SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Unicompartmental Knee Prothesis

Device Trade Name: Oxford™ Cementless Partial Knee System

Device Procode: NRA

Applicant's Name and Address: BIOMET MANUFACTURING CORP.
Waterton Industrial Estate
Bridgend, Wales
CF31 3XA
United Kingdom

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P010014/S105

Date of FDA Notice of Approval: November 22, 2024

The original PMA P010014 was approved on April 21, 2004, and is intended for use in individuals with osteoarthritis or avascular necrosis limited to the medial compartment of the knee and is intended to be implanted with bone cement. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Oxford™ Cementless Partial Knee System.

II. INDICATIONS FOR USE

The Oxford™ Cementless Partial Knee System is indicated for use in unilateral knee procedures with osteoarthritis or avascular necrosis limited to the medial compartment of the knee. It is intended to be implanted without the application of bone cement for patients whose clinical condition would benefit from a shorter surgical time compared to the cemented implant.

The device system is for prescription use.

III. CONTRAINDICATIONS

- Infection, sepsis, and osteomyelitis
- Use in simultaneous bilateral surgery or planned staged bilateral procedures
- Use in the lateral compartment of the knee
- Rheumatoid arthritis or other forms of inflammatory joint disease

- Revision of a failed prosthesis
- Insufficiency of the collateral, anterior or posterior cruciate ligaments which would preclude stability of the device
- Disease or damage to the lateral compartment of the knee except for a medial ulcer
- Uncooperative patient or patient with neurologic disorders who are incapable of following directions
- Osteoporosis
- Metabolic disorders which may impair bone formation
- Osteomalacia
- Distant foci of infections which may spread to the implant site
- Rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram
- Vascular insufficiency, muscular atrophy, neuromuscular disease
- Incomplete or deficient soft tissue surrounding the knee
- Charcot's disease
- A fixed varus deformity (not passively correctable) of greater than 15 degrees
- A fixed flexion deformity (not passively correctable) of greater than 15 degrees

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Oxford™ Cementless Partial Knee System labeling.

V. DEVICE DESCRIPTION

The Oxford™ Cementless Partial Knee System is a medial, unicompartmental knee prosthesis consisting of three components: a femoral component to substitute the distal femoral bone; a tibial component to substitute the proximal tibial bone; and an unconstrained mobile meniscal bearing which is placed between the two components. The femoral and tibial components of the Oxford™ Cementless Partial Knee System are intended to be implanted without bone cement.

Figure 1: Oxford™ Cementless Partial Knee System

The Oxford™ Cementless Partial Knee femoral and tibial components are manufactured from CoCrMo alloy (ASTM F75), and the bone contacting surfaces of the implants are coated with a plasma sprayed titanium alloy powder (Ti-6Al-4V per ASTM F1580). The femoral and tibial components bone contacting surfaces are then coated a second time

with a plasma sprayed hydroxyapatite (HA) powder (ASTM F1185 and ISO 13779-6). The meniscal bearing is made of ultra-high molecular weight polyethylene (UHMWPE per ASTM F648), embedded with a titanium (Ti-6Al-4V per ASTM F136 and ISO 5832-3) wire and two tantalum balls (ASTM F560 and ISO 13782) to act as radiological markers.

Device Components

Femoral Component

The cementless femoral component is available in five sizes (Extra Small, Small, Medium, Large, and Extra Large) which may be used on either the left or right knee. The femoral component has two pegs incorporated into the design to provide location to the patients prepared bone. The femoral component features a primary stepped peg with a distal diameter sufficient to provide initial fixation through a press-fit in the patient's prepared femur.

Tibial Component

The tibial components are anatomic in design with specific variants intended for use in each of the left and right knee. Each component is approximately semi-circular in shape, extending anteriorly for optimum bone coverage. The tibial component is available in seven size and in left and right configurations (AA, A, B, C, D, E, F), which increases in the medial lateral (M/L) and anterior-posterior (A/P) dimensions. The inferior surface of the tibial component features a distally protruding keel for initial location of the implant to the patient's prepared bone. The underside surface of the tibial component features the same dual coating as the femoral component.

Meniscal Bearings

The meniscal bearing is available in a range of sizes to match the femoral component sizes and is available in eight thicknesses (ranging from 3mm to 9mm). The meniscal bearings are anatomical in design and have separate variants for implantation in the left and right knee.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of osteoarthritis or avascular necrosis limited to the medial compartment of the knee. Each alternative has its own

advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

The following alternative practices and procedures can be used to treat osteoarthritis or avascular necrosis limited to the medial compartment of the knee:

Alternative Surgical Procedures

- Hemi-arthroplasty: Only one joint surface is replaced
- Osteotomy: Realignment of the bone with or without removal of a portion of the bone
- Knee arthrodesis: Surgical immobilization of the knee joint
- Total Knee Arthroplasty: the entire knee joint is replaced

Non-Surgical Treatments

- Alternative non-surgical procedures
- Cortisone injection
- Hyaluronic injection
- Physical therapy
- Ambulatory (walking) aides
- Arthritis medication

VII. MARKETING HISTORY

The Oxford™ Cementless Partial Knee System is commercially available in the following countries outside the USA:

- Albania
- Argentina
- Bosnia and Herzegovina
- Canada
- China
- Ecuador
- Egypt
- EU
- Hong Kong
- Indonesia
- Iran
- Israel
- Japan
- Kazakhstan
- Lebanon
- Malaysia
- Mexico
- New Zealand
- Russia
- Serbia
- Singapore
- Sri Lanka
- Thailand
- Turkey
- UAE
- Ukraine
- Vietnam

The Oxford™ Cementless Partial Knee System has been implanted in over 300,000 procedures outside the U.S. since 2013. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

Avascular Necrosis
Bearing Dislocation/Disassociation
Clicking/Popping/Crepitus/Grinding
Effusion/Swelling/Edema
Femoral Implant Loosening
Instability
Other Ipsilateral Knee Related Adverse Event
Pain (progressive/persistent)
Stiffness/Limited ROM (progressive/persistent)
Subsidence
Tibial Fracture
Tibial Implant loosening

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Performance testing was conducted for the Oxford™ Cementless Partial Knee System and testing from the currently approved Oxford™ Meniscal Unicompartmental Knee System was leveraged to demonstrate that the Oxford™ Cementless Partial Knee System will perform as intended. Tests performed are listed here:

- Contact Area & Contact Pressure
- Range of motion evaluation
- Femoral Component Fatigue Strength
- Tibial Component Fatigue Strength
- Constrain/Dislocation
- Wear simulation testing
- MR Compatibility evaluation
- Cadaveric study

A summary of each test is provided in the Table below.

Table 1: Summary of Non-Clinical Performance Testing

Evaluation	Test	Acceptance Criteria	Results
Contact Area & Contact Pressure	Analysis of CAD models using Siemens NX12. CAD models of Extra Small and Extra Large Oxford Tibial Bearings articulating against compatible sizes of Femoral and Tibial components.	The contact area and contact stress of the femoral implant and Oxford cemented bearing shall be documented, through a knee range of motion of 0°, 15°, 30°, 60°, 90°. The contact area and contact stress of the tibial implant and Oxford cemented bearing shall be documented, through a knee range of motion of 0°, 15°, 30°, 60°, 90°.	Femoral implant to bearing contact area was found to be 381.68mm^2 and 714.43mm^2 for the Extra Small and Extra Large implants respectively. Tibial implant to bearing contact area was found to be a maximum of 462.42mm^2 and 889.49 mm^2 for the Extra Small and Extra Large bearing implants respectively.
Range of Motion	Analysis of CAD models using Siemens NX12. CAD models of Extra Small and Extra Large Oxford Tibial Bearings articulating against compatible sizes of Femoral and Tibial components.	The femoral and bearing range of motion must have a range that covers at least 0° – 110°.	The analysis of contact area shows that full contact is maintained between the bearing and femoral component up to at least 90° flexion. At 135° flexion, the Extra Small and Extra Large bearings respectively provide contact areas of 223.28mm^2 and 413.18mm^2, which remains greater than half the contact area at 0° flexion. The femoral component and the bearing have spherical articulating surfaces with no positive features protruding beyond the spherical surfaces. The devices do not limit range of motion and a high level of contact is maintained to at least 135°.
Femoral Component Fatigue Strength	Physical testing, with load based on ISO 7206-	Femoral implant shall withstand a peak load of 1.61 kN for 5 million cycles without crack formation, visual damage or articular surface dimensional deformation greater than manufacturing tolerances.	All samples survived 5 million cycles at 1.61kN peak load without cracks or visual damage, and remained within the manufacturing tolerance.
Tibial Component Fatigue Strength	Physical with load based on ISO 7206.	Tibial implant shall withstand a peak load of 1.61 kN under cyclic loading for 5 million cycles without crack formation, visual damage or articular surface dimensional deformation greater than manufacturing tolerances.	All samples survived 5 million cycles at 1.61kN peak load without cracks, visual damage, or dimensional deformation that would take them outside the manufacturing tolerance.
Constraint / Dislocation	Empirical data review: Review of device geometry, indications/ contraindications, and Post Market Surveillance data	The load required to induce A/P subluxation shall be documented. The load required to induce M/L subluxation shall be documented. The torque required to induce I/E rotational subluxation shall be documented.	The design of the Oxford Partial Knee was found to provide no constraints on relative motion of the implants. The sphere-on-sphere articulation of the femoral component on the bearing, and the flat-on-flat articulation of the bearing on the tibial implant, allow the bearing and femoral component to translate freely in the A/P and M/L direction relative to the tibia, and allow the bearing, femoral component, and tibial component to rotate freely internally and externally relative to each other. The loads required to induce subluxation are dependent on the patient's anatomy and not on the device design.

Wear	1.Wear testing per ISO 14243-1:2002 with amendments to reflect some changes in ISO 14243-1:2009 2.Wear testing was performed under ISO 14243-1 load control derived kinematics over 10 million test cycles on worst cased aged bearing per ASTM F2003	1.Tibiofemoral wear shall be evaluated per ISO 14243. Mean wear rate for the medial compartment shall be no greater than 21.70mm³/10⁶ cycles. 2. Informative test, no acceptance criteria applied	1.Mean wear rate of 19.57mm^3/10^6 cycles for the medial compartment specimens. The acceptance criteria were satisfied. 2. Mean linear gravimetric wear rate of 8.60 mg/Mc ± 3.76 mg/Mc
MR Compatibility Evaluation	Research Analysis/Adoption	Suitable for labeling as "MR Conditional".	Suitable for MRI use under the following conditions: Static Magnetic Field (B0) Orientation: Horizontal, Cylindrical Bore Static Magnetic Field Strength (B_0): 1.5 T or 3.0 T Maximum Spatial Field Gradient: 25 T/m (2500 Gauss/cm) RF Polarization (Formerly RF Excitation): Circularly Polarized (CP) RF Transmit Coil Type: Integrated Whole Body Transmit Coil Operating Mode: Normal Operating Mode Maximum Whole-Body SAR: 2 W/kg 15 minutes continuous RF followed by a wait time of 6 minutes

Coating Characterization

Characterization of the plasma spray and bilayer coating was performed according to FDA *Guidance for Industry on the Testing of Metallic Plasma Sprayed Coatings on Orthopedic Implants to Support Reconsideration of Postmarket Surveillance Requirements* (February 2, 2020). The following mechanical testing conducted:

- Microstructure of the modified surface
  - Surface thickness per ASTM F1854
  - Void size per ASTM F1854
  - Mean volume percent of voids per ASTM F1854
- Mechanical Properties of the modified surface
  - Shear fatigue strength per ASTM F1160
  - Static shear strength per ASTM F1044
  - Static tensile strength per ASTM F1147
  - Abrasion resistance per ASTM F1978

A summary of the Oxford™ Femur and Oxford™ Tibia component validation is provided in the table below.

Table 2: Mechanical Testing of Coatings

Test Method / Applicable Standards	**Acceptance Criteria**	**Results : Femur Plasma Spray Titanium coating**	**Results : Tibia Plasma Spray Titanium coating**
ASTM F1044 (Shear Static)	≥ 20 MPa	27.97 ± 0.34 MPa	41.95 ± 9.01 MPa

ASTM F1160 (Shear Fatigue)	≥ 10,000,000 cycles	All samples met 10,000,000 cycles	All samples met 10,000,000 cycles
ASTM F1147 (Static Tensile Adhesion)	≥ 22 MPa	47.49 ± 9.06 MPa	33.13 ± 5.98 MPa
ASTM F1854 (Thickness)	386 µm to 1,010 µm	802.56 ± 45.32 µm	757.22 ± 71.37 µm
ASTM F1854 (Porosity)	30% to 70%	38.08 ± 2.53 %	41.44 ± 4.72 %
ASTM F1854 (Pore Size)	100 µm to 1,000 µm	137.51 ± 7.85 µm	170.02 ± 13.34 µm
ASTM F1978 (Taber Abrasion)	Weight loss max. 65mg	29.03 ± 8.48 mg	34.78 ± 3.16 mg

In addition, the hydroxyapatite coating was characterized according to FDA guidance *510(k) Information Needed for Hydroxyapatite Coated Orthopedic Implants* (February 20, 1997). The hydroxyapatite coating met all applicable characterization requirements.

Biocompatibility

The implants are manufactured using implant grade materials and the instruments are manufactured using standard instrumentation materials. The biological evaluation per ISO-10993 was based on review of the materials, manufacturing vendors, manufacturing validation testing (cytotoxicity, sensitization, systemic toxicity, pyrogen testing, intracutaneous irritation), and manufacturing reagents. The risk assessment confirmed that there are no risks associated with the biocompatibility of the Oxford™ Cementless Partial Knee System.

