to evaluate the correct size for the final NUsurface implant. The Trial is implanted interpositionally between the medial femur and tibia. Correct placement and proper movement of the Trial through range of motion is confirmed by fluoroscopy (Figure 9).

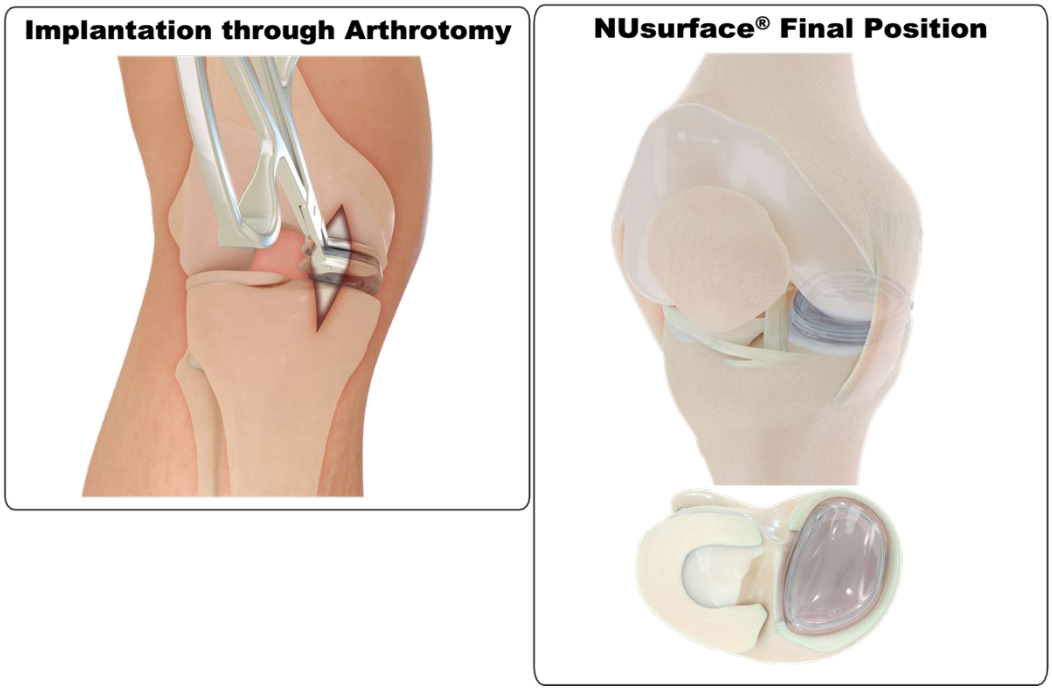
Figure 9



The Trial implant is removed with the extraction tool.

The definitive NUsurface Implant is implanted. Final range of motion testing and measurement is performed (Figure 10).

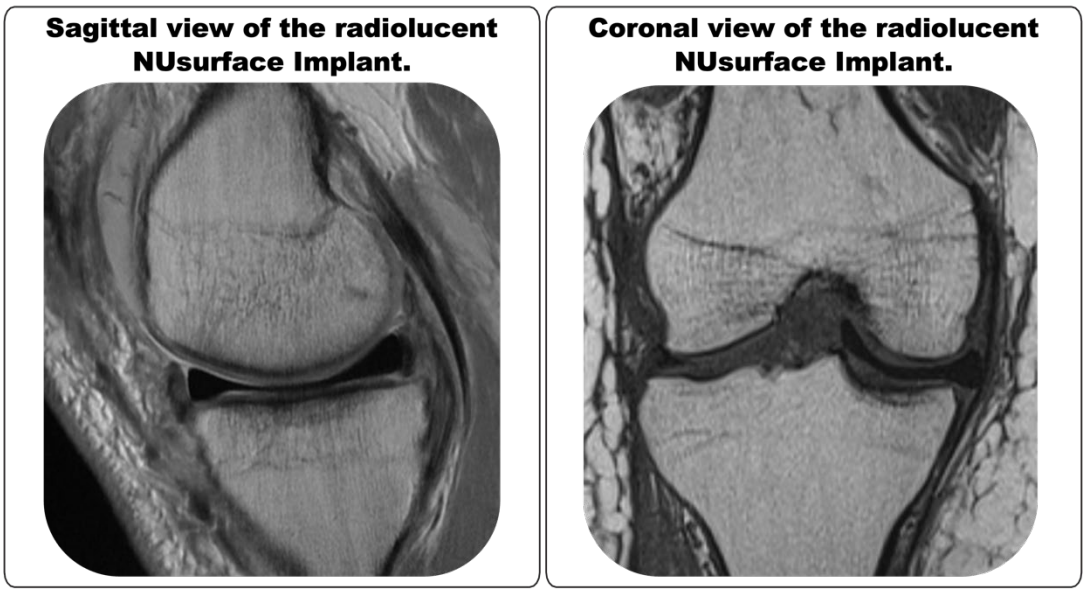
Figure 10



After wound closure, a dressing and straight-knee immobilizer are applied.

The NUsurface implant is radiolucent on X-ray. Postoperative evaluation should be performed using MRI. The figures below depict the ideal sizing and placement of the NUsurface Meniscus Implant for a typical patient (Figure 11).

Figure 11



More details of the surgical technique are available in Appendix C.

4 Indications For Use (Proposed)

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.

5 Contraindications

Contraindications for the NUsurface meniscus implant are below. The complete instructions for use including warning and precautions are in Appendix D

1. 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;
2. 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;

3. Patients with extrusion of the medial meniscus 5mm or greater;
4. >5° loss of extension and >15° loss of flexion difference between index and contralateral knee; greater than ±5° of varus/valgus femoral/tibial alignment.
5. 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;
6. Grossly distorted anatomy or neuropathic joint such as Charcot joint;
7. Knee joint bone resorption, avascular necrosis, or rapid joint destruction;
8. Skeletally immature;
9. 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;
10. Morbid obesity;
11. Patients with inflammatory or systemic disease such as psoriatic arthritis or rheumatoid arthritis;
12. Patients with an allergy to any of the materials used to construct the implant;
13. Patients with insufficient quantities of synovial fluid to allow for proper lubrication of the knee, such as occurs with Sjogren's Syndrome;
14. Active Infection, sepsis, or osteomyelitis;
15. Medial compartment anatomy requiring a NUsurface device size larger or smaller than available;
16. Use of the NUsurface device in the lateral compartment of the knee or in any part of the body other than the medial knee;
17. Patients incapable of following instructions, such as having certain types of mental illnesses, or unwilling or unable to be compliant with directions.

6 Regulatory and Marketing History

6.1 CE Marking and Marketing History

The first surgical implantation of the NUsurface Meniscus Implant took place in Italy May 2008, following receipt of the CE mark and marketing authorization in the European Union in March 2008. NUsurface has never been withdrawn from any markets for safety reasons. The NUsurface Meniscus Implant is currently marketed in the following countries:

- Belgium
- France
- Germany
- Israel

- Italy
- Netherlands
- Switzerland
- United Kingdom

The NUsurface Implant in the EU and Israel is offered under a different, broader indication for use than the proposed US labeling. The CE marked indication states that the NUsurface device is for: Primary or post-meniscectomy patients with acute or chronic medial compartment pain who have or have had a traumatic or degenerative meniscal tear(s) and/or meniscal insufficiency.

6.2 US Regulatory History

510(k) filings

The Sponsor submitted two 510(k) applications. (b) (4) was filed in May 2008, and (b) (4) was filed in November 2013. Both claimed substantial equivalence to 21 CFR 888.3590, a metal interpositional spacer. FDA found both submissions to be Not Substantially Equivalent because the material used to make the NUsurface device differs from previously cleared metallic devices. The Not Substantially Equivalent letter for (b) (4) stated,

> *"This decision is based on the fact that your device has new technological characteristics, that could affect safety and effectiveness, and raises new types safety and effectiveness questions. Specifically, how do the characteristics of the NUSurface Resurfacing System (including its swelling behavior, composite structure, strain-history dependence, ability to adsorb biological materials, and novel breakdown mechanisms and products) allow it to perform as safely and effectively as predicates?"* (Emphasis added)

IDE (b) (4)

From 2010 to 2013, the Sponsor submitted 6 Pre-IDE Supplements and had a face-to-face meeting regarding the additional information required to approve the IDE to begin the clinical study. In August 2012, the Sponsor submitted (b) (4) requesting approval to perform a randomized controlled trial, called VENUS. In May 2013, the FDA approved the VENUS IDE. The first U.S. NUsurface surgery in the VENUS Trial was in January 2015 under (b) (4).

First De Novo Petition

In February 2014, FDA denied a de novo petition that contained clinical data collected outside the U.S. The Sponsor filed that de novo petition on December 30, 2008. The main reasons given for the denial were that the OUS clinical dataset was incomplete, the data lacked an analysis of the MRI's taken in the European/Israeli multi-center trial, and lacked a control group to interpret the results.

IDE (b) (4)

In March 2015, Active Implant submitted a second IDE, called SUN ((b) (4)). The SUN trial was a single arm study of the NUsurface device. The inclusion/exclusion criteria for the SUN trial were the same as for the VENUS Trial. This IDE was approved without conditions in April 2015.

Combination of (b) (4)

In October 2017, the Sponsor met with the review team to confirm de novo status and discuss data availability and timing. FDA suggested pooling SUN and VENUS subjects to increase the safety information regarding the device. The Agency confirmed the device was de novo eligible and suggested that 24-month data would be required. Throughout 2017, 2018, and into 2019, Active Implants worked with the agency to combine the studies. In March 2019, in VENUS IDE Supplement (b) (4) the agency agreed with the revised SAP and proposed propensity analysis to adjust the combined studies before any 24-month data was obtained. The combined study was named MERCURY.

Breakthrough Designation

In September 2019, FDA granted the NUsurface Meniscus Implant Breakthrough Device designation (b) (4) . The basis of the decision was acknowledgment that the device treated patients with an irreversibly debilitating condition and had the potential to be a more effective treatment of their condition compared to available options.

DEN (b) (4)

Active Implants submitted De Novo Petition DEN (b) (4) on July 30, 2020. Following additional correspondence with FDA and response to questions, in May 2021, the company received a denial letter for the reasons discussed above. Active Implants appealed the denial of DEN (b) (4) in August of 2021. The denial decision was upheld in September 2021. Following the appeal, the Sponsor discussed with FDA management and the review team outcomes of a subpopulation that reduced the risk of secondary surgeries.

In November of 2021, Active Implants submitted a Sprint Meeting request to discuss radiographic baseline measurements that identify patients at a greater risk of secondary surgery. The sprint meeting took place on January 26, 2022 and FDA feedback informed the subpopulation submitted in DEN (b) (4) .

DEN (b) (4)

Active Implants filed DEN (b) (4) with clinical data from a subpopulation of 74 NUsurface subjects and 35 matched control subjects in June 2022. FDA provided 75 Day feedback in August 2022. In November of 2022, the Sponsor and FDA met to discuss the clinical deficiency questions. In this meeting, it was clear that an advisory panel could help inform the assessment of benefit versus risk. The request for this Panel Meeting was agreed to in December of 2022.

7 The Clinical Need

The NUsurface has been developed for the treatment of a patient population that suffers from pain and loss of function of the knee joint caused by degeneration of the cartilage in the medial compartment. Patients enrolled in clinical trials to evaluate the NUsurface are a salvage

population who have already undergone one or more failed meniscectomies and repeated non-operative regimens of therapy and are symptomatic at least 6 months later.

Arthroscopic partial meniscectomy (APM) is the most commonly performed surgical procedure in orthopaedic surgery and in the U.S. over 1 million are performed per year[40], making it the third most common surgical procedure in adults[41]. The rationale for partial meniscectomy is that removing the source of pain will result in symptom relief.

Typically, the more severe the disease, the greater the improvement when the pathology is removed. Yet results from 12 randomized trials confirm that repeat meniscectomies are not effective in patients who have failed one or more previous meniscectomies, and these surgeries are not statistically better than nonoperative therapy at 2 years.[42] Despite these results, "failed nonoperative treatment" is still considered an indication for surgery, leading to a downward cascade in which the severity of the disease is actually made worse by the surgery to treat it.

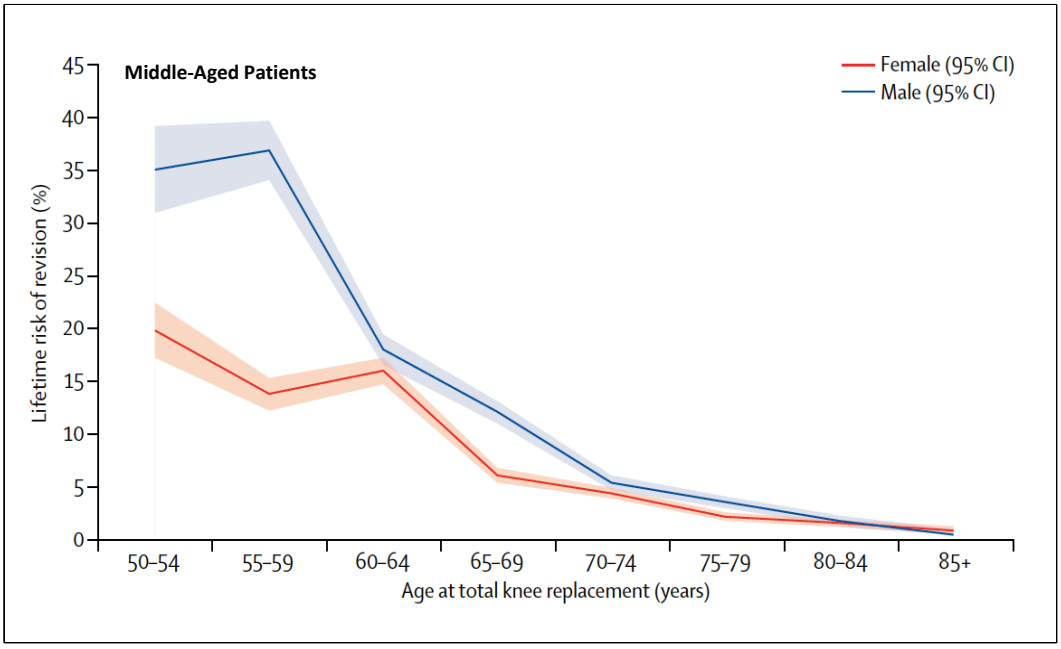
Patients are 132 times more likely to undergo arthroplasty if they have had a meniscectomy than if they have not, demonstrating the causal relationship between meniscal insufficiency and cartilage degeneration[43]. These patients have a history of knee surgery failure and will be at an increased risk of failure and complications from any subsequent surgical intervention. Operative treatments such as meniscal allograft, which are indicated in a younger population, are no longer an option for these patients,[44] and patients who are indicated for NUsurface are not considered good candidates for arthroplasty.[45]

According to a 2018 American Academy of Orthopaedic Surgeons (AAOS) instruction course lecture, U.S. surgeons perform over 680,000 TKA procedures per year. AAOS projects the number of primary TKA procedures in the U.S. will double to 1.28 million a year[46] by 2030. Not only is the frequency of TKA procedures increasing, but the average age of patients receiving TKA is getting younger. Arthroplasty at age 50, the mean age of the subjects enrolled in the MERCURY study, is not a desirable option for people with knee pain. A well-established finding regarding total knee

[40] Hutchinson ID, Moran CJ, Potter HG, Warren RF, Rodeo SA. (2013) Restoration of the meniscus. Form and function. AJSM.
[41] Only heart and eye surgeries are more common. The definition of surgery means the cutting of tissue.
[42] Section 23.10, page 3991 of DEN(b) (4) contains all 24 citations associated with these 12 clinical studies.
[43] Pengas LP et al. (2012) Total meniscectomy in adolescents. A 40-year follow-up. J Bone Jt Surg;94B(12):1649-1654.
[44] American Academy of Orthopaedic Surgeons (AAOS) Meniscus transplantation: indications, techniques, clinical outcomes. Instruction Course Lecture 54:341-353, Feb 2005.
[45] AAOS "What are the AAOS guidelines for total knee arthroplasty in the treatment of osteoarthritis (OA)? October 12, 2020.
[46]Projected volume of primary and revision total joint replacement in the U.S. 2030 to 2060. AAOS March 6, 2018.

replacement is that patient dissatisfaction is more likely when OA is mild[47,48,49,50,51,52,53]. A 2017 Lancet publication estimated that men and women who undergo total knee arthroplasty in their 50s have a 20% to 37% lifetime risk of revision total knee arthroplasty (Figure 12). For this reason, TKA is typically delayed in younger patients to reduce the risk of a second arthroplasty[54].

Figure 12. Plot estimating lifetime risk of total knee replacement revision against age at the time of primary total knee replacement surgery (in 5-year bands) and stratified by gender.



For the reasons discussed above, the standard of care for the NUsurface eligible population is non-operative therapy, including activity restrictions, weight loss, bracing, over-the-counter analgesics, non-steroidal anti-inflammatory drugs, physical therapy, steroid and visco-

[47] Niemeläinen M, Moilanen T, Huhtala H, Eskelinen A. Outcome of knee arthroplasty in patients aged 65 years or less: a prospective study of 232 patients with 2-year follow-up. *Scandinavian Journal of Surgery*. 2019;108(4):313-320. doi:10.1177/1457496918816918

[48] Jacobs CA, Christensen CP, Karthikeyan T. Chronic Non-Orthopedic Conditions More Common in Patients with Less Severe Degenerative Changes That Have Elected to Undergo Total Knee Arthroplasty. *J Arthroplasty*. 2015;30(7):1146-1149. doi:10.1016/j.arth.2015.01.051

[49] Peck CN, Childs J, McLauchlan GJ. Inferior outcomes of total knee replacement in early radiological stages of osteoarthritis. *Knee*. 2014;21(6):1229-1232. doi:10.1016/j.knee.2014.08.018

[50] Nakano N, Shoman H, Olavarria F, Matsumoto T, Kuroda R, Khanduja V. Why are patients dissatisfied following a total knee replacement? A systematic review. *Int Orthop*. 2020;44(10):1971-2007. doi:10.1007/s00264-020-04607-9

[51] Scott CE, Oliver WM, MacDonald D, Wade FA, Moran M, Breusch SJ. Predicting dissatisfaction following total knee arthroplasty in patients under 55 years of age. *Bone Joint J*. 2016;98-B(12):1625-1634. doi:10.1302/0301-620X.98B12.BJJ-2016-0375.R1

[52] Stone O D, Duckworth A D, Curran D P, Ballantyne J A, Brenkel I J. Severe arthritis predicts greater improvements in function following total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2017b; 25(8): 2573-9.

[53] van de Water R B, Leichtenberg C S, Nelissen R G H H, Kroon H M, Kaptijn H H, Onstenk R, et al. Preoperative radiographic osteoarthritis severity modifies the effect of preoperative pain on pain/function after total knee arthroplasty: results at 1 and 2 years postoperatively. J Bone Joint Surg Am 2019; 101(10): 879-87.

[54] Bayliss LE, Culliford D, Monk AP, et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study [published correction appears in Lancet. 2017 Apr 8;389(10077):1398]. *Lancet*. 2017;389(10077):1424-1430. doi:10.1016/S0140-6736(17)30059-4

supplementation injections, and prescription drugs. This leaves a substantial gap in treatment options between NSAIDs and arthroplasty for the NUsurface patient population.

In the absence of a device that can replicate the function of the meniscus, patients typically undergo multiple surgeries with limited efficacy until they are faced with a choice that offers diminishing results: continue to suffer from pain or, at the time the pain becomes intolerable, undergo arthroplasty at an age that places them at higher lifetime risk for future revision arthroplasty. There is a need for a new treatment option that is able to address the pain and symptoms experienced by these patients.

8 Summary of Non-Clinical Data

The following is a summary of the major *in vitro* or benchtop testing, animal *ex vivo* and *in vivo* testing, and cadaveric testing submitted to the FDA prior to initiating the two NUsurface IDE's, (b) (4) . *In vitro* testing includes biocompatibility, biodegradation risk assessment, Finite Element Analysis (FEA), and mechanical testing, including fatigue (uniaxial environment and mixed mode (shear environment). Ex vivo animal testing includes a study of freshly harvested bovine cartilage cells, *in vivo* animal testing represents a 3, 6, and 9-month sheep study. Finally, cadaveric testing assessed the surgical technique, instrumentation, correlation of the native meniscus to the NUsurface Meniscus Implant shape and contact mechanics, as well as surgical technique.

Biocompatibility and Biodegradation

As part of the approval process for IDE (b) (4) , in April 2013, the Sponsor requested North American Science Associates (NAMSA) perform a review and assessment of the biological risk of the biocompatibility and biodegradation associated with the clinical exposure of the NUsurface® Meniscus Implant. NAMSA reviewed the literature, safety testing data, additional pre-clinical testing, and clinical data available regarding the biological safety of the NUsurface Meniscus Implant and the possible impact of the processing and manufacturing changes on the safety of the product. The risk assessment performed by NAMSA only occurred after a review of the information gathered from biological testing data on the material components intended for incorporation into the finished device, the relevant published literature, and the long history of use of the materials used in the manufacture of the NUsurface Meniscus Implant.

Literature Review

A literature review discussed Degradation Resistance of polycarbonate-urethane, Resistance to hydrolytic degradation, Resistance of polycarbonate urethane to metal ion oxidation, Resistance of polycarbonate-urethane to enzymatic degradation, Resistance of polycarbonate-urethane to mineralization, Existing data from previous long-term animal studies of polycarbonate urethane, and In vivo degradation data from other clinical studies.

Ex vivo cartilage study

Under certain test conditions, chondrocyte cells in bovine cartilage explants remain alive for 11-14 days. Cylinders made of metal and Bionate 80A pressed on the cartilage explants using the same load. The results confirmed that cartilage samples loaded with Bionate 80A had statistically more chondrocytes remaining alive than samples loaded with metal. A peer-reviewed publication[6] documented the results.

In vivo sheep study

The results of a 6-month study of a fixed Bionate® 80A PCU Implant in six sheep have been published. Further discussion of the study and protocol are provided in (b) (4) . Histological analysis showed relatively mild cartilage degeneration that was dominated by loss of proteoglycan content and cartilage structure. However, the total osteoarthritis score (The Modified Mankin Scale) did not significantly differ between the control and operated knees, and there were no differences in the severity of degenerative changes between 3 and 6-months post-surgery. The experimental joints showed few macroscopic changes relative to the non-operated controls, and the main pathological changes present at 6-months post-implantation were similar to those observed at 3months post-implantation. Macroscopically, cartilage in direct contact with the implant was well preserved and did not show significant degeneration. Inflammation, other than that seen in association with the small amount of foreign matter occasionally observed, was negligible.

Finite Element Testing

Finite Element (FE) modeling of the implant in the medial knee under loading was conducted to develop an optimal design in terms of composition and geometry, whose contact pressure with the tibial plateau (TP) would be similar to that of the natural meniscus and also be able resist mechanical failure of any of its components.

Three-dimensional finite element (FE) models of the knee and PCU-based implant were analyzed under physiological loads to calculate internal loads and other functional characteristics of the implant. For each configuration, peak and average TP contact pressures were calculated. In addition, peak and average von Mises and tensile stresses were calculated for the PCU and the UHMWPE fibers, respectively. The model was validated by comparing calculated pressures, determined from FE analysis, to tibial plateau contact pressures measured in a cadaveric knee *in vitro*.

An optimal implant configuration was then selected based on the ability to restore pressure distribution in the knee, manufacturability of the design, and long-term safety of the constituent materials. This design produces an optimal pressure distribution, similar in shape

and values to that of natural meniscus and it could be manufactured in various sizes, without risking its integrity of the construct under joint loads.

Viscoelastic properties of the device

A large study characterized the strain-rate response and viscoelastic properties of the NUsurface device by measuring its creep, stress relaxation, and hysteresis properties after simulated use.

Mechanical testing of the device conducted in a chamber containing heated (37ºC) simulated physiological fluid (bovine serum diluted with water 4:1) used specially designed polyethylene replicas of the tibia and femur to mimic the distribution of joint compressive forces on the device in vivo.

The results were the NUsurface meniscus implant behaved as a non-linear viscoelastic material, with mechanical load-deformation compression properties similar to those of the natural meniscus. The implant maintained its geometry when subjected to soaking in fluid. The combination of soaking, together with fatigue loading, resulted in mild geometrical changes as a result of creep. These changes, a fraction of a millimeter, can be considered as long-term adaptation of the implant under load. All of the mechanical characterization tests showed a mild transition in the mechanical properties during the first 300,000 load cycles, which then stabilized for the rest of the duration of 2 million cycles. These relatively small changes in geometry reflect the adaptation measured after 2 million cycles and appear to represent the effects of long-term use. A peer reviewed publication[55] summarized these test results.

In vitro stability testing using cadaver legs

An *in vitro* study simulated the dynamic performance of the NUsurface meniscus implant during daily activities by subjecting the device to various loading conditions in cadaver knee joints. To quantify the effects of important variables, this study measured gross implant motion as a function of joint loading, implant size, joint laxity, and the amount of posterior horn excised during the meniscectomy procedure. Such characterization was necessary since the implant is a non- fixed device and is designed to be self-centering to prevent dislocation.

Mixed-mode wear testing

A study evaluated the long- term performance of the NUsurface device by using a full mixed-mode loading regime; loading in more than on direction.

In summary, the implant successfully underwent the simulation of 5 million human leg load cycles under full mixed-mode conditions without dislocating or undergoing significant

[55] Shemesh M, Asher R, Zylberberg E, Guilak F, Linder-Ganz E, Elsner JJ. (2014) Viscoelastic properties of a synthetic meniscus implant. J Mech Behav Biomed Mater;29:42-55.

degradation. The NUsurface implant was able to withstand long-term loading in simulated body environment. Five million cycles of simulated loads did not affect the structural, mechanical, chemical, or functional properties of the device.

Fatigue Testing and Material Testing

Fatigue testing of the NUsurface Implant applied 5 million human gait cycles under cyclic loading using simulated femoral and tibial condyles. The device was able to withstand the anticipated fatigue loading. Moreover, the device showed the same functionality after the experiment, in terms of pressure distribution ability.

Cadaver Testing

Implantations in multiple cadaver knees in multiple test centers around the world confirmed the sizing protocol of the implant for each cadaveric knee. The cadaver tests validated the surgical technique for how to use the trials and implant the device.

Correlation Study

A geometrical analysis and correlation study used a database of 118 MRI scans of American patient knees to determine the average dimensions/geometric relations in normative knees. These measurements help develop a normative meniscus geometry and helped predict the number of NUsurface sizes needed to cover the candidate population. The theoretical analysis was complemented with experimental and computational studies to validate the results. A peer reviewed publication[56] documented the results.

Knee Contact Mechanics

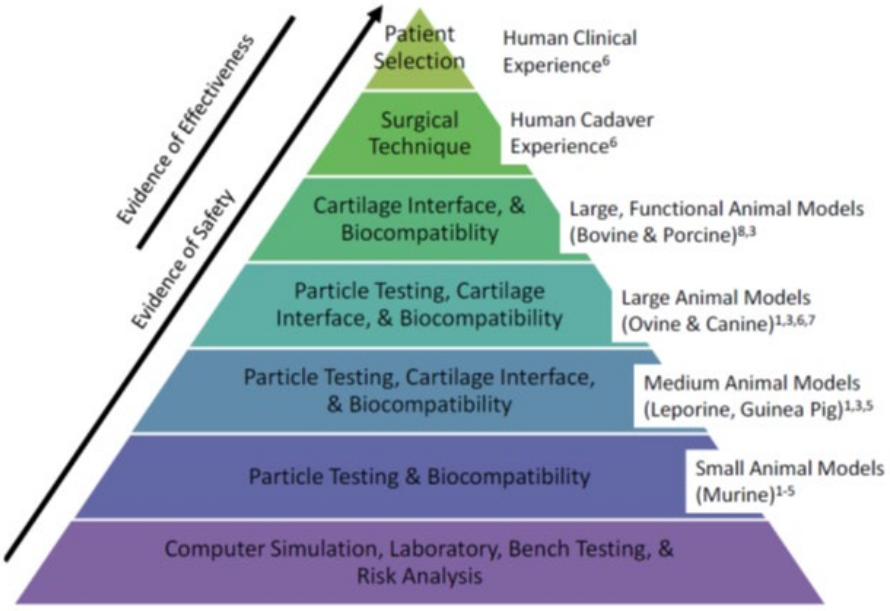
Design parameters of an artificial meniscus, such as geometry, size, and materials, affect the contact area between it and the femur and tibia. The contact pressure values and distribution maps on the tibial plateau may be studied both experimentally and computationally while under compression and during typical gait cycles. The results were used during the implant development process to help confirm the final implant design. A peer review publication[57] documented the results of this study.

Summary of All Pre-Clinical Testing

[56]Elsner JJ, Portnoy S, Guilak F, Shterling A, Linder-Ganz E. (2010) MRI-based characterization of bone anatomy in the human knee for size matching of a medial meniscal implant. J Biomech Eng;132.
[57]Linder-Ganz E, Elsner JJ, Danino A, Guilak F, and Shterling A. A novel quantitative approach for evaluating contact mechanics of meniscal replacements. J Biomech. Eng 2010; 132(2): 024501.

All the above pre-clinical testing, as well as animal model testing of Bionate 80A, built a foundation of proof leading to human clinical experience. The pyramid below is a pictorial summary of data from the lab bench testing and finite element studies, to progressively higher animal models, then to the feasibility, pilot, control evaluation, then two pivotal IDE studies in humans.

Table 2 Summary of NUsurface Pre-Clinical Testing



NUsurface® Meniscus Implant Burden of Proof

1. PTG Master File (Bionate®)- See Attachment 9
2. PTG-DSM Master File (Dyneema Purity®)- See Attachment 9
3. TriboFit® PCU Testing- See Previous Submissions (referenced in Application)
4. Schwarz and Smith et al.- See Previous Submissions and Attachment 11
5. NAMSA Testing- See Previous Submissions and Attachment 12
6. AIC (Sponsor) Testing- See Attachment 21
7. Carbone et al. and Field (2012)- See Attachments 11 and 14
8. Pöllänen et al., University of Kuopio- See Attachments 16 and 17

More details of non-clinical testing of the NUsurface meniscus implant are provided in Appendix F. Peer reviewed presentations and publications of the NUsurface implant are provided in Appendix G.

9 Summary of the IDE Study

9.1 Investigation Plan

9.1.1 Inclusion/Exclusion Criteria

Eight inclusion criteria and 35 exclusion criteria were used to identify the patient population in the two IDE studies that comprise MERCURY. The main eligibility criteria are listed in Table 3. The complete eligibility criteria are provided in the protocol included in Appendix A.

Table 3: MERCURY Principal Eligibility Criteria

Inclusion criteria	Exclusion criteria
• have a previous medial meniscectomy as confirmed by diagnostic MRI and subject history at least 6 months prior to the start of study treatment, • have a pain score of 75 or less on the KOOS (Knee injury Osteoarthritis Outcome Score) pain scale, with 100 being normal, • have ≥ 2 mm intact meniscal rim and is capable of receiving a NUsurface device, if used, • have a subject age between age 30 and 75 at the time of the start of study treatment, • enter subjects willing and able to follow the study protocol • have subjects willing to receive, if used, non-surgical care therapy • be able to read and understand English	• have 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), • have a varus/valgus knee deformity > 5 degrees, • have 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), • have patellar compartment pain and/or patellar articular cartilage damage greater than Grade II, • have an ACL reconstruction performed less than 9 months before implanting the NUsurface® implant, • be excessively obese (BMI > 32.5)

9.1.2 Study Design

The MERCURY trial was designed to evaluate the safety and efficacy of the NUsurface Meniscus Implant in patients with knee pain following failed medial compartment meniscectomy. The MERCURY study tested the hypothesis that the NUsurface Meniscus Implant would be superior to the standard of care for this patient population is multimodal non-operative therapy, in patients who have failed one or more previous meniscectomy procedures.

To standardize this control Group treatment across all sites, a treatment algorithm was established based on literature and input from clinicians in the field. Each patient randomized to the control treatment began care with a list of pharmacological and non-surgical treatment options. These treatment options were administered throughout the length of the study. The investigator had the flexibility to start and/or stop these acceptable treatments at his or her discretion.

Therapy allowed:

- Injections with corticosteroids
- Injections with Hyaluronic Acid (HA)

- 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 clinical data for MERCURY are a combination of outcomes from two IDE studies; (b) (4), known as VENUS, and (b) (4), known as SUN. VENUS enrolled 127 randomized subjects (61 in the NUsurface treatment arm and 66 in the control group) and the single-arm SUN enrolled 114 subjects treated with the NUsurface. The statistical analysis plan for combining the studies was reviewed by FDA and approved. Both IDE studies used identical devices implanted with the same surgical technique. Both studies had a common set of inclusion and exclusion criteria and evaluated study subjects with the same outcome instruments at the same time points. Written informed consent was obtained from all subjects. Patients were treated at 20 sites geographically distributed throughout the United States, which are listed below. The subpopulation includes data from 19 clinical sites.

VENUS Trial

SUN Trial

(b) (4), (b) (6)

Five Patient Reported Outcome (PRO) questionnaires were used in the MERCURY study. The validated outcome instrument used to determine the primary endpoint was the Knee Injury and Osteoarthritis Outcome Score, or KOOS[58,59,60,61,62]. KOOS consists of 42 questions divided into 5 subscales measuring pain, function and quality of life. Another validated PRO used in the study

[58] Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003;1:64.

[59] Roos EM. 3 steps to improve reporting and interpretation of patient-reported outcome scores in orthopedic studies. Acta Orthop. 2018;89(1):1-2.

[60] Collins NJ, Prinsen CA, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis Cartilage. 2016;24(8):1317-1329.

[61] Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. Osteoarthritis Cartilage. 2009;17(11):1434-1439.

[62] Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcomes. 2003;1:17.

was the Western Ontario Meniscal Evaluation Tool (WOMET)[63,64]. All 242 subjects completed the PRO questions at pre-specified time points: baseline, 1.5 months, 6 months, 12 months, and 24-months. MRI scans were obtained at baseline, 1.5, 12, and 24-months. First treatment date was January 21, 2015, last treatment date was June 14, 2018, and all subjects were followed for at least 2 years.

The clinical investigation followed the Clinical Investigational Plans (CIP). The MERCURY study collected 5 Subject Reported Outcome (PRO) measurements (KOOS, VAS, WOMET, IKDC, and EQ-5D) for 242 subjects at 5 time points, baseline, 1.5, 6, 12, and 24 months. Please see the table below for the follow-up schedule (Figure 13).

Figure 13. Study Visit Schedule for Subject PRO Assessments and MRI

	Baseline	Visit 1 1.5 Month	Visit 2 6 Month	Visit 3 12 Month	Visit 4 24 Month
MRI	✓	✓		✓	✓
KOOS (Knee injury and Osteoarthritis Outcome Score)	✓	✓	✓	✓	✓
Pain Visual Analog Scale (VAS)	✓	✓	✓	✓	✓
International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form	✓		✓	✓	✓
WOMET	✓	✓	✓	✓	✓
EQ-5D	✓	✓	✓	✓	✓

9.1.3 Primary Objective

The objective of the MERCURY trial was to evaluate the safety and effectiveness of the NUsurface Meniscus Implant in treating the target population. The hypothesis tested was whether surgical implantation of the study device yielded results superior to the standard of care, non-surgical therapy.

[63] Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken).* 2011;63 Suppl 11:S208-228.

[64] Sihvonen R, Jarvela T, Aho H, Jarvinen TL. Validation of the Western Ontario Meniscal Evaluation Tool (WOMET) for patients with a degenerative meniscal tear: a meniscal pathology-specific quality-of-life index. J Bone Joint Surg Am. 2012;94(10):e65.

The 24 month composite primary endpoint included all of the following components:

1. ≥20-point improvement in the KOOS Overall score, the average of the 5 KOOS domains, which includes the Pain domain.
2. ≥20-point improvement in KOOS Pain considered independently
3. Confirmation of the position and condition of the NUsurface device on MRI
4. Absence of protocol-defined secondary surgical interventions that qualified as an automatic failure of study, defined as:
    a. NUsurface subjects who had surgery to remove the device, with or without replacement, for any reason.
    b. Control group subjects who underwent any surgical procedure on the medial compartment of the index knee.

9.1.4 Secondary Objectives

In total, 19 hierarchical ranked secondary outcomes for superiority were prespecified in the Clinical Investigation Plan (Table 4).

Table 4. Primary and Secondary Outcome Variables

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)

9.1.5 Radiographic Observations

Joint-related MRI observations were analyzed during the study period of the first 24 months of therapy for the control and treatment arms. The reviewer was (b) (6), Department of Radiology, University of (b) (4). The following observations were assessed:

- Subchondral bone: presence and patterns of bone marrow edema (BME)
- Synovial proliferation: presence and degree
- Joint Effusion: presence and degree
- MCL sprain pattern: presence and degree
- Medial joint space measurements
- Medial meniscus/implant extrusion measurements
- Cartilage integrity

9.1.6 Randomization and Statistical Analysis Plan

Randomization Process

The randomization process was central and only performed after the patient signed the informed consent. The randomization process used blocks of 4. However, to prevent possible bias, no site personnel knew the size of the randomization blocks.

The (b) (4) pivotal randomized study planned to enroll a total of 124-128 subjects using a 1:1 randomization ratio. The final enrollment was 127 (61 NUsurface cases and 66 non-surgical controls). Added to the (b) (4) randomized study were the clinical data from the single arm 115 subject, (b) (4) IDE for a total of 176 NUsurface patients and 66 Non-Surgical controls for a final investigational to non-surgical control ratio of 2.7 to 1.

Blinding

Patients and surgeons could not be blinded about receiving surgical or non-surgical treatment since it was obvious whether the patient had surgery or not. The randomization process worked as intended since the baseline analysis did not find any statistical differences between the two treatment arms of the study in terms of the major patient characteristics such as gender, weight, treated knee side, and baseline pain.

Statistical Methods

Because of the addition of one set of IDE data to another set, the final data needed a propensity adjustment for the PROM data reported. The (b) (4) IDE had a superiority study design using

an alpha spending limit of 0.05. To control and limit the Type 1 error, the primary and secondary endpoints used a rank order hierarchical approach of 20 variables that allowed superiority claims until the superiority in favor of the NUsurface Arm disappeared. The statistical analysis also used a modified intent-to-treat (mITT) method that only used the data of the patients who actually received treatment. A separate Statistical Analysis Plan contains additional details about the data analysis such as how the study would handle missing data.

Hypothesis

The study tested the following hypothesis for superiority of the primary endpoint: two years after treatment, recipients of the NUsurface Meniscus Implant will have a statistically higher (>95% chance) probability of "Overall Success" vs. "Overall Failure" than recipients of the Non-Surgical Standard of Care. The null hypothesis was the converse: two years after treatment, the statistically probability of "Overall Success" will not be greater in NUsurface Meniscus Implant recipients.

Propensity Score Adjustment

The statistical analysis of all outcomes used SAS programming. This clinical reports provides the time course adjusted results of the analyses of the outcome measurement tools used. Propensity score adjustments were created from baseline comparisons of NUsurface to controls. A table describing the basis of propensity score adjustments is below.

Table 5 Basis of Propensity Score Adjustments

	All Patients		Subpopulation	
Variables used in Propensity Score (Control vs NUsurface) Logistic Regression (with p values)				
Intervention: Physical therapy	<0.001		.	
Intervention: Glucos/Chond	0.002		.	
Current: Chronic problem	0.002		.	
Prior: Cartilage surgery	0.007		0.019	
Intervention: Analgesics	0.017		.	
Usual activities	0.097		.	
Sports/Recreation baseline category	.		.	
Intervention: Steroid injection	.		0.034	
Current: Subacute problem	.		.	
Binary Propensity Score Category				
	Control	**NUsurface**	**Control**	**NUsurface**
Low propensity score	15	105	11	44
High propensity score	51	71	24	30

Patient (b) (6) (infection) was dropped from all Evaluability groups.

Initially, all variables with statistically significant p values (p<0.05) 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.

9.2 IDE Supplements: Changes to the Investigation Plan

In March 2019, in VENUS IDE Supplement (b) (4) the agency agreed with the revised Statistical Analysis Plan and proposed propensity analysis to adjust the combined studies (b) (4) before any 24-month data was obtained.

9.3 Protocol Deviations

No protocol deviations jeopardized subject health. All protocol deviations were monitored annually by an independent Data Safety Monitoring Board. All protocol deviations were reported to the FDA though annual study reports.

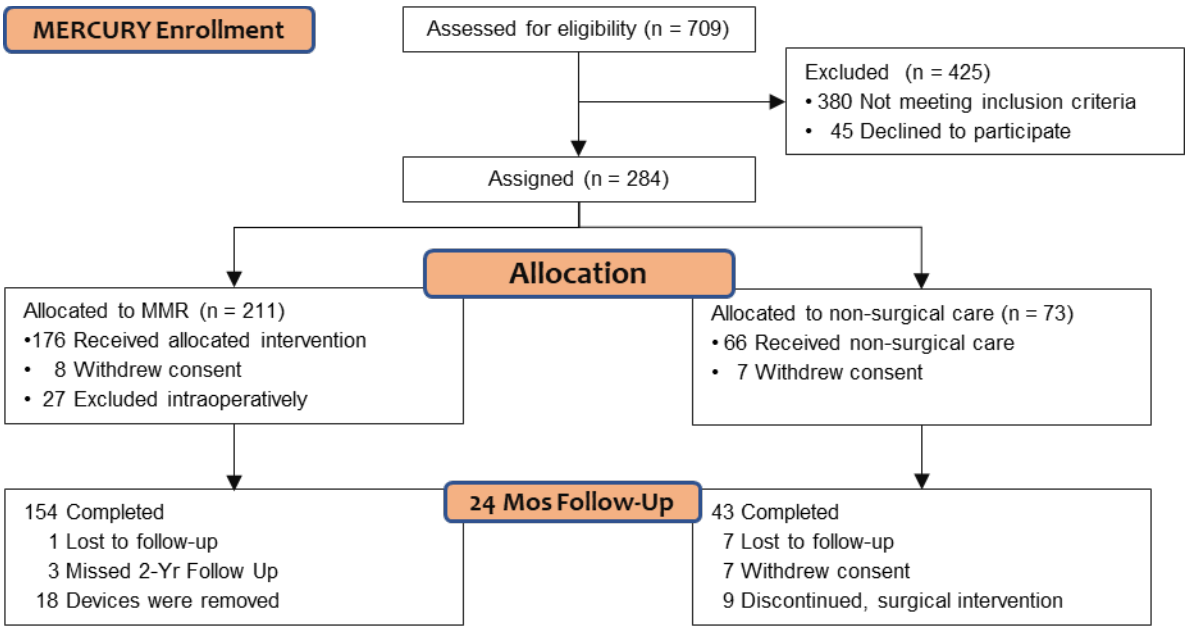
10 Summary of Clinical Data included in the Total Population

10.1 Patient Population

10.1.1 Patient Accounting

Figure 14 describes the patient accounting for the MERCURY study.

Figure 14



10.1.2 Patient Demographics / Baseline Characteristics

Characteristics of the MERCURY subjects are summarized in Table 6.

Table 6. ***Baseline Demographic Characteristics: Mercury***

	Measure	*NUsurface n= 176*	*Control n= 66*	*p*
1	Age - yr	49.78 ±10.06	49.82 ±10.27	0.9814
2	Body Mass Index (BMI)	27.04 ±3.13	26.83 ±3.64	0.6558
3	Male Gender - n (%)	130 (73.9%)	48 (72.7%)	0.8709
4	Left Index Knee - n (%)	89 (50.6%)	31 (47.0%)	0.6662
5	Median (range) months since last meniscectomy	81.34 ±89.68	67.02 ±76.81	0.2519
6	One Previous Partial Meniscectomy - n(%)	123 (69.9%)	46 (69.7%)	1.0000
7	Two or More Previous Partial Meniscectomies - n(%)	53 (30.1%)	20 (30.3%)	1.0000
8	KOOS Subscore - Pain	52.95 ±12.97	54.17 ±15.57	0.5400
9	KOOS Subscore - Symptoms	61.32 ±16.54	62.55 ±16.54	0.6065
10	KOOS Subscore - ADL	62.60 ±17.30	65.26 ±19.88	0.3081
11	KOOS Subscore - Sports and Recreation	32.16 ±21.50	39.28 ±21.65	**0.0229**
12	KOOS Subscore - Quality of Life	25.67 ±16.47	30.02 ±13.53	0.0568
13	KOOS Overall Score	46.94 ±13.66	50.26 ±14.29	0.0983
14	WOMET Norm Score	34.71 ±16.64	39.05 ±16.58	0.0711
15	IKDC Score	40.64 ±12.42	45.43 ±13.97	**0.0106**
17	Ethnicity: Hispanic or Latino	5 (2.8%)	2 (3.0%)	.
	Ethnicity: Not Hispanic or Latino	171 (97.2%)	64 (97.0%)	.
18	Race: American Indian or Alaskan Native	2 (1.1%)	0 (0.0%)	.
	Race: Asian	1 (0.6%)	1 (1.5%)	.
	Race: Asian,Native Hawaiian or Other Pacific Islander	1 (0.6%)	0 (0.0%)	.
	Race: Asian,White	0 (0.0%)	1 (1.5%)	.
	Race: Black or African American	2 (1.1%)	3 (4.5%)	.
	Race: White	170 (96.6%)	61 (92.4%)	.
19	Education: Graduated from college	70 (39.8%)	26 (39.4%)	.
	Education: Graduated from high school	14 (8.0%)	8 (12.1%)	.
	Education: Postgraduate school or degree	33 (18.8%)	20 (30.3%)	.
	Education: Some college	59 (33.5%)	12 (18.2%)	.
20	Activity: High competitive sports	1 (0.6%)	1 (1.5%)	.
	Activity: No athletic activities	33 (18.8%)	10 (15.2%)	.
	Activity: Occasional athletic activities	97 (55.1%)	30 (45.5%)	.
	Activity: Well-trained and frequent athletic activities	45 (25.6%)	25 (37.9%)	.

10.2 Primary Endpoint (Overall Success) and Analysis—Overall Population

Although the overall population is no longer the indicated population for use of the device, results are presented in this section for the overall group to provide context for the analysis in the indicated population in Section 11.

In the overall population of the MERCURY study the NUsurface met its primary endpoint (Table 7). The overall success rate at 24- months, using the dichotomized propensity scores to combine the studies was 43% in the NUsurface group compared to 23% in the control group. FDA recommended in IDE supplement (b) (4) that the propensity analysis at baseline should determine the adjustment for the primary

analysis. These rates are similar to the unadjusted and SAP-adjusted rates. In all three analyses, the superiority of the NUsurface was demonstrated to be statistically significant beginning at 6 months, and maintained at both 12, and 24-month timepoints.

Table 7: MERCURY Primary Endpoint Calculations

Baseline KOOS Sports/Recreation	Success Rates	p value
Unadjusted	Control = 12/52 = 23.1% NUsurface = 77/172 = 44.8%	**p = 0.006**
Adjusted According to (b) (4) Statistical Analysis Plan (Per Protocol)	Control = 12/52 → 23.6% NUsurface= 77/172 → 44.3%	**p = 0.010**
Adjusted Using Dichotomized Propensity Score to Account for Prior Physical Therapy and Cartilage Surgery	Control = 12/52 → 23.3% NUsurface = 77/172 →43.1%	**p = 0.013**

10.3 Secondary Endpoints

The NUsurface met an additional 17 secondary endpoints (Table 8). Description of each patient reported outcome measure is provided in Appendix E.

- NUsurface was superior on the PRO questionnaires KOOS, VAS and EQ-5D.
- NUsurface was superior on the subjective IKDC-SKEF knee form.
- NUsurface subjects achieved statistically significant superiority over the control group in secondary endpoints as early as at 6 months.
- There was a consistent duration of benefit on the KOOS, VAS, IKDC-SKEF, and EQ-5D at the 6-month, 12-month, and 24-month follow-up visits.

Table 8: Summary of MERCURY Primary and Secondary Endpoints—NUsurface vs. Control

Hierarchical Rank Order	Endpoint Description in the Statistical Analysis Plan	P-Value
1	**Overall Success at 24-Months**	0.013
2	24-Month VAS vs Baseline	0.002
3	24-Month MRI vs Baseline of Cartilage Condition In Medial Compartment	<0.001
4	24-Month IKDC SKEF Score vs Baseline	<0.001
5	24-Month QALY Score vs Baseline (using EQ-5D)	0.028
6	24-Month KOOS Pain	<0.001
7	24-Month KOOS Overall	0.003
8	12-Month KOOS Pain	<0.001
9	12-Month KOOS Pain vs Baseline	0.001
10	12-Month VAS vs Baseline	<0.001
11	12-Month KOOS Overall vs Baseline	<0.001
12	12-Month MRI vs Baseline Cartilage Thickness at Center of Medial Tibial Plateau	N/A*
13	12-Month IKDC SKEF Score vs Baseline	<0.001
14	12-Month QALY Score vs Baseline (using EQ-5D)	0.012
15	24-Month Return to Work	N/A*
16	6-Month KOOS Pain	<0.001
17	6-Month VAS vs Baseline	<0.001
18	6-Month IKDC SKEF Score vs Baseline	<0.001
19	6-Month KOOS Overall	<0.001
20	6-Month QALY Score vs Baseline (using EQ-5D)	0.028

*The 12th variable is a measurement of cartilage thickness at the center of medial tibial plateau, comparing 12-Month MRI scans to baseline. This proved to be technically beyond the capability of MRI scans to provide reliable data and no measurements were possible. Also return to work proved difficult to calculate given the way the data were recorded and no comparison between the two arms was made.

All secondary endpoints were calculated using the same criteria which defined an automatic study failure as used for the primary endpoint. To control and limit the Type 1 error, the primary and secondary endpoints used a rank order hierarchical approach of 20 variables that allowed superiority claims until the superiority in favor of the NUsurface Arm disappeared. All available patients were included.

The PRO components of the primary endpoint are KOOS Pain and KOOS Overall. A 20-point improvement in each was required for a patient to be a success. This threshold was selected because a 10-point improvement is considered minimally detectable, while a 20-point improvement is clinically meaningful[65,66,67,68,69].

[65] Liu JN, Gowd AK, Redondo ML, et al. Establishing Clinically Significant Outcomes After Meniscal Allograft Transplantation. Orthop J Sports Med. 2019;7(1):2325967118818462. Published 2019 Jan 4. doi:10.1177/2325967118818462

[66] Monticone M, Ferrante S, Salvaderi S, Motta L, Cerri C. Responsiveness and minimal important changes for the Knee Injury and Osteoarthritis Outcome Score in subjects undergoing rehabilitation after total knee arthroplasty. Am J Phys Med Rehabil. 2013;92(10):864-870.

[67] Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. J Orthop Surg Res. 2015;10:24.

[68] Collins NJ, Prinsen CA, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis Cartilage. 2016;24(8):1317-1329.

[69] Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003;1:64.

To visualize the magnitude and duration of the NUsurface benefits, KOOS Pain and KOOS Overall improvements are plotted on the following two graphs. Subjects with a permanent device removal or a control with a surgical intervention are excluded from the graph. Subjects with an exchanged NUsurface device are included. As shown in Figure 15, subjects treated with NUsurface achieved a statistically significant and clinically meaningful reduction in pain as early as 6 months, which was sustained through the 24-month follow-up. The advantage of the NUsurface compared to the control in terms of KOOS improvement was also very similar over time from 6 to 24-months.

Figure 15

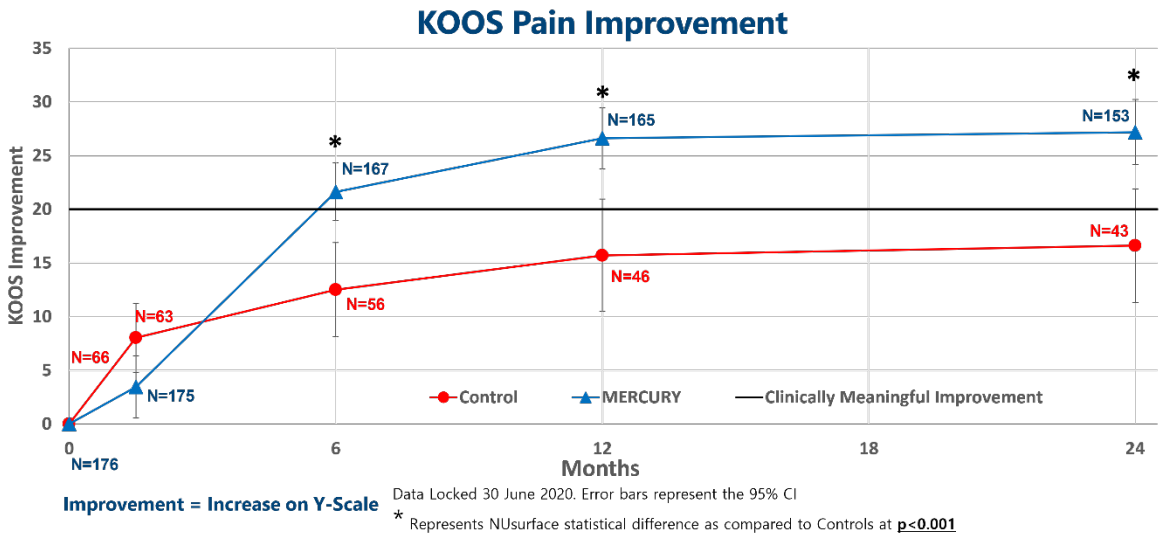
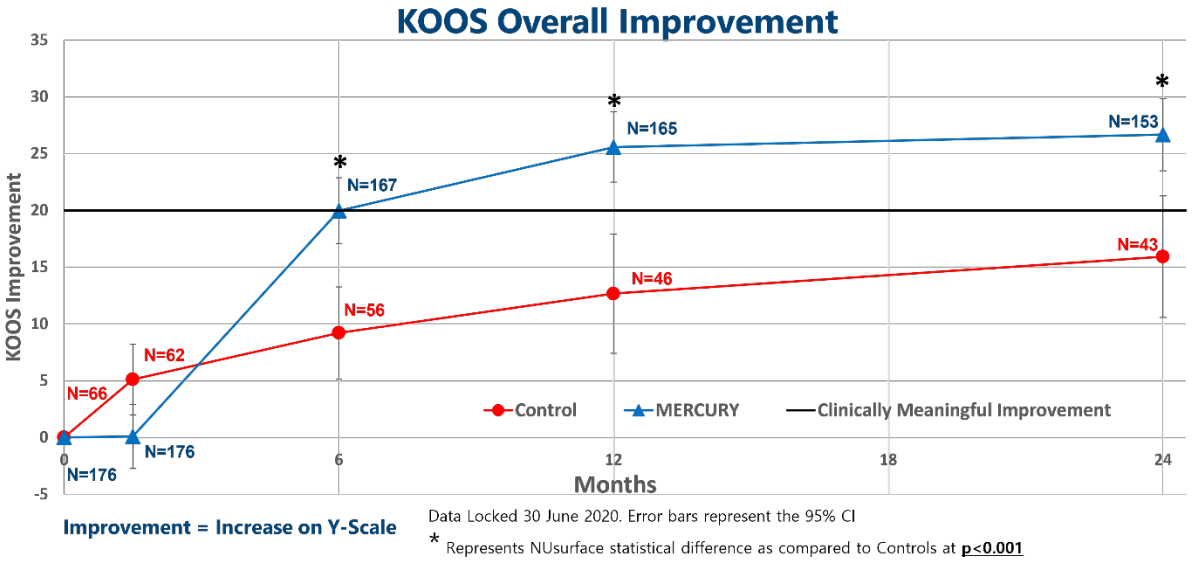


Figure 16 shows the same magnitude and duration measurements of KOOS Overall improvement. All PROMs used in the MERCURY study consistently confirmed that the benefit of NUsurface began as early as 6 months and was maintained throughout the study.

Figure 16



MRIs taken at baseline were compared with those taken at the 24-month follow-up. The condition of the cartilage in the medial compartment was the third pre-specified endpoint of the study. The results showed that subjects in the control group had more than twice the rate of cartilage degeneration on the medial femoral condyle compared to subjects in the NUsurface group. At baseline, full thickness lesions were present in 26% of the control patients and 27% of the NUsurface patients. By 24-months, the number of patients with these lesions had increased to 56% in the control group and decreased to 21% in the NUsurface group. This difference was highly significant ($p<0.001$).

The results of the MERCURY trial confirm the very poor clinical prognosis of patients treated with the current standard of care. Of the 66 patients who were randomized to nonoperative treatment, 14 withdrew from the study or were lost to follow-up. Using the last observations for these 14 subjects, the mean KOOS Pain and KOOS Overall scores were worse than at baseline. The unadjusted success rate would have been reduced to 17% if these control subjects had been included in the analysis.

The MERCURY clinical trial included MRI's at baseline, 6-week, 12-month and 24-month time points and is one of the first studies to document degenerative changes to the knees in subjects treated with non-surgical therapy. A significant finding was a twofold increase in the incidence of full-thickness femoral condyle lesions at two years from baseline in these patients. The incidence of these lesions more than tripled in a subgroup of control subjects who had undergone more than one meniscectomy prior to enrollment.

10.4 Radiological Evaluations

Cartilage loss and degeneration

Progressive degeneration and loss of articular cartilage leads to joint space narrowing, pain and loss of function and is considered an objective clinical endpoint in measuring osteoarthritis of the knee[70]. The correlation between lesions on the femoral condyle and poor outcomes has also been confirmed in clinical studies[71,72,73]. Non-surgical therapy does not alter the natural progression of degenerative changes, and this study demonstrated the significant risk of accelerated knee degeneration in control subjects[74,75,76,77,78,79,80,81,82,83].

The NUsurface has been developed for the treatment of a patient population that suffers from pain and loss of function of the knee joint after surgical resection of a part of their medial meniscus. The rationale for partial meniscectomy is that removal of the source of pain will result in symptom relief or improvement in pain. Typically, the more severe the disease, the more relief or improvement is achieved by removing the pathology yet results from 12 randomized trials confirm that repeat meniscectomies are not effective in patients who have failed one or more previous meniscectomies, and that these surgeries are not statistically better than nonoperative therapy at 2 years.[84] Despite these results, "failed nonoperative treatment" is still considered an indication for surgery, leading to a downward cascade in which the severity of the disease is actually being made worse by the outcome of the surgery to treat it.

[70] Wirth W, Hunter DJ, Nevitt MC, Sharma L, Kwoh CK, Ladel C, Eckstein F. (2017) Predictive and concurrent validity of cartilage thickness change as a marker of knee osteoarthritis progression: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage;25(12):2063-2071. doi:10.1016/j.joca.2017.08.005.

[71] Kijowski R, Woods MA, McGuine TA, Wilson JJ, Graf BK, De Smet AA. Arthroscopic partial meniscectomy: MR imaging for prediction of outcome in middle-aged and elderly patients. *Radiology*. 2011;259(1):203-212. doi:10.1148/radiol.11101392

[72] Hong SY, Han W, Jang J, et al. Prognostic Factors of Mid- to Long-term Clinical Outcomes after Arthroscopic Partial Meniscectomy for Medial Meniscal Tears. *Clin Orthop Surg*. 2022;14(2):227-235. doi:10.4055/cios20185

[73] Sgroi M, Gninka J, Fuchs M, Seitz AM, Reichel H, Kappe T. Chondral lesions at the medial femoral condyle, meniscal degeneration, anterior cruciate ligament insufficiency, and lateral meniscal tears impair the middle-term results after arthroscopic partial meniscectomy. *Knee Surg Sports Traumatol Arthrosc*. 2020;28(11):3488-3496. doi:10.1007/s00167-020-05883-z

[74] Englund M, Guermazi A, Roemer FW, et al. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The Multicenter Osteoarthritis Study. Arthritis Rheum. 2009;60(3):831-839.

[75] Englund M, Niu J, Guermazi A, et al. Effect of meniscal damage on the development of frequent knee pain, aching, or stiffness. Arthritis Rheum. 2007;56(12):4048-4054.

[76] Hart HF, Crossley KM, Felson D, et al. Relation of meniscus pathology to prevalence and worsening of patellofemoral joint osteoarthritis: the Multicenter Osteoarthritis Study. Osteoarthritis Cartilage. 2018;26(7):912-919.

[77] Berthiaume MJ, Raynauld JP, Martel-Pelletier J, et al. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis. 2005;64(4):556-563.

[78] Hunter DJ, Zhang YQ, Niu JB, et al. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis Rheum. 2006;54(3):795-801.

[79] Englund M, Guermazi A, Roemer FW, et al. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The Multicenter Osteoarthritis Study. Arthritis Rheum. 2009;60(3):831-839.

[80] Guermazi A, Eckstein F, Hayashi D, et al. Baseline radiographic osteoarthritis and semi-quantitatively assessed meniscal damage and extrusion and cartilage damage on MRI is related to quantitatively defined cartilage thickness loss in knee osteoarthritis: the Multicenter Osteoarthritis Study. *Osteoarthritis Cartilage*. 2015;23(12):2191-2198. doi:10.1016/j.joca.2015.06.017

[81] Sharma L, Nevitt M, Hochberg M, et al. Clinical significance of worsening versus stable preradiographic MRI lesions in a cohort study of persons at higher risk for knee osteoarthritis. *Ann Rheum Dis*. 2016;75(9):1630-1636. doi:10.1136/annrheumdis-2015-208129

[82] Arno S, Bell CP, Xia D, et al. Relationship between meniscal integrity and risk factors for cartilage degeneration. *Knee*. 2016;23(4):686-691. doi:10.1016/j.knee.2015.11.004.

[83] Kijowski R, Woods MA, McGuine TA, Wilson JJ, Graf BK, De Smet AA. Arthroscopic partial meniscectomy: MR imaging for prediction of outcome in middle-aged and elderly patients. *Radiology*. 2011;259(1):203-212. doi:10.1148/radiol.11101392

[84] Section 23.10, page 3991 of DEN(b) (4) contains all 24 citations associated with these 12 clinical studies.

From a disease model perspective, the most plausible model and theory that explains what causes knee pain in these patients is that a degenerative, dysfunctional meniscus is not an isolated disease entity (meniscopathy) but one of several different entities that form the etiopathogenesis of the degenerative process in osteoarthritis.

Pain in OA is explained by a variety of different entities that interact as a continuum.

1. Bone marrow lesions are well described radiological findings adjacent to degenerative joint diseases and strong evidence from longitudinal studies show that progressive bone marrow lesion development is associated with development of knee pain[85].
2. Synovitis is also a plausible cause for pain since knee synovium, especially in non-arthritic knees, is highly innervated[86]. Synovitis has been associated with progressive OA, development of symptoms, and chemokine expression related to nociceptive stimuli in multiple longitudinal studies[87,88].
3. On a molecular level, degradation of cartilage results in release of damage-associated molecular pattern molecules and alarmins, which in turn is associated with the release of proinflammatory cytokines, such as tumor necrosis factor and interleukins[89,90].
4. These mediators, as with other proinflammatory mediators, have the potential to reduce the excitation threshold in high threshold nociceptive neurons, thus making them more likely to respond to noxious and non-noxious stimuli explaining the most plausible pain-generating process[91,92].

Under this framework, the most common biomechanical factor underlying this process is the increased loading and stress to the femoral condyle of the knee after the meniscus has become damaged or resected by meniscectomy. This is because the meniscus distributes the load across the knee, and when it is removed, this increased load leads to repetitive micro-injury of the subchondral bone and articular cartilage that exceed the ability of the joint to repair the damage.

The capacity for intrinsic repair of damaged articular cartilage is limited, but if the local environment permits, cells that are extrinsic to the cartilage can provide a mechanism for repair.[93] Although the new cartilage they produce, fibrocartilage, is not histologically, biochemically, or biomechanically comparable to normal hyaline articular cartilage, in the presence of physiologic loading it nonetheless permits normal joint function, prevents further deterioration, and, most important, permits the patient to function asymptomatically[21]. Data

[85] Felson D T, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum 2007; 56(9): 2986-92. Fu K, Robbins

[86] MAPP P I. INNERVATION OF THE SYNOVIUM. ANN RHEUM DIS 1995; 54(5): 398- 403.

[87] Ayral X, Pickering E H, Woodworth T G, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis—results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthr Cartil 2005; 13(5): 361-7.

[88] Scanzello C R, McKeon B, Swaim B H, DiCarlo E, Asomugha E U, Kanda V, et al. Synovial inflammation in patients undergoing arthroscopic meniscectomy: molecular characterization and relationship to symptoms. Arthritis Rheum 2011; 63(2): 391-400.

[89] Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory pro- cess in osteoarthritis. Nat Rev Rh

[90] Eitner A, Hofmann G O, Schaible H-G. Mechanisms of osteoarthritic pain: studies in humans and experimental models. Front Mol Neurosci 2017; 10: 349.

[91] Miller R E, Tran P B, Obeidat A M, Raghu P, Ishihara S, Miller R J, et al. The role of peripheral nociceptive neurons in the pathophysiology of osteoarthritis pain. Curr Osteoporos Rep 2015; 13(5): 318-26.

[92] Fu K, Robbins S R, McDougall J J. Osteoarthritis: the genesis of pain. Rheumatology 2018; 57(Suppl_4): iv43-iv50.

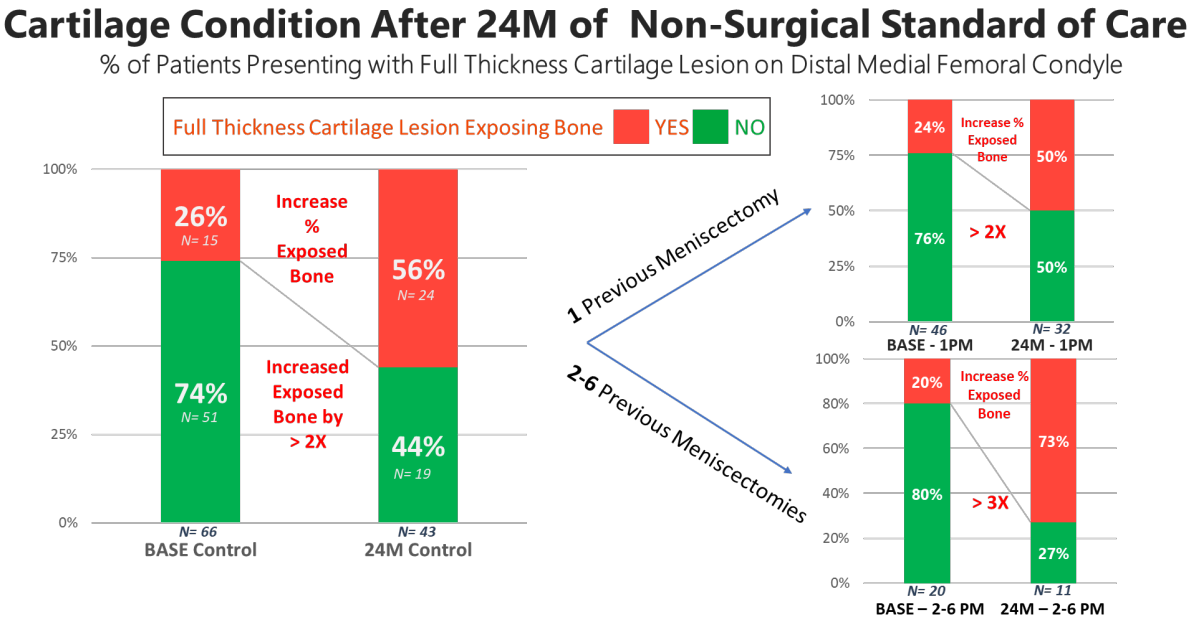
[93] *Radin EL, Burr DB. Hypothesis: joints can heal. Semin Arthritis Rheum 1984;13:293–302.*

indicate that joint healing in OA depends not only on a source of cells but also on normalization of intra-articular stress and movement of the joint.[94]

Cartilage Results

Cartilage lesion results for the control arm are shown in Figure 17. On the left, the increase in cartilage lesions from 26% at baseline to 56% at 24 months can be seen. More information on the increase in full thickness cartilage lesions is evident when these controls subjects are separated into a group of only 1 previous meniscectomy (top right) and more than one previous meniscectomy (bottom right). Control subjects with 1 previous meniscectomy doubled in full thickness lesions at 24 months. Control subjects with more than 1 previous meniscectomy more than tripled in full thickness lesions at 24 months.