B. Animal Studies

A nonclinical Good Laboratory Practice (GLP) implantation study was performed to evaluate the local effects including bone healing response of the two-representative bone-contacting samples of the Oxford™ Cementless Partial Knee System, i.e. CoCr plasma sprayed with HA (Test Article 1 (T1)) and CoCr plasma sprayed with Ti6Al4V alloy and HA on top (Test Article 2 (T2)). The test articles were compared to the bone-contacting material compounds of the marketed Oxford™ Cemented Partial Knee System (control article (C), polished CoCr). Articles were tested in a femoral condyle and humeral model in sheep for 4, 13 and 26 weeks. Local tissue effects including bone healing response were evaluated based on macroscopic, histopathologic and histomorphometric analyses. Local tissue effects evaluation showed a slight to moderate inflammatory reaction, which was similarly observed in the three groups, leading to minimal to no reaction of both T1 and T2 when compared to C, at the three time points. Slight to moderate numbers of macrophages containing blue/grey granular material of unknown nature were rarely observed in draining lymph nodes mainly for the Tl and T2 articles (but also suspected in the C group). Even though it is doubtful due to their probable observation in the C group, there is a possibility that these macrophages might correspond to drained macrophages containing phagocytosed hydroxyapatite from the

implantation sites. The hydroxyapatite coating of T1 and T2 seemed less thick and sometimes discontinuous over time. Following the complete necropsy, no findings on the organs could be linked to the implanted articles. Regarding bone healing response, bone neoformation was similar for all articles. Osteoconduction was similar for T1 compared to C, and slightly less advanced for T2 after 26 weeks. Osseointegration was greater for T1 and T2 compared to C after 26 weeks. Bone remodeling similarly progressed among the three groups over time. Based on the Reactivity Ranking, at four weeks, thirteen weeks and twenty-six weeks after implantation, the test articles scored <3 and were considered to have minimal to no reaction when compared to the control article.

Further animal studies were not necessary to support the safety and effectiveness of the Oxford™ Cementless Partial Knee System implants.

C. Additional Studies

Additional testing was performed as outlined in the table below.

Table 3: Additional Testing Summary

Test	Acceptance Criteria	Results	Analysis Type
Sterilization	Gamma irradiation sterilization process is used. The sterilization dose is established in accordance with Method VDmax20 from ISO/TS 13004:2022 and Method VDmax25 from ISO 11137-2:2015. Devices must have a sterility assurance of at least 10^{-6}.	Passed	Validation was performed on the largest size Femoral which was determined to create the worst case conditions for the coated metal components.
Endotoxin	Total endotoxin should be less than 20 endotoxin units (EU)/Device.	Passed	ANSI/AAMI ST72:2019 Limulus amebocyte lysate (LAL) test performed on Cementless Oxford Femoral and Tibial component. Results confirms that the testing limit of 20 endotoxin units per construct is met.

Package performance	Packaging integrity tests conducted in simulated testing at baseline, 1, 3, 5, 7, and 10 years, and real time aging at 1, 3, 5, 7, and 10 years: 1.Peel strength; 2.bubble testing; 3.visual heat seal inspection; 4.visual inspection / label copy.	Passed	Samples processed under normal conditions at the minimum sealing parameters were evaluated via visual inspection, seal integrity (ASTM F-1886), bubble leak testing (ASTM F-2096), aseptic presentation (ISO 11607), peel strength (ASTM F-88), and label legibility. Validation was completed for Nylon pouch Primary sterile barrier packaging.
Package stability testing	Seal strength values must generate a Ppk process capability minimum value of 0.68 utilizing 0.75lb/inch as the LSL per interval per location	Passed	Seal strength testing was completed for Nylon pouch Primary sterile barrier packaging. Seal Strength demonstrated a Ppk capability of 2.09.
Cleaning validation	Visually free of manufacturing material or cosmetic defects. Total Organic Carbon ≤1.25 mg/part Non-Polar Solvent Extractable ≤2.0 mg/part Non-Soluble Water Extractable ≤3.0 mg/part Soluble Water Extractable ≤4.0mg/part	Passed	Cleaning validation was conducted on the implants based on worst case for geometry and surface area, therefore one tibia and one femur parts were used.

	Bacterial Endotoxin Test (BET) ≤20 EU/device Cytotoxicity, MEM elution method ≤ Grade 2		

The shelf life for the Oxford™ Cementless Partial Knee System based on the testing above is 10 years for the metal components and 5 years for the polyethylene components.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of unicompartmental knee arthroplasty with the Oxford™ Cementless Partial Knee System originally for use in individuals with osteoarthritis or avascular necrosis limited to the medial compartment in the knee in the US under IDE # G100123 (the "Oxford™ Cementless IDE Study"). Data from this clinical study were the basis for the PMA approval decision for the following modified Intended Use/Indications for Use statement: The Oxford™ Cementless Partial Knee System is indicated for use in unilateral knee procedures with osteoarthritis or avascular necrosis limited to the medial compartment of the knee. It is intended to be implanted without the application of bone cement for patients whose clinical condition would benefit from a shorter surgical time compared to the cemented implant. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between October 2013 and November 2018. The database for this Panel Track Supplement reflected data collected through November 2020 and included 378 patients. There were 9 investigational sites.

The study was a prospective, multi-center, two-arm, single-blinded, randomized, controlled clinical study. Each knee included in the study was randomized to receive treatment with either a Oxford™ Cementless Partial Knee (Investigational arm) or a Oxford™ Meniscal Unicompartmental Knee (Control arm). An imbalanced, blocked randomization (2:1, Cementless vs. Cemented) was used. The study included both Unilateral and Bilateral knees. In the case of Bilateral knees, the subject received the same knee implant for the second surgery as was prescribed by the randomization assigned for the first knee.

Unilateral and bilateral cases were determined retrospectively. Subjects receiving a single implant were classified as a unilateral case. Subjects receiving two study devices (staged or simultaneously) were considered as bilateral cases from the start of the first knee being implanted, such that all case data was considered and analyzed as

a bilateral case. Subjects implanted with a single study device and later receiving a non-study device in the contralateral knee were also considered bilateral cases.

The study was designed to show that the investigational device (Cementless) was non-inferior to the Control device using four co-primary study endpoints. This was shown using a closed testing method in which each of the primary endpoints (described below) are compared using $\alpha=0.05$. Study success required that the Cementless group successfully demonstrated non-inferiority when compared to the Control group for all four of the individual primary endpoints.

The sample size was calculated based on the endpoint of Radiographic Success, which was the endpoint which required the largest sample size to maintain 90% power. A success rate of 95% was used for the estimate of Radiographic Success, which resulted in a sample size of 191 Cementless device vs. 96 Control (5% type I error rate, 90% power). The sample size was increased by 10% to allow for possible exclusions in the primary analysis due to bilateral patients who may not be poolable with the unilateral cases, as well as attrition of up to 15%. This gave a theoretical sample size of 383 total subjects (255 Cementless vs. 128 Control). After completion of enrollment, it was discovered that five (5) subjects were implanted with an earlier version of the device and had to be excluded from the data analysis. This resulted in a final sample size of 378 subjects. The actual per-group sample size is slightly different from the theoretical per-group sample size due to the randomization scheme which was blocked within-site and per-patient. The per group, Per Protocol final sample sizes were 241 Cementless vs. 137 Control.

An independent laboratory was contracted to review, analyze and report laboratory findings including the condition of the explanted devices.

All radiographs were reviewed by an independent primary reviewer. If the primary reviewer identified a radiographic failure, the films deemed a failure, along with a randomly selected statistical sample of current non-failures were sent to a qualified, independent second reviewer. If the results of the second review differed significantly from the first, an independent, qualified third reviewer was employed to review the films.

All knee-related adverse events (AEs) were reviewed by an independent Clinical Events Committee (CEC) consisting of three independent orthopaedic surgeons and adjudicated for seriousness, device-relatedness, severity, and outcome. For completeness, all general AEs were examined by one of the CEC members to determine if any of those events should have been classified as a knee-related event and adjudicated accordingly.

The control group was the Oxford™ Cemented Partial Knee, which is a legally marketed alternative.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Oxford™ Cementless IDE study was limited to patients who met the following inclusion criteria:

- Patients with a pre-operative Knee Society Assessment Score of <70
- Patients undergoing primary partial knee arthroplasty as Unilateral arthroplasty or Bilateral arthroplasty, simultaneously or otherwise
- Patients diagnosed with osteoarthritis or avascular necrosis limited to the medial compartment of the operative knee joint
- Male or female patients who are at least 21 years of age at the time of surgery
- Patients with full thickness cartilage loss, with or without bone loss in the medial compartment
- Patients with functionally intact ACL and PCL
- Patients who need to obtain relief of pain and/or improved function in their knee
- Patients with fixed flexion deformity < 15°
- Patients who are able to follow post operative care instructions
- Patients who are willing and able to return for scheduled follow-up evaluations
- Patients in which natural alignment can be restored
- Patients who have completed a valid, IRB approved Informed Consent Form
- Patients with childbearing potential who voluntarily agree to prevent pregnancy for 2 years following device implantation

Patients were not permitted to enroll in the Oxford™ Cementless IDE study if they met any of the following exclusion criteria:

- Patients with a pre-operative Knee Society Assessment Score of ≥ 70
- Patients in which the device would be used to revise a failed prosthesis
- Patients who are less than 21 years of age at the time of surgery
- Disease or damage to the lateral part of the knee that in the investigator's opinion contraindicates a partial knee replacement
- Patients diagnosed with rheumatoid arthritis or other forms of inflammatory joint disease
- Patients diagnosed with a failed upper tibial osteotomy in the operative knee
- Patients diagnosed with post-traumatic arthritis after tibial plateau fracture
- Patients who have had a patellectomy
- Patients with a flexion deformity > 15°
- Patients with a fixed varus deformity > 15°
- Patients who have rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram
- Patients with a fused knee on operative side
- Patients who have active or suspected infection, local or systemic, that, in the opinion of the investigator, may put patients at undue risk.

- Patient with pre-existing condition(s) that may interfere with the survival of the implant or their outcomes, including:
    - Sickle Cell Anemia
    - Lower extremity muscular atrophy
    - Neuromuscular disease
    - Vascular insufficiency
    - Metabolic Disorders which impair bone formation
    - Paget's Disease
    - Charcot's Disease
    - Osteomalacia
    - Severe Osteoporosis
- Patients with clinical conditions that may limit follow-up (in the opinion of the investigator) including;
    - Immuno-compromised conditions (i.e. HIV)
    - Hepatitis
    - Tuberculosis
    - Neoplastic disease such as cancer of the prostate, lung, stomach, cervix, etc.
- Chronic renal failure
- Organ transplant (i.e. heart, liver, lung, etc.) recipients
- Known disease process that in the opinion of the investigator may limit long term (4 year) follow up (i.e. multiple sclerosis, leukemia, lymphoma, etc.)
- Patients diagnosed with Parkinson's or Alzheimer's Disease
- Patients who have had an above-knee amputation in the contralateral leg
- Instability or deformity of the ligaments and/or surrounding soft tissue, which would preclude stability of the prostheses
- Patients with a known metal allergy
- Prisoners or, individuals who are known to be abusing drugs or alcohol or are mentally incompetent
- Patients who have received systemic steroids within the past 6 months or steroid injection into the affected knee within the previous 6 weeks prior to enrollment
- Patients who are pregnant
- Patients with severe valgus or varus knees (valgus or varus angulation of more than 20°) where collateral ligament, iliotibial band, or popliteal release is required
- Patients who refuse to sign the IRB approved Informed Consent Form
- Participation in an interventional clinical research study procedure, other than a Bilateral knee arthroplasty in this study, within the past 12 months
- Patients with a history of osteomyelitis or sepsis of the index knee
- Patients who require patellar resurfacing
- Patients who are not skeletally mature
- Patients who have had a total hip replacement procedure <18 months prior to entering the study

- Patients who have had a contralateral non-study knee replacement procedure <18 months prior to entering the study
- Patients who are found intraoperatively to have inadequate bone stock or other conditions that contraindicate a partial knee replacement

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 6 weeks (±3 weeks), 6 months (±1 month), 1 year (±2 months), 2 years (±2 months) and annually (±2 months) until all subjects completed the 2-year follow-up visit postoperatively. After the 2-year follow-up, patients were examined clinically and radiographically on an annual basis until all available study patients completed the 2-year follow-up.

Preoperative information collected and assessments performed included informed consent, medical history, demographics, concomitant medications, Knee Society Assessment Score (KSSA), Knee Society Function Score (KSSF), and Oxford Knee Score (OKS). Postoperatively, the objective parameters measured during the study included a radiographic evaluation, KSSA, KSSF, OKS, and a patient satisfaction questionnaire, which were all collected at all visits. Adverse events and complications were recorded at all visits. The Study Assessment Schedule and Follow-Up Windows Table outlines the study data collection.

Table 4: Study Assessment Schedule

Form Name	Pre-op	Operative	6 Week	6 Month	1 Year	2 Year	Annually*
Informed Consent	X						
Patient History & Record of Medications	X						
Patient Operation		X					
Knee Society Score (KSS)	X		X	X	X	X	X
Oxford Knee Score	X		X	X	X	X	X
Patient Satisfaction Questionnaire			X	X	X	X	X
Radiographic Evaluation (Independent Reviewer)			X	X	X	X	X
Protocol Deviation	As appropriate						
Adverse Event	As appropriate						
Study Completion	As appropriate						
Adverse Event Determination	As appropriate						

Table 5: Follow-Up Visit Windows

Interval	Follow-up Window	Months Post-op	Days Post-op
6 Week	+/- 3 weeks	1-2	21-63
6 Month	+/- 1 month	5-7	153-214
1 Year	+/- 2 months	10-14	304-426
2 Years	+/- 2 months	22-26	669-791
3 Years	+/- 2 months	34-38	1035-1157
4 Years	+/- 2 months	46-50	1400-1522
5 Years	+/- 2 months	58-62	1765-1887
6 Years	+/- 2 months	70-74	2130-2252
7 Years	+/- 2 months	82-86	2495-2617
8 Years	+/- 2 months	94-98	2860-2982
9 Years	+/- 2 months	106-110	3226-3347
10 Years	+/- 2 months	118-122	3591-3712

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Safety:
With regards to safety, all adverse events were recorded, described, and compared for Cementless vs. Control Groups.