Figure 17. Control Arm Cartilage Lesion Results



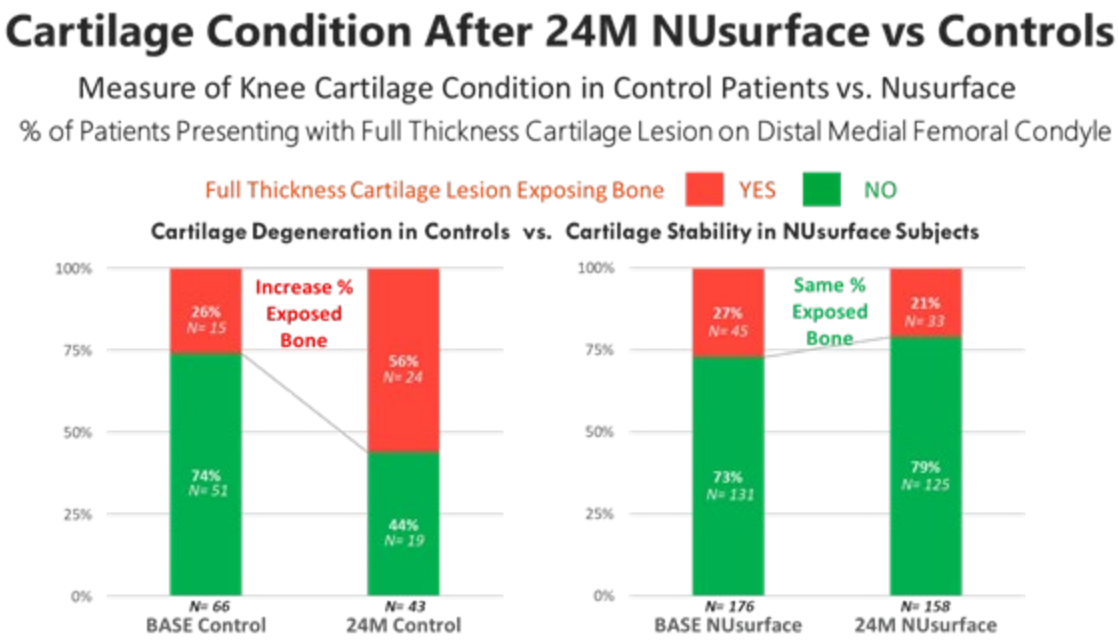
The MERCURY study control arm confirmed a direct correlation between the condition of the femoral cartilage at 24-month follow-up and pain relief and functional recovery. Subjects with a full thickness lesion at 24-month follow-up had a success rate of 16.7% compared to subjects without a full thickness lesions, who had a success rate of 36.8%.

Figure 18 compares the cartilage condition of the control arm to the NUsurface arm. The graph on the left shows the increase of cartilage lesions in controls from baseline (26%) to 24-months (56%). The graph on the right shows there was an improvement in the cartilage of the medial

[94] *Convery FR, Akeson WH, Keown GH. The repair of large osteochondral defects. An experimental study in horses. Clin Orthop Relat Res 1972;82:253–62.*

femoral condyle in the NUsurface group; at baseline, 27% of subjects had thickness lesions in comparison to 21% at 24 months.

Figure 18



Patient level analysis of the radiographic data of the femoral condyle demonstrate that:

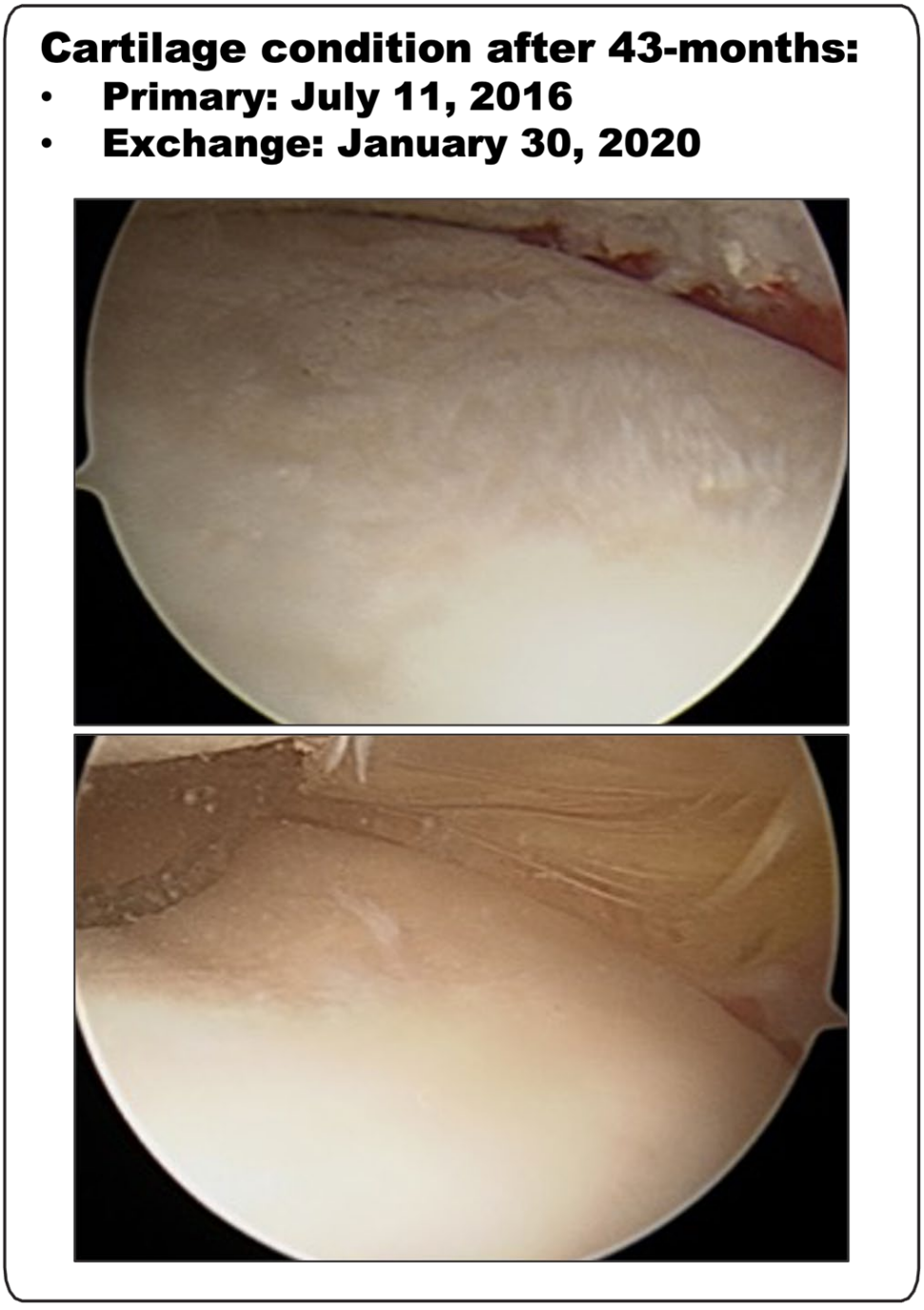
Fewer NUsurface patients experienced cartilage deterioration at 24-months compared to controls, 14.7% vs 43.8% (p=0.001).

- NUsurface preserved the cartilage in patients with full thickness lesions compared to controls, 85.3% vs 56.3% (p = 0.001).
- NUsurface improved the cartilage in patients with full thickness lesions at baseline compared to controls, 62% vs 9% (p=0.002).

These results are consistent with surgeon observations in the clinical trial and with animal data from a study conducted by the sponsor.[11]. As noted above, the Company has been researching the chondroprotective properties of the implant material for over 15 years.

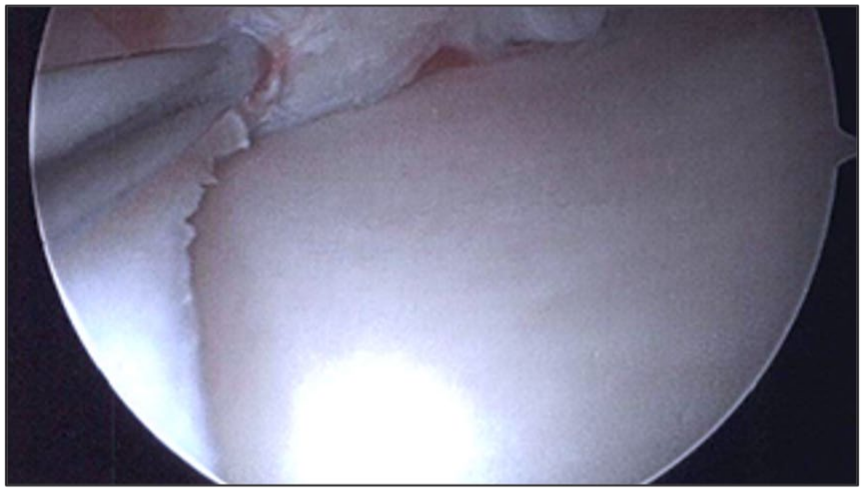
Images 1 & 2 are arthroscopic images of the condition of a subject's medial tibial plateau at baseline and after the 24-month visit. In both cases, at 43 and 53 months with the NUsurface implant the cartilage condition has not deteriorated.

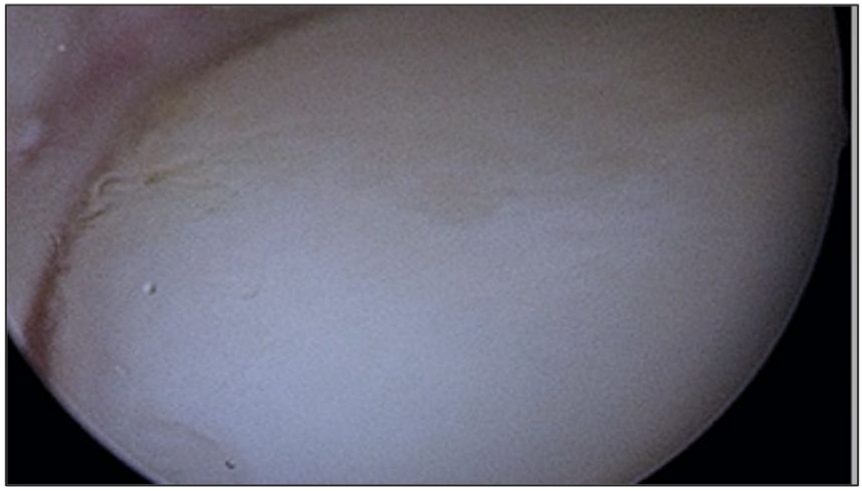
Images 1 & 2 Cartilage condition before implantation and after 43 & 53 months



Cartilage condition after 53-months:

- **Primary: Dec. 1, 2015**
- **Exchange: April 17, 2020**





In addition to the cartilage observations described above, other radiological observations were recorded. Both arms were matched at baseline not only in terms of demographics but also in terms of radiological observations including the MR grading of the cartilage, bone marrow lesions of all types, synovial proliferation, effusion, medial joint space and meniscus extrusion. The only difference at baseline between the two arms was for higher prevalence of MCL sprain in the control arm.

In addition to the cartilage observations, the treatment arm also had less peripheral bone marrow edema signal in the tibia compared to controls. There was no difference between the arms in all of other evaluated observations.

In the NUsurface arm, some findings were consistently seen in the short-term postoperative follow-up visit (1.5 months post-op) which then resolved. These included bone marrow edema (both subchondral bone marrow edema and peripheral bone marrow edema) and medial collateral ligament sprain patterns as well as synovial proliferation and effusion.

The summary of MRI results observed in the MERCURY study are as follows:

- Superiority of the NUsurface Meniscus Implant at 24-months
    - Lower prevalence of full-thickness cartilage defect in the medial femoral condyle
    - Higher rate of regression from full thickness to non-full thickness cartilage defects in the medial femoral condyle
    - Lower prevalence of peripheral BME signal in the medial tibial plateau
    - Increase of the medial joint space
- Inferiority of the NUsurface Meniscus Implant at 24-months
    - No significant results
- No difference between NUsurface device and controls at 24-months
    - Subchondral bone marrow edema-like signal
    - Subchondral cysts
    - Synovial proliferation and joint effusion
    - Medial collateral ligament grade 1 sprain pattern
- Normal transient short-term post- implantation MR-appearance
    - Peripheral and subchondral bone marrow edema-like signal
    - Synovial proliferation and joint effusion
    - MCL sprain pattern

10.5 Safety

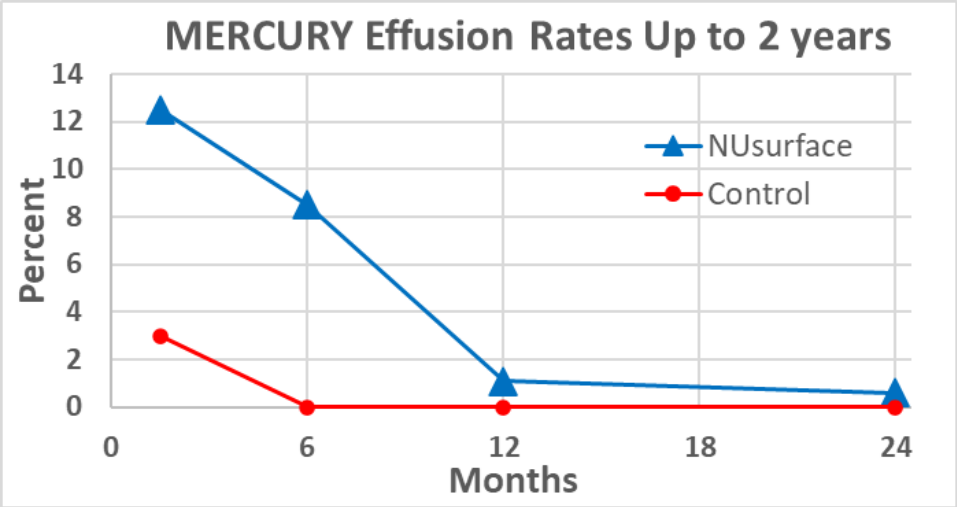
10.5.1 Adverse Events

Beginning with enrollment in 2015, all adverse events in the MERCURY trial were reviewed annually by an independent DSMB. At each annual meeting, the DSMB concluded that all adverse events were of low to moderate risk and recommended that patients should continue to be evaluated according to the study protocol. The Sponsor pre-specified that adverse events in the study would be compared between the two arms and that events that were statistically different would be analyzed.

In the total population, there were 5 types of AEs that occurred at statistically different rates between the two arms.

Four were device-specific: damage, dislocation, dislocation and damage, and noise. The rate of effusion was the only clinical outcome recorded by the investigators for which there was a statistically significant difference between the two arms. Effusion seen in the NUsurface arm resolved without clinical sequelae and the rate of effusion compares favorably to the rates of effusion seen following meniscectomy and arthroscopy as reported in the literature[95,96,97,98,99]. At the 12-month and 24-month follow-up, there was no difference in the rate of effusion between the two groups (Figure 19). The increased frequency of effusion in the NUsurface arm was an effect of a surgical procedure when compared to the non-operative arm.

Figure 19



All adverse events at the index knee are provided in Table 9

[95] Paschos NK, Giotis D, Abuhemoud K, Georgoulis AD. Effectiveness of aspiration in knee joint effusion management: a prospective randomized controlled study. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(1):226-232. doi:10.1007/s00167-013-2379-1

[96] Jawish, R., Najdi, H., Abi Safi, C., & Chameseddine, A. (2015). The effect of intra-articular Tenoxicam on knee effusion after arthroscopy. International Orthopaedics, 39(7), 1423–1426. doi:10.1007/s00264-014-2640-3

[97] Shahid MS, Murphy D, O'Donnell T, et al. A prospective study for evaluation of knee effusion after hip surgery. Irish Medical Journal. 2002 May;95(5):140-141. PMID: 12092694

[98] Akan K, Unay K, Berkem L, Guven M, Poyanli O. (2011) Suction drainage influence on knee effusion following partial meniscectomy with partial fat pad or synovium resection. Acta Orthop Traumatol Turc;45(4):221-224.

[99] Yakin DE, Rogers VP. (1999) Convention instrument vs. laser-assisted arthroscopic meniscectomy. Lasers in Surgery and Medicine;25(5):435-437.

TABLE 9: All Adverse Events at Index Knee or Possibly Related to Treatment (1 of 2)

	Control (N=66)			NUsurface (N=176)			
Body System / Preferred Term	n*	n**	%	n*	n**	%	p
Any Adverse Event							
All	24	21	31.8%	308	131	74.4%	<0.001
CARDIOVASCULAR							
All	0	0	0.0%	6	6	3.4%	0.193
DEEP VEIN THROMBOSIS	0	0	0.0%	6	6	3.4%	0.193
GASTROINTESTINAL							
All	0	0	0.0%	2	2	1.1%	1.000
OTHER GASTROINTESTINAL ILLNESS / DISORDER	0	0	0.0%	2	2	1.1%	1.000
KNEE							
All	23	20	30.3%	296	128	72.7%	<0.001
ADHESIONS (*)	0	0	0.0%	6	6	3.4%	0.193
ARTHROFIBROSIS	0	0	0.0%	3	2	1.1%	1.000
BAKER'S CYST	0	0	0.0%	4	4	2.3%	0.577
DAMAGE	0	0	0.0%	57	50	28.4%	**<0.001**
DEHISCENCE	0	0	0.0%	4	4	2.3%	0.577
DISLOCATION	0	0	0.0%	23	19	10.8%	**0.002**
DISLOCATION AND DAMAGE	0	0	0.0%	18	18	10.2%	**0.004**
EFFUSION (*)	2	2	3.0%	47	37	21.0%	**<0.001**
FAT PAD SYNDROME / PLICA	0	0	0.0%	2	2	1.1%	1.000
FEMORAL OSTEONECROSIS	0	0	0.0%	2	2	1.1%	1.000
INFECTION	0	0	0.0%	2	2	1.1%	1.000
KNEE ABRASION	0	0	0.0%	1	1	0.6%	1.000
KNEE GENERALIZED OSTEOARTHRITIS	2	2	3.0%	1	1	0.6%	0.181
KNEE SYNOVITIS	1	1	1.5%	4	4	2.3%	1.000
LATERAL COLLATERAL LIGAMENT 1° SPRAIN-CHRONIC	0	0	0.0%	1	1	0.6%	1.000
LATERAL MENISCAL TEAR	1	1	1.5%	2	2	1.1%	1.000
LIMITED ROM (*)	0	0	0.0%	8	7	4.0%	0.194
MECHANICAL SYMPTOMS	0	0	0.0%	10	9	5.1%	0.119
MEDIAL MENISCAL TEAR	2	2	3.0%	0	0	0.0%	0.074

File: TADV1.RTF Extracted: 28JUL2020(17:07) Executed: 28JUL2020(17:40).

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

TABLE 9 (Continued): All Adverse Events at Index Knee or Possibly Related to Treatment (2 of 2)

	Control (N=66)			NUsurface (N=176)			
Body System / Preferred Term	n*	n**	%	n*	n**	%	p
KNEE							
NOISE	0	0	0.0%	26	22	12.5%	**0.001**
NON-SPECIFIC KNEE PAIN (*)	9	9	13.6%	33	28	15.9%	0.841
OTHER KNEE INJURY	3	3	4.5%	14	13	7.4%	0.568
PATELLAR TENDINOPATHY	1	1	1.5%	0	0	0.0%	0.273
PATELLAR TENDON TEAR/RUPTURE	0	0	0.0%	1	1	0.6%	1.000
PATELLOFEMORAL PAIN SYNDROME	1	1	1.5%	3	2	1.1%	1.000
POST-TRAUMATIC PATELLOFEMORAL PAIN	0	0	0.0%	2	2	1.1%	1.000
RASH	0	0	0.0%	2	2	1.1%	1.000
ROTATION	0	0	0.0%	15	10	5.7%	**0.066**
ROTATION AND DAMAGE	0	0	0.0%	1	1	0.6%	**1.000**
SAPHENOUS NEUROMA	0	0	0.0%	1	1	0.6%	1.000
STIFFNESS (*)	0	0	0.0%	2	2	1.1%	1.000
SUBLUXATION	0	0	0.0%	1	1	0.6%	1.000
TIBIAL-FEMORAL FUNCTIONAL INSTABILITY	1	1	1.5%	0	0	0.0%	0.273
LOWER LEG							
All	0	0	0.0%	2	2	1.1%	1.000
COMMON PERONEAL NERVE INJURY	0	0	0.0%	2	2	1.1%	1.000
LUMBOSACRAL SPINE							
All	0	0	0.0%	1	1	0.6%	1.000
NON-SPECIFIC LOW BACK PAIN / MECHANICAL PAIN	0	0	0.0%	1	1	0.6%	1.000
THIGH							
All	1	1	1.5%	1	1	0.6%	0.472
HAMSTRING STRAIN	1	1	1.5%	1	1	0.6%	0.472

File: TADV1.RTF Extracted: 28JUL2020(17:07) Executed: 28JUL2020(17:40).
p values determined using the Fisher exact test. n*=Total number of reported events. n**=number of subjects with a reported event.

10.5.2 Additional Surgical Procedures and Surgical Interventions

Secondary surgical procedures in the NUsurface arm are categorized in Table 10 below. Most were attributable to the device being damaged or dislodged. The implant was permanently removed in 10.3% of patients and replaced in 20.6%. Twelve patients (7%) were treated without implant removal or replacement. The device was repositioned in 4 of the patients. In 8 patients, the secondary procedure was a result of trauma or arthroscopic release of adhesions, which is an anticipated complication of any knee procedure.

Table 10 NUsurface Secondary Surgical Interventions by Type

Secondary Surgical Interventions	NUsurface Arm
Secondary Surgical Interventions other than Device Exchanges or Removals	12/175 = 6.9%
Permanently Removed Device	18/175 = 10.3%
Device Exchanges	36/175 = 20.6%

Of the patients in whom the implant was permanently removed, 8 (4.6%) converted to a reconstructive knee procedure, while the remaining 10 (5.5%) continued to function without an implant.

The second surgery rate for the NUsurface may appear high when compared to present-day arthroplasty surgery. However, this rate is in line with non-arthroplasty knee treatments as it is the unfortunate reality that there is no single definitive intervention for meniscal deficiency and subsequent arthritis[100]. Knee pain is a lifelong disease process that requires longitudinal management, with different interventions at different times.

However, the concept that reoperation is synonymous with "failure" is not supported in clinical practice[101,102]. The vast majority of patients experience excellent outcomes following post-MAT (i.e., revision) arthroscopy[103]. Revision arthroscopy or surgical procedures are a relatively low risk option for patients who have already undergone the procedures. The subjects in whom the device was replaced had the same opportunity and the same potential to benefit from the device as they did after their initial surgery. As described further in this document, the overall secondary surgery rate is comparable to other knee preservation procedures, is acceptable to surgeons based on their professional experience, and is acceptable to patients, as confirmed by the 7 patient preference (PPI) surveys or focus groups conducted by the sponsor in over 700 patients.

11 Summary of Clinical Data included in the Subpopulation

The results for the indicated subpopulation are presented below.

11.1 Patient Population

Meniscal extrusion, in which the meniscus is partially or completely displaced from the tibial cartilage surface, is a well-known hallmark of degenerative changes in the knee that signals the development of osteoarthritis. Several studies confirm that a displaced meniscus alters the weight-bearing capacity of the knee joint, leading to cartilage loss and increased bone marrow

[100] Sochacki KR, Varshneya K, Safran MR, et al. Reoperation Rates Following Meniscus Transplantation Using the Truven Database. *Arthroscopy*. 2020;36(10):2731-2735. doi:10.1016/j.arthro.2020.06.031

[101] Spalding T, Getgood A. Defining outcome after meniscal allograft transplantation: Is buying time a valid measure of success?. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(5):1424-1426. doi:10.1007/s00167-016-4128-8

[102] Searle, H., Asopa, V., Coleman, S. *et al.* The results of meniscal allograft transplantation surgery: what is success?. *BMC Musculoskelet Disord* **21**, 159 (2020). https://doi.org/10.1186/s12891-020-3165-0

[103] Frank RM, Cole BJ. Meniscus transplantation. Curr Rev Musculoskelet Med. 2015;8(4):443-450. doi:10.1007/s12178-015-9309-4.

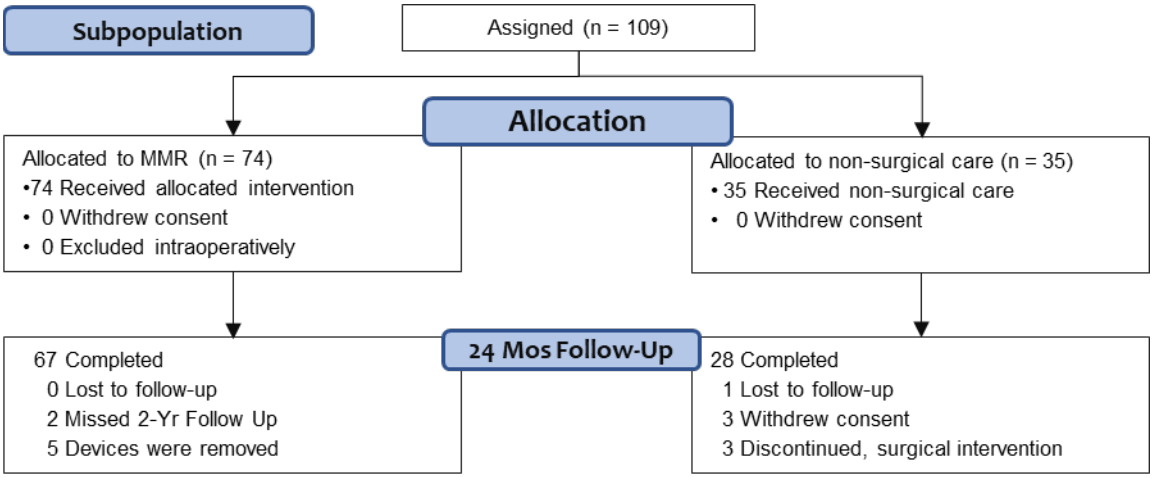
lesions[104]. Data from the MERCURY study showed that patients with more severe disease in the NUsurface group were more likely to undergo secondary surgical procedures including total knee replacement compared to patients with less severe disease.

Twenty-eight NUsurface subjects (16%) had meniscal extrusion of 5mm or greater at baseline. Of these, 22 underwent a device related second surgical procedure during the trial and were automatic study failures (Figure 31). Four of the 28 NUsurface subjects with more severe extrusion (>5mm) underwent arthroplasty, for a rate of 14.3%. Four of the 148 NUsurface subjects with less severe extrusion (<5mm) underwent arthroplasty, a rate of 2.7%. This is a statistically significant difference (p=0.023).

11.1.1 Patient Accounting

Figure 20 describes the patient accounting for the MERCURY subpopulation.

Figure 20



11.1.2 Patient Demographics/Baseline Characteristics

Table 11 gives the characteristics of the 109 subjects in the study population. None of the major baseline variables was statistically different between the two arms.

[104] Pache S, Aman ZS, Kennedy M, Nakama GY, Moatshe G, Ziegler C, LaPrade RF. (2018) Meniscal root tears: current concepts review. Arch Bone Jt Surg;6(4):250-259.

Table 11 Baseline Demographic Characteristics: Subpopulation

	Measure	*NUsurface n= 74*	*Control n= 35*	*p*
1	Age - yr	51.01 ±9.94	50.69 ±9.47	0.8707
2	Body Mass Index (BMI)	26.86 ±2.70	27.01 ±3.88	0.8278
3	Male Gender - n (%)	61 (82.4%)	28 (80.0%)	0.7941
4	Left Index Knee - n (%)	40 (54.1%)	14 (40.0%)	0.2191
5	Median (range) months since last meniscectomy	86.82 ±90.31	58.77 ±80.61	0.1204
6	Two or More Previous Partial Meniscectomies - n(%)	17 (23.0%)	12 (34.3%)	0.2488
7	KOOS Subscore - Pain	54.17 ±12.77	55.40 ±15.71	0.6642
8	KOOS Subscore - Symptoms	62.97 ±15.88	62.14 ±16.39	0.8029
9	KOOS Subscore - ADL	64.61 ±17.42	67.27 ±18.48	0.4663
10	KOOS Subscore - Sports and Recreation	35.95 ±22.46	41.21 ±22.49	0.2557
11	KOOS Subscore - Quality of Life	27.03 ±17.68	32.14 ±13.82	0.1349
12	KOOS Overall Score	48.94 ±13.68	51.63 ±14.18	0.3454
13	VAS Pain Score	52.35 ±21.15	50.03 ±25.29	0.6165
14	WOMET Norm Score	38.24 ±17.75	39.67 ±17.63	0.6949
15	IKDC Score	42.32 ±13.08	44.75 ±12.58	0.3629
17	Ethnicity: Hispanic or Latino	4 (5.4%)	2 (5.7%)	.
	Ethnicity: Not Hispanic or Latino	70 (94.6%)	33 (94.3%)	.
18	Race: Black or African American	1 (1.4%)	2 (5.7%)	.
	Race: White	73 (98.6%)	33 (94.3%)	.
19	Education: Graduated from college	32 (43.2%)	15 (42.9%)	.
	Education: Graduated from high school	8 (10.8%)	6 (17.1%)	.
	Education: Postgraduate school or degree	11 (14.9%)	9 (25.7%)	.
	Education: Some college	23 (31.1%)	5 (14.3%)	.
20	Activity: High competitive sports	0 (0.0%)	1 (2.9%)	.
	Activity: No athletic activities	14 (18.9%)	5 (14.3%)	.
	Activity: Occasional athletic activities	37 (50.0%)	14 (40.0%)	.
	Activity: Well-trained and frequent athletic activities	23 (31.1%)	15 (42.9%)	.

11.2 Primary Endpoint (Overall Success) and Analysis

Overall Success was the primary variable for both arms and is a combination endpoint based on two KOOS improvements (a double responder), comparing baseline calculations to values at 24 month follow-up. A 20-point minimum benefit improvement in KOOS Pain and KOOS Overall, subject to floor and ceiling thresholds described in the study protocols, were part of the protocol definition for a study Overall Success. To be a success, each subject could not have an Automatic Study Failure (ASF). The two arms of the study had different definitions for an ASF. For the Controls, an ASF was any surgery of the index knee indicating failure of the non-surgical therapy. The FDA defined a NUsurface ASF as ≤ 24-month device removal with or without replacement or surgery for dislocation or rotation without replacement.

The propensity score adjustment, described above, is applied to all benefit PRO data collected in the study and contained in the tables in this report. The following table describes the primary variable, Overall Success, at 24-months. As described in the (b) (4) protocol, the study had a null hypothesis: After 2 years of treatment the probability of Overall Success will not be greater in the NUsurface® Meniscus Implant recipients. Each subject at 2 years was either an Overall Success or an Overall Failure.

Table 12 below describes the Overall Success rate for the subpopulation. At 24-months, the NUsurface arm was statistically superior to the standard of care Control arm at p=0.011. Last observation carried forward (LOCF) to account for missing data analysis is also provided at each timepoint. Again, at all LOCF timepoints, the NUsurface arm was statistically superior at p = 0.003, 0.009, or 0.011.

Table 12 Adjusted Overall Success Rates based on KOOS, and Surgical Failure - Subpopulation

	Control		NUsurface		
Variable	n/N	Percent (adjusted percent)	n/N	Percent (adjusted percent)	p
6 Weeks	2/34	5.9% (5.0%)	6/72	8.3% (8.5%)	0.516
6 Months	6/34	17.6% (17.4%)	26/72	36.1% (36.3%)	0.059
12 Months	5/30	16.7% (16.5%)	33/73	45.2% (45.4%)	**0.010**
24 Months	5/31	16.1% (18.2%)	37/72	51.4% (48.1%)	**0.011**
LOCF 24 Months	5/31	16.1% (18.2%)	37/72	51.4% (48.1%)	**0.011**
LOCF 12-24 Months	5/31	16.1% (18.2%)	38/74	51.4% (48.7%)	**0.009**
LOCF 6-24 Months	5/34	14.7% (16.0%)	38/74	51.4% (48.8%)	**0.003**
LOCF 6Wk-24 Months	5/35	14.3% (15.7%)	38/74	51.4% (48.8%)	**0.003**
For NUsurface patients, surgical failure is defined as device removal, replacement, repositioning, reinsertion or MRI failure.					
p values calculated using logistic regression adjusted for propensity score strata.					
LOCF adds one 24-month patient with a post-24-month visit. Only KOOS scores are carried forward so surgical failures do not change.					

Thus, the statistical analysis of the primary endpoint for the subpopulation rejects the null hypothesis stated in the protocol. The control arm was not superior to the NUsurface arm of the 2-year clinical study.

11.3 Secondary Endpoints

All other variables analysed in the MERCURY clinical trial were secondary. The following tables give the results of these calculations for the subpopulation, after adjusting the data to combine the two IDE studies (Table 13)

Table 13 Primary and Secondary Endpoint Measurements for the MERCURY Subpopulation

Number	Hierarchical Rank Order	Calculated p Value
1	**Overall Success at 24 Months**	0.011
2	24 Month VAS vs Baseline	0.036
3	24 Month MRI vs. Baseline of Cartilage Condition in Medial Compartment	0.006
4	24 Month IKDC SKEF Score vs Baseline	0.003

The first 4 variables were superior in favor of the NUsurface arm. The tables below provide data for the 3 secondary endpoints.