The twenty-four months safety endpoint data for the Cementless vs. Control Groups was independently adjudicated by a Clinical Events Committee in accordance with applicable FDA guidance documents to ensure appropriate classification.[1, 2] The twenty-four month safety endpoint data was compared and analyzed for all index knee-related adverse events. These adverse events were summarized by knee and included the number of adverse events involving the index knee for each patient. The safety adverse event reporting was performed for the type of knee procedure to include All Knees, Bilateral Knees, and Unilateral Knee procedures. The safety and adverse event reporting was also performed for the Per-Protocol (PP) and Intent-to-Treat (ITT) populations.

The summary of adverse event data for the Cementless vs. Control Groups and the proportions of index knees experiencing adverse events for both groups and relative risk with associated 95% Confidence Intervals (CI) were reported for the following parameters.

- Subjects with Adverse Events of the index knee, n (%)
- Subjects with Device-Related Adverse Events of the index knee, n (%)
- Total number of Adverse Events of the index knee, n (%)
    - Device Non-Related Non-Serious
    - Device Non-Related Serious
    - Device-Related Non-Serious
    - Device-Related Serious
    - Subjects with device revision/removal
    - Subjects with device removal/conversion to total knee arthroplasty

The twenty-four months safety endpoint data for the Cementless vs. Control Group was then independently adjudicated by a Clinical Events Committee in accordance with applicable FDA guidance documents to ensure appropriate classification. The summary of Adverse Event data for the Cementless vs. Control Groups and the proportions of index knees experiencing adverse events were reported for the following parameters.

- Adverse Event Severity, n (%)
    - Mild
    - Moderate
    - Severe
- Adverse Event Outcome
    - Device Revision/Removal/Reoperation
    - Study Withdrawal

- Tolerated
- Not Tolerated
- Resolved
- Not Resolved

This was performed for all adverse events and for those adverse events that were classified as device-related. An index knee had to have all adverse events classified as either Tolerated or Resolved to be classified within that category.

Effectiveness:

With regards to effectiveness, the primary endpoints in this study consisted of four individual co-primary endpoints:

1. Absence of Revision/Removal/Unanticipated Adverse Device Effect (UADE) at any time point through 24 months follow-up
2. Radiographic Success at 22+ months
3. The Knee Society Assessment Score (KSSA) at 22+ months
4. The Knee Society Function Score (KSSF) at 22+ months

The 22+ Month interval was defined as the first availability of data for that endpoint starting at 22 months after the index procedure.

The Radiographic Success at 22+ months co-primary endpoint was modified to allow the use of radiographs that were completed outside of the 22-26 months study interval window to follow the protocol-defined plan for analysis (use of 22+ month radiographic data). The reason for the missed assessment within the study interval window at 24-months was shown along with the other adverse event data reported for these subjects to support the use of this specific datapoint beyond the 24-month scheduled assessment. The radiographic success is based upon the proportion of radiographically successful knees and all device revisions and removals that are classified as failures. Additionally, the KSSA and KSSF co-primary endpoints for all cases (combined, unilateral, and bilateral) were evaluated with 22+ month data and therefore also modified from the original co-primary endpoints. The Absence of Revision/Removal/Unanticipated Adverse Device Effect (UADE) endpoint was evaluated at the 24-month timepoint.

With regard to success/failure criteria, a successful radiographic endpoint was defined as a knee that met the following criteria at 22+ months:

1. Absence of osteolysis
2. No migration/subsidence of any femoral or tibial component
3. Absence of fractured component

Conversely, a radiographic failure is defined as follows:

1. Presence of osteolysis defined as a radiolucency that is both progressive and is greater than 3 mm at its maximum interface in two or more contiguous zones OR a bony destructive lesion that is progressive in nature.

2. Migration/subsidence of any femoral or tibial component defined as a component migration/subsidence of > 3 mm as compared to 6 week radiographs.
3. A component fracture.

Each co-primary effectiveness endpoint was considered successful for the study overall if the Cementless group was non-inferior to the Control Group, according to the following parameters:

1. Absence of revision/removal/UADE: The proportion of knees that were free from revision/removal/UADE in the Cementless group was non-inferior to that of Control knees using a 10% margin of non-inferiority at 24 Months.
2. Radiographic Success at 22+ Months: The proportion of radiographically successful knees in the Cementless group was non-inferior to the proportion of radiographically successful knees in the Control group using an 8% margin of non-inferiority.
3. KSSA at 22+ Months: The mean KSSA for the Cementless group was non-inferior to the mean KSSA for the Control group using a 6.4-point margin of non-inferiority.
4. KSSF at 22+ Months: The mean KSSF for the Cementless group is non-inferior to the mean KSSF for the Control group using a 9.2-point margin of non-inferiority.

Overall study success requires that the Cementless group successfully demonstrate non-inferiority when compared to the Control group for all four of the individual primary endpoints.

B. Accountability of PMA Cohort

At the time of database lock, of 378 patients enrolled in the PMA study, 82% (309) patients are available for analysis at the completion of the study, the 24-month post-operative visit. Over the first two years there were 7 deaths and 16 Device removal/reoperations. There were five subjects in the Investigational Group that were originally randomized to receive the Investigational cementless device (Intent-to-Treat population) but due to an intraoperative protocol deviation had the Control cemented device implanted (Per Protocol population) done primarily because of concerns of inadequate device to bone fixation with the cementless subject device. Therefore, in the Cementless Group there are 246 knees in the ITT population and 241 knees in the PP population while the Cemented Group there are 132 knees in the ITT population and 137 knees in the PP population. Details are shown in Figure 2 below.

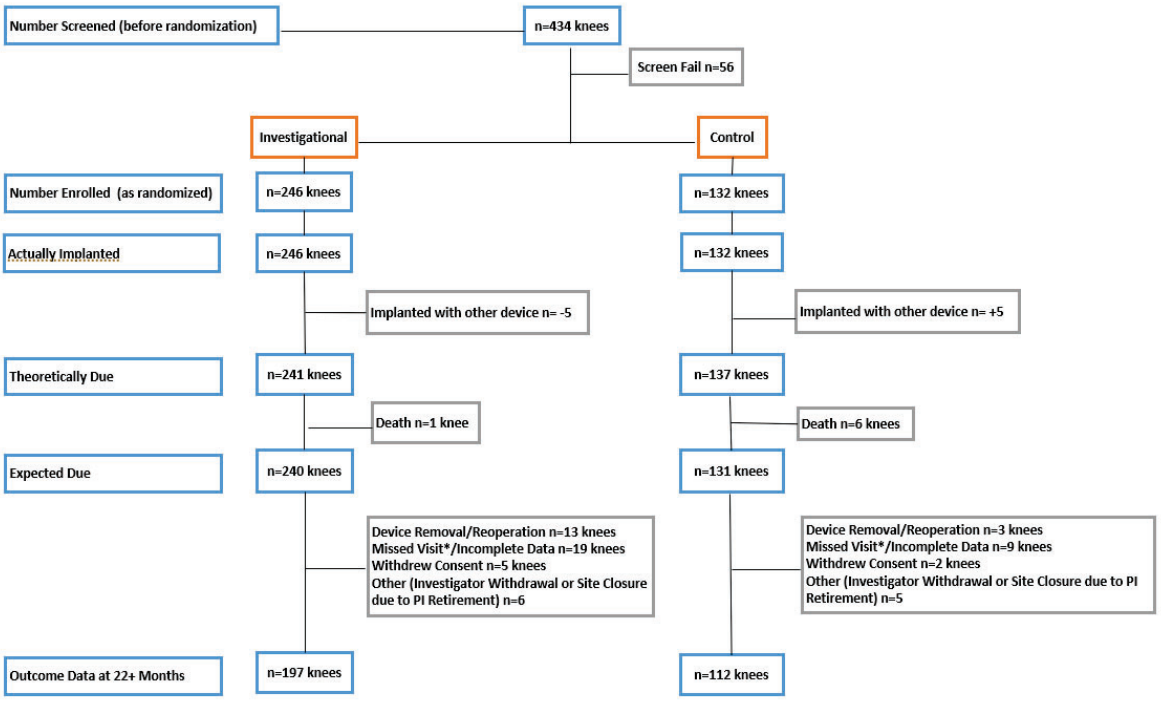

Figure 2: Patient Accountability Tree

The patient accountability summary by knee is presented for Month 12-, 24-, and 36-month clinical evaluations for the PP (Table 6) and ITT (Table 7) populations. The percentage of patients in each group with complete follow-up data at the 24-month evaluation in the PP population was for All Knees (Investigational: 79%; Control: 79%), Unilateral Knees (Investigational: 81%; Control: 78%), and Bilateral Knees (Investigational: 73%; Control: 82%). The percentage of patients in each group with complete follow-up data at the 24-month evaluation in the ITT population was for All Knees (Investigational: 79%; Control: 79%), Unilateral Knees (Investigational: 81%; Control 77%), and Bilateral Knees (Investigational: 74%; Control: 81%).

Table 6: Follow-up Compliance and Subject Accountability for the Per Protocol Population

	Preoperative		12 Months		24 Months		36 Months	
Protocol Window	C	I	C	I	C	I	C	I
All Knees								
Theoretical	137	241	137	241	137	241	137	241
Deaths (Cumulative)	0	0	2	1	4	1	7	3
Failures (Cumulative)	0	0	0	11	3	13	4	15
Expected	137	241	132	229	130	227	126	223
Actual[A]	137	241	111	203	103	179	78	142
% Follow-up[A]	100.0%	100.0%	82.2%	88.6%	79.2%	78.9%	61.9%	63.7%
Actual[B]	137	241	116	207	114	192	83	161
% Follow-up[B]	100.0%	100.0%	85.9%	90.4%	87.7%	84.6%	65.9%	72.2%
Unilateral								
Theoretical	106	199	92	182	90	175	90	173
Deaths (Cumulative)	0	0	1	1	2	1	3	1
Failures (Cumulative)	0	0	0	6	2	7	3	9
Expected	106	199	91	175	86	167	84	163
Actual[A]	106	199	78	157	67	135	48	101
% Follow-up[A]	100.0%	100.0%	85.7%	89.7%	77.9%	80.8%	57.1%	62.0%
Actual[B]	106	199	79	159	73	144	52	116
% Follow-up[B]	100.0%	100.0%	86.8%	90.9%	84.9%	86.2%	61.9%	71.2%
Bilateral								
Theoretical	31	42	45	59	47	66	47	68
Deaths (Cumulative)	0	0	1	0	2	0	4	2
Failures (Cumulative)	0	0	0	5	1	6	1	6
Expected	31	42	44	54	44	60	42	60
Actual[A]	31	42	32	45	36	44	30	41
% Follow-up[A]	100.0%	100.0%	72.7%	83.3%	81.8%	73.3%	71.4%	68.3%
Actual[B]	31	42	36	47	41	48	31	45
% Follow-up[B]	100.0%	100.0%	81.8%	87.0%	93.2%	80.0%	73.8%	75.0%

[A]Patients with complete data for each endpoint in the window time frame

[B]Patients with any follow-up data reviewed or evaluated by investigator ("all evaluated" accounting)

Failures = Revision or removals of any component of the device or an unanticipated, device-related adverse event

I = Investigational Device

C = Control Device

Table 7: Follow-up Compliance and Subject Accountability for the Intent to Treat Population (ITT Population)

	Preoperative		12 Months		24 Months		36 Months	
Protocol Window	C	I	C	I	C	I	C	I
All Knees								
Theoretical	132	246	132	246	132	246	132	246
Deaths (Cumulative)	0	0	2	1	4	1	7	3
Failures (Cumulative)	0	0	0	11	2	14	3	16
Expected	132	246	130	234	126	231	122	227
Actual[A]	132	246	106	208	99	183	76	144
% Follow-up[A]	100.0%	100.0%	81.5%	88.9%	78.6%	79.2%	62.3%	63.4%
Actual[B]	132	246	111	212	110	196	81	163
% Follow-up[B]	100.0%	100.0%	85.4%	90.6%	87.3%	84.8%	66.4%	71.8%
Unilateral								
Theoretical	102	203	88	186	86	179	86	177
Deaths (Cumulative)	0	0	1	1	2	1	3	1
Failures (Cumulative)	0	0	0	6	1	8	2	10
Expected	102	203	87	179	83	170	81	166
Actual[A]	102	203	74	161	64	138	46	103
% Follow-up[A]	100.0%	100.0%	85.1%	89.9%	77.1%	81.2%	56.8%	62.0%
Actual[B]	102	203	75	163	70	147	50	118
% Follow-up[B]	100.0%	100.0%	86.2%	91.1%	84.3%	86.5%	61.7%	71.1%
Bilateral								
Theoretical	30	43	44	60	46	67	46	69
Deaths (Cumulative)	0	0	1	0	2	0	4	2
Failures (Cumulative)	0	0	0	5	1	6	1	6
Expected	30	43	43	55	43	61	41	61
Actual[A]	30	43	31	46	35	45	30	41
% Follow-up[A]	100.0%	100.0%	72.1%	83.6%	81.4%	73.8%	73.2%	67.2%
Actual[B]	30	43	35	48	40	49	31	45
% Follow-up[B]	100.0%	100.0%	81.4%	87.3%	93.0%	80.3%	75.6%	73.8%

[A]Patients with complete data for each endpoint in the window time frame

[B]Patients with any follow-up data reviewed or evaluated by investigator ("all evaluated" accounting)

Failures = Revision or removals of any component of the device or an unanticipated, device-related adverse event

I = Investigational Device

C = Control Device

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a clinical study of subjects undergoing a unicondylar knee arthroplasty performed in the US.

Demographic data collected at baseline for the clinical study are presented in the tables below. There are 113 patients (137 knees) for the control and 207 patients (241 knees) for the investigational device. The mean age was 66.4 years for the control and 65.8 years for the investigational. For the control, the gender breakdown was 54% male and 46% women. For the investigational, the gender breakdown was 61.8% male and 38.2% women. The mean BMI for the control was 31.4 and for the investigational was 31.5. The table below summarizes the clinical study demographic by race breakdown.

Table 8: Oxford IDE Demographic by Race

Outcome	Number of Patients (out of 378)
Black or African American	3 (0.79%)
Hispanic or Latino	1 (0.26%)
White	277 (73.28%)
Other	1 (0.26%)
Missing or Unknown	96 (25.40%)

The tables below summarize the patient demographics in the clinical study by treatment.

Table 9: Demographics (Summary/Average by Treatment Group)

	Control	Investigational	P-Value
Number of Knees	137	241	
Number of Patients	113	207	
At Time of Procedure:			
Age			
N	137	241	
mean +/- SD	66.4 +/- 8.5	65.8 +/- 8.7	0.5365
Range (Min, Max)	(45.0, 81.0)	(37.0, 84.0)	

	Control	Investigational	P-Value
Gender			
Male	54.0% (74/137)	61.8% (149/241)	0.1575
Female	46.0% (63/137)	38.2% (92/241)	
Height in			
N	137	241	
mean +/- SD	67.5 +/- 3.9	67.3 +/- 3.9	0.7847
Range (Min, Max)	(59.0, 78.0)	(58.0, 76.0)	
Weight lbs			
N	137	241	
mean +/- SD	204.2 +/- 41.2	203.1 +/- 37.0	0.7922
Range (Min, Max)	(119.0, 320.0)	(127.0, 310.0)	
BMI			
N	137	241	
mean +/- SD	31.4 +/- 4.8	31.5 +/- 5.2	0.8791
Range (Min, Max)	(21.8, 44.6)	(22.3, 51.0)	
	Control	**Investigational**	**P-Value**
Preoperative Diagnosis			
Osteoarthritis	99.3% (136/137)	97.9% (236/241)	0.4239
Avascular Necrosis	0.7% (1/137)	2.1% (5/241)	
Side of Surgery			
Left	50.4% (69/137)	48.1% (116/241)	0.7482
Right	49.6% (68/137)	51.9% (125/241)	
Knee Involvement			
Unilateral	63.5% (87/137)	65.1% (157/241)	0.4606
Bilateral (Unilateral Presenting)*	26.3% (36/137)	28.2% (68/241)	
Bilateral (Bilateral Presenting)**	10.2% (14/137)	6.6% (16/241)	

*__Unilateral Presenting__-The subject presented as a unilateral knee and later had the contralateral knee replaced. Note: the contralateral knee may or may not have been enrolled in the study.

**__Bilateral Presenting__- The subject had both knees replaced during the same surgery.

Table 10: Demographics (Category by Treatment Group Overall)

Patient Demographics – Overall by Treatment (Unilateral and Bilateral)			C	I
Demographic Measure	**Gender**	**Response**	**N (%)**	**N (%)**
Age				
		<20.0	0	0
		20.0-29.9	0	0
		30.0-39.9	0	1(0.4%)
		40.0-49.9	6(4.4%)	10(4.1%)
		50.0-59.9	23(16.8%)	45(18.7%)
		60.0-69.9	59(43.1%)	101(41.9%)
		70.0-79.9	46(33.6%)	73(30.3%)
		80.0-89.9	3(2.2%)	11(4.6%)
		90.0-99.9	0	0
		>=100.0	0	0
Height				
	Female	<60.0	2(3.2%)	3(3.3%)
		60.0-62.9	11(17.5%)	26(28.3%)
		63.0-65.9	32(50.8%)	37(40.2%)
		66.0-68.9	17(27.0%)	23(25.0%)
		69.0-71.9	1(1.6%)	3(3.3%)
		72.0-74.9	0	0
		75.0-77.9	0	0
		>=78.0	0	0
	Male	<60.0	0	1(0.7%)
		60.0-62.9	0	2(1.3%)
		63.0-65.9	3(4.1%)	10(6.7%)
		66.0-68.9	13(17.6%)	39(26.2%)
		69.0-71.9	37(50.0%)	60(40.3%)
		72.0-74.9	19(25.7%)	33(22.1%)
		75.0-77.9	0	5(3.4%)
		>=78.0	2(2.7%)	0
Operative Difficulty				
		NO	133(97.1%)	237(98.3%)

Patient Demographics – Overall by Treatment (Unilateral and Bilateral)			C	I
Demographic Measure	**Gender**	**Response**	**N (%)**	**N (%)**
		YES	4(2.9%)	4(1.7%)
Gender- Operative Difficulty		Male	3	2
Gender- Operative Difficulty		Female	1	2
Operative Difficulty (Specific)				
		LACK OF FEMORAL BONE	1(0.7%)	1(0.4%)
		OSTEOPOROTIC BONE	1(0.7%)	0
		OTHER	2(1.5%)	4(1.7%)
Operative Side				
		LEFT	69(50.4%)	116(48.1%)
		RIGHT	68(49.6%)	125(51.9%)
Weight				
	Female	<100.0	0	0
		100.0-124.9	1(1.6%)	0
		125.0-149.9	5(7.9%)	15(16.3%)
		150.0-174.9	21(33.3%)	22(23.9%)
		175.0-199.9	20(31.7%)	26(28.3%)
		200.0-224.9	9(14.3%)	16(17.4%)
		225.0-249.9	5(7.9%)	10(10.9%)
		250.0-274.9	2(3.2%)	1(1.1%)
		275.0-299.9	0	2(2.2%)
		>=300	0	0
	Male	<100.0	0	0
		100.0-124.9	0	0
		125.0-149.9	1(1.4%)	2(1.3%)
		150.0-174.9	6(8.1%)	12(8.1%)
		175.0-199.9	20(27.0%)	42(28.2%)
		200.0-224.9	14(18.9%)	38(25.5%)
		225.0-249.9	16(21.6%)	26(17.4%)
		250.0-274.9	6(8.1%)	23(15.4%)

Patient Demographics – Overall by Treatment (Unilateral and Bilateral)			C	I
Demographic Measure	Gender	Response	N (%)	N (%)
		275.0-299.9	7(9.5%)	3(2.0%)
		>=300	4(5.4%)	3(2.0%)

Table 11: Demographics (Category by Treatment Group for Bilateral Patients)

Patient Demographics – Bilateral by Treatment			C	I
Demographic Measure	Gender	Response	N (%)	N (%)
Age				
		<20.0	0	0
		20.0-29.9	0	0
		30.0-39.9	0	0
		40.0-49.9	3(6.0%)	5(6.0%)
		50.0-59.9	13(26.0%)	15(17.9%)
		60.0-69.9	20(40.0%)	35(41.7%)
		70.0-79.9	12(24.0%)	29(34.5%)
		80.0-89.9	2(4.0%)	0
		90.0-99.9	0	0
		>=100.0	0	0
Gender				
		Female	19(38.0%)	33(39.3%)
		Male	31(62.0%)	51(60.7%)
Height				
	Female	<60.0	0	0
		60.0-62.9	0	12(36.4%)
		63.0-65.9	7(36.8%)	13(39.4%)
		66.0-68.9	12(63.2%)	8(24.2%)
		69.0-71.9	0	0
		72.0-74.9	0	0
		75.0-77.9	0	0
		>=78.0	0	0
	Male	<60.0	0	0
		60.0-62.9	0	0

Patient Demographics – Bilateral by Treatment			C	I
Demographic Measure	**Gender**	**Response**	**N (%)**	**N (%)**
		63.0-65.9	2(6.5%)	4(7.8%)
		66.0-68.9	5(16.1%)	16(31.4%)
		69.0-71.9	14(45.2%)	22(43.1%)
		72.0-74.9	10(32.3%)	9(17.6%)
		75.0-77.9	0	0
		>=78.0	0	0
Operative Difficulty				
		NO	50(100.0%)	83(98.8%)
		YES	0	1(1.2%)
Gender- Operative Difficulty	Female			1
Operative Difficulty (Specify)				
		OTHER		1(1.2%)
Operative Side				
		LEFT	25(50.0%)	43(51.2%)
		RIGHT	25(50.0%)	41(48.8%)
Weight				
	Female	<100.0	0	0
		100.0-124.9	0	0
		125.0-149.9	0	5(15.2%)
		150.0-174.9	4(21.1%)	9(27.3%)
		175.0-199.9	6(31.6%)	6(18.2%)
		200.0-224.9	4(21.1%)	8(24.2%)
		225.0-249.9	5(26.3%)	5(15.2%)
		250.0-274.9	0	0
		275.0-299.9	0	0
		>=300	0	0
	Male	<100.0	0	0
		100.0-124.9	0	0
		125.0-149.9	0	0
		150.0-174.9	2(6.5%)	6(11.8%)
		175.0-199.9	10(32.3%)	8(15.7%)

Patient Demographics – Bilateral by Treatment			C	I
Demographic Measure	Gender	Response	N (%)	N (%)
		200.0-224.9	6(19.4%)	13(25.5%)
		225.0-249.9	5(16.1%)	11(21.6%)
		250.0-274.9	4(12.9%)	12(23.5%)
		275.0-299.9	2(6.5%)	1(2.0%)
		>=300	2(6.5%)	0

No analyses were performed for sex-, gender-, age-, race-, ethnicity-specific subgroups.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Investigational and Control study cohorts at 24-months follow-up. In the PP population there were 209 Investigational and 114 Control subjects (knees) while in the ITT population there were 214 Investigational and 109 Control subjects (knees) who were available for the 24-month evaluation. The key safety outcomes for this study are presented below in Tables 12 to 15, 20-27, and 32. Supplementary safety outcomes for this study are presented in Tables 28 to 31 consisting of safety data over the course of the study. Over the course of the study in the PP population there were 241 Investigational and 137 Control subjects (knees) while in the ITT population there were 246 Investigational and 132 Control subjects (knees) who were potentially available for safety data past the 24-month evaluation. Adverse effects are reported in Tables 16 to 19.

Adverse effects that occurred in the PMA clinical study:

Combined Data (All Knees) Safety Data – 24 Months

A summary of key findings of the 24-month Safety Data concerning the categorization of adverse events (AEs) by device-relatedness and serious/non-serious is provided in Table 12 for the PP and Table 13 for the ITT populations.

Table 12: All Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (PP) at 24 Months

	24 Months			
Parameter	**Investigational (N=209)**	**Control (N=114)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	198	80		
Subjects with AEs of the index knee, n %	115 (55%)	46 (40%)	1.36	1.06, 1.76
Device-Related AEs of the index knee	45	24		
Subjects with device-related AEs of the index knee, n %	34 (16%)	12 (11%)	1.55	0.83, 2.87
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	88 (42%)	38 (33%)	1.26	0.93, 1.71
Device Non-Related Serious	7 (3.3%)	3 (2.6%)	1.27	0.34, 4.83
Device-Related Non-Serious	28 (13.4%)	11 (9.6%)	1.39	0.72, 2.68
Device-Related Serious	8 (3.8%)	3 (2.6%)	1.45	0.39, 5.38
All Subjects with Device Revision/Removal	13 (6.2%)	3 (2.6%)	2.36	0.69, 8.12
All Subjects with Device Removal/Conversion to TKA	8 (3.8%)	1 (0.9%)	4.36	0.55, 34.45

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

Table 13: All Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (ITT) at 24 Months

	24 Months			
Parameter	**Investigational (N=214)**	**Control (N=109)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	207	71		
Subjects with AEs of the index knee, n %	119 (56%)	42 (39%)	1.44	1.11, 1.88
Device-Related AEs of the index knee	50	19		
Subjects with device-related AEs of the index knee, n %	37 (17%)	9 (8.3%)	2.09	1.05, 4.18
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	90 (42%)	36 (33%)	1.27	0.93, 1.74
Device Non-Related Serious	8 (3.7%)	2 (1.8%)	2.04	0.44, 9.43
Device-Related Non-Serious	31 (14%)	8 (7.3%)	1.97	0.94, 4.15
Device-Related Serious	9 (4.2%)	2 (1.8%)	2.29	0.50, 10.42
All Subjects with Device Revision/Removal	14 (6.5%)	2 (1.8%)	3.57	0.83, 15.41
All Subjects with Device Removal/Conversion to TKA	9 (4.2%)	0 (0%)	N/A	N/A

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

In the ITT population the data shows that 37 of 214 knees in the Investigational group (17%) had a device-related adverse event (AE) of the index knee, and 9 of 109 knees in the Control group (8.3%) had a device-related AE involving the index knee (RR 2.09; 95% CI 1.05, 4.18). In the PP population the data show that 34 of 209 knees in the Investigational group (16%) had a device-related adverse event (AE) of the index knee, and 12 of 114 knees in the Control group (11%) had a device-related AE involving the index knee (RR 1.55; 95% CI 0.83, 2.87). In the PP population, the Investigational group compared to the Control group had a clinically but not statistically significant over two-fold risk of sustaining a device revision or removal (RR 2.36; 95% CI 0.69, 8.12) and over four-fold risk of being converted to a total TKA (RR 4.36; 95% CI 0.55, 34.45).