VAS Pain

The Visual Analog Scale (VAS). VAS is a validated measurement tool to assess pain level in a study. The scale uses a 10cm line. One end of the line represents “no pain,” while the other end of the line represents “Pain as bad as it could possibly be”. The subject marks on the line their evaluation of their current level of pain. A lower absolute score is a reduction in pain. This protocol required the VAS Pain be measured at baseline and at 1.5, 6, 12, & 24-months. The results are in Table 14.

Table 14 Secondary Efficacy Variables - VAS pain scores (higher absolute scores=worse)							
	Control			NUsurface			
Variable	**N**	**Mean (adjusted mean)**	**SD**	**N**	**Mean (adjusted mean)**	**SD**	**p**
Adjusted Absolute values – Subpopulation							
Baseline	35	50.0 (49.7)	25.3	74	52.4 (52.5)	21.2	0.552
6 Weeks	34	39.4 (39.0)	25.7	73	38.1 (38.3)	24.9	0.901
6 Months	33	34.6 (33.5)	28.0	72	17.3 (17.8)	17.4	**0.001**
12 Months	28	34.6 (33.5)	31.0	74	20.9 (21.4)	24.6	**0.049**
24 Months	29	29.4 (28.7)	26.2	68	22.5 (23.0)	27.8	0.375
Last visit	35	35.0 (34.0)	28.0	74	22.9 (23.4)	28.1	**0.077**
Adjusted Improvement from baseline - Subpopulation (higher improvement scores=better)							
6 Weeks	34	11.5 (11.6)	25.0	73	14.7 (14.6)	29.7	0.619
6 Months	33	14.0 (14.7)	23.1	72	34.7 (34.4)	25.6	**<0.001**
12 Months	28	9.4 (10.2)	31.7	74	31.5 (31.1)	26.9	**0.002**
24 Months	29	15.7 (15.9)	20.4	68	29.9 (29.7)	30.3	**0.036**
Last visit	35	15.1 (15.6)	20.1	74	29.4 (29.2)	30.7	**0.024**
p values calculated using ANOVA stratified by baseline propensity score strata.							

As can be seen in the table, at baseline the VAS Pain in both arms of the subpopulation are not statistically different (p=0.552). For VAS absolute pain measurements, lower scores mean a subjects report less pain. For VAS pain improvement measurements, data is represented by the magnitude of VAS score reduction. After the start of treatment, the clinical improvement from baseline is statistically significantly in favor of the NUsurface arm at 6 (p=<0.001), 12 (p=0.002), and 24- months (p=0.036).

Cartilage Condition

The cartilage condition of subjects treated with the NUsurface were compared to non-surgical controls at baseline, 12, and 24-months (Table 15). Full thickness cartilage defects were identified using the Outerbridge grading system. All cartilage readings were measured by (b) (6) (b) (6), MD, Department of Radiology, University of (b) (4).

Table 15 Adjusted Secondary Efficacy Variables - Cartilage Defect Rates (Subpopulation)					
	Control		NUsurface		
Variable	**n / N**	**Percent**	**n / N**	**Percent**	**p**
Any Defect in the MFC or MTP					
Baseline	10 / 35	28.6%	22 / 74	29.7%	0.982
6 Weeks	8 / 34	23.5%	26 / 74	35.1%	0.300
12 Months	18 / 29	62.1%	33 / 73	45.2%	0.053
24 Months	20 / 29	69.0%	29 / 63	46.0%	**0.006**
LOCF All	22 / 35	62.9%	34 / 74	45.9%	0.061
LOCF 12/24	21 / 30	70.0%	34 / 74	45.9%	**0.008**
Femoral Defect					
Baseline	10 / 35	28.6%	16 / 74	21.6%	0.359
6 Weeks	8 / 34	23.5%	20 / 74	27.0%	0.544
12 Months	16 / 29	55.2%	19 / 73	26.0%	**0.007**
24 Months	17 / 29	58.6%	16 / 63	25.4%	**<0.001**
LOCF All	19 / 35	54.3%	19 / 74	25.7%	**0.004**
LOCF 12/24	18 / 30	60.0%	19 / 74	25.7%	**<0.001**
Tibial Defect					
Baseline	0 / 35	0.0%	8 / 74	10.8%	0.041
6 Weeks	0 / 34	0.0%	15 / 74	20.3%	0.016
12 Months	4 / 29	13.8%	21 / 73	28.8%	0.241
24 Months	4 / 29	13.8%	18 / 63	28.6%	0.533
LOCF All	4 / 35	11.4%	21 / 74	28.4%	0.177
LOCF 12/24	4 / 30	13.3%	21 / 74	28.4%	0.353
Adjusted p values calculated using the Cochran-Mantel-Haenszel test stratified by Baseline Value.					
LOCF: Last Observation Carried Forward.					

Cartilage defects in the medial compartment were not statistically different at baseline with a p-value of 0.982. At 24-months, the NUsurface arm had statistically fewer cartilage defects in the entire medial compartment (p=0.006). This statistical difference was even stronger in the femoral condyle at both 12-months (p=0.007) and 24-months (p<0.001).

Describe below in the Radiological Evaluations section are additional data of cartilage condition measured with a second and third reader.

IKDC SKEF

The IKDC (International Knee Documentation Committee) includes a demographic form, current health assessment form, Subjective Knee Evaluation Form (SKEF), knee history form, surgical documentation form, and knee examination form. The knee history form and surgical documentation form are only used at baseline. The Subjective Knee Evaluation Form is completed at 6, 12, & 24-months. The results are in Table 16.

Table 16 Secondary Efficacy Variables - IKDC score

	Control			NUsurface			
Variable	**N**	**Mean (adjusted mean)**	**SD**	**N**	**Mean (adjusted mean)**	**SD**	**p**
Adjusted Improvement from baseline - Subpopulation							
6 Months	34	7.1 (7.1)	14.4	70	19.6 (19.6)	20.5	**0.003**
12 Months	27	10.8 (11.2)	19.7	72	21.3 (21.1)	20.4	**0.039**
24 Months	29	8.4 (9.0)	13.0	8	23.4 (23.0)	22.2	**0.003**
Last visit	34	6.3 (7.2)	13.3	3	22.3 (21.8)	22.3	**0.001**

p values calculated using ANOVA stratified by baseline propensity score strata.

As can be seen in the table, for the IKDC post-treatment, the clinical results are statistically significantly ($p \leq 0.039$) in favor of the NUsurface arm at 6, 12 and 24 months in the change from baseline.

Hierarchical Rank Order

The original and final Statistical Analysis Plan contained a hierarchical rank order for superiority tests. Table 17 contains a list of 20 variables and the results for the subpopulation. Ten of a possible 18 secondary measurements were statistically superior, although no claim of superiority will be made for the endpoints after number 4, due to the lack of superiority on the EQ-5D (endpoint 5).

Table 17 Primary and Secondary Endpoint Measurements for the MERCURY Subpopulation

Number	Hierarchical Rank Order	Calculated p Value
1	**Overall Success at 24 Months**	0.011
2	24 Month VAS vs Baseline	0.036
3	24 Month MRI vs. Baseline of Cartilage Condition in Medial Compartment	0.006
4	24 Month IKDC SKEF Score vs Baseline	0.003
5	24 Month QALY Score (using EQ-5D)	0.810
6	24 Month KOOS Pain	0.101
7	24 Month KOOS Overall	0.273
8	12 Month KOOS Pain	0.107
9	12 Month KOOS Pain vs Baseline	0.019
10	12 Month VAS vs Baseline	0.002
11	12 Month KOOS Overall vs Baseline	0.004
12	12 Month MRI vs Baseline Cartilage Thickness at Center of Medial Tibial Plateau	-
13	12 Month IKDC SKEF Score vs Baseline	0.039
14	12 Month QALY Score (using EQ-5D)	0.850
15	24 Month Return to Work	-
16	6 Month KOOS Pain	0.054
17	6 Month VAS vs Baseline	<0.001
18	6 Month IKDC SKEF Score vs Baseline	0.003
19	6 Month KOOS Overall	0.034
20	6 Month QALY Score (using EQ-5D)	0.155

Key: Green box = Significant p–values included in the hierarchical rank order

Orange box = p-values < 0.05 not included in the hierarchical rank order

11.4 Other Evaluations - Confirmatory Study

The radiographic criteria which defined the subpopulation in MERCURY were applied to data from the Multi-Center Trial (MCT) study, a 24-month, single arm clinical trial of NUsurface in 128 subjects from the EU and Israel that began enrollment in 2011.

The MCT study followed clinical protocol 00017 entitled “Treatment of the Medial Meniscus with the NUsurface Meniscus Implant”. Section 21.1 of the 00017 protocol states the purpose of the Multi-Center Trial:

- Demonstrate safety and performance of the study device
- Confirm the sizing and surgical technique

- Demonstrate comparative clinical effectiveness to the literature
- Demonstrate comparative economic benefit to the healthcare system/payors

MCT Study Design and Duration

Seven sites in Europe (one each in Italy, Sweden, The Netherlands, two in Belgium, and two in Germany) and 3 sites in Israel approved the Multi-Center Trial protocol. Before being enrolled in the study, all subjects gave written informed consent to participate. During the period from February 2011 through December 2013, 154 subjects enrolled in the study and 128 received the NUsurface device. Not included in this number are 26 patients in which the surgeons decided intraoperatively not to implant the NUsurface device. As allowed in Section 7.7 of the study protocol, these cases, called bailouts, did not receive the study treatment.

The major inclusion and exclusion criteria for the MCT clinical study are in **Table 18.**

Table 18 *Multi-Center Trial Major Inclusion and Exclusion Criteria.*

Inclusion Criteria	Exclusion Criteria
· have a degenerative and/or torn meniscus and/or previous meniscectomy as confirmed by diagnostic MRI · have a pain score of 75 or less on the KOOS pain scale, with 100 being normal · be in neutral alignment ±5 degrees of the mechanical axis · be between age 35 and 75 at the time of the planned surgery	· have evidence of a Grade IV (Outerbridge) articular cartilage loss on the medial tibial plateau or femoral condyle that could contact the NUsurface® implant · have a varus/valgus knee deformity > 5 degrees · have a knee laxity level of more than ICRS (International Cartilage Research Society) Grade II, 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) · have patellar compartment pain and/or patellar articular cartilage damage greater than Grade II · have an ACL reconstruction performed less than 9 months before implanting the NUsurface® implant · be morbidly obese (BMI [Body Mass Index] >35

Routine radiographic images taken during pre-operative (baseline) screening measured the leg axis alignment and the size of the device prior to surgery. In addition, the surgeon evaluated the MRI scans of the index knee pre-operatively, as did an independent musculoskeletal radiologist.

At each follow-up visit, an exam and evaluation of each patient took place. The recording of any adverse events since the patient's last clinical visit also occurred.

Data were collected at each site according to the schedule in **Table 19** and documented on the Case Report Forms (CRF's). The evaluation means listed in **Table 19** assessed the patient's knee, implant, pain, function, and/or quality of life before, during, and after surgery.

Table 19 Visit schedule for each type of assessment

	Screening	Surgery	Visit 1 1.5 Mo*	Visit 2 6 Mo*	Visit 3 12 Mo*	Visit 4 24 Mo*
X-ray	✓					
MRI	✓		✓		✓	✓
Fluoroscopy		✓				
Physical exam	✓		✓	✓	✓	✓
KOOS	✓		✓	✓	✓	✓
Pain VAS	✓		✓	✓	✓	✓
IKDC	✓			✓	✓	✓
EQ-5D	✓			✓	✓	✓

*Protocol window for 1.5 months = 1-4 months, 6 months = 5-8 months,
12 months =9-17 months, 24 months = 18-30 months.

Study Population

Table 20 contains the baseline demographic information for the 128-patient population who received the NUsurface Meniscus Implant.

Table 20 Demographic information of the patients included in the single arm, prospective, Multi-Center Trial of the NUsurface® Meniscus Implant. The data are either a number or a mean ± 95% Confidence Interval of the mean. Numbers in parentheses are either the minimum-maximum range or a percentage.

Number of patients	128
Age	50.4 ± 1.6 (30-73)
Gender (female / male)	54 (42.2%) / 74 (57.8%)
Index knee (right / left)	63 (49.2%) / 65 (50.8%)
History of previous treatment to index knee: • previous partial meniscectomy: • non-surgical care:	 104 (81.3%) 24 (18.8%)
BMI (Body Mass Index, kg/m^2)	26.7 ± 0.7 (18.8 – 35.1)

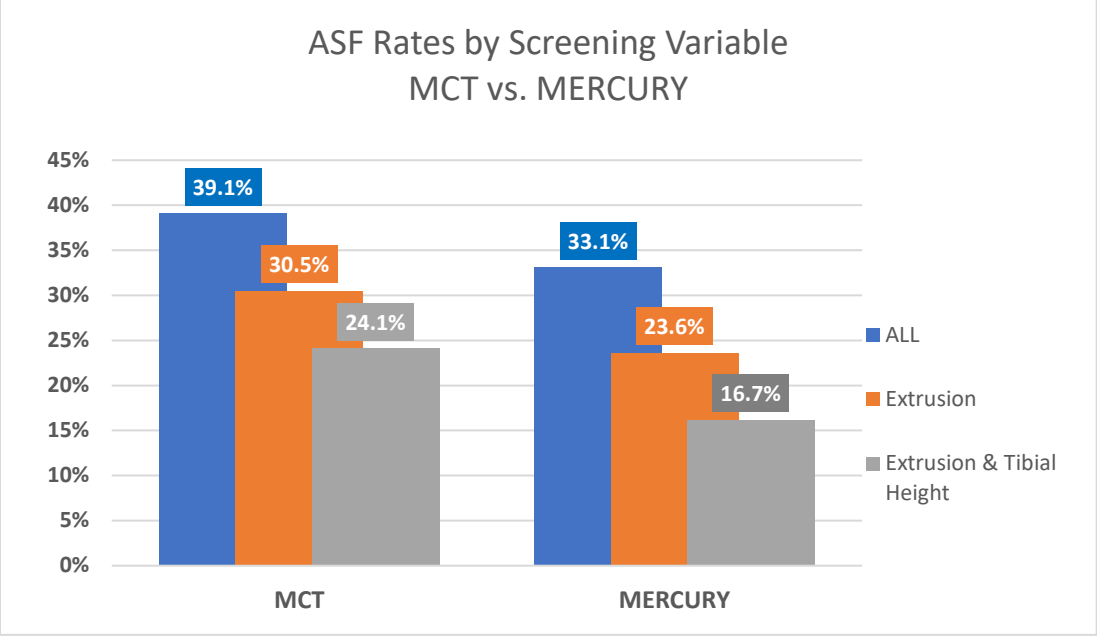
The subjects in both the MERCURY and MCT studies were comparable in age (50 years) and BMI (27). The definition of an ASF used in the MERCURY trial was applied to MCT outcomes and 39.1%

of MCT would have been ASF's based on this criterion.

Results

Removing subjects from the analysis with meniscus extrusion 5mm or greater and subjects with tibial height <11mm reduces the ASF rate from 39.1% to 24.1%. Thus, the two factors that impact secondary surgery rates in MERCURY were confirmed in the MCT study, and the magnitude of impact on the secondary surgery rate was similar in the two studies. Figure 21 compares reduction in the ASF rates of the two studies.

Figure 21: Comparison of MERCURY and MCT ASF Rates



KOOS Pain improvement in the total populations and the subpopulations of MCT and MERCURY at 24-months compared to baseline was similar (Table 21).

Table 21: KOOS Pain Measurements of MCT and MERCURY Subpopulations

	Baseline	24 months	KOOS Point Improvement
MCT Total Population (N=128)	42.1	72.0	30
MERCURY Total Population (N=175)	53.0	80.7	27.7
MCT Subgroup (N=54)	43.4	70.8	27.4
MERCURY Subgroup (N=74)	54.2	78.5	24.3

Conclusions

- NUsurface patients with <5mm of meniscus extrusion have a significantly decreased rate of device related second surgeries compared to subjects with 5mm or greater extrusion ($p<0.001$).
- MCT and MERCURY subjects with 5mm or greater meniscus extrusion had similar rates of secondary procedures; 77% and 79%.
- The average medial tibial spine height was 11mm in MCT and MERCURY subjects.
- KOOS Pain and KOOS Overall averages increased at 24-months in subjects in the subpopulation compared to the total population.
- 46% of subjects in the MCT study and 42% of subjects in the MERCURY study are included in the subpopulation, indicating comparability between the two studies.

11.4.1 Surgeon and Patient Perception

In addition to the clinical data presented in the de novo application, the Sponsor submitted the results of 7 patient perspective and preference studies, one of which included measurements of patients' risk tolerance for a second surgical intervention by 2 years.

For the 7th study, the Sponsor commissioned a professional survey organization to perform the patient perspective study using the final results from the subpopulation. The investigation was well-controlled and collected evidence from 207 respondents who matched the major NUsurface clinical study demographics. Presented with the final minimum benefit and maximum risk data from the MERCURY trial, 100% of these prospective patients said they found the maximum NUsurface risk rate in the subpopulation acceptable.

The result of the 7th study parallels the results of the previous 6 surveys, the results of which are in Table 22. Patient Preference Information is a way to gauge the level of benefit versus risk a patient would consider acceptable and mirrors the decision a patient would make after reading the disclosures in an IFU and discussing options with a clinician. The NUsurface Patient Preference Information surveys included in the de novo petition provides valid evidence that an overwhelming majority of the target patient population believes the benefit outweighs the risk and would proceed with NUsurface surgery, when presented with the results of the MERCURY Trial.

Table 22 Results of 7 Patient Preference Studies

PPI Study Number	Number of Respondents	Proportion Choosing NUsurface Device over No Surgery	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:60-88%

Patient Perspective information may also be obtained from Patient Reported Outcome Measurements (PROM). While Patient Preference and Patient Reported Outcome Measures (PROM) sound similar, they are different in that preference measures the comparisons between alternative treatment options and PROMs measure a report that comes directly from the patient about the status of a patient's health condition[105]. Of the 65 PROM questions answered at various time points of the MERCURY study, 8 dealt with emotional or mental health aspects of health-related quality of life. Four of the 8 were in the Quality of Life section of the KOOS that asked about a patient's awareness, fear, confidence, and difficulty as related to knee functions. Three WOMET questions dealt with fear, worry, and frustration or discouragement. One EQ-5D question dealt with mental anxiety or depression.

This PROM data found multiple cases in which the NUsurface statistically was superior at 24- months compared to controls. The statistical benefits were numerous, of large magnitude, and for long duration, all attributes listed in the FDA's De Novo guidance document as needed to grant a De Novo marketing authorization. The most striking patient perspective data are the KOOS Quality of Life measurements comparing 24-months to baseline, which evaluate a patient's awareness, fear, confidence, and difficulty as related to knee functions. The NUsurface subpopulation was statistically superior to controls at p=0.004.

The surgeons' perspective of the NUsurface device is also relevant. A letter submitted to FDA summarizes the experience and observations of 22 surgeon investigators representing all sites in the MERCURY study. The key section in that letter states:

> *"…patients overwhelmingly choosing to undergo re-implantation with NUsurface is the strongest indicator that this procedure strikes the right balance. We have a great deal of experience discussing the risks of repeat surgery for similar procedures that we now offer*

[105] Best Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/

patients who are not indicated for NUsurface, such as Meniscal Allograft Transplant, ACL reconstruction, meniscus repair and meniscectomy. Patients make informed decisions to accept these risks when they are presented to them."

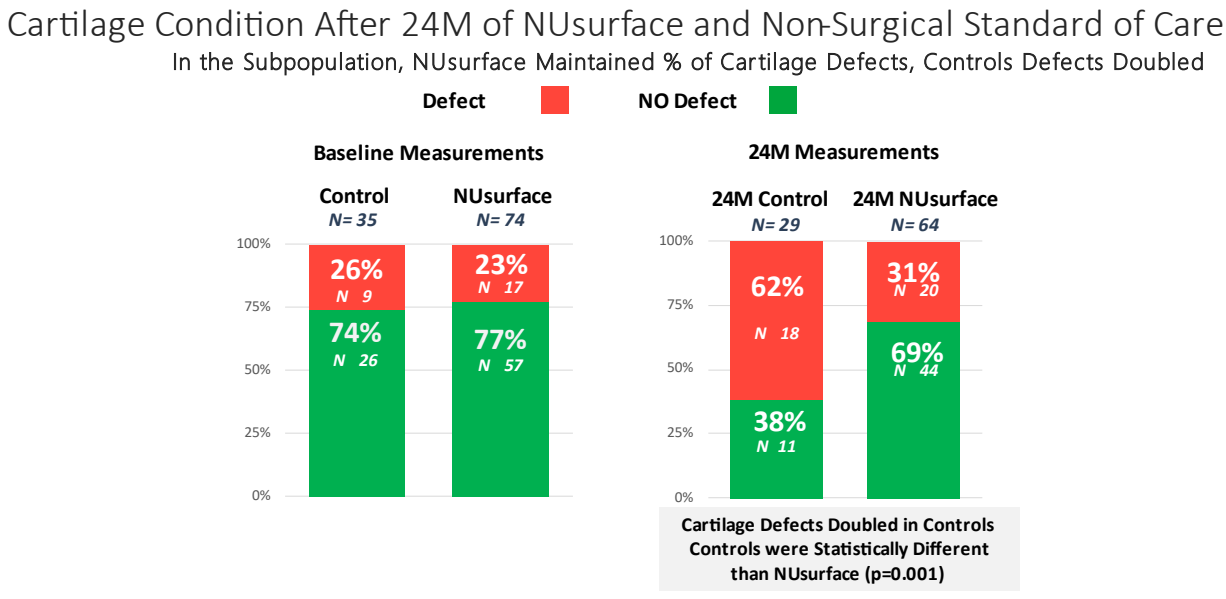
11.5 Radiological Evaluations

To confirm the results of the subpopulation with respect to impact of the NUsurface on cartilage, MRI measurements from two additional readers have been included into the dataset. All MRI readers were blinded to the patient's name, the treating surgeon, and the patient's clinical conditions including pain and function scores as well as the patient's outcome. The second reader is a fellowship trained musculoskeletal radiologist and read all baseline and 24 months MRIs in the subpopulation. In the event a 24-month MRI was not available, a 12-month MRI was read. The results of the 12-month read are only reflected in Last Observation Carried Forward (LOCF) results. The third reader is a licensed orthopedic surgeon and read the MRIs of any disagreements between the first and second readers. Results below reflect the 3 reader MRI analysis. The readers were:

- (b) (6), MD, Department of Radiology, University of (b) (4)
- (b) (6) MD, Department of Radiology, University of (b) (4)
- (b) (6), MD, (b) (4) Medical Center, Hadera Israel

In the NUsurface subpopulation, the rate of defects on either the medial femoral condyle (MFC) or the medial tibial plateau (MTP) was 23% at baseline and 31% at 24 months. Lesions in the control subpopulation increased from 26% at baseline to 62% at 24 months. Controls more than doubled the progression of full thickness lesions at 24 months compared to NUsurface. The difference at 24 months between study groups was statistically different at p=0.001 (Figure 22).

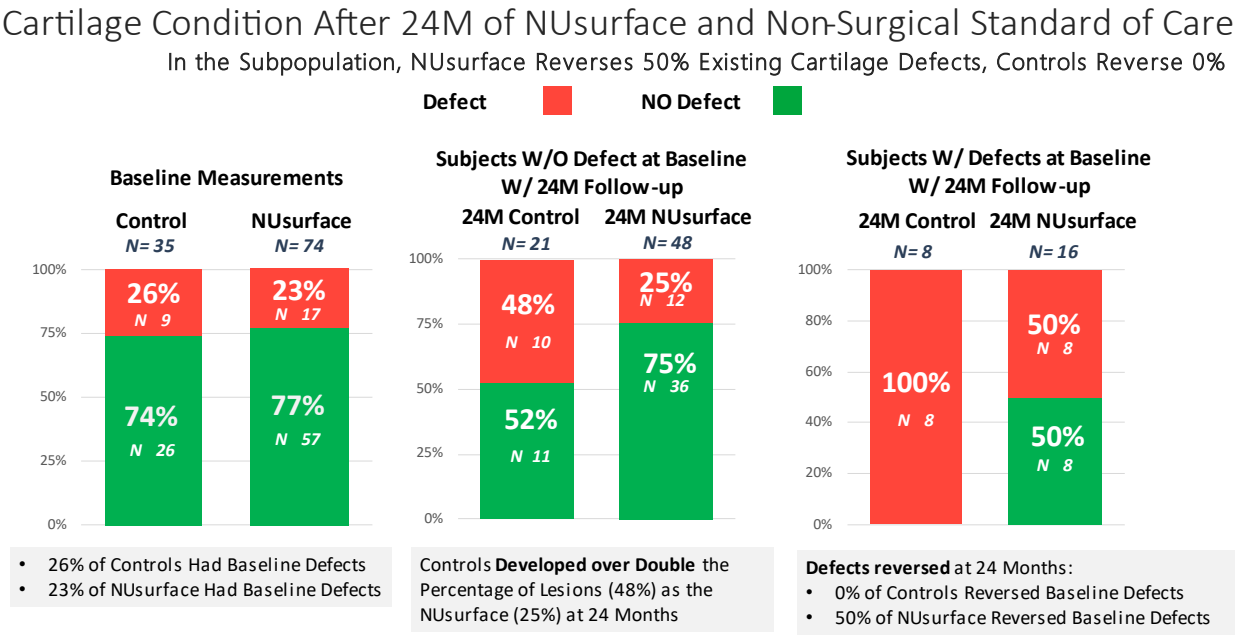
Figure 22



In the subpopulation, full thickness lesion were reversed in 50% of NUsurface subjects and 0% of controls. The bar graphs below illustrate results for the subpopulation, showing the incidence of full thickness lesions on either the MFC or MTP for controls subjects compared to NUsurface subjects (Figure 23):

- Subjects without a lesion at baseline developed cartilage lesions in the control group at double the rate compared to NUsurface, 48% compared 25%.
- At 24-months, 50% of full thickness lesions observed in NUsurface patients at baseline had reversed. This was not seen in any control subject.

Figure 23



The Table 22 provides more details regarding the 24 month and LOCF subpopulation results. Cartilage measurements were analyzed in 3 regions:

1. On either the MFC or the MTP, labeled any defect
2. On the femur
3. On the tibia

Results with 3 MRI readers were similar to the cartilage results with a single reader in that a statistical difference in favor of the NUsurface arm was seen on the femur or on either the femur or tibial (any defect). No statistical difference was observed on the tibia alone.

TABLE 22: Adjusted Secondary Efficacy Variables - Cartilage Defect Rates (Subpopulation subjects)					
	Control		NUsurface		
Variable	**n / N**	**Percent**	**n / N**	**Percent**	**p**
Any Defect					
Baseline	9 / 35	25.7%	17 / 74	23.0%	0.816
24 Months	18 / 29	62.1%	20 / 64	31.3%	**0.001**
LOCF All	19 / 35	54.3%	25 / 74	33.8%	**0.029**
LOCF 12/24	18 / 30	60.0%	25 / 74	33.8%	**0.007**
Femoral Defect					
Baseline	9 / 35	25.7%	12 / 74	16.2%	0.252
24 Months	16 / 29	55.2%	11 / 64	17.2%	**<0.001**
LOCF All	17 / 35	48.6%	14 / 74	18.9%	**0.001**
LOCF 12/24	16 / 30	53.3%	14 / 74	18.9%	**<0.001**
Tibial Defect					
Baseline	0 / 35	0.0%	5 / 74	6.8%	0.096
24 Months	4 / 29	13.8%	11 / 64	17.2%	0.940
LOCF All	4 / 35	11.4%	14 / 74	18.9%	0.490
LOCF 12/24	4 / 30	13.3%	14 / 74	18.9%	0.698
Adjusted p values calculated using the Cochran-Mantel-Haenszel test stratified by Baseline Value.					
LOCF: Last Observation Carried Forward.					

Table 23 Provides a more in-depth analysis of cartilage defects by observing the effect of cartilage lesions at 24-months if the subjects had a baseline defect (initial defect) or did not have a baseline defect (no defect). The Table represents cartilage defects on either the MFC or the MTP. In all 24-month and last observation carried forward measurements, NUsurface subjects reversed lesions at baseline by a range of 50% to 47% (highlighted in bold).

TABLE 23: Secondary Efficacy Variables - Cartilage Defect Rates (Subpopulation subjects any defect)					
	Control		NUsurface		
Variable	**n / N**	**Percent**	**n / N**	**Percent**	**p**
Baseline	9 / 35	25.7%	17 / 74	23.0%	0.812
24 Months	18 / 29	62.1%	20 / 64	31.3%	0.005
Initial defect	8 / 8	100%	**8 / 16**	**50.0%**	
No defect	10 / 21	47.6%	12 / 48	25.0%	
LOCF All	19 / 35	54.3%	25 / 74	33.8%	0.042
Initial defect	9 / 9	100%	**9 / 17**	**52.9%**	
No defect	10 / 26	38.5%	16 / 57	28.1%	
LOCF 12/24	18 / 30	60.0%	25 / 74	33.8%	0.015
Initial defect	8 / 8	100%	**9 / 17**	**52.9%**	
No defect	10 / 22	45.5%	16 / 57	28.1%	
p values calculated using the Cochran-Mantel-Haenszel test stratified by Baseline Value for Post-treatment values.					
LOCF: Last Observation Carried Forward.					

These data support the conclusion that the NUsurface device is protective of the cartilage when compared to the control group, in which there is a significant decline in the condition of the cartilage.

11.6 Safety

11.6.1 Adverse Events

At specified post-treatment visits and annual visits thereafter, the study documented adverse events in the clinical trial. The adverse events were either serious device/procedure-related, serious non-device-related, non-serious device/procedure-related, or non-serious non-device-related adverse events. The Medical Director and an independent Data and Safety Monitoring Board reviewed a comprehensive analysis of the adverse events when all subjects reached 2-year follow-up. All this analysis and review determined the absolute risk of receiving treatment with either the NUsurface device or non-surgical therapy.

There were no unanticipated device-related adverse events. The variety and type of all device-related adverse events observed were of an anticipated type and rate (i.e., expected and not out of the ordinary for the study population) and listed as possible adverse events in the patient informed consent. Removing the NUsurface Meniscus Implant and replacing it proved to be straightforward and without clinical sequelae. This is attributable in part to the minimal amount of tissue removed in preparing the joint. In those patients in whom the device was exchanged,

the average time of surgery was 37 minutes. All adverse events in the index knee are in Table 24.

Table 24 Adverse Events at Index Knee or Possibly Related to Treatment 0-60 months (Subpopulation) (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 24 (continued) Adverse Events at Index Knee or Possibly Related to Treatment 0-60 months (Subpopulation) (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.

11.6.2 Additional Surgical Procedures and Surgical Interventions

The Automatic Study Failure rate in the NUsurface subgroup was 16.7%.

- The implant was permanently removed in 6.9% (N=5).
- The Implant was replaced or repositioned in 9.7% (N=7).

The ASF rate in the control subgroup was 9.7%.

- This was not statistically different from the NUsurface ASF rate of 16.7% (p=0.173, Table 25).

In evaluating the rate of secondary surgery to assess whether it is acceptable, both the benefits of NUsurface and the consequences and burden of the secondary surgery must be considered. The benefits of NUsurface in terms of superiority to the current standard of care have been discussed above, and include both improvement in pain and symptoms as well as cartilage

protection. Because tissue is preserved and the NUsurface does not require fixation, the replacement procedure is simple, short, and does not limit future treatment options.

Table 25. Surgical Failure - Subpopulation Subjects					
	Control		NUsurface		
Variable	**n/N**	**Percent (Adjusted Percent)**	**n/N**	**Percent (Adjusted 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.					

Incidence of Secondary Surgical Procedures

The NUsurface implant was removed or exchanged in 16.7% of subjects in the subpopulation. This can be compared to the rates of secondary procedures in comparable procedures on the knee.

Summary of Comparable Surgical Procedures

Meniscal allograft transplantation, Unispacer, and ACI (Autologous Chondrocyte Implantation) are comparable procedures for subjects with meniscal or chondral deficiencies in the knee. The comparators have been either PMA approved, 510(k) cleared, or determined to be a human tissue product by the FDA. Published literature as well as publicly available IFU safety information show that the second surgery rates of the NUsurface Meniscus Implant are lower than these surgical procedures. Rehabilitation following NUsurface implantation is also shorter. Eligibility criteria, rehabilitation times, and surgery rates are provided in Table 26.

Table 26 Summary of Comparable Knee Preservation Interventions

Knee Preservation Interventions	Eligibility Criteria	Procedure Rehabilitation	24 Month or Earlier Reported Reoperation Rates	Citations
Unispacer (Metal Meniscus)	Skeletally mature	Bracing for 3-4 weeks	56%	Bailie et al. 2008
Meniscal Allograft Transplantation	Younger than 40	Bracing with crutches for 4-6 weeks, Physical Therapy for 3-12 months	58.8%	Sochacki et al. 2020/AAOS
Carticel (Autologous Chondrocyte Implantation)	Younger than 65	Bracing for 6-8 weeks	40%	Carticel IFU
NUsurface (Synthetic Meniscus)	**Skeletally mature**	**Bracing for 1-2 weeks**	**16.7%**	**MERCURY Subpopulation**

Multiple surgeries are common in patients with knee pain resulting from meniscal insufficiency and cartilage degeneration. The rate of repeat meniscectomies and arthroscopic examinations in this patient population reflects the relatively low risks associated with these surgeries and is in keeping with the principle of performing the least invasive intervention necessary to achieve the desired clinical outcome.

Prior to enrollment, all subjects in the MERCURY study had failed between 1 to 6 previous meniscectomy procedures, with approximately 30% of subjects having undergone 2 or more previous meniscectomies. The probability of a secondary surgical intervention is consistent with patients' expectations with regard to their outcomes from knee surgery. While additional surgery is not desirable, the population indicated for NUsurface is better able to assess the risks inherent in an additional surgery if needed, based on their own experience.

Adverse Events and Outcomes of Secondary Surgery in the NUsurface Population

NUsurface was replaced in 7 patients in the subpopulation. KOOS Pain was 20-points or greater in 4 of 6 subjects for whom 24-month outcomes are available. Regarding risk:

- Exchange procedures required minimal or no tissue resection. The medial compartment, having adapted to the implant, accommodated the replacement more readily than after the initial surgery. Because the implant is not anchored, it is easy to remove.
- Adverse events recorded for patients were lower than after the primary surgery.
- Mean surgical time was 37 minutes for the exchange procedure compared to 91 minutes for the initial procedure.
- Study investigators noted that post-operative recovery was also faster than after the primary implantation.

This analysis confirms that the risk of an exchanged device is similar to, or lower than, the risk of the primary procedure.

The Risk of Arthroplasty

The NUsurface subpopulation had similar rates of arthroplasty compared to controls. In the control subpopulation, there was one UNI in 35 subjects for a rate of 2.9%. This compares to 3 NUsurface subjects out of 74, two UNI's and one TKA, for a rate of 4.1%. These rates are not statistically different (p=1.0). There was also one high tibial osteotomy in the control group, increasing the reconstructive surgery rate from 2.9% to 5.7%. In the subpopulation, the reconstructive surgery rate was higher in the control group than in the NUsurface group, although not statistically different (Table 27).

Table 27. Reconstructive Surgery Rates for the MERCURY Subpopulation

Conversion Rate by 24-Months	Control Arm	NUsurface Arm
Total Knee Arthroplasty	0/35 = 0.0%	1/74 = 1.4%
Uni Knee Arthroplasty	1/35 = 2.9%	2/74 = 2.7%
High Tibial Osteotomy	1/35 = 2.9%	0/74 = 0.0%
Total Reconstructions	2/35 = 5.7%	3/74 = 4.1%

In addition to the rate of reconstructive surgery at 24 months, the time to reconstructive surgery was also recorded. The control Uni occurred 162 days after the start of treatment in the study. The average of both control reconstructive surgeries was 192 (+/- 43) days. The 3 NUsurface subjects converted to a reconstructive surgery at an average of 510 (+/- 69) days. On average, NUsurface subjects converted nearly 1 year after controls subjects. The difference in time to reconstructive surgery was statistically different in favor of NUsurface (p=0.008). Degenerative changes documented in the medial compartment also represent a significant additional risk for control patients. Lesions on the medial femoral condyle are directly linked to poor clinical outcomes[106].

In the context of other knee interventions, including metallic meniscal implants most similar to NUsurface, where a 32% conversion to TKA/UKA rate is common, the 4.1% conversion rate to TKA/UKA of the NUsurface device is relatively low (Table 28).

Table 28. Arthroplasty Rates for the Unispacer Metallic Meniscus vs NUsurface

	Unispacer Publications					NUsurface MERCURY
	Bailie et al. 2008	Sisto and Mitchell 2005	Australian National Joint Registry 2005, 2015		Catier 2011	
Number of Devices	18	37	40		17	**74**
Mean Age	49	55	54.7		58	**50.9**
TKA/UKA Rate (%)	33%	32%	33.7%	50.6%	35%	**4.1%**
Mean follow-up in months	19	26	12	36	40	**24**

[106] Sgroi, M, Gninka, J, Fuchs, M, Seitz AM, Reichel H, Kappe T. (2020) Chondral lesions at the medial femoral condyle, meniscal degeneration, anterior cruciate ligament insufficiency, and lateral meniscal tears impair the middle-term results after arthroscopic partial meniscectomy. Knee Surg Sports Traumatol Arthrosc;28(11):3488-3496.

In summary:

- The NUsurface and the control arms of the study were statistically different in 1 adverse event category, effusion.
- All other known or potential adverse event categories were not statistically different between the two arms of the study. The absence of any other statistical differences in any medical area demonstrates the relatively benign nature of the surgical procedure and implant. This finding in a large sample size with 2-year minimum follow-up is confirmatory evidence of the overall safety of the NUsurface Meniscus Implant.
- There were no unanticipated adverse device-related events or high-risk adverse events during the course of the MERCURY clinical study.
- The type and rate of all of the device-related adverse events observed in the 74 NUsurface subjects were anticipated, low-to-moderate risk, and treatable.
- This comprehensive analysis of the adverse event dataset of the MERCURY trial provides reasonable assurance the NUsurface Meniscus Implant is safe.

11.7 Benefit-Risk Considerations

Subject to general and special controls, the probable benefits of implanting the NUsurface implant in patients with medial knee compartment pain outweigh the potential risks.

11.7.1 Summary of Benefits

The MERCURY trial demonstrated that patients can achieve pain relief and recover function with the NUsurface meniscus implant. This patient population is at significant risk of accelerated degeneration of the medial compartment cartilage and continued pain and loss of function. The risk to cartilage was shown in control subjects of the MERCURY study.

The MERCURY trial demonstrated the safety and performance of the NUsurface meniscus implant in a randomized controlled trial. In a subpopulation of the trial, 74 subjects received the NUsurface implant and 35 subjects were treated with non-surgical therapy. The primary endpoint included a 24-month dual responder requirement of ≥20-point KOOS Pain improvement, ≥20-point KOOS Overall, MRI analysis of implant position and condition, and lack of automatic surgical failure. Thus, the primary endpoint incorporated both safety and performance metrics. The unadjusted overall study success rate for the NUsurface arm was 51.4% compared to the control success rate of 16.1%. The NUsurface arm met the statistical criterion for superiority (p=0.011).

The MERCURY study also measured secondary endpoints at 24-months. The NUsurface implant was superior to Controls in the first 3 secondary endpoint 24-month measurements of:

- VAS pain (p=0.036)
- cartilage condition in the medial compartment (p=0.006)
- IKDC SKEF score (p=0.003)

NUsurface was also superior in 7 additional secondary endpoints at 6 and 12-months. Although no claims of superiority will be made, superiority at timepoints before 24-months provide evidence of the duration of the benefit of NUsurface.

The MERCURY study also measured the magnitude of the treatment benefit. A 20-point change in the KOOS scale is considered clinically meaningful. The success rate in the NUsurface arm was nearly three times greater than the success rate in the control arm. 83% of subjects in the NUsurface arm had some level of improvement in either KOOS Pain or KOOS Overall at 24-months. Mean improvements from baseline to 24-months was:

- 112% in KOOS Quality of life (26.6 at Baseline vs. 56.4 at 24-months)
- 71% in KOOS Sports and Recreation (35.5 at Baseline vs. 60.8 at 24-months)
- 44% in KOOS Overall (48.5 at Baseline vs. 69.9 at 24-months)
- 43% in KOOS Pain (53.7 at Baseline vs. 76.6 at 24-months)

The MERCURY trial demonstrated that the NUsurface implant provides statistically superior improvements in pain relief, function recovery, and quality of life compared to non-surgical therapy at 6, 12, and 24-months.

Although the subpopulation for which the device is indicated was identified post hoc, this is mitigated by two key considerations: (1) the study also met its prespecified endpoints in the overall population; and (2) the improvement in outcomes as a result excluding from the analysis patients at higher risk of second surgeries was confirmed in a separate population of patients from a well controlled study outside the United States.

This conclusion is also supported by nonclinical testing demonstrating positive effects on cartilage and both clinical and commercial experience outside the United States, where the product has been CE marked since 2008.

11.7.2 Summary of Risks

Risks in the Subpopulation

Adverse events in the NUsurface arm were all anticipated and consistent with other knee interventions in similar populations; there were no unanticipated adverse events in the MERCURY study. The rate of effusion was statistically different between the NUsurface and controls, the only non-device specific adverse event in which there was a difference between the two arms. This difference disappeared after 6-months follow-up. In the control group, progressive degeneration of the cartilage places patients at a high risk of arthroplasty or reconstructive surgery at an age that then puts them at an increased risk of revision surgery.

The NUsurface implant was removed or exchanged in 16.7% of subjects in the subpopulation. There were no long-term sequelae as a consequence of removing the device or exchanging it. Exchanging the device is either reversible, in the case of an implant exchange, or treatable in the case of an implant removal. Removal or exchange of the NUsurface implant is straight forward. A small incision is required to retrieve it. Some additional preparation to the medial

compartment may be needed if the device is exchanged. However, surgical time is one third that of the initial surgery and rehabilitation is faster than the original surgery.

The 16.7% reoperation rate for NUsurface was not statistically different than the 9.7% operation rate in the control arm (p=0.173). The reconstructive surgery rate of 4.1% in the NUsurface arm not statistically different than the 5.7% in the control arm (p=0.655). The average time to a reconstructive surgery was 11 months earlier in the control arm compared to the NUsurface arm. Measured against comparable knee surgeries, the NUsurface arm reoperation rate of 16.7% was well below the 56% reoperation rate for the metal meniscus, 58.8% rate for meniscal allograft, and 40% rate for autologous chondrocyte implantation[107,108,109,110,111,112,113].

Results from surveys of over 700 patients with knee pain conclude that patients understand the value of the NUsurface treatment and are willing to accept the risks of this treatment, including the potential for reoperation, to achieve the pain relief and function recovery benefit, including overall quality of life.

11.7.3 Benefit-Risk Summary and Conclusions

Data from the MERCURY trial support a positive benefit-risk assessment of the NUsurface Meniscus implant. Patients eligible for the NUsurface have a critical unmet medical need for effective "bridging" treatments between non-operative management and reconstructive knee surgery or arthroplasty, that alleviate pain and functional limitations in patients with symptomatic post-meniscectomy knees. This current gap in the continuum of care has led to the current trend[114] to perform knee replacement procedures in ever younger patients that is driven by patient demand and the promise shown by the short-term outcomes in the first few years after surgery[115,116,117]. Current estimates predict that by 2030 over 50% of knee

[107] Catier C, Turcat M, Jacquel A, Baulot E. The Unispacer unicompartmental knee implant: its outcomes in medial compartment knee osteoarthritis. Orthop Traumatol Surg Res. 2011;97(4):410-417.
[108] Saltzman BM, Meyer MA, Weber AE, Poland SG, Yanke AB, Cole BJ. Prospective Clinical and Radiographic Outcomes After Concomitant Anterior Cruciate Ligament Reconstruction and Meniscal Allograft Transplantation at a Mean 5-Year Follow-up. *Am J Sports Med*. 2017;45(3):550-562. doi:10.1177/0363546516669934
[109] Frank RM, McCormick F, Rosas S, et al. Reoperation Rates After Cartilage Restoration Procedures in the Knee: Analysis of a Large US Commercial Database. *Am J Orthop (Belle Mead NJ)*. 2018;47(6):10.12788/ajo.2018.0040. doi:10.12788/ajo.2018.0040
[110] Bailie AG, Lewis PL, Brumby SA, Roy S, Paterson RS, Campbell DG. The Unispacer knee implant: early clinical results. J Bone Joint Surg Br. 2008;90(4):446-450.
[111] Clarius M, Becker JF, Schmitt H, Seeger JB. The UniSpacer: correcting varus malalignment in medial gonarthrosis. Int Orthop. 2010;34(8):1175-1179.
[112] Brooks F, Akram T, Roy S, Pemberton D, Chandatreya A. Early results with a patient specific interpositional knee device. Acta Orthop Belg. 2012;78(4):500-505.
[113] Kempshall, P. J., Parkinson, B., Thomas, M., Robb, C., Standell, H., Getgood, A., & Spalding, T. (2014). *Outcome of meniscal allograft transplantation related to articular cartilage status: advanced chondral damage should not be a contraindication. Knee Surgery, Sports Traumatology, Arthroscopy, 23(1), 280–289.* doi:10.1007/s00167-014-3431-5
[114] Projected volume of primary and revision total joint replacement in the U.S. 2030 to 2060. AAOS March 6, 2018.
[115] Gaudiani MA, Samuel LT, Diana JN, et al. 5-Year Survivorship and Outcomes of Robotic-Arm-Assisted Medial Unicompartmental Knee Arthroplasty. *Appl Bionics Biomech*. 2022;2022:8995358. Published 2022 May 6. doi:10.1155/2022/8995358
[116] Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet*. 2018;392(10158):1672-1682. doi:10.1016/S0140-6736(18)32344-4
[117] Casper DS, Fleischman AN, Papas PV, Grossman J, Scuderi GR, Lonner JH. Unicompartmental Knee Arthroplasty Provides Significantly Greater Improvement in Function than Total Knee Arthroplasty Despite Equivalent Satisfaction for Isolated Medial Compartment Osteoarthritis. *J Arthroplasty*. 2019;34(8):1611-1616. doi:10.1016/j.arth.2019.04.005

replacements will be implanted in patients younger than 65 years, with the largest increase in patents aged 45–55 years[118,119].

Because age at the time of primary knee replacement is a significant predictor of survival, revision and failure rates, the number of revisions is expected to increase dramatically and could lead to many patients ceasing to be revisable, creating a large burden to society in terms of cost and disability[120]. Middle-aged patients undergoing their first knee replacement surgery have up to a 35% lifetime risk of revision knee surgery with the median time to revision only 4.4 years[121]. Patients under 50 are at a significantly higher risk of undergoing revision due to periprosthetic joint infection or to aseptic mechanical failure, even at one year after primary knee arthroplasty[122,123].

If a patient undergoes a primary unicompartmental knee replacement, the chance of revision is approximately 30% within 25 years[124], and if the primary knee undergoes a first revision to a second prosthetic knee, there is a 20% chance that this second knee will need replacing within 13 years requiring a second revision (implantation of a third prosthetic knee). The second revision has a 20% chance of needing a third revision within 5 years (a fourth prosthetic knee) which in turn has a 20% chance of undergoing a fourth revision (fifth prosthetic knee) within 3 years. Furthermore, the longer the primary prosthetic knee lasts, the longer the first revision (second prosthetic knee) is likely to last, while the risk of needing further revision is higher in males and younger patients.[125]

The medical literature above describes the need for an effective interim treatment for these patients that would allow them to delay reconstructive knee surgery until they are age appropriate. Patients who fail non-operative care are faced with the prospect of prolonged pain and symptoms.

[118] Kurtz SM, Lau E, Ong K, Zhao K, Kelly M, Bozic KJ. Future young patient demand for primary and revision joint replacement: national projections from 2010 to 2030. *Clin Orthop Relat Res*. 2009;467(10):2606-2612. doi:10.1007/s11999-009-0834-6

[119] Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;89(4):780-785. doi:10.2106/JBJS.F.00222

[120] Schreurs BW, Hannink G. Total joint arthroplasty in younger patients: heading for trouble? [published correction appears in Lancet. 2017 Apr 8;389(10077):1398]. *Lancet*. 2017;389(10077):1374-1375. doi:10.1016/S0140-6736(17)30190-3

[121] Bayliss LE, Culliford D, Monk AP, et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study [published correction appears in Lancet. 2017 Apr 8;389(10077):1398]. *Lancet*. 2017;389(10077):1424-1430. doi:10.1016/S0140-6736(17)30059-4

[122] Meehan JP, Danielsen B, Kim SH, Jamali AA, White RH. Younger age is associated with a higher risk of early periprosthetic joint infection and aseptic mechanical failure after total knee arthroplasty. *J Bone Joint Surg Am*. 2014;96(7):529-535. doi:10.2106/JBJS.M.00545

[123] Chalmers BP, Pallante GD, Sierra RJ, Lewallen DG, Pagnano MW, Trousdale RT. Contemporary Revision Total Knee Arthroplasty in Patients Younger Than 50 Years: 1 in 3 Risk of Re-Revision by 10 Years. *J Arthroplasty*. 2019;34(7S):S266-S270. doi:10.1016/j.arth.2019.02.001

[124] Evans JT, Walker RW, Evans JP, Blom AW, Sayers A, Whitehouse MR. How long does a knee replacement last? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up [published correction appears in Lancet. 2019 Feb 20;:]. Lancet. 2019;393(10172):655-663. doi:10.1016/S0140-6736(18)32531-5

[125] Paul RW, Osman A, Clements A, Tjoumakaris FP, Lonner JH, Freedman KB. What Are the All-Cause Survivorship Rates and Functional Outcomes in Patients Younger Than 55 Years Undergoing Primary Knee Arthroplasty? A Systematic Review. *Clin Orthop Relat Res*. 2022;480(3):507-522. doi:10.1097/CORR.0000000000002023

FDA guidance on benefit/risk determinations for de novo submissions highlights the need to consider risks and benefits both with respect to the level of uncertainty and the alternatives available to patients. In this instance, there is a high degree of certainty with respect to benefit, based on the following evidence from the company's clinical studies:

- The MERCURY study met its primary and many secondary endpoints, including radiological evidence of cartilage protection.
- NUsurface had nearly three times the success rate compared to controls.
- Risks to subjects implanted with the NUsurface device were well characterized in the MERCURY study.
- Secondary surgery was straightforward, with short operative time, and good outcomes and did not expose patients to higher risk of adverse events.
- Over 75% of patients who had already undergone NUsurface elected a replacement rather than other surgical options, in full appreciation of the procedure and rehabilitation.

Thus, the MERCURY study provided a high degree of certainty of risks in terms of magnitude and severity.

The special controls that Active Implants proposed include appropriate labeling, training, and clinical and non-clinical testing, similar to other previously FDA cleared implants in de novo petitions. Special controls have been designed for further optimization based on learnings from the MERCURY study and commercial experience outside the United States.

12 Conclusion

Active Implants firmly believes that sufficient information has been submitted to support classification of NUsurface into class II. For the indicated patient population, data submitted in the de novo application demonstrate that the probable benefits of NUsurface outweigh its probable risks of illness or injury when used as intended, and the risk of a secondary surgery does not preclude a positive benefit-risk assessment. Moreover, sufficient information has been submitted to establish special controls that, which along with general controls, provide a reasonable assurance of the safety and effectiveness of the NUsurface implant for its intended use, similar to special controls in the labeling of orthopedic implants cleared through the de novo process with similar risks. NUsurface provides significant patient benefit to a patient population with otherwise poor prognosis.

Appendix A: VENUS Study Protocol

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Appendix B: Pre-Clinical Chondroprotective Publications

J Appl Biomater Biomech 2011; Vol. 9 no. 1, 47-53
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ORIGINAL ARTICLE

The effect of loading and material on the biomechanical properties and vitality of bovine cartilage in vitro

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ABSTRACT

Purpose: **New methodology for long-term (270 h) biomechanical testing with living cartilage was developed. Polyurethane (PU) implant material was compared with stainless steel and reference samples in static unconfined compressive loading conditions on cartilage to provide a basis for dynamic testing of novel PU implant materials under conditions that simulate an articulating human knee joint.**

Methods: **Custom-made tools and techniques were developed to prepare cylindrical samples from bovine patella with cartilage including subchondral bone. Specific incubator cups with static loading setups for a culture incubator were manufactured to keep bovine cartilage explants alive in cell culture conditions under unconfined static compressive loading (0.25 MPa) for 270 h (11.25 d). Four loading conditions of cartilage were studied: free (FREE), restrained minimal loading (RESTR), loading with a metal plate (MEW) and loading with polyurethane (PUW).**

Results: **After static loading for 270 h, cartilage biomechanical tests indicated clear differences between the groups in frequency dependent dynamic stiffness curves. Surprisingly, the PU curves were closest to the FREE sample curves. Those with load and direct contact with metal (MEW) became significantly stiffer, while restrained samples became softer. Significant differences ($p<0.05$, Mann-Whitney's U test) in cell vitality between samples from various groups could be seen in fluorescein diacetate (FDA) and propidium iodide (PI) stained samples by confocal microscopic analysis. The approximate mean percentages of living cells after 270 hours cultivation were: FREE 87%, MEW 3%, PUW 35%, and RESTR 66%. Test results indicate that it is possible to keep cartilage cells alive in cell culture incubator conditions for two weeks period under a 0.25 MPa unconfined static loading. The FREE samples were most successful and cells loaded with PU were more vital than cells loaded with metal.**

Conclusions: **Based on the results, PU seems to be more compatible material than surgical steel in contact with living cartilage. Because of a large variation in the quality of bovine cartilage material from different animals, special care is necessary when selecting specimens to guarantee reliable and reproducible results.**

Key words: Biomechanical testing, Polyurethane, Biomaterial, Cartilage, Vitality

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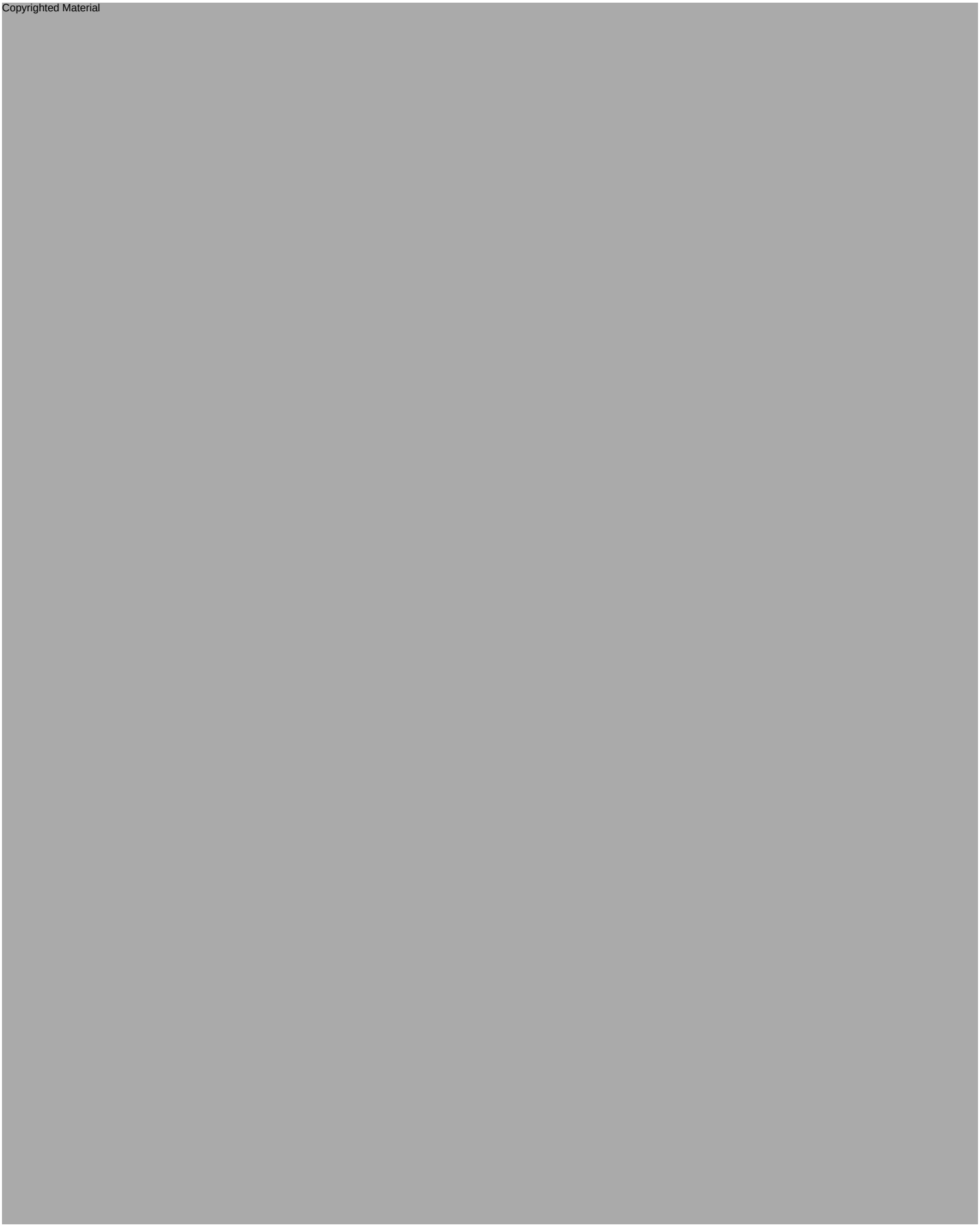

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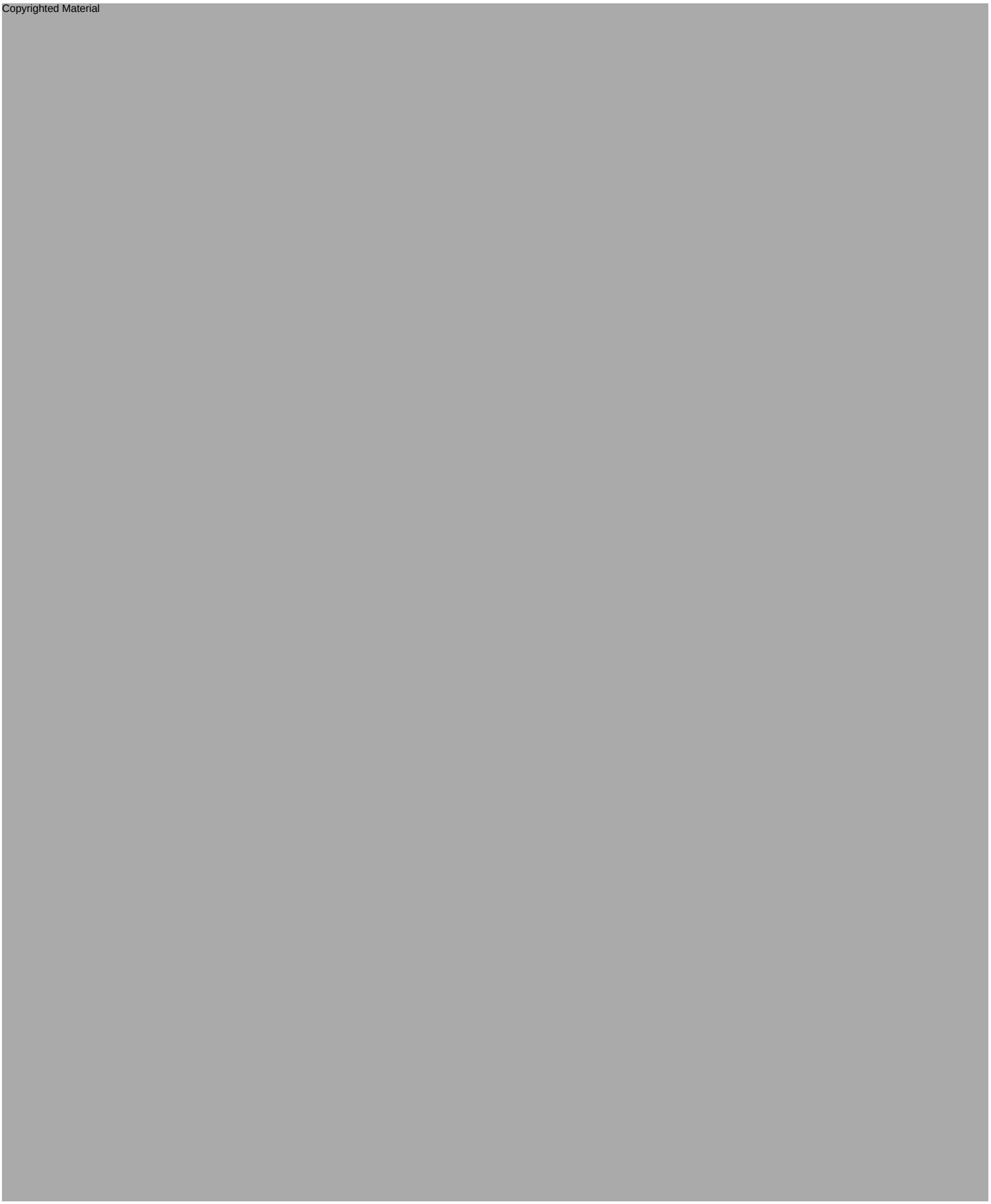

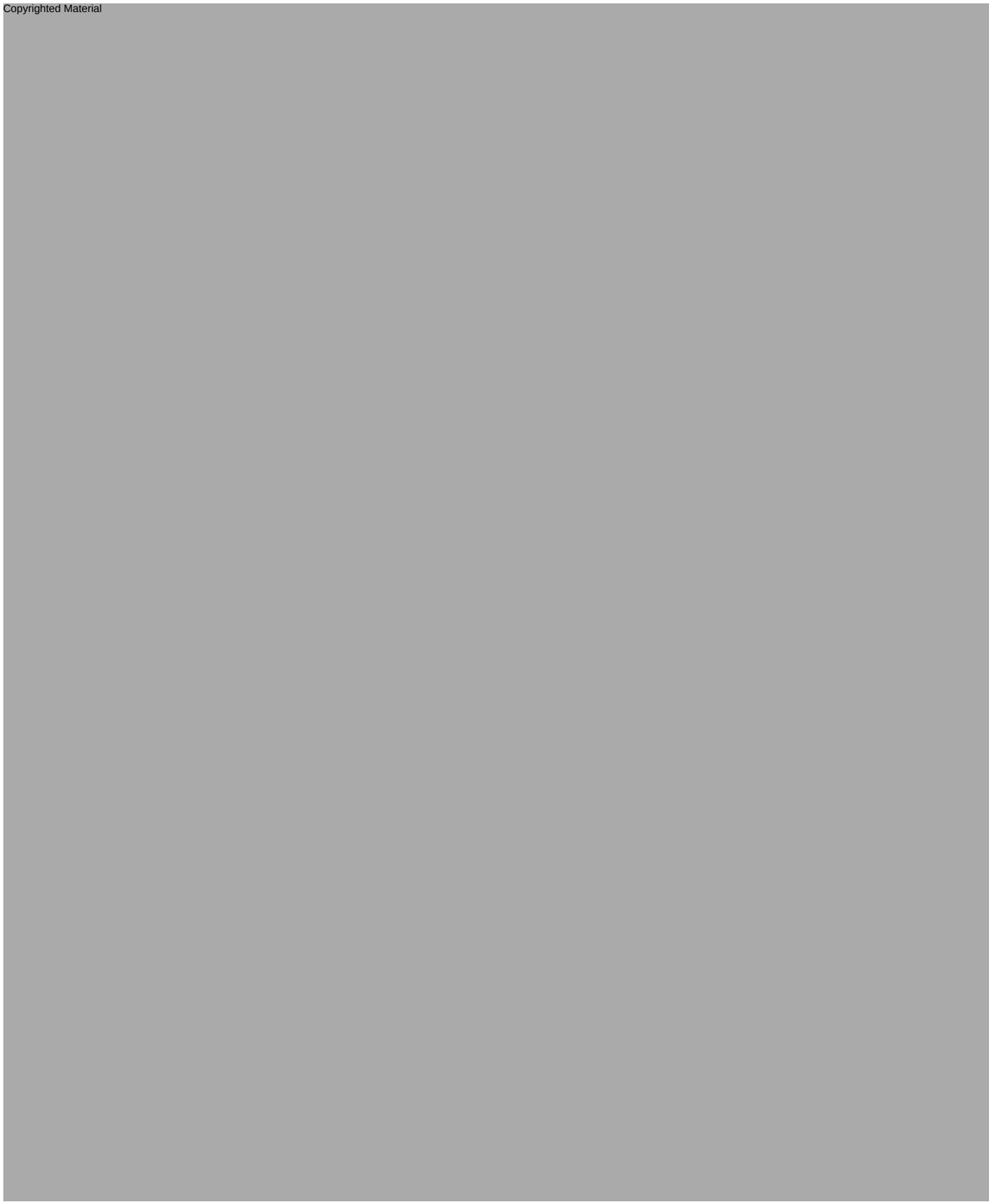

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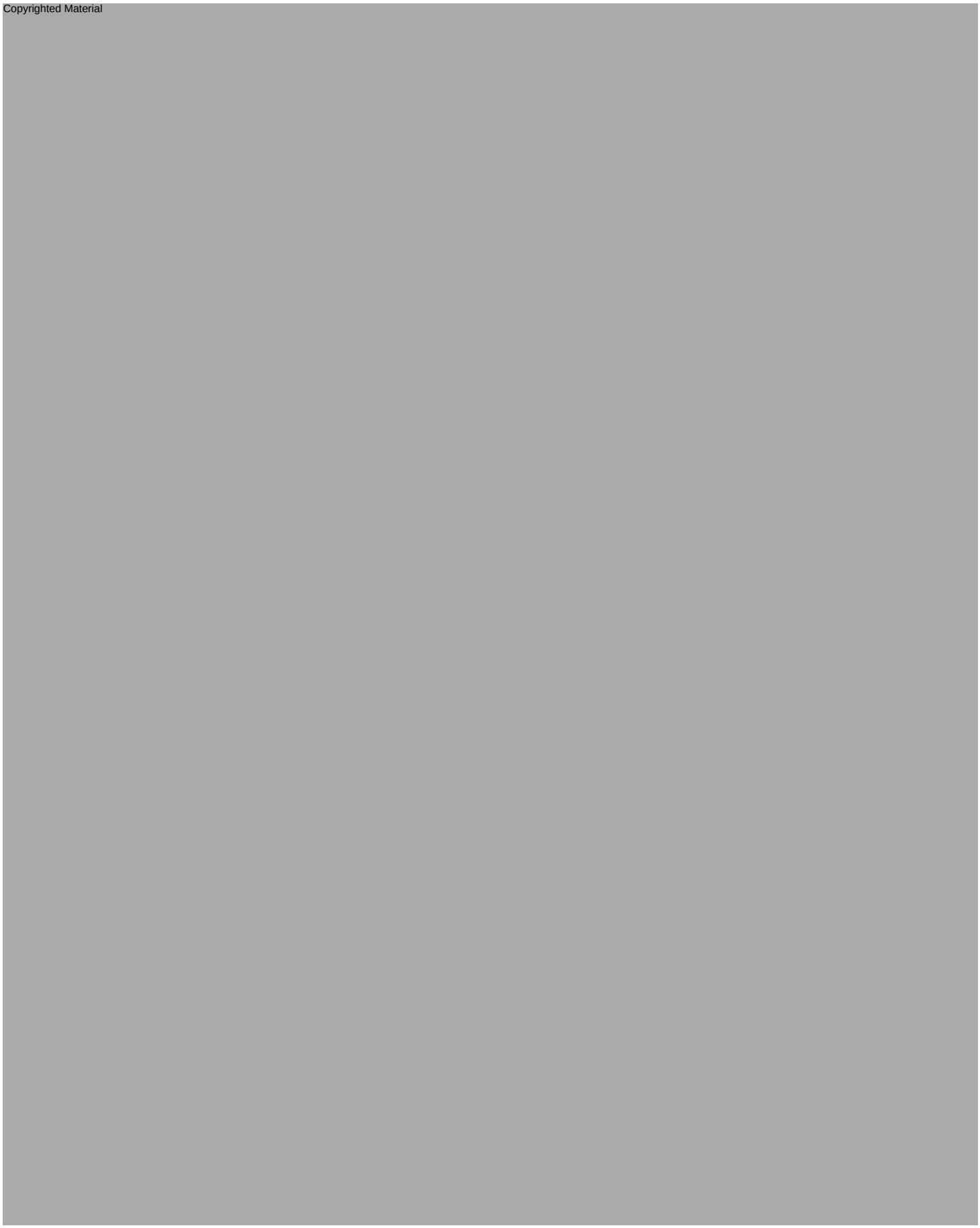