The increased relative risk for a knee sustaining a device-related AE was both clinically and statistically significant in the ITT population while it was clinically significant in the PP population. The overall increased rates for a subject to sustain an AE of the index knee in the Investigational versus Control group and the additional failure that required a Subject Device Revision/Removal and conversion to a total knee arthroplasty (TKA) is due to intraoperative protocol deviations. As outlined in the section X.B – Accountability of the PMA Cohort, there were five subjects that were originally randomized to receive the cementless subject investigational device but were instead implanted with the control cemented subject device because of concerns of inadequate device to bone fixation with the cementless subject device. Noteworthy, is that the five subjects that were intraoperative protocol deviations are part of both the PP and ITT population, have a substantial number of AEs to include 4 device non-related non-serious, 1 non-related serious, 4 device-related non-serious, 1 device-related serious and 4 AEs deemed not to require adjudication. Subject PLA1051 was randomized to the Investigational group but the surgeon determined fixation of the tibial component was inadequate and implanted the Control device. PLA1051 was the only device in the Control Group that required a removal of all components and a subsequent total knee arthroplasty because of the onset of rheumatoid arthritis. These five intraoperative protocol deviation patients that were implanted with the control instead of subject device because of concerns of inadequate device to bone fixation should not be only counted as AEs in the subject device group within the PP population because the data does not demonstrate a reasonable assurance of safety and effectiveness to implant a cemented device instead of a cementless device when there is potentially inadequate device to bone-prosthesis fixation. Based on the data from the pivotal IDE Study, when there is concern about the adequacy of the Investigational cementless subject device bone fixation, a TKA should likely be performed instead of a mobile bearing cemented unicondylar knee arthroplasty. Because of the substantial number of AEs and their degree of seriousness in these five subjects that were originally randomized to the subject device but were implanted

with the control device, the FDA deems that both the ITT and PP populations should be used to provide the best estimate of the safety of the subject device.[3, 4]

A summary of key findings of the 24-month Safety Data concerning the categorization of AEs by device-relatedness, AE severity, and AE outcome is provided in Table 14 for the PP and Table 15 for the ITT populations.

Table 14: All Knee-Related Adverse Events (AEs) (Severity and AE Outcome) (PP) at 24 Months

	24 Months	
	Based on Knees	
Characteristic	Investigational (N=209)	Control (N=114)
Total number of AEs of the index knee	198	80
Subjects with AEs of the index knee, n %	115 (55%)	46 (40%)
Device-Related AEs of the index knee	45	24
Subjects with device-related AEs of the index knee, n %	34 (16%)	12 (11%)
Adverse Events Severity*, n %		
Mild, number of AEs	86 (41%)	36 (32%)
Moderate, number of AEs	35 (17%)	14 (12%)
Severe, number of AEs	17 (8.1%)	6 (5.3%)
Device-Related Adverse Events Severity*, n %		
Mild, number of AEs	22 (11%)	9 (7.9%)
Moderate, number of AEs	8 (3.8%)	3 (2.6%)
Severe, number of AEs	8 (3.8%)	3 (2.6%)
Adverse Events Outcome, n %		
Device Revision/Removal/Reoperation	15 (7.2%)	5 (4.4%)
Study Withdrawal	0 (0%)	1 (0.9%)
Tolerated	36 (17%)	16 (14%)
Not Tolerated	79 (38%)	30 (26%)
Resolved	53 (25%)	21 (18%)
Not Resolved	62 (30%)	25 (22%)
Device-Related AEs Outcome, n %		
Device Revision/Removal/Reoperation	8 (3.8%)	3 (2.6%)
Study Withdrawal	0 (0%)	0 (0%)
Tolerated	19 (9.1%)	8 (7.0%)
Not Tolerated	15 (7.2%)	4 (3.5%)
Resolved	6 (2.9%)	1 (0.9%)
Not Resolved	28 (13.4%)	11 (9.6%)

*Each index knee is classified by adverse event severity and device-related outcomes. Calculations were based on the number of knees in each category. For example, if a case presented with 3 mild adverse events they were counted once for that category.

Table 15: All Knee-Related Adverse Events (AEs) (Severity and AE Outcome) (ITT) at 24 Months

	24 Months	
	Based on Knees	
Characteristic	Investigational (N=214)	Control (N=109)
Total number of AEs of the index knee	207	71
Subjects with AEs of the index knee, n %	119 (56%)	42 (39%)
Device-Related AEs of the index knee	50	19
Subjects with device-related AEs of the index knee, n %	37 (17%)	9 (8.3%)
Adverse Events Severity*, n %		
Mild, number of AEs	90 (42%)	32 (29%)
Moderate, number of AEs	36 (17%)	13 (12%)
Severe, number of AEs	19 (8.9%)	4 (3.7%)
Device-Related Adverse Events Severity*, n %		
Mild, number of AEs	25 (12%)	6 (5.5%)
Moderate, number of AEs	8 (3.7%)	3 (2.8%)
Severe, number of AEs	9 (4.2%)	2 (1.8%)
Adverse Events Outcome, n %		
Device Revision/Removal/Reoperation	17 (7.9%)	3 (2.8%)
Study Withdrawal	0 (0%)	1 (0.9%)
Tolerated	38 (18%)	14 (13%)
Not Tolerated	81 (38%)	28 (26%)
Resolved	53 (25%)	21 (19%)
Not Resolved	66 (31%)	21 (19%)
Device-Related AEs Outcome, n %		
Device Revision/Removal/Reoperation	9 (4.2%)	2 (1.8%)
Study Withdrawal	0 (0%)	0 (0%)
Tolerated	21 (9.8%)	6 (5.5%)
Not Tolerated	16 (7.5%)	3 (2.8%)
Resolved	6 (2.8%)	1 (0.9%)
Not Resolved	31 (14%)	8 (7.3%)

*Each index knee is classified by adverse event severity and device-related outcomes. Calculations were based on the number of knees in each category. For example, if a case presented with 3 mild adverse events they were counted once for that category.

In the PP population the percentage of device-related AEs in a knee was higher overall and for each severity subgroup in the Investigational group (N=209 [Mild: n=22, (11%); Moderate: n=8 (3.8%); Severe: n=8 (3.8%)] compared to the Control Group (N=114) [Mild: n=9, (7.9%); Moderate: n=3 (2.6%); Severe: n=3 (2.6%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Tolerated and Not Tolerated was higher in the Investigational group [Tolerated: n=19, (9.1%); Not Tolerated: n=15 (7.2%)] compared to the

Control Group [Tolerated: n=8, (7.0%); Not Tolerated: n=4 (3.5%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Resolved and Not Resolved was higher overall in the Investigational group [Resolved: n=6, (2.9%); Not Resolved: n=28 (13.4%)] compared to the Control Group [Resolved: n=1, 0.9%); Not Resolved: n=11 (9.6%)]. Similar findings were reported in the ITT concerning device-related AEs classification by severity and AE outcomes.

A summary of key findings of the 24-month Safety Data concerning the Description of All Knee-Related Adverse Events Description by the Index Knee is provided in Table 16 for the PP and Table 17 for the ITT populations.

Table 16: All Knee-Related Adverse Events Description by the Index Knee (PP) at 24 Months

	24 Months			
Adverse Event	**Investigational (N=209)**	**Control (N=114)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	198	80		
Subjects with AEs of the index knee, n %	115 (55%)	46 (40%)	1.36	1.06, 1.76
Adverse Event Description, n %				
Deep Wound Infection	2 (1.0%)	0 (0.0%)	N/A	N/A
Femoral Implant Loosening	1 (0.5%)	0 (0.0%)	N/A	N/A
Instability	6 (2.9%)	0 (0.0%)	N/A	N/A
MCL/ACL/PCL/Meniscal Injury	2 (1.0%)	1 (0.9%)	1.09	0.10, 11.90
Stiffness/Limited ROM (progressive/persistent)	7 (3.3%)	3 (2.6%)	1.27	0.34, 4.83
Tibial Implant Loosening	2 (1.0%)	0 (0.0%)	N/A	N/A
Tibial Fracture	4 (1.9%)	0 (0.0%)	N/A	N/A
Patellar Subluxation	0 (0.0%)	1 (0.9%)	N/A	N/A
Delayed Wound Healing	3 (1.4%)	0 (0.0%)	N/A	N/A
Hematoma	6 (2.9%)	2 (1.8%)	1.64	0.34, 7.98
Wound Dehiscence	4 (1.9%)	0 (0.0%)	N/A	N/A
Wound Drainage	4 (1.9%)	0 (0.0%)	N/A	N/A
Superficial Infection	2 (1.0%)	1 (0.9%)	1.09	0.10, 11.90
Clicking/Popping/Crepitus/Grinding	11 (5.3%)	3 (2.6%)	2	0.57, 7.02
Pain (progressive/persistent)	37 (17.7%)	18 (15.8%)	1.12	0.67, 1.88
Subsidence	2 (1.0%)	0 (0.0%)	N/A	N/A
Progressive Disease in Contralateral Compartment	3 (1.4%)	3 (2.6%)	0.55	0.11, 2.66
Avascular Necrosis	1 (0.5%)	0 (0.0%)	N/A	N/A
Bakers Cyst	1 (0.5%)	0 (0.0%)	N/A	N/A
Bearing Dislocation/Disassociation	3 (1.4%)	1 (0.9%)	1.64	0.17, 15.55
Cellulitis/Redness/Blistering	1 (0.5%)	1 (0.9%)	0.55	0.03, 8.64
Effusion/Swelling/Edema	28 (13.4%)	8 (7.0%)	1.91	0.90, 4.05
Hemarthrosis/Hemarthritis	0 (0.0%)	1 (0.9%)	N/A	N/A
Synovitis	3 (1.4%)	1 (0.9%)	1.64	0.17, 15.55
Traumatic Injury (Study Knee)	9 (4.3%)	5 (4.4%)	0.98	0.34, 2.86
Other Ipsilateral Knee Related AE	34 (16.3%)	17 (14.9%)	1.09	0.64, 1.86

Table 17: All Knee-Related Adverse Events Description by the Index Knee (ITT) at 24 Months

	24 Months			
Adverse Event	**Investigational (N=214)**	**Control (N=109)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	207	71		
Subjects with AEs of the index knee, n %	119 (56%)	42 (39%)	1.44	1.11, 1.88
Adverse Event Description, n %				
Deep Wound Infection	2 (0.9%)	0 (0.0%)	N/A	N/A
Femoral Implant Loosening	1 (0.5%)	0 (0.0%)	N/A	N/A
Instability	6 (2.8%)	0 (0.0%)	N/A	N/A
MCL/ACL/PCL/Meniscal Injury	2 (0.9%)	1 (0.9%)	1.02	0.09, 11.11
Stiffness/Limited ROM (progressive/persistent)	8 (3.7%)	2 (1.8%)	2.04	0.44, 9.43
Tibial Implant Loosening	2 (0.9%)	0 (0.0%)	N/A	N/A
Tibial Fracture	4 (1.9%)	0 (0.0%)	N/A	N/A
Patellar Subluxation	0 (0.0%)	1 (0.9%)	N/A	N/A
Delayed Wound Healing	3 (1.4%)	0 (0.0%)	N/A	N/A
Hematoma	6 (2.8%)	2 (1.8%)	1.53	0.31, 7.45
Wound Dehiscence	4 (1.9%)	0 (0.0%)	N/A	N/A
Wound Drainage	4 (1.9%)	0 (0.0%)	N/A	N/A
Superficial Infection	2 (0.9%)	1 (0.9%)	1.02	0.09, 11.11
Clicking/Popping/Crepitus/Grinding	12 (5.6%)	2 (1.8%)	3.06	0.70, 13.41
Pain (progressive/persistent)	39 (18.2%)	16 (14.7%)	1.24	0.73, 2.12
Subsidence	2 (0.9%)	0 (0.0%)	N/A	N/A
Progressive Disease in Contralateral Compartment	4 (1.9%)	2 (1.8%)	1.02	0.19, 5.47
Avascular Necrosis	1 (0.5%)	0 (0.0%)	N/A	N/A
Bakers Cyst	1 (0.5%)	0 (0.0%)	N/A	N/A
Bearing Dislocation/Disassociation	3 (1.4%)	1 (0.9%)	1.53	0.16, 14.52
Cellulitis/Redness/Blistering	1 (0.5%)	1 (0.9%)	0.51	0.03, 8.07
Effusion/Swelling/Edema	29 (13.6%)	7 (6.4%)	2.11	0.96, 4.66
Hemarthrosis/Hemarthritis	0 (0.0%)	1 (0.9%)	N/A	N/A
Synovitis	3 (1.4%)	1 (0.9%)	1.53	0.16, 14.52
Traumatic Injury (Study Knee)	10 (4.7%)	4 (3.7%)	1.27	0.41, 3.97
Other Ipsilateral Knee Related AE	35 (16.4%)	16 (14.7%)	1.11	0.65, 1.92

When examining the Description of All Knee-Related Adverse Events by the Index Knee, both the PP and ITT populations had several adverse event types with increased incidence rates in the Investigational compared to the Control group. Higher noteworthy incidence rates in the Investigational compared to the Control group were reported for femoral implant loosening, instability, stiffness/limited range of motion, tibial implant loosening, tibial fracture, delayed

wound healing, hematoma, wound dehiscence, wound drainage, clicking/popping/crepitus/grinding, pain, subsidence, avascular necrosis, bearing dislocation/disassociation, effusion/swelling/edema, synovitis, deep wound infection, and other ipsilateral Knee Related AE. In summary, the relative risk of the Investigational Group compared to Control Group for AEs of the index knees is 1.44 with a 95% confidence interval (CI) (1.11, 1.88) in the ITT and 1.36 with 95% CI (1.06, 1.76) in the PP populations that is both clinically and statistically significant.

A summary of key findings of the 24-month Safety Data concerning the Description of All Knee-Related and Device-Related Adverse Events by the Index Knee is provided in Table 18 for the PP and Table 19 for the ITT populations.

Table 18: All Knee-Related and Device-Related Adverse Events Description by the Index Knee (PP) at 24 Months

	24 Months			
Adverse Event	**Investigational (N=209)**	**Control (N=114)**	**Relative Risk**	**95% CI**
Device-Related AEs of the index knee	45	24		
Subjects with device-related AEs of the index knee, n %	34 (16%)	12 (11%)	1.55	0.83, 2.87
Adverse Event Description, n %				
Femoral Implant Loosening	1 (0.5%)	0 (0.0%)	N/A	N/A
Instability	2 (1.0%)	0 (0.0%)	N/A	N/A
Stiffness/Limited ROM (progressive/persistent)	2 (1.0%)	1 (0.9%)	1.09	0.10, 11.90
Tibial Implant Loosening	2 (1.0%)	0 (0.0%)	N/A	N/A
Tibial Fracture	2 (1.0%)	0 (0.0%)	N/A	N/A
Patellar Subluxation	0 (0.0%)	1 (0.9%)	N/A	N/A
Clicking/Popping/Crepitus/Grinding	2 (1.0%)	2 (1.8%)	0.55	0.08, 3.82
Pain (progressive/persistent)	5 (2.4%)	4 (3.5%)	0.68	0.19, 2.49
Subsidence	2 (1.0%)	0 (0.0%)	N/A	N/A
Progressive Disease in Contralateral Compartment	0 (0.0%)	1 (0.9%)	N/A	N/A
Avascular Necrosis	1 (0.5%)	0 (0.0%)	N/A	N/A
Bearing Dislocation/Disassociation	3 (1.4%)	1 (0.9%)	1.64	0.17, 15.55
Effusion/Swelling/Edema	5 (2.4%)	4 (3.5%)	0.68	0.19, 2.49
Hemarthrosis/Hemarthritis	0 (0.0%)	1 (0.9%)	N/A	N/A
Other Ipsilateral Knee Related AE	13 (6.2%)	3 (2.6%)	2.36	0.69, 8.12

Table 19: All Knee-Related and Device-Related Adverse Events Description by the Index Knee (ITT) at 24 Months

	24 Months			
Adverse Event	**Investigational (N=214)**	**Control (N=109)**	**Relative Risk**	**95% CI**
Device-Related AEs of the index knee	50	19		
Subjects with device-related AEs of the index knee, n %	37 (17%)	9 (8.3%)	2.09	1.05, 4.18
Adverse Event Description, n %				
Femoral Implant Loosening	1 (0.5%)	0 (0.0%)	N/A	N/A
Instability	2 (0.9%)	0 (0.0%)	N/A	N/A
Stiffness/Limited ROM (progressive/persistent)	3 (1.4%)	0 (0.0%)	N/A	N/A
Tibial Implant Loosening	2 (0.9%)	0 (0.0%)	N/A	N/A
Tibial Fracture	2 (0.9%)	0 (0.0%)	N/A	N/A
Patellar Subluxation	0 (0.0%)	1 (0.9%)	N/A	N/A
Clicking/Popping/Crepitus/Grinding	3 (1.4%)	1 (0.9%)	1.53	0.16, 14.52
Pain (progressive/persistent)	6 (2.8%)	3 (2.8%)	1.02	0.26, 4.00
Subsidence	2 (0.9%)	0 (0.0%)	N/A	N/A
Progressive Disease in Contralateral Compartment	1 (0.5%)	0 (0.0%)	N/A	N/A
Avascular Necrosis	1 (0.5%)	0 (0.0%)	N/A	N/A
Bearing Dislocation/Disassociation	3 (1.4%)	1 (0.9%)	1.53	0.16, 14.52
Effusion/Swelling/Edema	6 (2.8%)	3 (2.8%)	1.02	0.26, 4.00
Hemarthrosis/Hemarthritis	0 (0.0%)	1 (0.9%)	N/A	N/A
Other Ipsilateral Knee Related AE	13 (6.1%)	3 (2.8%)	2.21	0.64, 7.58

When examining the Description of All Knee-Related and Device-Related Adverse Events by the Index Knee, both the PP and ITT populations had several adverse event types with increased incidence rates in the Investigational compared to the Control group. Higher noteworthy incidence rates in the Investigational compared to the Control group were reported for femoral implant loosening, instability, stiffness/limited range of motion, tibial implant loosening, tibial fracture, subsidence, avascular necrosis, bearing dislocation/disassociation, and other ipsilateral Knee Related AE. Among patients categorized with the adverse event description Other Ipsilateral Knee Related AE, in the Investigational Group there were 13 adverse events in 11 unilateral knees (device-related non-serious = 10; device-related serious = 1) and 3 adverse events in 3 bilateral knees (device-related non-serious = 3). The Investigational subject with a device-related serious adverse event was noted to have a tibial radiolucency at the 6-week radiographic assessment and subsequently underwent removal of all components at the 2-year safety follow-up. In the Control Group there were 6 adverse events in 3 unilateral knees and all were classified as device-related non-serious adverse events.

In summary, the relative risk of the Investigational Group compared to Control Group for device-related AEs of the index knees is 2.09 with a 95% CI of (1.05, 4.18) in the ITT and 1.55 with a 95% CI (0.83, 2.87) in the PP populations, showing that the risk of a device-related AE for the Investigational is statistically significantly higher than the Control group in the ITT population. Additionally, the relative risk of the Investigational Group compared to the Control Group for AEs of the index knees is 1.44 with 95% CI (1.11, 1.88) in the ITT and 1.36 with 95% CI (1.06, 1.76) in the PP populations that is both clinically and statistically significant. In both the PP and ITT populations the percentage of device-related AEs in a knee was higher overall and for each severity subgroup in the Investigational group compared to the Control Group. In both the PP and ITT populations the percentage of device-related AE outcomes in a knee that were both Tolerated and Not Tolerated was higher overall in the Investigational group compared to the Control Group. In both the PP and ITT populations the percentage of device-related AE outcomes in a knee that were both Resolved and Not Resolved was higher overall in the Investigational group compared to the Control Group. In the PP population, the Investigational group compared to the Control group had a clinically but not statistically significant over two-fold risk of sustaining a device revision or removal and over four-fold risk of being converted to a total TKA. Overall, the Investigational compared to the Control Group had both clinically and statistically significant increased safety data concerns.

Unilateral Knees Safety Data – 24 Months

A summary of key findings of the 24-month Safety Data concerning the categorization of adverse events (AEs) by device-relatedness and serious/non-serious is provided in Table 20 for the PP and Table 21 for the ITT populations for Unilateral Knees.

Table 20: Unilateral Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (PP) at 24 Months

	24 Months			
Parameter	**Investigational (N=154)**	**Control (N=73)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	141	65		
Subjects with AEs of the index knee, n %	83 (54%)	36 (49%)	1.09	0.83, 1.44
Device-Related AEs of the index knee	30	21		
Subjects with device-related AEs of the index knee, n %	21 (14%)	10 (14%)	1.00	0.49, 2.00
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	64 (42%)	30 (41%)	1.01	0.73, 1.41
Device Non-Related Serious	5 (3.2%)	3 (4.1%)	0.79	0.19, 3.22
Device-Related Non-Serious	17 (11%)	9 (12%)	0.90	0.42, 1.91
Device-Related Serious	5 (3.2%)	2 (2.7%)	1.19	0.24, 5.96
All Subjects with Device Revision/Removal	7 (4.5%)	2 (2.7%)	1.66	0.35, 7.79
All Subjects with Device Removal/Conversion to TKA	5 (3.2%)	1 (1.4%)	2.37	0.28, 19.92

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

Table 21: Unilateral Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (ITT) at 24 Months

	24 Months			
Parameter	**Investigational (N=158)**	**Control (N=69)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	150	56		
Subjects with AEs of the index knee, n %	87 (55%)	32 (46%)	1.19	0.89, 1.59
Device-Related AEs of the index knee	35	16		
Subjects with device-related AEs of the index knee, n %	24 (15%)	7 (10%)	1.50	0.68, 3.31
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	66 (42%)	28 (41%)	1.03	0.73, 1.45
Device Non-Related Serious	6 (3.8%)	2 (2.9%)	1.31	0.27, 6.33
Device-Related Non-Serious	20 (13%)	6 (8.7%)	1.46	0.61, 3.47
Device-Related Serious	6 (3.8%)	1 (1.4%)	2.62	0.32, 21.36
All Subjects with Device Revision/Removal	8 (5.1%)	1 (1.4%)	3.49	0.45, 27.40
All Subjects with Device Removal/Conversion to TKA	6 (3.8%)	0 (0%)	N/A	N/A

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

In the PP population the data show that 21 of 154 unilateral knees in the Investigational group (14%) had a device-related adverse event (AE) of the index knee, and 10 of 73 unilateral knees in the Control group (14%) had a device-related AE involving the index knee (RR 1.00; 95% CI 0.49, 2.00). In the ITT population the data show that 24 of 158 unilateral knees in the Investigational group (15%) had a device-related adverse event (AE) of the index knee, and 7 of 69 unilateral knees in the Control group (10%) had a device-related AE involving the index knee (RR 1.50; 95% CI 0.68, 3.31). In the PP population, the Investigational group compared to the Control group had a clinically but not statistically significant increased risk of sustaining a device revision or removal (RR 1.66; 95% CI 0.35, 7.79) and over two-fold risk of being converted to a total TKA (RR 2.37; 95% CI 0.28, 19.92). In the ITT population, the Control Group of unilateral knees had one device revision/removal and no conversions to a TKA. Overall, the unilateral knee subpopulation when compared to the All Knees dataset had considerably improved safety data regarding device-relatedness and serious/non-serious adverse event reporting.

A summary of key findings of the 24-month Safety Data concerning the categorization of AEs by device-relatedness, AE severity, and AE outcome is

provided in Table 22 for the PP and Table 23 for the ITT populations for unilateral knees.

Table 22: Unilateral Knee-Related Adverse Events (Severity and AE Outcome) (PP) at 24 Months

	24 Months	
	Based on Knees	
Characteristic	**Investigational (N=154)**	**Control (N=73)**
Total number of AEs of the index knee	141	65
Subjects with AEs of the index knee, n %	83 (54%)	36 (49%)
Device-Related AEs of the index knee	30	21
Subjects with device-related AEs of the index knee, n %	21 (14%)	10 (14%)
Adverse Events Severity*, n %		
Mild, number of AEs	65 (42%)	28 (38%)
Moderate, number of AEs	21 (14%)	10 (14%)
Severe, number of AEs	11 (7.1%)	5 (6.8%)
Device-Related Adverse Events Severity*, n %		
Mild, number of AEs	15 (9.7%)	8 (11%)
Moderate, number of AEs	4 (2.6%)	2 (2.7%)
Severe, number of AEs	5 (3.2%)	2 (2.7%)
Adverse Events Outcome, n %		
Device Revision/Removal/Reoperation	10 (6.5%)	4 (5.5%)
Study Withdrawal	0 (0%)	1 (1.4%)
Tolerated	27 (18%)	13 (18%)
Not Tolerated	56 (36%)	23 (32%)
Resolved	38 (25%)	15 (21%)
Not Resolved	45 (29%)	21 (29%)
Device-Related AEs Outcome, n %		
Device Revision/Removal/Reoperation	5 (3.2%)	2 (2.7%)
Study Withdrawal	0 (0%)	0 (0%)
Tolerated	13 (8.4%)	7 (9.6%)
Not Tolerated	8 (5.2%)	3 (4.1%)
Resolved	2 (1.3%)	1 (1.4%)
Not Resolved	19 (12%)	9 (12%)

*Each index knee is classified by adverse event severity and device-related outcomes. Calculations were based on the number of knees in each category. For example, if a case presented with 3 mild adverse events they were counted once for that category.

Table 23: Unilateral Knee-Related Adverse Events (Severity and AE Outcome) (ITT) at 24 Months

	24 Months	
	Based on Knees	
Characteristic	Investigational (N=158)	Control (N=69)
Total number of AEs of the index knee	150	56
Subjects with AEs of the index knee, n %	87 (55%)	32 (46%)
Device-Related AEs of the index knee	35	16
Subjects with device-related AEs of the index knee, n %	24 (15%)	7 (10%)
Adverse Events Severity*, n %		
Mild, number of AEs	69 (44%)	24 (35%)
Moderate, number of AEs	22 (14%)	9 (13%)
Severe, number of AEs	13 (8.2%)	3 (4.3%)
Device-Related Adverse Events Severity*, n %		
Mild, number of AEs	18 (11%)	5 (7.2%)
Moderate, number of AEs	4 (2.5%)	2 (2.9%)
Severe, number of AEs	6 (3.8%)	1 (1.4%)
Adverse Events Outcome, n %		
Device Revision/Removal/Reoperation	12 (7.6%)	2 (2.9%)
Study Withdrawal	0 (0%)	1 (1.4%)
Tolerated	29 (18%)	11 (16%)
Not Tolerated	58 (37%)	21 (30%)
Resolved	38 (24%)	15 (22%)
Not Resolved	49 (31%)	17 (25%)
Device-Related AEs Outcome, n %		
Device Revision/Removal/Reoperation	6 (3.8%)	1 (1.4%)
Study Withdrawal	0 (0%)	0 (0%)
Tolerated	15 (9.5%)	5 (7.2%)
Not Tolerated	9 (5.7%)	2 (2.9%)
Resolved	2 (1.3%)	1 (1.4%)
Not Resolved	22 (14%)	6 (8.7%)

*Each index knee is classified by adverse event severity and device-related outcomes. Calculations were based on the number of knees in each category. For example, if a case presented with 3 mild adverse events they were counted once for that category.