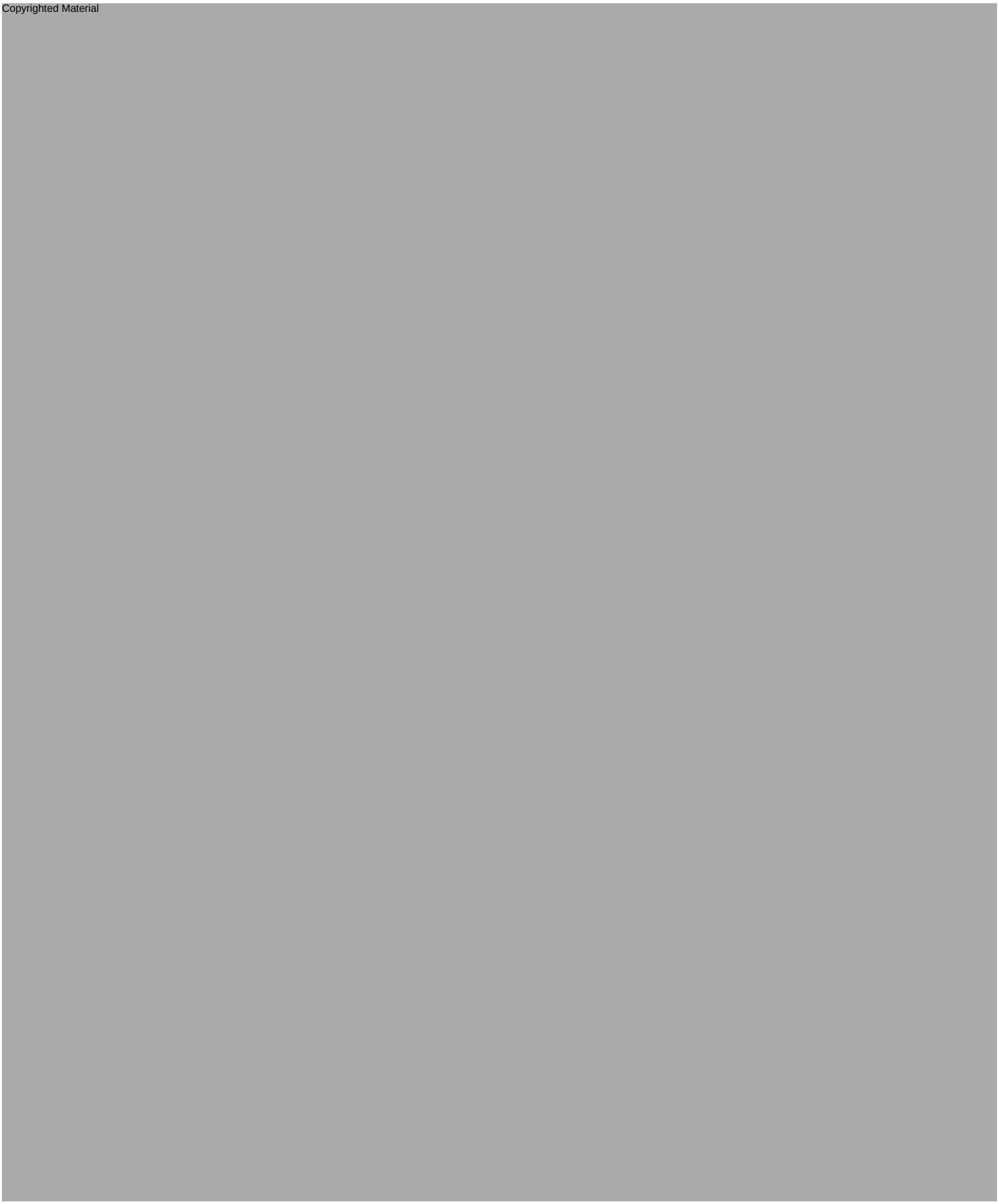

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KNEE

Chondroprotective effects of a polycarbonate-urethane meniscal implant: histopathological results in a sheep model

Gal Zur · Eran Linder-Ganz · Jonathan J. Elsner · Jonathan Shani · Ori Brenner · Gabriel Agar · Elliott B. Hershman · Steven P. Arnoczky · Farshid Guilak · Avi Shterling

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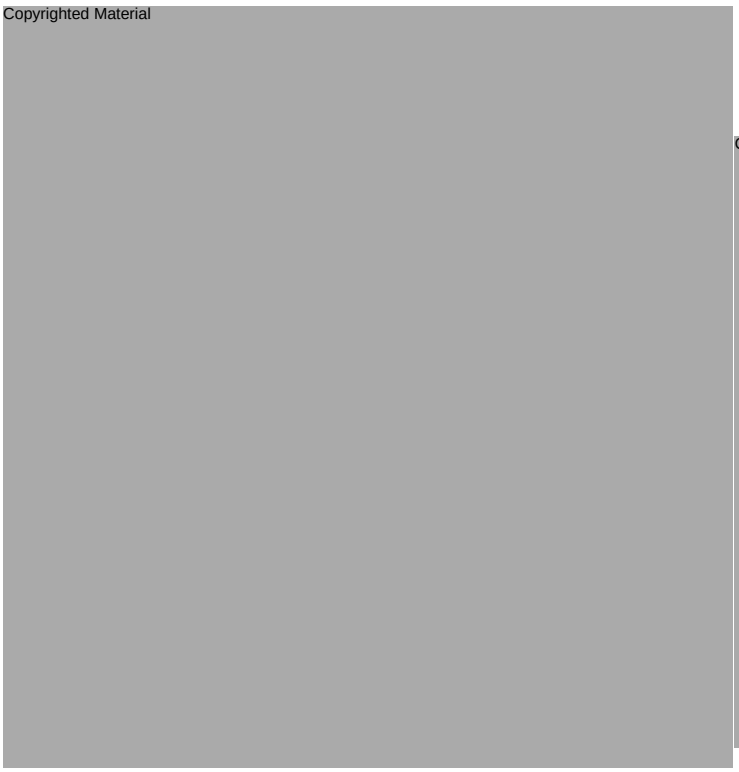
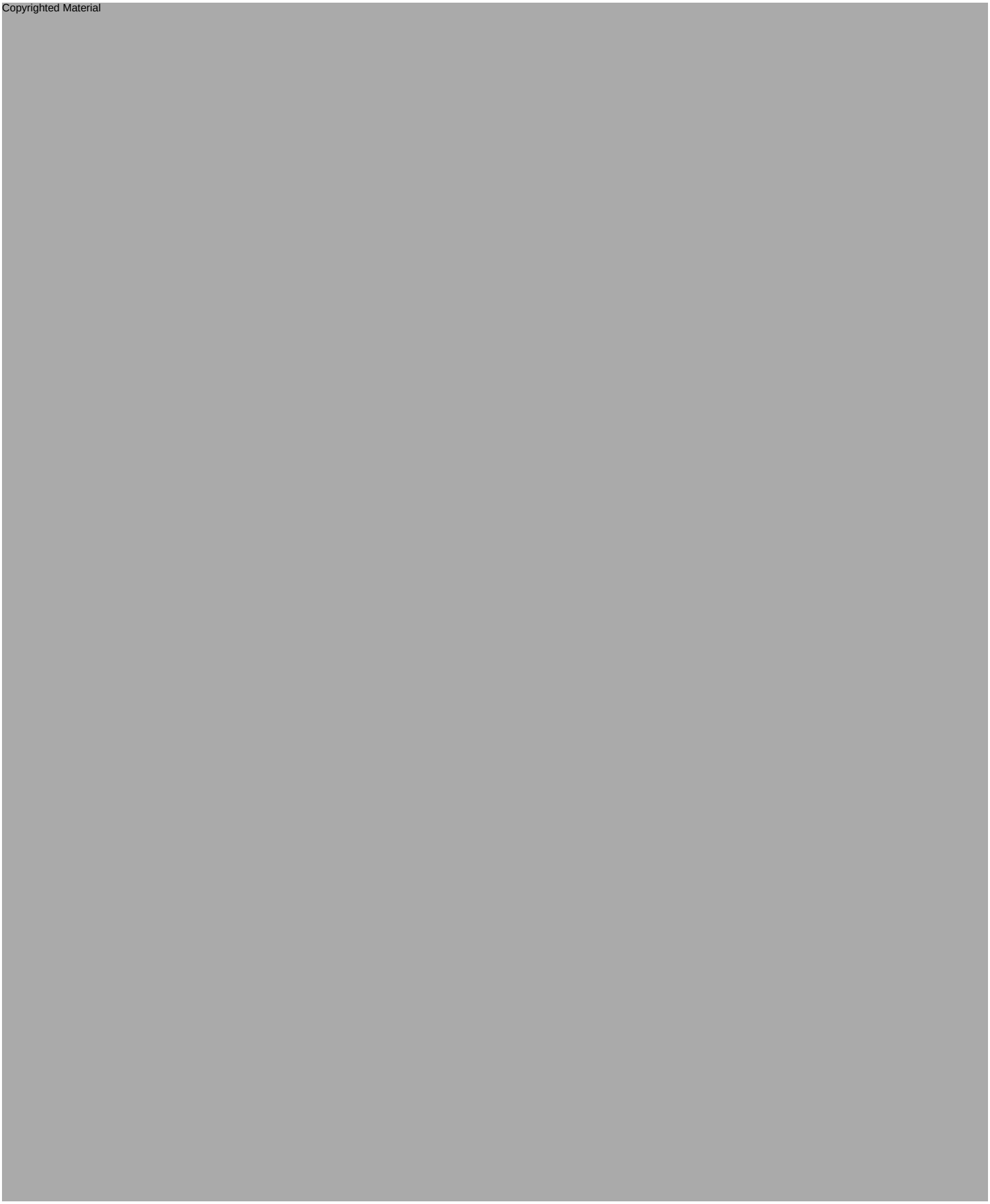
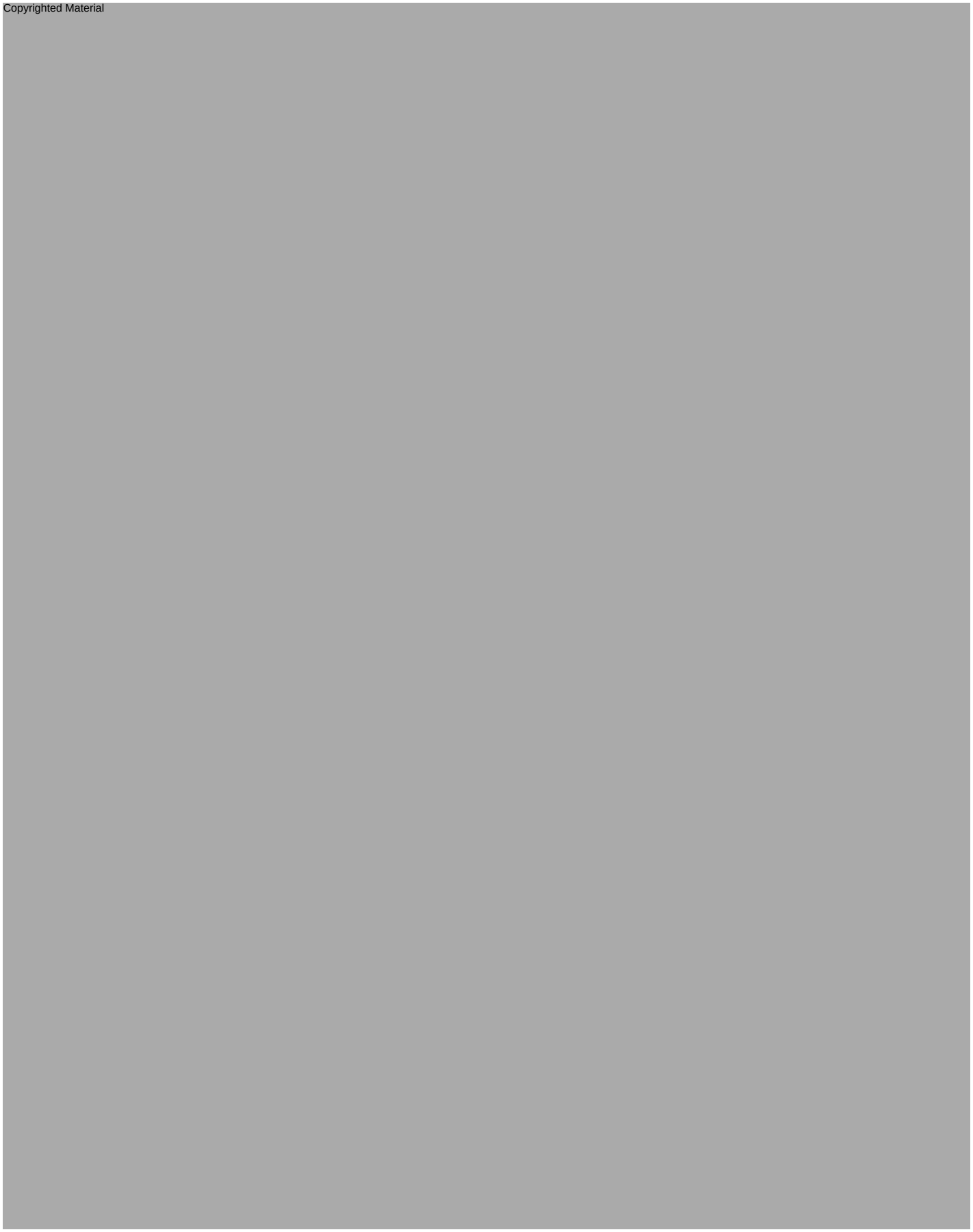
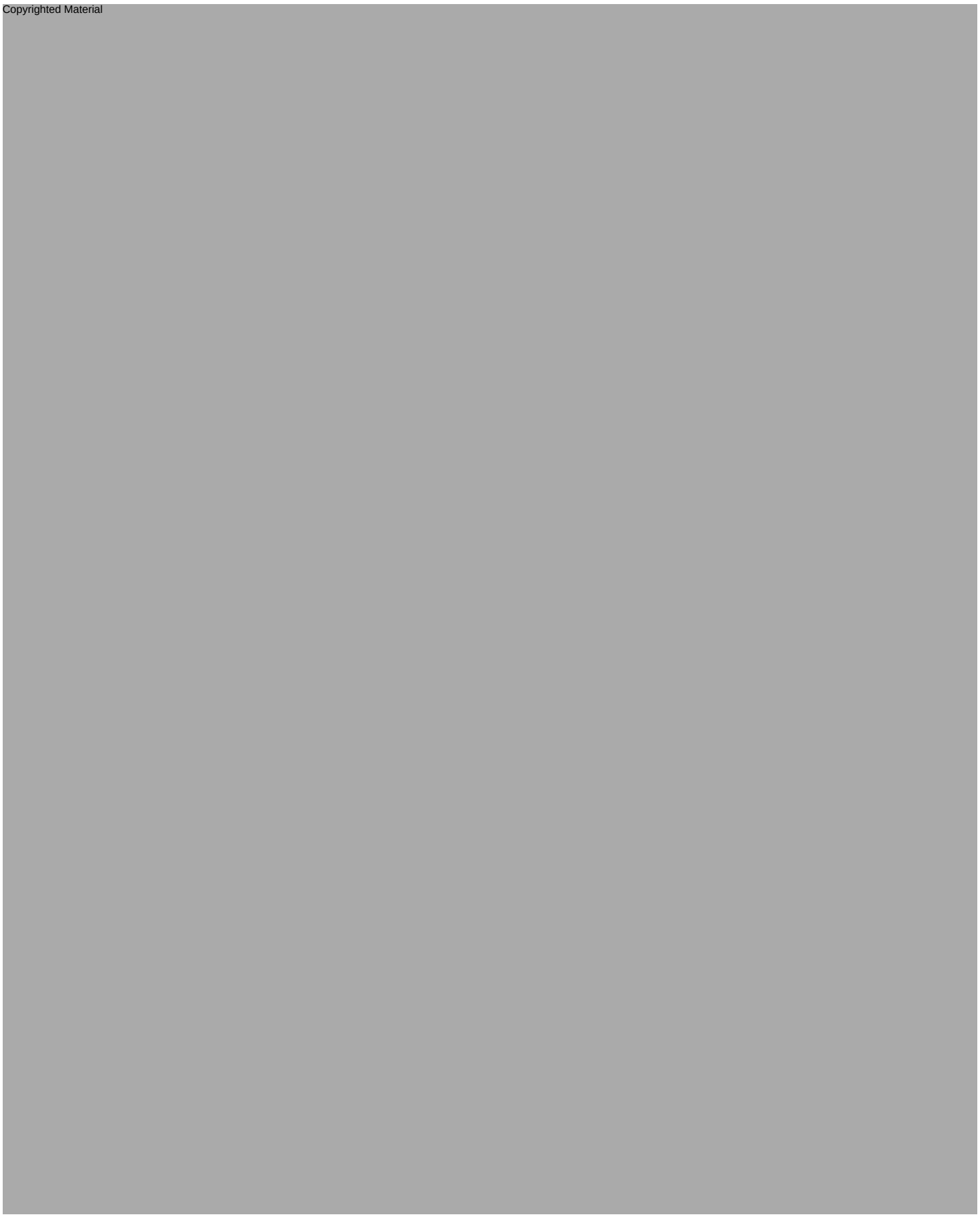
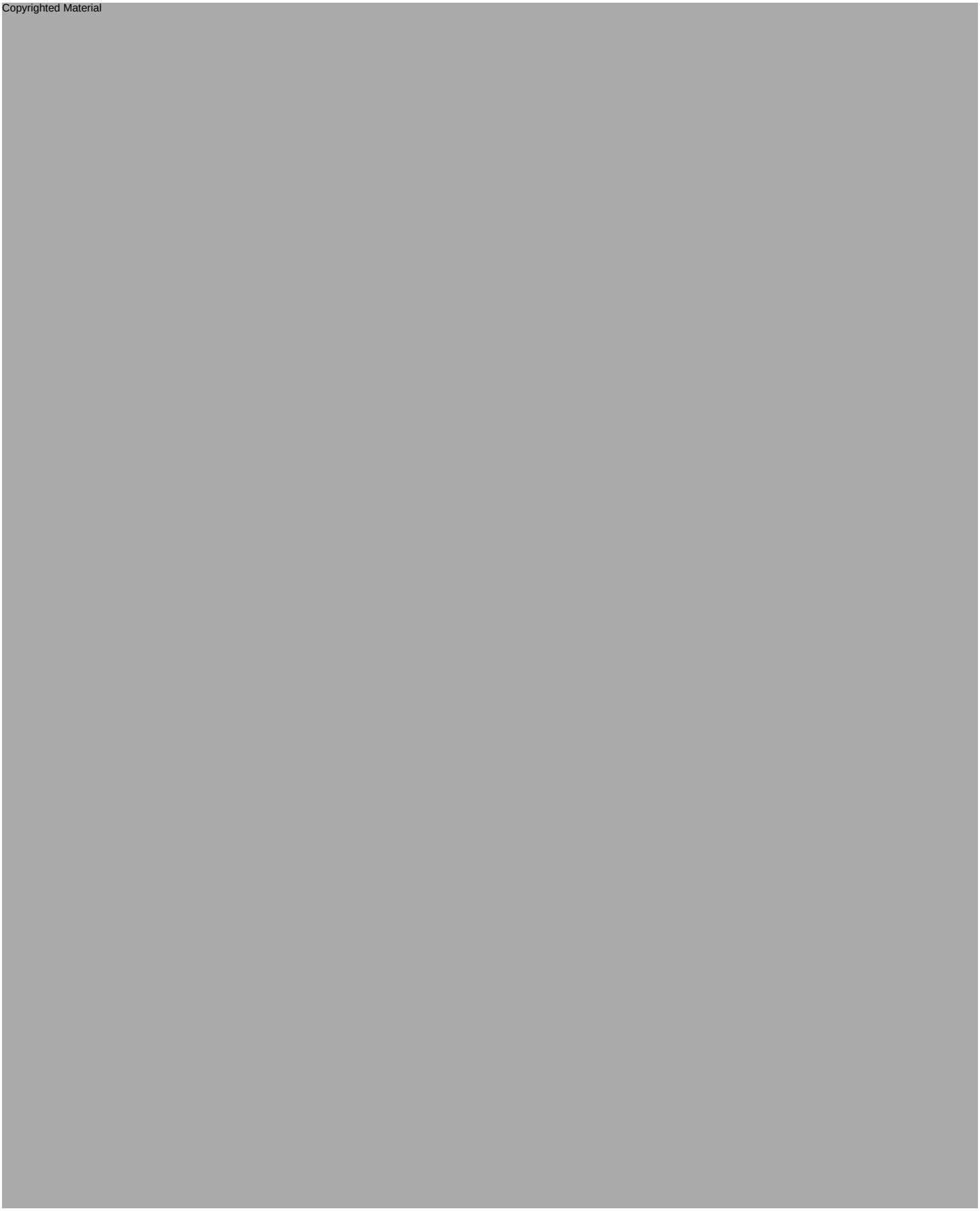
Abstract
Purpose Injury or loss of the meniscus generally leads to degenerative osteoarthritic changes in the knee joint. However, few surgical options exist for meniscal replacement. The goal of this study was to examine the ability of a non-degradable, anatomically shaped artificial meniscal implant, composed of Kevlar®-reinforced polycarbonate-urethane (PCU), to prevent progressive cartilage degeneration following complete meniscectomy.
Methods The artificial meniscus was implanted in the knees of mature female sheep following total medial meniscectomy, and the animals were killed at 3- and 6-months post-surgery. Macroscopic analysis and semi-quantitative histological analysis were performed on the cartilage of the operated knee and unoperated contralateral control joint.
Results The PCU implants remained well secured throughout the experimental period and showed no signs of wear or changes in structural or material properties. Histological analysis showed relatively mild cartilage degeneration that was dominated by loss of proteoglycan content and cartilage structure. However, the total osteoarthritis score did not significantly differ between the control and operated knees, and there were no differences in the severity of degenerative changes between 3 and 6 months post-surgery.
Conclusion Current findings provide preliminary evidence for the ability of an artificial PCU meniscal implant to delay or prevent osteoarthritic changes in knee joint following complete medial meniscectomy.