In the PP population the percentage of device-related AEs in unilateral knees was similar for each severity subgroup in the Investigational group (N=154) [Mild: n=15, (9.7%); Moderate: n=4 (2.6%); Severe: n=5 (3.2%)] compared to the Control Group (N=73) [Mild: n=8, (11%); Moderate: n=2 (2.7%); Severe: n=2 (2.7%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Tolerated and Not Tolerated was similar overall in the Investigational group [Tolerated: n=13, (8.4%); Not Tolerated: n=8 (5.2%)]

compared to the Control Group [Tolerated: n=7, (9.6%); Not Tolerated: n=3 (4.1%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Resolved and Not Resolved was similar in the Investigational group [Resolved: n=2, (1.3%); Not Resolved: n=19 (12%)] compared to the Control Group [Resolved: n=1, (1.4%); Not Resolved: n=9 (12%)]. Slightly higher rates were reported in the Investigational compared to the Control Group of device-related AEs classification in the ITT population for mild and severe severity classification groups and AE outcomes that were Not Tolerated or Not Resolved. Overall, the unilateral knee subpopulation when compared to the All Knees dataset had substantially improved safety data regarding device-related AE severity classification and device-related AE Outcomes adverse event reporting.

Bilateral Knees Safety Data – 24 Months

A summary of key findings of the 24-month Safety Data concerning the categorization of adverse events (AEs) by device-relatedness and serious/non-serious is provided in Table 24 for the PP and Table 25 for the ITT populations for bilateral knees.

Table 24: Bilateral Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (PP) at 24 Months

	24 Months			
Parameter	**Investigational (N=55)**	**Control (N=41)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	57	15		
Subjects with AEs of the index knee, n %	32 (58%)	10 (24%)	2.39	1.33, 4.28
Device-Related AEs of the index knee	15	3		
Subjects with device-related AEs of the index knee, n %	13 (24%)	2 (4.9%)	4.85	1.16, 20.30
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	24 (44%)	8 (20%)	2.24	1.12, 4.46
Device Non-Related Serious	2 (3.6%)	0 (0%)	N/A	N/A
Device-Related Non-Serious	11 (20%)	2 (4.9%)	4.10	0.96, 17.50
Device-Related Serious	3 (5.5%)	1 (2.4%)	2.24	0.24, 20.73
All Subjects with Device Revision/Removal	6 (11%)	1 (2.4%)	4.47	0.56, 35.73
All Subjects with Device Removal/Conversion to TKA	3 (5.5%)	0 (0%)	N/A	N/A

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

Table 25: Bilateral Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (ITT) at 24 Months

	24 Months			
Parameter	**Investigational (N=56)**	**Control (N=40)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	67	15		
Subjects with AEs of the index knee, n %	32 (57%)	10 (25%)	2.29	1.28, 4.09
Device-Related AEs of the index knee	15	3		
Subjects with device-related AEs of the index knee, n %	13 (23%)	2 (5.0%)	4.64	1.11, 19.45
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	24 (43%)	8 (20%)	2.14	1.08, 4.27
Device Non-Related Serious	2 (3.6%)	0 (0%)	N/A	N/A
Device-Related Non-Serious	11 (20%)	2 (5.0%)	3.93	0.92, 16.76
Device-Related Serious	3 (5.4%)	1 (2.5%)	2.14	0.23, 19.86
All Subjects with Device Revision/Removal	6 (11%)	1 (2.5%)	4.29	0.54, 34.23
All Subjects with Device Removal/Conversion to TKA	3 (5.4%)	0 (0%)	N/A	N/A

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

In the PP population the data show that 13 of 55 bilateral knees in the Investigational group (24%) had a device-related adverse event (AE) of the index knee, and 2 of 41 bilateral knees in the Control group (4.9%) had a device-related AE involving the index knee (RR 4.85; 95% CI 1.16, 20.30) which was clinically and statistically significant. In the ITT population the data show that 13 of 56 bilateral knees in the Investigational group (23%) had a device-related adverse event (AE) of the index knee, and 2 of 40 bilateral knees in the Control group (5%) had a device-related AE involving the index knee (RR 4.64; 95% CI 1.11, 19.45). In the PP population, the Investigational group compared to the Control group had a clinically but not statistically significant over four-fold increased risk of sustaining a device revision or removal (RR 4.47; 95% CI 0.56, 35.73). Additionally, in the Investigational group 3 patients (5.5%) compared to none in the Control group were converted to a total TKA. Overall, the bilateral knee subpopulation when compared to the All Knees dataset had clinically and statistically significant increased safety data concerns regarding device-relatedness and serious/non-serious adverse event reporting.

A summary of key findings of the 24-month Safety Data concerning the categorization of AEs by device-relatedness, AE severity, and AE outcome is provided in Table 26 for the PP and Table 27 for the ITT populations for bilateral Knees.

Table 26: Bilateral Knee-Related Adverse Events (Severity and AE Outcome) (PP) at 24 Months

	24 Months	
	Based on Knees	
Characteristic	Investigational (N=55)	Control (N=41)
Total number of AEs of the index knee	57	15
Subjects with AEs of the index knee, n %	32 (58%)	10 (24%)
Device-Related AEs of the index knee	15	3
Subjects with device-related AEs of the index knee, n %	13 (24%)	2 (4.9%)
Adverse Events Severity*, n %		
Mild, number of AEs	21 (38%)	8 (20%)
Moderate, number of AEs	14 (25%)	4 (9.8%)
Severe, number of AEs	6 (11%)	1 (2.4%)
Device-Related Adverse Events Severity*, n %		
Mild, number of AEs	7 (13%)	1 (2.4%)
Moderate, number of AEs	4 (7.3%)	1 (2.4%)
Severe, number of AEs	3 (5.5%)	1 (2.4%)
Adverse Events Outcome, n %		
Device Revision/Removal/Reoperation	5 (9.1%)	1 (2.4%)
Study Withdrawal	0 (0%)	0 (0%)
Tolerated	9 (16%)	3 (7.3%)
Not Tolerated	23 (42%)	7 (17%)
Resolved	15 (27%)	6 (15%)
Not Resolved	17 (31%)	4 (10%)
Device-Related AEs Outcome, n %		
Device Revision/Removal/Reoperation	3 (5.5%)	1 (2.4%)
Study Withdrawal	0 (0%)	0 (0%)
Tolerated	6 (11%)	1 (2.4%)
Not Tolerated	7 (13%)	1 (2.4%)
Resolved	4 (7.3%)	0 (0%)
Not Resolved	9 (16%)	2 (4.9%)

*Each index knee is classified by adverse event severity and device-related outcomes. Calculations were based on the number of knees in each category. For example, if a case presented with 3 mild adverse events they were counted once for that category.

Table 27: Bilateral Knee-Related Adverse Events (Severity and AE Outcome) (ITT) at 24 Months

	24 Months	
	Based on Knees	
Characteristic	**Investigational (N=56)**	**Control (N=40)**
Total number of AEs of the index knee	67	15
Subjects with AEs of the index knee, n %	32 (57%)	10 (25%)
Device-Related AEs of the index knee	15	3
Subjects with device-related AEs of the index knee, n %	13 (23%)	2 (5.0%)
Adverse Events Severity*, n %		
Mild, number of AEs	21 (38%)	8 (20%)
Moderate, number of AEs	14 (25%)	4 (10%)
Severe, number of AEs	6 (11%)	1 (2.5%)
Device-Related Adverse Events Severity*, n %		
Mild, number of AEs	7 (13%)	1 (2.5%)
Moderate, number of AEs	4 (7.1%)	1 (2.5%)
Severe, number of AEs	3 (5.4%)	1 (2.5%)
Adverse Events Outcome, n %		
Device Revision/Removal/Reoperation	5 (8.9%)	1 (2.5%)
Study Withdrawal	0 (0%)	0 (0%)
Tolerated	9 (16%)	3 (7.5%)
Not Tolerated	23 (41%)	7 (18%)
Resolved	15 (27%)	6 (15%)
Not Resolved	17 (30%)	4 (10%)
Device-Related AEs Outcome, n %		
Device Revision/Removal/Reoperation	3 (5.4%)	1 (2.5%)
Study Withdrawal	0 (0%)	0 (0%)
Tolerated	6 (11%)	1 (2.5%)
Not Tolerated	7 (13%)	1 (2.5%)
Resolved	4 (7.1%)	0 (0%)
Not Resolved	9 (16%)	2 (5.0%)

*Each index knee is classified by adverse event severity and device-related outcomes. Calculations were based on the number of knees in each category. For example, if a case presented with 3 mild adverse events they were counted once for that category.

In the PP population the percentage of device-related AEs in bilateral knees was substantially increased for each severity subgroup in the Investigational group (N=55) [Mild: n=7, (13%); Moderate: n=4 (7.3%); Severe: n=3 (5.5%)] compared to the Control Group (N=41) [Mild: n=1, (2.4%); Moderate: n=1 2.4%); Severe: n=1 (2.4%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Tolerated and Not Tolerated was higher overall in the Investigational group [Tolerated: n=6, (11%); Not Tolerated: n=7 (13%)]

compared to the Control Group [Tolerated: n=1, (2.4%); Not Tolerated: n=1 (2.4%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Resolved and Not Resolved was higher overall in the Investigational group [Resolved: n=4, (7.3%); Not Resolved: n=9 (16%)] compared to the Control Group [Resolved: n=0, 0%); Not Resolved: n=2 (4.9%)]. Similar findings were reported in the ITT concerning device-related AEs classification by severity and AE outcomes. Overall, the bilateral knee subpopulation when compared to the All Knees dataset had clinically significant increased safety data concerns regarding device-related AE severity classification and device-related AE Outcomes adverse event reporting.

Unilateral and Bilateral Knees Safety Data – Over the Course of the Study
A summary of the key findings of the Safety Data – Over the Course of the Study concerning the categorization of adverse events (AEs) by device-relatedness and serious/non-serious is provided in Table 28 for the PP and Table 29 for the ITT populations for Unilateral Knees.

Table 28: Unilateral Knee-Related Adverse Events (Device-Relatedness and Seriou/Non-Serious) (PP) Over the Course of the Study

	Over the Course of the Study			
Parameter	**Investigational (N=172)**	**Control (N=91)**	**Relative Risk**	**95% CI**
Adverse Events (AEs) of the index knee	184	86		
Subjects with AEs of the index knee, n %	95 (55%)	44 (48%)	1.14	0.89, 1.47
Device-Related AEs of the index knee	36	24		
Subjects with device-related AEs of the index knee, n %	22 (13%)	13 (14%)	0.90	0.47, 1.69
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	78 (45%)	38 (42%)	1.09	0.81, 1.46
Device Non-Related Serious	6 (3.5%)	5 (5.5%)	0.63	0.20, 2.02
Device-Related Non-Serious	18 (10%)	11 (12%)	0.87	0.43, 1.75
Device-Related Serious	7 (4.1%)	3 (3.3%)	1.23	0.33, 4.66
All Subjects with Device Revision/Removal	10 (5.8%)	4 (4.4%)	1.32	0.43, 4.10
All Subjects with Device Removal/Conversion to TKA	7 (4.1%)	2 (2.2%)	1.85	0.39, 8.73

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

Table 29: Unilateral Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (ITT) Over the Course of the Study

	Over the Course of the Study			
Parameter	Investigational (N=176)	Control (N=87)	Relative Risk	95% CI
Adverse Events (AEs) of the index knee	174	76		
Subjects with AEs of the index knee, n %	99 (56%)	40 (46%)	1.22	0.94, 1.59
Device-Related AEs of the index knee	41	19		
Subjects with device-related AEs of the index knee, n %	25 (14%)	10 (11%)	1.24	0.62, 2.46
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	81 (46%)	35 (40%)	1.14	0.85, 1.55
Device Non-Related Serious	7 (4.0%)	4 (4.6%)	0.87	0.26, 2.88
Device-Related Non-Serious	21 (12%)	8 (9.2%)	1.30	0.60, 2.81
Device-Related Serious	8 (4.5%)	2 (2.3%)	1.98	0.43, 9.11
All Subjects with Device Revision/Removal	11 (6.3%)	3 (3.4%)	1.81	0.52, 6.33
All Subjects with Device Removal/Conversion to TKA	8 (4.5%)	1 (1.1%)	3.95	0.50, 31.12

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

In the PP population the data shows that 22 of 172 unilateral knees in the Investigational Group (13%) had a device-related adverse event (AE) of the index knee, and 13 of 91 unilateral knees in the Control Group (14%) had a device-related AE involving the index knee (RR 0.90; 95% CI 0.47, 1.69). In the ITT population the data shows that 25 of 176 unilateral knees in the Investigational Group (14%) had a device-related adverse event (AE) of the index knee, and 10 of 87 unilateral knees in the Control Group (11%) had a device-related AE involving the index knee (RR 1.24; 95% CI 0.62, 2.46). In the PP population, the Investigational Group compared to the Control Group had a clinically by not statistically significant increased risk of sustaining a device revision or removal (RR 1.32; 95% CI 0.43, 4.10) and being converted to a total TKA (RR 1.85; 95% CI 0.39, 8.73). In the ITT population, the Investigational group compared to the Control Group had a clinically but not statistically significant increased risk of sustaining a device revision or removal (RR 1.81; 95% CI 0.52, 6.33) and being converted to a total TKA (RR 3.95; 95% CI 0.50, 31.12). Overall, the unilateral knee subpopulation Over the Course of the Study compared to the 24-month dataset had similar safety data regarding device-relatedness and serious/non-serious adverse event reporting. There is greater uncertainty with the safety data when it is presented over the course of the study because the length of follow-up for patients is different, and this may be different for the Control and Investigational groups. The amount of missing data may significantly limit conclusions regarding subject device safety.