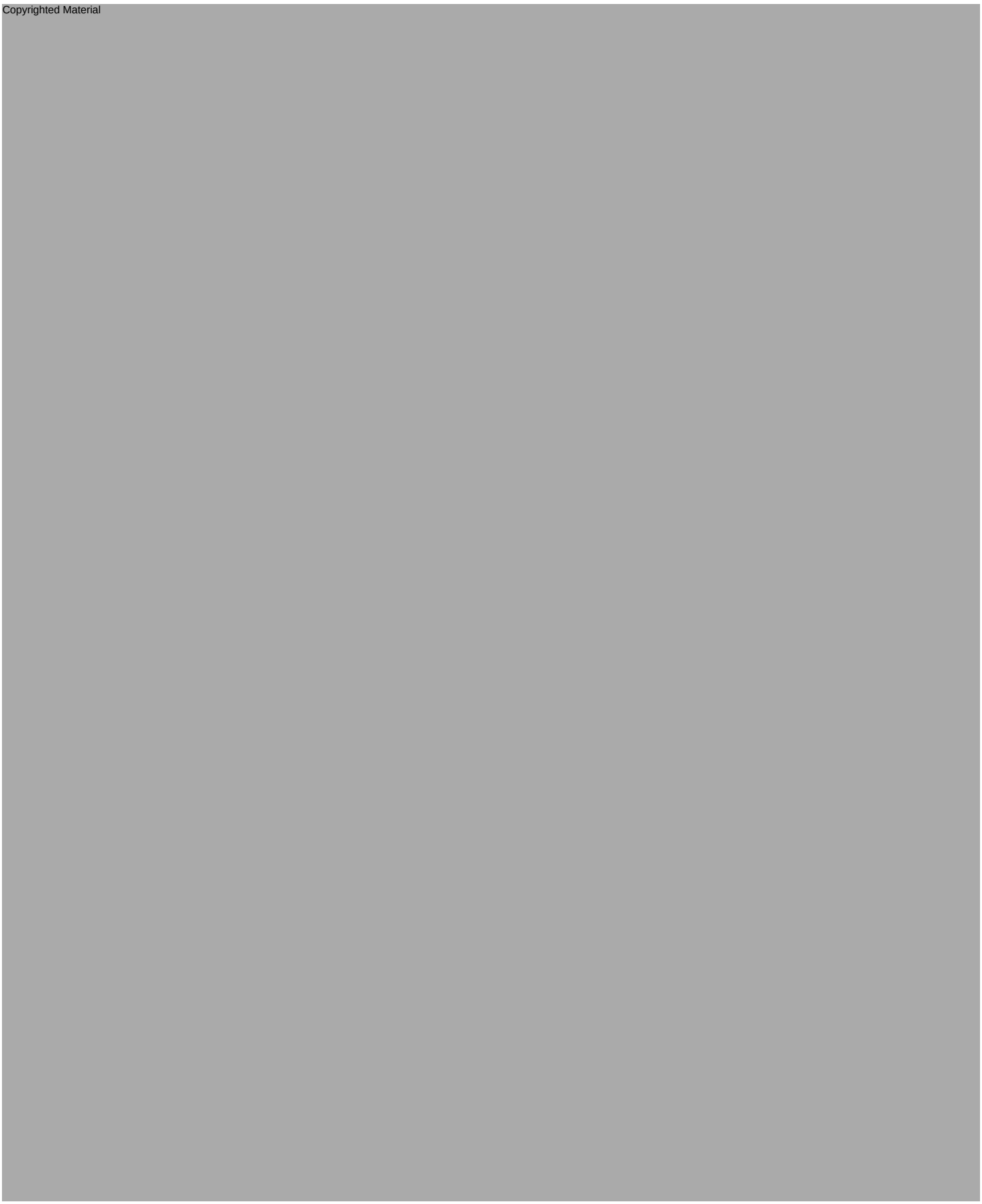


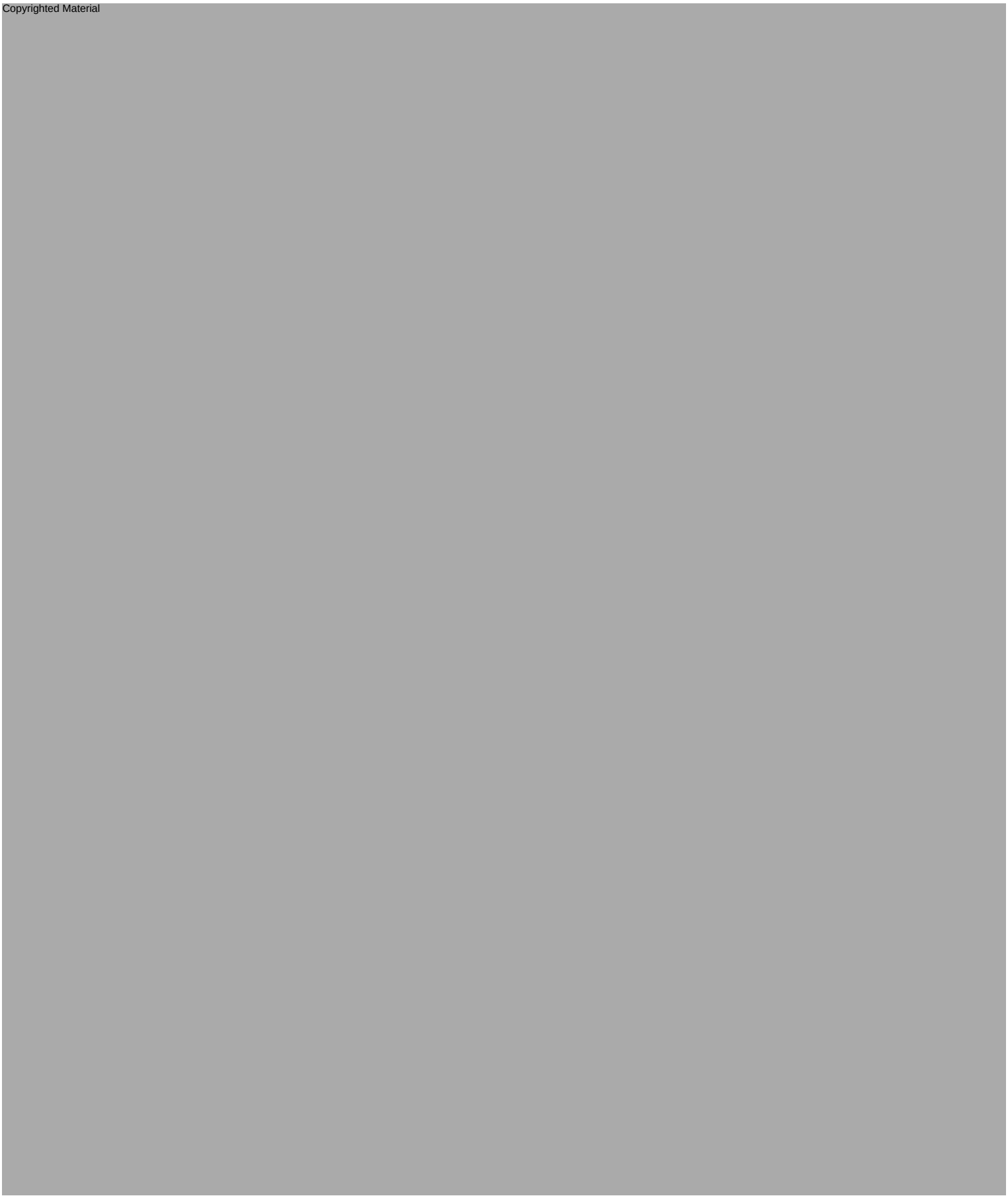


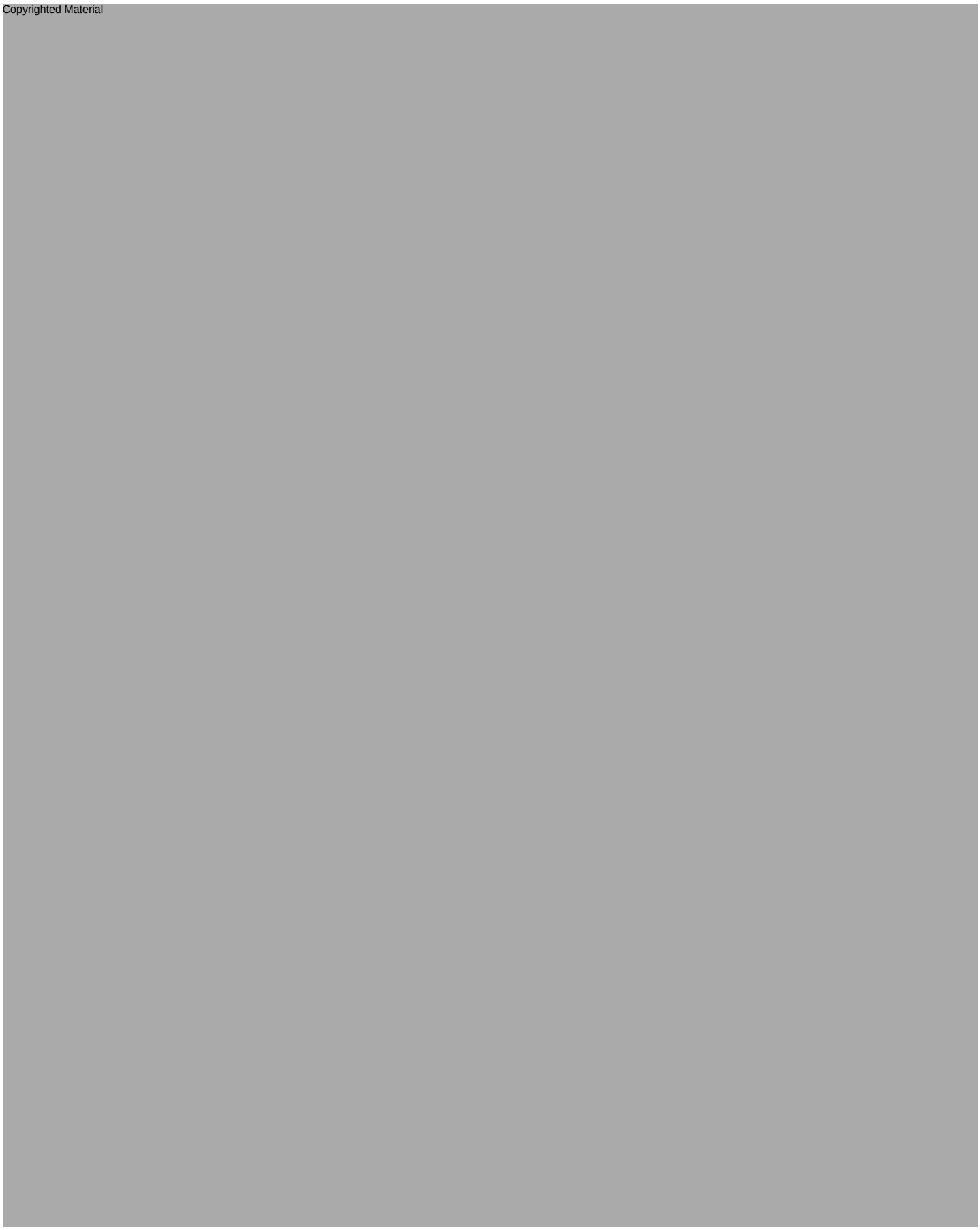


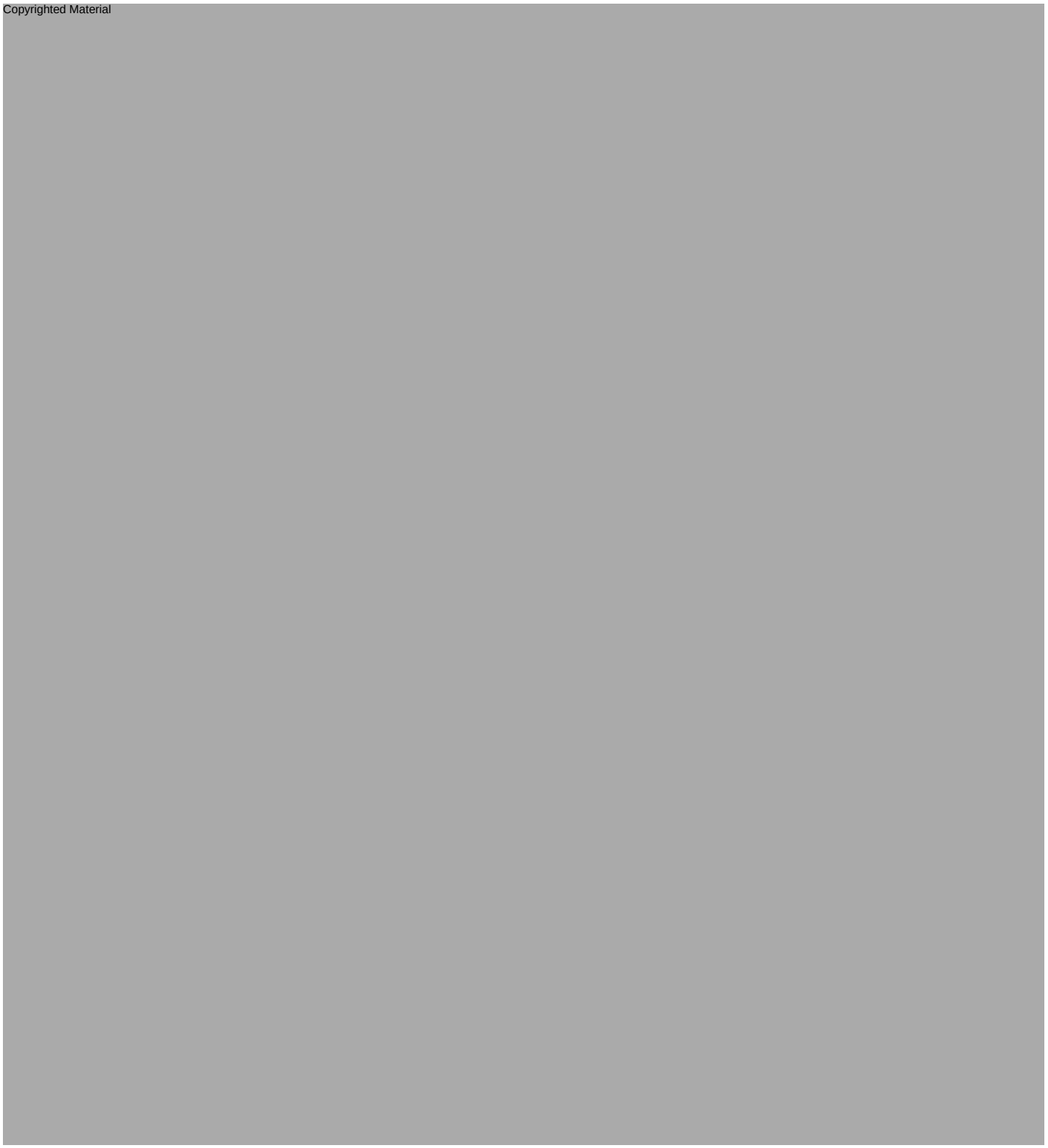












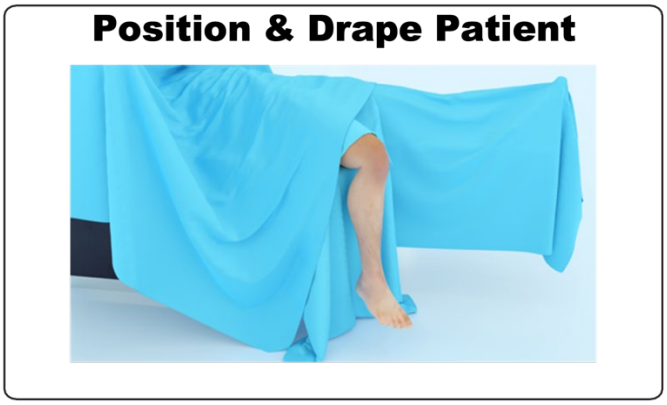
Appendix C: NUsurface Surgical Technique

Position and drape the patient.

The surgical procedure begins by placing the subject in a standard knee arthroscopy position, per the surgeon's preference, under general or regional anesthesia.

The patient is positioned and draped for an arthroscopic knee procedure.

A tourniquet, circumferential leg holder or lateral post is used.

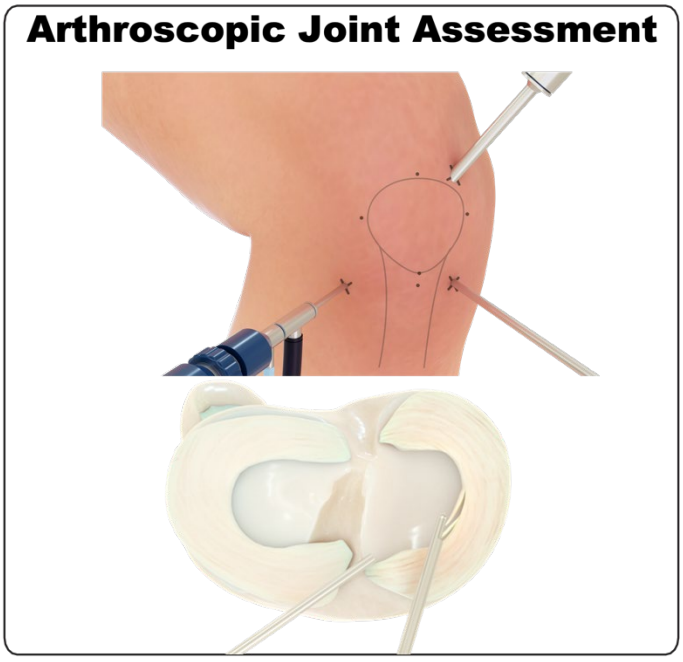


Arthroscopically inspect the joint.

Using an arthroscopic camera and meniscus probe the medial and lateral compartments, the medial meniscal root, articular cartilage, and intercondylar notch are evaluated. Unstable tissue or articular cartilage should be debrided carefully to ensure stable margins.

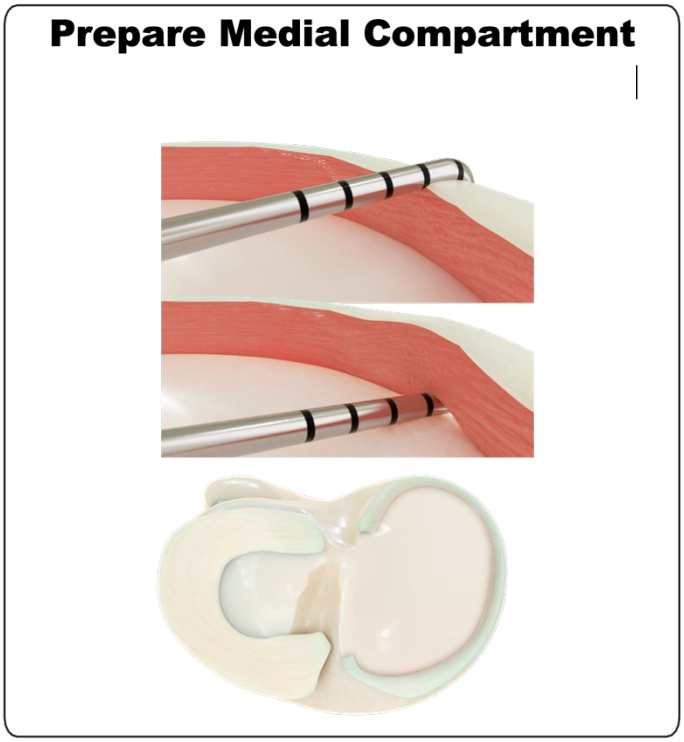
The location and grade of any chondral lesions noted on the preoperative MRI, should be confirmed, and directly observed. Chondral lesions that are located in the center of the medial femoral condyle (MFC) and medial tibial plateau (MTP) are probed and evaluated using a meniscus probe.

Chondral lesions in the medial compartment are evaluated, especially on the periphery, to ensure no exposed bone will come into contact with the device. Rough and unstable cartilage lesion margins are debrided to create stable margins.

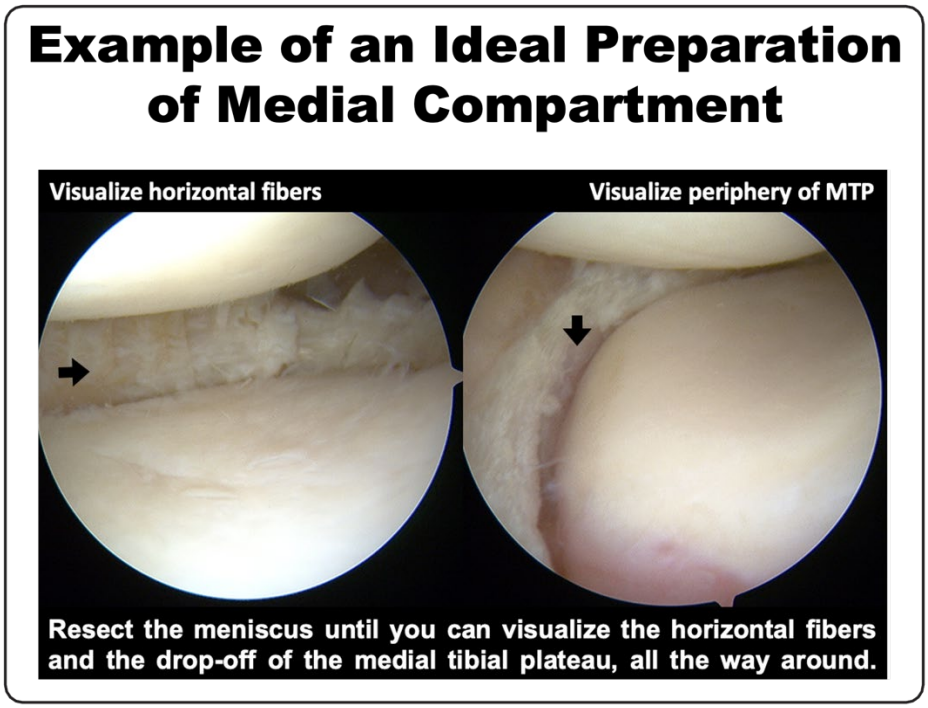


Prepare the medial compartment.

A circumferential meniscectomy in the avascular region of the medial meniscus is performed to create a 2mm vertical margin (rim) around the periphery.



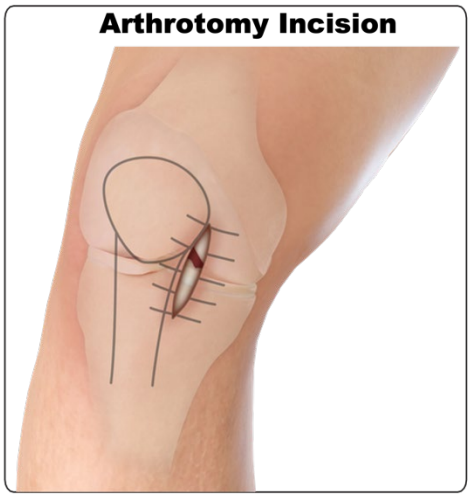
Preparation is complete after the remaining meniscus is stable and horizontal meniscus fibers are visible along with the drop-off of the MTP.



Prepare the intercondylar fossa. Depending on the intercondylar notch morphology, stenosis, and osteophyte formation, it may be necessary to remove osteophytes from the intercondylar femoral notch.

Create an Arthrotomy.

Create a 4-6 cm medial parapatellar arthrotomy adjacent to the medial border of patellar tendon, extending through the medial portal from the proximal inferior third of the patella to the tibial metaphysis as depicted in the figure below.

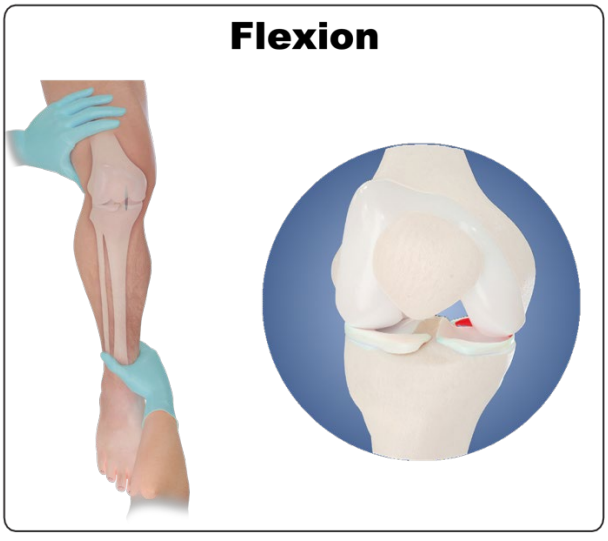


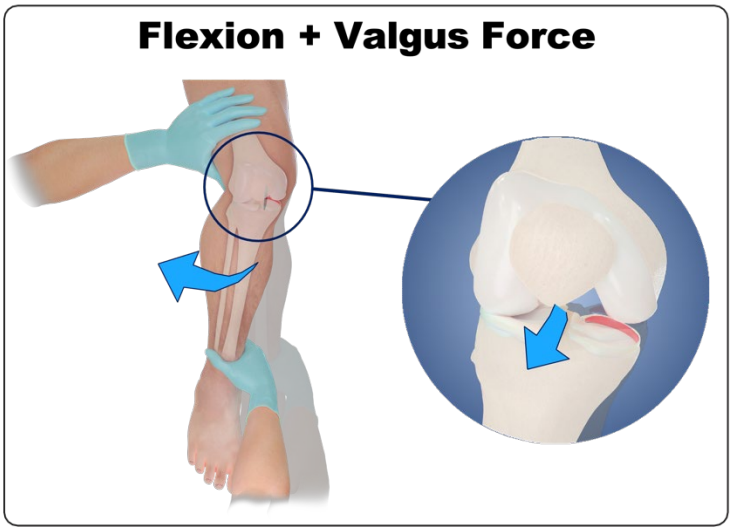
Soft tissue should be dissected to expose the medial compartment, resecting the fat pad and any scarring from past surgeries, as needed. The vertical wall of the meniscus is viewed under direct visualization, confirming a steep vertical wall no more than 2mm thick.

Implant the Trial Implant.

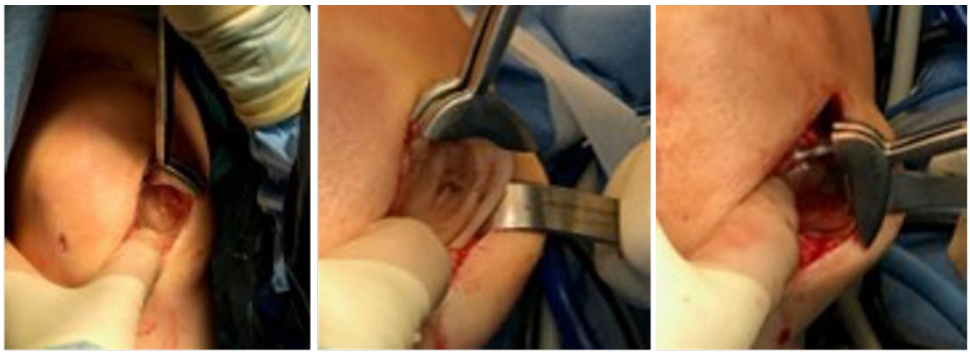
Once the appropriate implant size is selected, trial implants are removed with the extraction tool. Finally, the NUsurface implant is placed, another range of motion test is performed and followed by a standard capsular closure, surgical site inspection, and application of postoperative dressings.

Confirm optimal knee positioning. Insertion techniques may vary depending on patient positioning and choice of leg holder. The optimal position and maneuver for insertion of the Trial is illustrated in the figures below: while the ankle is held (1) a valgus stress is applied (2).

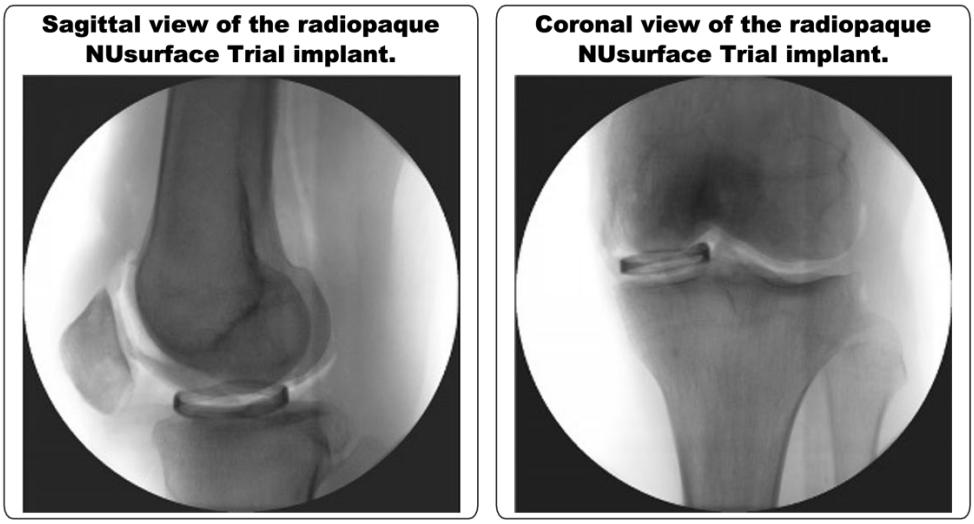




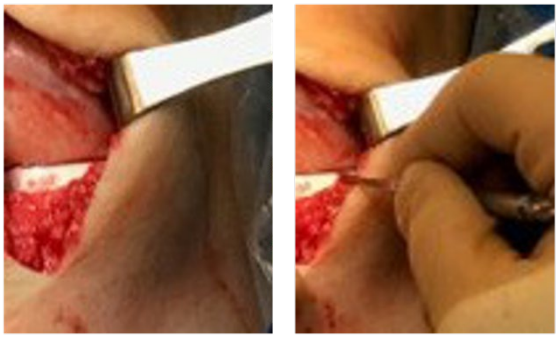
The Trial is implanted interpositionally between the medial femur and tibia by slowly extending the knee and exerting a strong posterior force on the insertion instrument while simultaneously pushing the instrument posteriorly. The Trial will be drawn into the medial compartment, interpositionally positioned between the medial femur and tibia.



Correct placement and proper movement of the Trial through range of motion is confirmed by fluoroscopy. The figures below depict the ideal sizing and placement of the NUsurface Meniscus Implant for a typical patient.



Under direct visualization complete several full range-of-motion cycles. Assess placement and confirm appropriate size. (Figure 13).



Remove the Trial implant.

The Trial implant is removed with the extraction tool.

Insert the Definitive NUsurface Implant

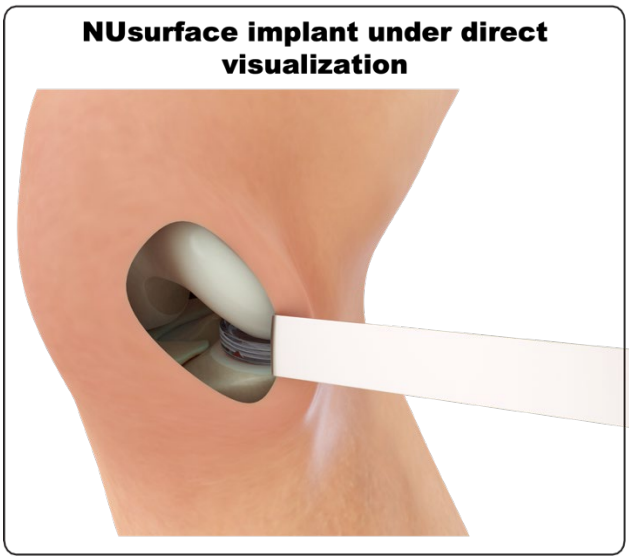
The NUsurface Implant is implanted interpositionally between the medial femur and tibia using the same technique described for the Trial Implant. Prior to insertion of the Implant, remove all loose debris using copious irrigation of the surgical site. Any surgical debris left may damage the Implant or cause damage to tissue.

Begin by slowly extending the knee and exerting a strong posterior force on the insertion instrument while simultaneously pushing the instrument posteriorly. The NUsurface Implant will be drawn into the medial compartment, interpositionally positioned between the medial femur and tibia.

Final NUsurface Confirmation and Wound Closure

Assess the placement and range of motion of the NUsurface Implant.

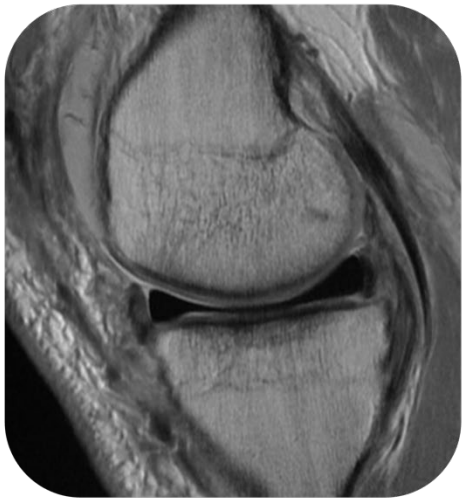
Perform a full range of motion to confirm proper positioning of the device and knee function. Confirm the Implant is stable, does not have any impingement in motion, or contact with exposed bone.



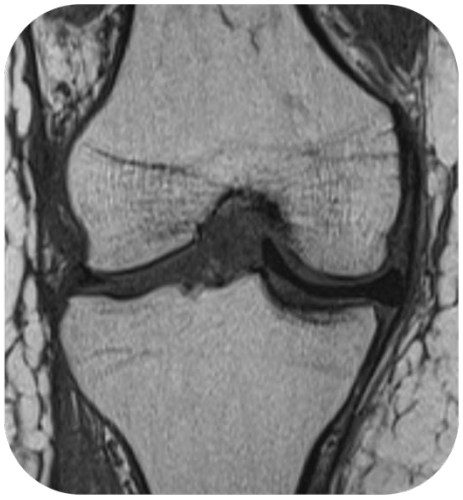
Prior to closing, flush the surgical site with copious antibiotic and saline irrigation. A drain may be placed in the wound. The incision is closed in layers, and a dressing applied. The patient is placed in a straight-leg brace

The NUsurface implant is radiolucent on X-ray. Postoperative evaluation should be performed using MRI. The figures below depict the ideal sizing and placement of the NUsurface Meniscus Implant for a typical patient.

Sagittal view of the radiolucent NUsurface Implant.



Coronal view of the radiolucent NUsurface Implant.



Appendix D: Draft Instructions For Use

DRAFT Instructions for Use

NUsurface® Meniscus Implant

Purpose:

The purpose 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.

Device Materials:

The NUsurface® Meniscus Implant is a discoid shaped device made of medical grade polycarbonate-urethane (PCU) reinforced peripherally with tensioned ultrahigh molecular weight polyethylene (UHMWPE) fibers:

• Polycarbonate-urethane, PCU (Medical Grade)	Matrix material of the meniscus implant
• UHMWPE fibers (Medical Grade)	Reinforcement fibers inside the PCU

Device Description:

NUsurface Meniscus Implants and Trials are available in both left and right versions in a variety of sizes. The size width and length vary in increments to allow the surgeon to select the one during surgery that best fits the patient. The surgeon approaches the knee using an arthroscopic approach and performs a mini-arthrotomy to insert the Trial and then Implant between the medial tibial plateau and femoral condyle.

Indications:

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.

Contraindications:

1. 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;
2. 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;
3. Patients with extrusion of the medial meniscus 5mm or greater;
4. >5° loss of extension and >15° loss of flexion difference between index and contralateral knee; greater than ±5° of varus/valgus femoral/tibial alignment.
5. 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;
6. Grossly distorted anatomy or neuropathic joint such as Charcot joint;
7. Knee joint bone resorption, avascular necrosis, or rapid joint destruction;
8. Skeletally immature;
9. 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;
10. Morbid obesity;
11. Patients with inflammatory or systemic disease such as psoriatic arthritis or rheumatoid arthritis;
12. Patients with an allergy to any of the materials used to construct the implant;
13. Patients with insufficient quantities of synovial fluid to allow for proper lubrication of the knee, such as occurs with Sjogren's Syndrome;
14. Active Infection, sepsis, or osteomyelitis;
15. Medial compartment anatomy requiring a NUsurface device size larger or smaller than available;
16. Use of the NUsurface device in the lateral compartment of the knee or in any part of the body other than the medial knee;
17. Patients incapable of following instructions, such as having certain types of mental illnesses, or unwilling or unable to be compliant with directions.

Warnings

1. Patients in which the height of the tibial spine is below 11mm are at a greater risk of device related adverse events.
2. 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.
3. The pivotal clinical study did not evaluate device effectiveness in patients with a complete disruption of the medial posterior

meniscal root, or with less than a 2 mm medial meniscal rim.

4. 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.

Possible Adverse Effects:

1. Bending, breaking, or tearing of the device, cartilage, or bone;
2. Dislocation, subluxation, and/or rotation of the device, which are types of dislodgement;
3. Device removal and/or exchange;
4. Device generated noise, clicking, or motion sensation perceived by the patient;
5. Foreign body reaction to the materials used or to wear debris created; synovitis
6. Osteolysis, bone resorption, remodeling, or excessive calcification around the Implant such as by osteophyte, ectopic, or heterotopic bone formation or re-formation;
7. Cartilage deterioration;
8. Infection;
9. Pain in or loss of or restriction in motion of the knee joint;
10. Lateral compartment or patella complications;
11. Leg length discrepancy or difficulty in walking;
12. All other complications associated with knee and implant surgery are possible such as:
    - Peripheral neuropathies, nerve damage, circulatory compromise and heterotopic bone formation may occur;
    - Genitourinary disorders; gastrointestinal disorders; vascular disorders, including thrombus; bronchopulmonary disorders, including emboli; myocardial infarction; infection; loss of consortium; and/or death;
    - With all orthopaedic implant devices, localized progressive bone resorption (osteolysis) or cartilage destruction may occur around the component because of use or foreign-body reaction to implant materials or particulate matter. Any of these conditions can lead to complications including dislocation, subluxation, rotation, and/or tear, or abrasive wear of the device that may necessitate the removal or exchange of the Implant;
    - Dislocation, rotation, and/or subluxation from proper position may result from: variant knee anatomy, large baseline varus or valgus angle deformities, less than ideal initial Implant size selection, exposed bone contacting the implant, lifting excessive loads, squatting, and/or twisting of the Implant; and/or malalignment. Device dislodgement may also result from trauma, infection, biological complications including osteolysis, bone or soft tissue remodeling, adhesions, and/or mechanical impingement;

The expected useful life of the NUsurface® Meniscus Implant in the human body is finite and varies depending upon biological, mechanical, anatomical, physicochemical, and/or other patient specific factors. The NUsurface® Meniscus Implant cannot be expected to and will not withstand the loads and motions of the knee joint indefinitely, especially if the adjacent cartilage degenerates over time and bone contacts the Implant. **Note:** Additional surgery including joint replacement or other types of advanced reconstructive knee surgery may be necessary to correct some of these possible anticipated adverse effects.

Precautions:

- Instruction for Use may be revised periodically.
- **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

side 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.

Utilization and Implantation:

- Use Trial components intraoperatively to help determine the final implant size, evaluate function, and confirm range of motion. Always remove the Trial before closing. The intended use of the Trial is only for sizing and brief contact with the patient.
- The Trial size matches the final Implant size. A five digits product code embedded on the medial-posterior edge of the Trial and Implant approximates its size in whole millimeters: the first two digits the length (LL), next 2 digits the width (WW), and last digit the minimum thickness (T). The final NUsurface® Implant size to select depends on intra-operative confirmation of correct range of motion, arthroscopy check for impingement, and fluoroscopy check for a smooth movement;
- Please refer to the latest operative technique for detailed pre-operative, intra-operative and post-operative instructions;
- Do not use an instrument with a sharp edge near the NUsurface® Meniscus Implant;
- Take care to protect device components from being marred, nicked, or notched from contact with abrasive or sharp objects;
- Mishandling a sterile Implant or Trial prior to or during the surgical procedure may compromise its sterility and/or damage the component. Have extra inventory on hand in case of an unexpected need.

Radiology and MRI Safety:

The Implant is radiolucent and not visible on an X-ray. The Implant is MR safe and visible in an MRI scan. During a clinical study, some MRI's taken around 6 weeks post-op showed Bone Marrow Lesion, MCL sprain, synovial proliferation, and/or effusion around the Implant. Any surgeon who orders an early post-surgery MRI should expect to see these types of MRI observations which the clinical study found to have no clinical significance and to be transient in nature.

Sterility & Packaging & Storage:

Active Implants sterilizes each NUsurface® Meniscus Implant package using ethylene oxide gas. Double blister packaging helps maintain the sterility of the product. All NUsurface Implants and Trials are sterile at the time of shipment. Inspect the integrity of each package upon receipt and again before opening. Store the NUsurface® Meniscus Implant in its original box at room temperature in a dry area protected from direct sunlight and extreme changes in temperature and humidity. Take care to prevent package damage or contamination during storage. If the package does become damaged, opened, or wet, assume any product inside is not sterile. In the event of contamination, package damage, or non-use after opening, discard the device according to hospital procedures. Never re-sterilize, re-implant, or re-use implants. To help achieve the best possible results, do not use any undamaged package after the expiry date (year-month-day) shown on the product packaging.

Complaints:

Any healthcare professional experiencing any problems with this product should call Active Implants LLC at phone number +901-762-0352, send an e-mail to: complaints@activeimplants.com, or mail a letter to the following address:

Address for Complaints and Returns:

Send complaints or returns to the following address:
Active Implants LLC
6060 Primacy Parkway, Suite 460
Memphis, TN 38119
USA

Explanation of symbols on packaging:

	DO NOT USE IF PACKAGE IS DAMAGED		STERILIZED USING ETHYLENE OXIDE
	DO NOT REUSE		KEEP AWAY FROM SUNLIGHT
	KEEP DRY		CONSULT INSTRUCTIONS FOR USE
	DO NOT RESTERILIZE		MRI SAFE
	DATE OF MANUFACTURE		USE BY DATE (YYYY-MM-DD)
	BATCH CODE		CATALOG NUMBER
	MANUFACTURER		PRESCRIPTION ONLY
	DOUBLE STERILE BARRIER SYSTEM		

Manufactured for and Distributed by: Active Implants LLC
Draft Insert, document number 01240. dated 5 June 2022

Appendix E: Description of Patient Reported Outcome Measures

KOOS

The KOOS (Knee injury and Osteoarthritis Outcome Score) is a validated outcome measurement for assessing knee related injuries and treatments. KOOS provides a comprehensive evaluation of the subject's pre-treatment and post-treatment condition including activity levels, pain, swelling, locking, stability, support, sports activity, and quality of life assessment. KOOS consists of 7 questions about symptoms, 9 questions related to pain, 17 questions related to function in daily activities, 5 questions related to function in sports activities, and 4 questions related to Quality of Life. All 42 questions have 5 possible answers. Subjects filled out the forms at baseline and at 1.5, 6, 12, 24 months, as described in

VAS Pain

The Visual Analog Scale (VAS) is a validated measurement tool to assess pain level in a study. The scale uses a 10cm line. One end of the line represents "no pain," while the other end of the line represents, "Pain as bad as it could possibly be". The subject marks on the line their evaluation of their current level of pain. This protocol required the VAS Pain be measured at baseline and at 1.5, 6, 12, & 24 months.

WOMET

WOMET is the Western Ontario Meniscus Evaluation Tool. As the name implies, this tool was developed to evaluate meniscal injuries. As indicated in Table 3, subjects filled out WOMET at baseline and 1.5, 6, 12, and 24 months after the start of treatment. The WOMET measurement tool consists of 16 Visual Analog Scale lines with "not at all" on the left end and "extremely bothered" or similar phrase on the right. Study subjects mark the line to record their status on the date they fill out the form. Their mark on the line then converts to a number between 0 and 100. The 16 questions are divided into three sections—the first 9 questions relate to physical symptoms (best score = 0, worst score = 900), the next 4 questions relate to Sports, Recreation, Work, & Lifestyle (best score = 0, worst score = 400), and the last 3 questions relate to Emotion (best score = 0, worst score = 300,). A Normalized Total Score subtracts the total score from 1600 (the maximum) and divides by 16 to get a percentage (worst score = 0, best score = 100%). Further details are in the WOMET instruction form (Kirkley and Griffin) and WOMET validation report (Kirkley et al. 2007). According to the WOMET developers, one of the meniscal conditions validated for the WOMET measurement tool is meniscal resection.

IKDC

The IKDC (International Knee Documentation Committee) includes a demographic form, current health assessment form, Subjective Knee Evaluation Form (SKEF), knee history form, surgical

documentation form, and knee examination form. The knee history form and surgical documentation form are only used at baseline.

EQ-5D

EuroQol-5D (EQ-5D) is a patient questionnaire used to measure Quality of Life. Subjects in the clinical study filled out this instrument at five observation points (baseline, 1.5-, 6-, 12- and 24-months). EQ-5D is a standardized measure of health status developed by the EuroQol (the "EQ") Research Foundation and provides a simple, generic measure of health. The EQ-5D has two components—a descriptive 5 question portion and a General Health Visual Analog Scale (VAS) where subjects make a mark on a line to represent their overall health assessment. The EQ-5D-3L asks subjects to grade their own health in 5 Dimensions (the "5D"), mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using three levels (the "3L") of possible responses, no problems, some problems, severe problems. Each of the 5 questions gets a score from 1 to 3, where 1 is the best possible score and 3 is the worst. Thus, a study subject who checks in the first box, "I have no problems," would be assigned a score of 1 for mobility. Filling out the entire questionnaire generates a series of five numbers with each digit between 1 and 3. For example, a score of 11111 means the subject has no problems, whereas a score of 11223 means the person has no problems with the first two questions (dimensions), some problems with the next two, and an extreme problem with the final question.

The subject's answers to the 5 questions on health converts into a single summary index by applying a formula that attaches a weight to each level in each dimension (question) of the questionnaire. The index deducts the appropriate weight from 1.0, the value assigned for full health. The VAS records the subject's self-rated health on the day completed on a vertical, Visual Analog Scale with the endpoints labelled "Worst Imaginable Health State" (assigned a value of 0) and "Best Imaginable Health State" (assigned a value of 100). The Sponsor evaluated the EQ-5D data according to the EQ-5D User Guide.

Appendix F: Development and Pre-clinical Testing of NUsurface

Anatomical Characterization of the Human Knee

One of the first steps toward designing a medial meniscus replacement device was to accurately characterize the anatomical size and shape of the medial meniscus, tibial plateau, and femoral condyle. To do this, Elsner et al.[94] studied MRI scans of the medial meniscus and knee bones from 118 subjects with no obvious knee pathologies. The mean age of the subjects was 62 years (range: 45-79 years) and average BMI was 28 kg/m^2 (range: 19-39 kg/m^2). The researchers used MRI measurements of the medial meniscus, tibial plateau, and femoral condyle in order to address 3 goals:

1. Compare the average dimensions of the medial meniscus and knee bones in male and female populations;
2. Develop a mathematical model representing all dimensions of the human knee;
3. Use the relationship between the dimensions of the knee to help size-match meniscus implants based on minimal, routine MRI measurements.

Results of the comparison between male and female knees were anticipated: the dimensions of male knees were significantly larger (17% on average) than female knees. For example, in males, femoral condyles were 15% larger, tibial plateaus were 13% larger, and the width and length of the medial meniscus were 16% and 17% larger, respectively, compared to female knees. Importantly, many of the relationships between the dimensions of the meniscus, tibia, and femur were not significantly different between male and female populations. In other words, differences between male and female knees could be explained by general scaling, rather than differences in shape or morphology. The researchers then used the relationships between the dimensions of the knee to develop a mathematical model of the entire joint. The advantage of the model is that all dimensions of the knee—including the dimensions of the articular surfaces in the medial compartment—can be determined from one routine MRI measurement: tibial plateau width.

Design and Pre-clinical Testing of NUsurface and PCU

The next step was to use measurements of the human knee to design a meniscus replacement device. In 2010, Elsner et al.[95] used computational modeling to design and test various configurations of the initial meniscus implant. To design the implant, the team used MRI scans of cadaver knees to build a 3D finite-element (FE) model representing the articular surfaces of the medial compartment and the meniscus implant (**Figure 2.1a**). Next, several configurations of the polycarbonate urethane (PCU) implant were tested in computational simulations of knee loading (i.e. 1,200 N of axial load) (**Figure 2.1b**). The various configurations of implant design included PCU-only implants; implants with circumferential reinforcement fibers made from polyethylene (PE), carbon, Kevlar, Nitinol, titanium, or stainless steel; and implants with 21 to

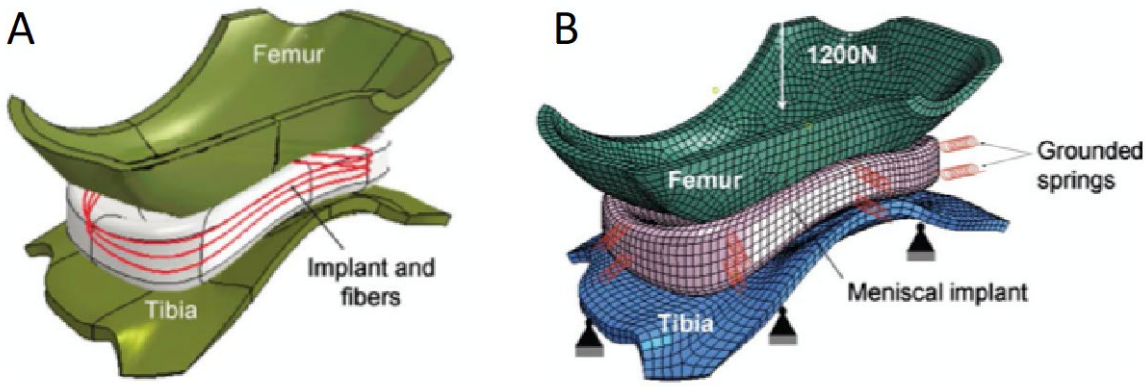


Figure 2.1. (A) 3D finite-element (FE) model of the femur, tibia, and meniscus implant. (B) FE model of the meniscus implant under 1,200 N of axial load.

39 loops of reinforcement fibers. Through simulations, the team determined how the various implant configurations impacted circumferential expansion of the implant as well as peak internal stress, contact pressure distribution, and contact area in the knee joint.

Results from stimulated compression testing revealed that PCU-only implants were highly distorted under load and resulted in peak internal stresses in the knee joint that were at least 2-times higher than reinforced implants.[95] Compression testing of the various implant configurations showed that the PCU implant with embedded PE fibers, with 3 loops of 7 fibers per loop, was the optimal design to limit implant distortion and stress in the knee joint. Further testing showed that this optimal design distributes pressure on the tibial plateau in a way that resembles the natural meniscus (**Figure 2.2**).

After the implant was designed using computational models, the team built the device and evaluated its biomechanical performance using cadaver knees. In the article from Linder-Ganz et al.[96], the research team obtained 3 human cadaver knees and fixed them to a compression apparatus. The apparatus was designed to apply load across the knee joint and measure pressure in the medial compartment. Biomechanical performance was evaluated using an overall score (range: 100 [best] to 0 [poor]) that took into account 3 separate measurements: peak contact area, utilization of area, and contact area. The biomechanical performance of optimally sized meniscus implants was compared to 1) the natural meniscus (set at a score of 100), 2) undersized implants, and 3) oversized implants. In all tests, the optimally sized implants attained higher scores (mean: 75; range: 80-65) than undersized (n=1; score: 65), and oversized (n=2; mean: 37.5; range: 35-40) implants. Tests of oversized Implants resulted in smaller contact area and concentrated regions of elevated pressure on the tibial plateau. A similar trend was also observed for undersized implants. Results from this pre-clinical study highlight the importance of implanting appropriately sized devices to minimize the risk of elevated contact pressure on the articular cartilage.

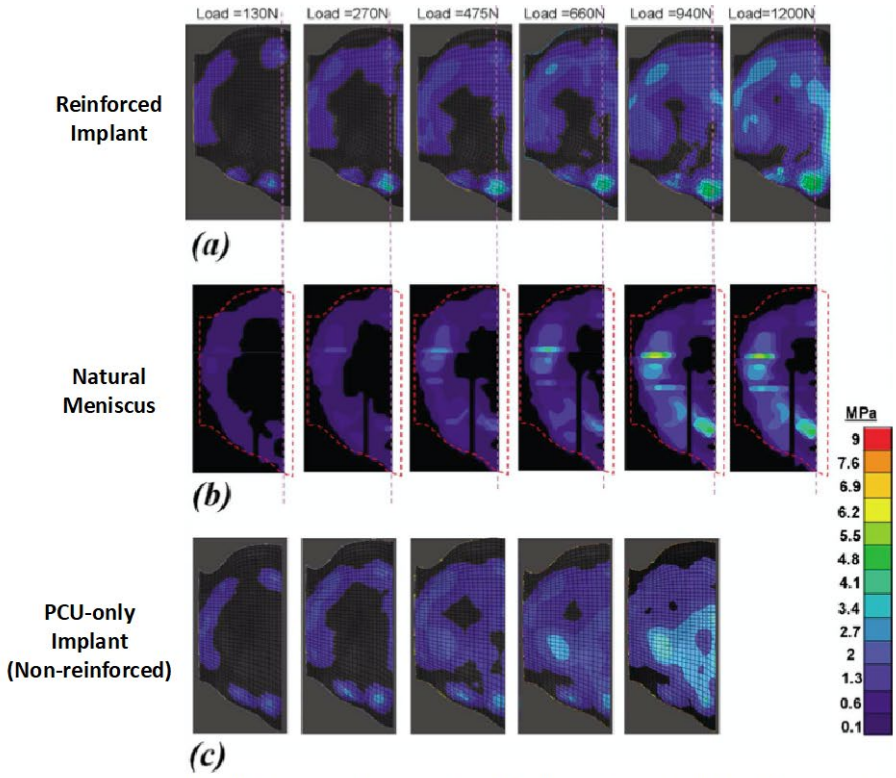


Figure 2.2. Contact pressure maps on the tibial plateau for a meniscus implant with embedded reinforcement fibers (a), the natural meniscus (b), and a PCU-only implant (c) from low load (left) to high load (right). Colors indicate contact pressure on the tibial plateau from low pressure (purple) to high pressure (red).

Additional static and dynamic load testing of NUsurface implants was reported in the 2014 article by Shemesh et al.[97] First, the research team tested fluid absorption capacity by soaking implants in simulated physiologic fluid (SPF) for up to 6 months. Implants gained 62 mg, or 0.75% of their original weight, over 6 months of soaking. Most of the weight gain (87%) occurred in the first week of soaking. Next, the viscoelastic properties of the implant were determined using a compression testing machine. The machine enabled 2 important measurements: 1) implant displacement and 2) contact area between the implant and a replica of the tibial plateau. Both measurements were obtained under applied static and dynamic loading conditions. Results showed that implants had a typical viscoelastic behavior; implants expanded slightly under increasing loads, resumed their original shape after the load was removed, and conformed to the tibial surface under gait-like conditions. Furthermore, implants that underwent 2 million dynamic load cycles over a 2-week period were slightly flattened; width increased by 0.9%, length increased by 1.1%, and thickness decreased by 1%. Time-series mechanical testing revealed that most of the flattening occurred during the first 300,000 cycles and implants underwent few additional changes between 300,000 and 2 million cycles. Overall, these studies showed that NUsurface implants are pliable and generally retain their size, structure, and viscoelastic properties over 2 million gait cycles.

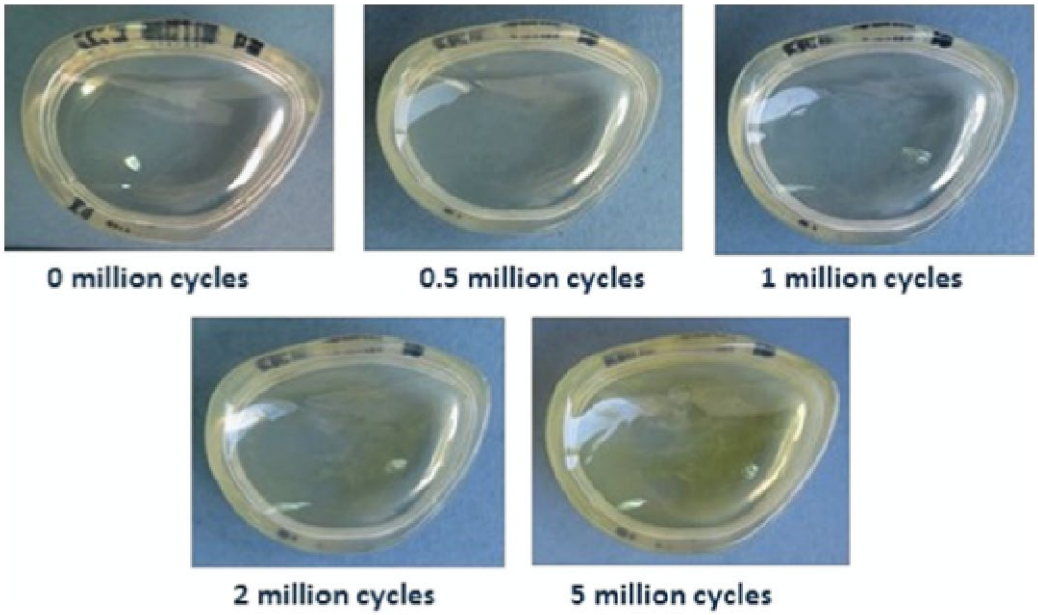


Figure 2.3. Photographs of NUsurface implants at baseline and after 0.5, 1, 2, and 5 million gait cycles

Expanding on work by Shemesh et al., Elsner et al.[98] evaluated long-term wear and volumetric changes to NUsurface implants after 5 million gait cycles. In this study, implants were loaded on a knee simulator machine capable of mimicking axial loading, flexion-extension motion, and tibial rotation. Throughout 5 million cycles, none of the implants dislodged from the knee simulator. Time-series studies revealed that the implant structure was resilient during 5 million gait cycles (**Figure 2.3**) and that they lost a very little amount of material during use (14.5 mg per million gait cycles). After 5 million cycles, implants lost 71.2 mg in weight, the reinforcement fibers did not change location and were intact, and only minor abrasive wear on the articulating surfaces of the implants was observed. Therefore, NUsurface implants are capable of withstanding 5 million gait cycles with minimal surface wear and material loss. Of note, the authors suggest gait testing with a knee simulator machine represents the worst-case scenario for evaluating long-term wear of the NUsurface implant. The team hypothesized that contact between the implant and surrounding soft tissue likely protects implants from extensive wear.

Several studies from other groups have also evaluated the durability of PCU. Incubation of PCU in cell culture with human monocytes and macrophages for 20 weeks revealed that PCU is subject to slight oxidative damage on the material surface.[99] Furthermore, analysis of PCU-based spine implants that were retrieved from patients after an average of 2.6 years (range: 0.7-6.5 years) revealed that 43% of implants had evidence of slight deformation, which, surprisingly, was not correlated to implantation time.[100] Furthermore, all surface damage was restricted to the first 10 µm and did not affect the mechanical properties of the implant.[100] These studies demonstrate that PCU is susceptible to slight oxidative damage on the material surface caused by the interaction of PCU implants and human monocytes and macrophages.

However, oxidative damage is limited to the surface and does not appear to significantly affect the mechanical properties of PCU.

Finally, as an implantable material, current evidence indicates that PCU does not elicit an immune response. Incubation of endotoxin-free PCU particles with cultured human macrophages did not elicit an inflammatory response (as measured by TNFa, IL-1b, and PGE_2) by macrophages,[101] indicating that there is no natural inflammatory response to PCU and that it may be well tolerated in the human body.

Animal Studies

Studies of PCU-based meniscal implants in sheep and goat models have shown that PCU implants are durable and may help decelerate the onset of degenerative knee conditions. In the 2010 study by Zur et al.,[102] a total of 6 adult sheep were subjected to a full meniscectomy of the medial meniscus in the left hindlimb followed by replacement with a size-matched meniscus implant. Animals were then allowed to move freely before being sacrificed for analysis at 3 months (n=3) or 6 months (n=3) of follow-up. Results of histological analyses showed that implanted knees had mild evidence of cartilage degeneration after 6 months, indicating that PCU meniscus implants slowed the onset of articular cartilage degeneration. Macroscopic inspection of control and implanted knees also revealed mild evidence of subchondral bone thickening, osteophyte formation, loss of proteoglycans, and cartilage degeneration in implanted knees. However, there were no significant differences in the histologic scores between groups at 3 months (implant: 29.2±6.8 versus control: 21.4±10.5; *P*>.05) or 6 months (implant: 34.0±10.6 versus control: 24.0±8.2; *P*>.05) (**Figure 2.4**).

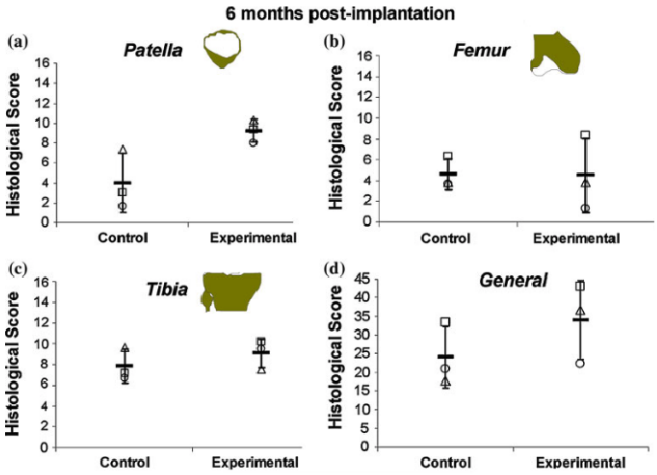


Figure 2.4. Histologic scores of the patella (a), femur (b), tibia (c), and general overall (d) in control and implant (experimental) knees at 6-months follow-up. No significant differences were observed between groups.

In addition, Vracken et al.[103] evaluated the performance of a custom-made PCU meniscus implant in a goat model. A total of 7 adult goats were subjected to a total meniscectomy in the medial compartment of the right hindlimb followed by replacement with a PCU meniscus implant. Of note, implants were attached to the tibia via sutures that were guided through transosseous tunnels, which was a technique that was markedly different than the fixation method used in Zur et al.[102] For a control group, another 6 goats were subjected to sham surgery. After 3 months, all animals were sacrificed for analysis. MRI analysis of implant and

control knees showed that all implants were intact but significantly extruded (2.5-3 mm) compared to control menisci ($P<.01$). In addition, compared to control knees, implant knees showed more severe signs of articular cartilage damage, chondral fibrillation, and scar tissue ossification. The authors concluded that the implant fixation method "could not withstand physiological loading in the goat knee, resulting in extrusion of the implant." However, no evidence of infection or an immunological response to the PCU implant was observed, which is further evidence indicating that PCU implants do not cause inflammation.

Appendix G: NUsurface Publications

CLINICAL & HEALTH ECONOMIC PAPERS:

Javanbakht M, Mashayekhi A, Carlson A, et al. Cost-Effectiveness Analysis of a Medial Meniscus Replacement Prosthesis for the Treatment of Patients with Medial Compartment Pain in the United Kingdom [published online ahead of print,May 2022]. Pharmacoecon Open. 2022;10.1007/s41669-022-00336-4. doi:10.1007/s41669-022-00336-4 (https://doi.org/10.1007/s41669-022-00336-4)

Hershman E, McKeon B, Kaeding C, Edelson R, Greenleaf J, Gersoff W. Superior Improvements in Knee Pain and Function with a Novel Synthetic Medial Meniscus Replacement Implant Compared to Non-surgical Care in Subjects with Knee Pain Following Partial Meniscectomy: Two-year Results from Two Prospective US Clinical Trials. Orthopaedic Journal of Sports Medicine. July 2021. doi:10.1177/2325967121S00206

(https://journals.sagepub.com/doi/10.1177/2325967121S00206)

Zaslav K, Farr J, Alfred R, Alley M, Dyle M, Gomoll A, Lattermann C, McKeon BP, Kaeding CC, Giel T, Hershman, EB. Treatment of post-meniscectomy knee symptoms with medial meniscus replacement results in greater pain reduction and functional improvement than non-surgical care. Knee Surgery, Sports Traumatology, Arthroscopy, April 2021. DOI: 10.1007/s00167-021-06573-0 (https://link.springer.com/article/10.1007/s00167-021-06573-0?)

McKeon BP, Zaslav K, Alfred R, Alley M, Edelson RH, Gersoff W, Greenleaf J, Kaeding C. Preliminary Results from a U.S. Clinical Trial of a Novel Synthetic Polymer Meniscus Implant. Orthopaedic Journal of Sports Medicine, September 2020. DOI: 10.1177/2325967120952414 (https://doi.org/10.1177/2325967120952414)

Alley R, Alfred R, Edelson R, Greenleaf J, Gersoff W, Gomoll A, Kaeding C, McKeon B, Zaslav K. Clinical Results of the NUsurface® Meniscus Implant versus Non-Surgical Controls at 24 months: Data from a Pooled cohort of a randomized controlled study and single arm study. Orthopaedic Journal of Sports Medicine. July 2020. doi:10.1177/2325967120S00367 (https://journals.sagepub.com/doi/10.1177/2325967120S00367)

Hershman EB, Jarvis JJ, Mick T, Dushaj K, Elsner JJ. Direct treatment cost outcomes among patients with medial meniscus deficiency: results from a 24-month surveillance study. Current Medical Research and Opinion, 2020 Jan 8; Vol. 36, Issue 3. DOI: 10.1080/03007995.2020.1713073 (https://doi.org/10.1080/03007995.2020.1713073)

De Coninck T, Elsner JJ, Linder-Ganz E, Cromheecke M, Shemesh M, Huysse W, Verdonk R, Verstraete K, Verdonk P. In-vivo evaluation of the kinematic behavior of an artificial medial meniscus implant: A pilot study using open-MRI. Clin Biomech (Bristol, Avon). 2014 Sep;29(8):898-905. (https://doi.org/10.1016/j.clinbiomech.2014.07.001)

Condello V, Ronga M, Linder-Ganz E, Zorzi C. Alternatives to Meniscus Transplantation Outside the United States. Cartilage Restoration, Practical Clinical Applications. Eds. Farr J and Gomoll

AH. Springer New York, 2014, pp 223-249. (https://link.springer.com/chapter/10.1007/978-1-4614-0427-9_19)

PODIUM & POSTER PRESENTATION:

Zaslav K Clinical Results of the NUsurface® Meniscus Implant versus Non-Surgical Controls at 24 months: Data from a Pooled cohort of a randomized controlled study and single arm study (First 100 MERCURY at 2 Years) Podium Presentation ICRS Focus Meeting, November 19, 2022; Miami, Florida. (https://cartilage.org/icrs-summit-miami/programm/#day2022-11-19)

Verdonk P, Zaslav k, Condello V, Arbel R, Kaeding C, Alfred R, Alley R, McKeon B.; Superior Improvements in Knee Pain and Function of a Novel Synthetic Medial Meniscus Prosthesis to Non-Surgical Care: 3 Year Results Podium Presentation # RE05-209; 39th AGA Congress; September 17, 2022; Vienna, Austria. (https://sepla.intercongress.de/0kW3tJkhguQDZCpxv1zMzW/)

Gersoff W, Gomoll A, Hacker S, Hershman E, Verdonk P.; Synthetic Medial Meniscus Replacement Superior to Non-Surgical Control: 3-Year RCT Results; ICRS 2022 Annual Meeting, April 15, 2022; Berlin, Germany (https://cslide.ctimeetingtech.com/icrs2021/attendee/confcal/presentation/list?q=Hershman#presentation-abstract-647433327644)

Shabshin N, Zaslav K, Lattermam C, Kaeding C.; Two-Year MRI Follow-Up on Medial Compartment Cartilage: Superiority of Implanted Synthetic Medial Meniscus Over Non-Surgical Care; ICRS 2022 Annual Meeting, April 15, 2022; Berlin, Germany (https://cslide.ctimeetingtech.com/icrs2021/attendee/confcal/presentation/list?q=kaeding#presentation-abstract-643170046066)

Cooper AD, Greenleaf J, Edelson R.; Superior Improvements in Knee Pain and Function with a Novel Synthetic Medial Meniscus Replacement Prosthesis Compared to Nonsurgical Care in Subjects with Knee Pain following Partial Meniscectomy: Three-Year Results from Two Prospective US Clinical Trials; AAOS 2022 Annual Meeting; March 24, 2022; Chicago, Illinois. (https://submissions.mirasmart.com/AAOS2022/Itinerary/PresentationDetail.aspx?evdid=1018)

Gersoff W, McKeon B, Kaeding C, Edelson R, Greenleaf J, Easton R, Bankston L, Cooper A, Latterman C, Alfred R, Alley R, Farr J, Zaslav K, Giel T, Inzana J, Montgomery W, McCarty E, Kurzweil P, Berman J, Carter T, Hacker S, Jones D, Gomoll A, Hershman E; Superior Improvements in Knee Pain and Function with a Novel Synthetic Medial Meniscus Replacement Implant Compared to Non-surgical Care in Subjects with Knee Pain Following Partial Meniscectomy: Two-year Results from Two Prospective US Clinical Trials; AANA-AOSSM Combined 2021 Annual Meeting; July 8, 2021; Nashville, Tennessee. (https://aossm-aana.sportsmed.org/program/instructional-courses)

Kurzweil P, Farr J, Geil T, Gomoll A, McCarty E, Zaslav K; Clinical Results of the NUsurface® Medial Meniscus Implant versus Non-Surgical Controls: All 242 Patients of a pooled Randomized Control Trial and Single-Arm Observational Study at 12 Months; Podium Presentation, Award-Winning Research Papers and Feature Lectures Session; AANA 2020

Annual Meeting; May 8, 2020; Grapevine, Texas. (https://www.aana.org/aanaimis/sitedownloads/education/annualmeeting/2020/preliminary.pdf)

McKeon B, Lattermann C, Gomoll A, Greenleaf J, Edelson R, Zaslav K, Giel T, Kaeding C, Gersoff W, Alfred R, Alley M, Farr J, Carter T, Bankston L, Easton R, Cooper A, Montgomery W; Early Clinical Results of a Synthetic Medial Meniscus Replacement Implant Versus Non-Surgical Controls: First 74 Patients of an FDA Investigational Device Exemption Randomized Controlled Trial at 2 Years Follow-Up; Podium Presentation, Sports Medicine VI Session; AAOS 2020 Annual Meeting; March 27, 2020; Orlando, Florida. (https://aaos.apprisor.org/epsSearchAAOS.cfm)

Agar G, Arbel R, Verdonk P, Condello V, McKeon BP, Zaslav KR, Kaeding C; Early Clinical Results of the NUsurface® Interpositional Knee Endoprosthesis versus Non-Surgical Controls: First 75 Patients of a Randomized Control Trial at 2 Years Follow-up; Podium Presentation, Sports Medicine Session; 39th IOA Annual Meeting; December 12, 2019; Tel Aviv, Israel. (https://ws.eventact.com/ioa2019/Program)

Gersoff W, McKeon B, Alfred R, Alley M, Edelson R, Greenleaf J; Clinical results of the NUsurface® Interpositional Endoprosthesis versus Non-Surgical Controls: First 100 Patients of a Pooled Randomized Control Trial and Single-Arm Observational Study; Podium Presentation #IN18-1227; DKOU 2019; October 22, 2019; Berlin, Germany. (https://dkou.org/en/programme/)

Zaslav K, McKeon B, Gersoff W, Alfred R, Alley M, Edelson R, Greenleaf J, Kaeding C; Clinical Results of the NUsurface® Implant vs Non-Surgical Controls: First 100 Patients from RCT and Single-Arm Observational Study at 12 Months; Podium Presentation #12.3.1; ICRS 15th World Congress; October 6, 2019; Vancouver, Canada. (https://cartilage.org/icrs2019-world-congress-vancouver/final-programme/)

Arbel R, Verdonk P, Condello V, McKeon BP, Zaslav KR, Kaeding C; Early Clinical Results of a Non- Anchored Interpositional Knee Endoprosthesis vs. Non-Surgical Controls: First 75 Patients of a Randomized Control Trial at 2 Years Follow-up; Podium Presentation # RE05-209; 36th AGA Congress; September 13, 2019; Manheim, Germany.

(https://kongressarchiv.aga-kongress.info/wp-content/uploads/2019/10/AGA19_Abstractband.pdf)

Kaeding C; Early Results of a Polycarbonate-Urethane Medial Meniscus Implant; Symposium: Beyond Meniscus Repair: A Case-Based Approach; Podium Presentation; 2019 ISAKOS 12th Biennial Congress; May 13, 2019; Cancun, Mexico. (https://www.isakos.com/meetings/2019Congress/InteractiveAgenda2019?ExpandSection=1338#Session2359)

Hershman EB, Jarvis JL, Mick T, Dushaj K, Elsner JJ; Real-World Treatment Cost Outcomes among Patients with Medial Meniscus Deficiency: Results from a 24-Month Surveillance Study; Podium Presentation; Paper #243; AAOS 2019 Annual Meeting; March 12, 2019; Las Vegas, Nevada, USA. (https://www.aaos.org/uploadedFiles/2019_FinalProgram.pdf)

Condello V; NUsurface: Where Are We?; Podium Presentation, Meniscus Reconstruction Session B12; The Meniscus 4th International Meeting; February 1, 2019; Bologna, Italy.

(https://www.the- meniscus.org/sites/default/files/meniscus2019.pdf)

Verdonk P; Menisci Novel Approach; Podium Presentation Session 5.2; 5th ICRS Summit: Bio-Orthopaedics in Sports Medicine; January 17, 2019; San Diego, California, USA. (https://drignaciodallo.com.ar/wp-content/uploads/ICRS_FinalProgrammeSanDiego_final.pdf)

Hershman EB, Jarvis JL, Mick T, Dushaj K, Elsner JJ; Direct Treatment Cost Outcomes among Patients with Medial Meniscus Deficiency: Results from a 24-Month Surveillance Study; Poster Presentation PMS26; ISPOR Europe 2018; November 10 – 14, 2018; Barcelona, Spain. (https://www.ispor.org/heor-resources/presentations-database/presentation/ispor-europe-2018/comparative- treatment-costs-of-surgical-vs-non-surgical-patients-with-medial-meniscus-deficiency-results-from-a-24- month-surveillance-study)

PRE-CLINICAL PODIUM PRESENTATIONS & PAPERS:

Sukopp M, Shemesh M, Pruech E, Linder-Ganz E, Hacker S, Condello V, Schwer J, Ingatius A, Dürselen L, Seitz A M; Biomechanical Evaluation of the In-Situ Stability of a Novel Artificial Medial Meniscus Implant; ORS 2021 Annual Meeting; February 12-16, 2021; Virtual Annual Meeting. (https://www.ors.org/2021annualmeeting/)

Shemesh M, Shefy-Peleg A, Levy A, Shabshin N, Condello V, Arbel R, Gefen A. Effects of a Novel Medial Meniscus Implant on the Knee Compartments: Imaging and Biomechanical Aspects. Biomechanics and Modeling in Mechanobiology, 2020 March 31. DOI: 10.1007/s10237-020-01323-6 (https://pubmed.ncbi.nlm.nih.gov/32236747/)

Elsner JJ, Shemesh M, Shefy-Peleg A, Gabet Y, Zylberberg E, Linder-Ganz E. Quantification of in vitro wear of a synthetic meniscus implant using gravimetric and micro-CT measurements. J Mech Behav Biomed Mater. 2015; 49:310-20. (https://doi.org/10.1016/j.jmbbm.2015.05.017)

Shemesh M, Asher R, Zylberberg E, Guilak F, Linder-Ganz E, Elsner JJ. Viscoelastic properties of a synthetic meniscus implant. J Mech Behav Biomed Mater. 2014 Jan;29:42-55. (https://doi.org/10.1016/j.jmbbm.2013.08.021)

Elsner JJ, Eliaz N, and Linder-Ganz E. The use of polyurethanes in joint replacement. Materials for Joint Arthroplasty - Biotribology of Potential Bearings. Eds. Sonntag R and Kretzer JP. Imperial College Press, London, 2014. (https://doi.org/10.1142/9781783267170_0009)

Zur G, Linder-Ganz E, Elsner JJ, Shani J, Brenner O, Agar G, Hershman EB, Arnoczky SP, Guilak F, Shterling A. Chondroprotective effects of a polycarbonate-urethane meniscal implant: histopathological results in a sheep model. Knee Surg Sports Traumatol Arthrosc. 2011 Feb;19(2):255-63. (https://link.springer.com/article/10.1007%2Fs00167-010-1210-5)

Linder-Ganz E, Elsner JJ, Zur G, Shterling A, Arbel R, Condello V, Zorzi C, Guilak F, Hershman E. A novel Polycarbonate-urethane meniscal implant: from bench to clinical use. Cartilage 2010; 1: 2S. DOI: 10.1177/1947603510386038 (https://online.boneandjoint.org.uk/doi/abs/10.1302/1358- 992X.94BSUPP_XL.ISTA2011-125)

Elsner JJ, Portnoy S, Guilak F, Shterling A, Linder-Ganz E. MRI-based characterization of bone anatomy in the human knee for size matching of a medial meniscal implant. J Biomech Eng. 2010 Oct;132(10):101008. (https://doi.org/10.1115/1.4002490)

Elsner JJ, Portnoy S, Zur G, Guilak F, Shterling A, Linder-Ganz E. Design of a free-floating polycarbonate-urethane meniscal implant using finite element modeling and experimental validation. J Biomech Eng. 2010 Sep;132(9):095001. (https://doi.org/10.1115/1.4001892)

Linder-Ganz E, Elsner JJ, Danino A, Guilak F, Shterling A. A novel quantitative approach for evaluating contact mechanics of meniscal replacements. J Biomech Eng. 2010 Feb;132(2):024501. (https://doi.org/10.1115/1.4000407)