A summary of the key findings of the Safety Data – Over the Course of the Study concerning the categorization of adverse events (AEs) by device-relatedness and

serious/non-serious is provided in Table 30 for the PP and Table 31 for the ITT populations for Bilateral Knees.

Table 30: Bilateral Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (PP) Over the Course of the Study

Parameter	Investigational (N=69)	Control (N=46)	Relative Risk	95% CI
Adverse Events (AEs) of the index knee	70	21		
Subjects with AEs of the index knee, n %	38 (55%)	12 (26%)	2.11	1.24, 3.59
Device-Related AEs of the index knee	18	3		
Subjects with device-related AEs of the index knee, n %	14 (20%)	2 (4.3%)	4.67	1.11, 19.58
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	29 (42%)	11 (24%)	1.76	0.98, 3.16
Device Non-Related Serious	2 (2.9%)	1 (2.2%)	1.33	0.12, 14.28
Device-Related Non-Serious	12 (17%)	2 (4.3%)	4.00	0.94, 17.05
Device-Related Serious	3 (4.3%)	1 (2.2%)	2.00	0.21, 18.64
All Subjects with Device Revision/Removal	6 (8.7%)	1 (2.2%)	4.00	0.50, 32.14
All Subjects with Device Removal/Conversion to TKA	3 (4.3%)	0 (0%)	N/A	N/A

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

Table 31: Bilateral Knee-Related Adverse Events (Device-Relatedness and Serious/Non-Serious) (ITT) Over the Course of the Study

	Over the Course of the Study			
Parameter	Investigational (N=70)	Control (N=45)	Relative Risk	95% CI
Adverse Events (AEs) of the index knee	70	18		
Subjects with AEs of the index knee, n %	38 (54%)	12 (27%)	2.04	1.20, 3.46
Device-Related AEs of the index knee	18	3		
Subjects with device-related AEs of the index knee, n %	14 (20%)	2 (4.4%)	4.50	1.07, 18.87
Total number of AEs of the index knee*, n%				
Device Non-Related Non-Serious	29 (41%)	11 (24%)	1.69	0.94, 3.04
Device Non-Related Serious	2 (2.9%)	1 (2.2%)	1.29	0.12, 13.77
Device-Related Non-Serious	12 (17%)	2 (4.4%)	3.86	0.91, 16.43
Device-Related Serious	3 (4.3%)	1 (2.2%)	1.93	0.21, 17.97
All Subjects with Device Revision/Removal	6 (8.6%)	1 (2.2%)	3.86	0.48, 30.99
All Subjects with Device Removal/Conversion to TKA	3 (4.3%)	0 (0%)	N/A	N/A

*Each index knee is classified by device-relatedness and serious versus non-serious. Calculations were based on the number of knees in each category. For example, if a case presented with 3 device- non-related non-serious adverse events they were counted once for that category.

In the PP population the data shows that 14 of 69 bilateral knees in the Investigational Group (20%) had a device-related adverse event (AE) of the index knee, and 2 of 46 bilateral knees in the Control Group (4.3%) had a device-related AE involving the index knee (RR 4.67; 95% CI 1.11, 19.58) which was clinically and statistically significant. In the ITT population the data shows that 14 of 70 bilateral knees in the Investigational group (20%) had a device-related adverse event (AE) of the index knee, and 2 of 45 bilateral knees in the Control group (4.4%) had a device-related AE involving the index knee (RR 4.50; 95% CI 1.07, 18.87). In the PP population, the Investigational group compared to the Control group had a clinically but not statistically significant four-fold increased risk of sustaining a device revision or removal (RR 4.00; 95% CI 0.50, 32.14). Additionally, in the Investigational group 3 patients (4.3%) compared to none in the Control group were converted to a total TKA. Overall, the bilateral knee subpopulation Over the Course of the Study compared to the 24-month dataset had similar safety data regarding device-relatedness and serious/non-serious adverse event reporting.

Device Revisions and Removals

A summary of the key findings of the 24-month Safety Data concerning the device revisions and removals is provided in Table 32.

Table 32: Device Revisions and Removals at 24 Months

Patient ID	Group Randomized	Group Implanted	Procedure Type	Days to Revision Surgery	Diagnosis	Treatment	Adverse Event Categorization
MOO1010	Investigational	Investigational	Unilateral	5	Hematoma	I&D/PE Exchange	SAE - Not Related
PLA1011	Investigational	Investigational	Unilateral	49	Infection	I&D/PE Exchange	SAE - Not Related
EDI1001L	Investigational	Investigational	Bilateral	56	Wound Dehiscence	I&D/PE Exchange	SAE - Not Related
ELK1066	Investigational	Investigational	Bilateral	234	Bearing Dislocation	PE Exchange	SAE - Related
ELK1037	Investigational	Investigational	Bilateral	513	Bearing Dislocation	PE Exchange	SAE - Related
ELK1063	Investigational	Investigational	Unilateral	50	Tibial Fracture - X-Rays at 6 weeks without fracture	TKA/Device Removal	SAE - Related
NEW1032	Investigational	Investigational	Unilateral	62	Tibial Fracture - X-Rays at 6 weeks without fracture	TKA/Device Removal	SAE - Not Related
ALE1017L	Investigational	Investigational	Bilateral	118	Tibial Fracture - Fracture at 6 weeks	TKA/Device Removal	SAE - Not Related
ALE1018R	Investigational	Investigational	Bilateral	133	Tibia Component Aseptic Loosening	TKA/Device Removal	SAE - Related
NEW1077	Investigational	Investigational	Unilateral	150	Femoral Component Loosening	TKA/Device Removal	SAE - Related
COB1001	Investigational	Investigational	Unilateral	186	Intraoperative Tibial Fracture/Pain	TKA/Device Removal	SAE - Related
HUN1059R	Investigational	Investigational	Bilateral	346	Lateral Compartment OA	TKA/Device Removal	AE - Not Related
NEW1038	Investigational	Investigational	Unilateral	598	Avascular Necrosis	TKA/Device Removal	SAE - Related
ALE1052	Control	Control	Unilateral	434	Bearing Dislocation	PE Exchange	SAE - Related
PLA1034R	Control	Control	Bilateral	463	Recurrent Hemarthrosis	PE Exchange	SAE - Related
PLA1051	Investigational	Control	Unilateral	529	Rheumatoid Arthritis	TKA/Device Removal	SAE - Related

Legend: I D = irrigation and debridement. PE = polyethylene. TKA total knee arthroplasty. AE = adverse event. SAE = serious adverse event.

There were 16 revisions used in the primary safety data and assessment of the Absence of Revision/Removal/UADE endpoint at 24 months. Among the 9 device removals that were converted to a total knee arthroplasty at 2 years, 8 were

in the Investigational Group and one subject, PLA 1051, was randomized to the Investigational Group but the surgeon determined fixation of the tibial component was inadequate and implanted the Control device.

There were an additional five revisions that took place after the 2-year assessment. In the Investigational Group after the 2-year assessment there were three additional device revisions to include one subject who had an irrigation and debridement and polyethylene exchange for infection and two subjects who had a total knee arthroplasty and device removal for tibial component loosening and tibial component radiolucent line/pain, respectively. In the Control Group after the 2-year assessment there were two additional device revisions to include a polyethylene exchange for bearing dislocation and a total knee arthroplasty and device removal for tibial fracture/component subsidence.

Surgical Technique Modification

During the study, there were four tibial fractures which occurred in the first year after the procedure. A modification to the surgical technique was implemented in September 2017 which included a warning which instructs the surgeon to take care when using the cementless pick, particularly in the posterior cortex region, to prepare the tibia. The Clinical Events Committee adjudication of these four tibial fractures reported that two Investigational Group cementless knee subjects were non-device-related serious adverse events, and two subjects were device-related serious adverse events. Two of the cementless knee subjects diagnosed with a tibial fracture had 6-week radiographs of the knee that were acceptable and did not identify a fracture at that time (Table 32). In the 22 Investigational cementless cases that were implanted after the updated surgical technique was in place there were no tibial fractures.

2. Effectiveness Results

The analysis of effectiveness was based on the PP and ITT populations for each of the four co-primary endpoints (Radiographic Success, Knee Society Score Assessment, and Knee Society Function Score at the 22+ Month time point and Absence of Revision/Removal/UADE at the 24-Month time points) as outlined in Table 33 for the PP population and Table 34 for the ITT population. For the PP population, there were 216 Investigational and 122 Control subjects evaluated for Absence of Revision/Removal/UADE, 211 Investigational and 115 Control subjects evaluated for Radiographic Success at 22+ Months, 241 Investigational and 137 Control subjects evaluated for KSSA Score at 22+ Months, and 241 Investigational and 137 Control subjects evaluated for KSSF Score at 22+ Months. For the ITT population, there were 221 Investigational and 117 Control subjects evaluated for Absence of Revision/Removal/UADE, 216 Investigational and 110 Control subjects evaluated for Radiographic Success at 22+ Months, 246 Investigational and 132 Control subjects evaluated for KSSA Score at 22+ Months, and 246 Investigational and 132 Control subjects evaluated for KSSF

Score at 22+ Months. Key effectiveness outcomes are presented in Tables 33 to 35.

Using the modified co-primary endpoints as outlined in Section X.A.1. Clinical Endpoints-Effectiveness there was an overall compliance rate of 87.3% for all four Co-Primary Effectiveness Endpoints with 316 of 362 subjects at the 22+ month follow-up for Radiographic Success, Knee Society Score Assessment, and Knee Society Function Score endpoints and 24-month follow-up for Revision/Removal/UADE Success endpoint. The overall compliance rate for the effectiveness endpoints as outlined above for the two groups was 114 of 130 Control subjects (87.7%) and 202 of 232 Investigational subjects (87.1%).

Combined Data (All Knees) Effectiveness Data

A summary of key findings of the 24-month Effectiveness Data for the four co-primary endpoints in Table 33 for the PP and Table 34 for the ITT populations.

Table 33: Co-Primary Effectiveness Endpoints Per Protocol (PP) by Knee at 24 Months

Population	Control	Investigational	Difference (95% CI)^	Non-Inferiority Margin	p value of NI test	Other Statistical Test
All						
Revision/Removal/UADE Success % (n/N)	97.5% (119/122)	94.0% (203/216)	3.6% (-0.6%, 7.8%)	10%	0.003	0.19*
Radiographic Success at 22+ Months % (n/N)	97.4% (112/115)	93.8% (198/211)	3.6% (-Inf, 7.4%)	8%	0.03	0.19*
KSSA Score at 22+ Months μ ± Std Dev, (n/N)	95.5 ± 7.0 (116/137)	95.6 ± 8.3 (204/241)	-0.03 (-Inf, 1.4)	6.4	<0.0001	<0.0001$
KSSF Score at 22+ Months μ ± Std, (n/N)	89.7 ± 14.1 (121/137)	89.4 ± 14.4 (206/241)	0.3 (-Inf, 3.0)	9.2	<0.0001	<0.0001$
Unilateral						
Revision/Removal/UADE Success % (n/N)	97.5% (77/79)	95.5% (148/155)	2.0% (-Inf, 6.6%)	10%	0.002	0.72*
Radiographic Success at 22+ Months % (n/N)	97.3% (72/74)	95.5% (149/156)	1.8% (-Inf, 6.2%)	8%	0.01	0.72*
KSSA Score at 22+ Months μ ± Std Dev, (n/N)	95.5 ± 7.2 (75/90)	95.5 ± 8.0 (150/175)	0.003 (-Inf, 1.8)	6.4	<0.0001	<0.0001$
KSSF Score at 22+ Months μ ± Std, (n/N)	88.1 ± 15.5 (78/90)	90.2 ± 14.4 (151/175)	-2.1 (-Inf, 1.3)	9.2	<0.0001	<0.0001$
Bilateral						
Revision/Removal/UADE Success % (n/N)	97.7% (42/43)	90.2% (55/61)	7.5% (-Inf, 15.1%)	10%	0.29	0.23*
Radiographic Success at 22+ Months % (n/N)	97.6% (40/41)	89.1% (49/55)	8.5% (-Inf, 16.4%)	8%	0.54	0.23*
KSSA Score at 22+ Months μ ± Std Dev, (n/N)	95.5 ± 6.5 (41/47)	95.6 ± 9.1 (54/66)	-0.1 (-Inf, 2.6)	6.4	<0.0001	<0.0001$
KSSF Score at 22+ Months μ ± Std, (n/N)	92.6 ± 10.5 (43/47)	87.1 ± 14.5 (55/66)	5.5 (-Inf, 9.7)	9.2	0.07	0.07$

Legend: μ = Mean. Std Standard Deviation. ^ One Sided 95% C.I. unless otherwise noted. #Two-sided 95% C.I.
*Indicates Fishers Exact Test. $Indicates T-test.

Table 34: Co-Primary Effectiveness Endpoints Intent to Treat (ITT) by Knee at 24 Months

Population	Control	Investigational	Difference (95% CI)^	Non-Inferiority Margin	p value of NI test	Other Statistical Test
All						
Revision/Removal/UADE Success % (n/N)	98.3% (115/117)	93.7% (207/221)	4.6% (0.7%, 8.6%)	10%	0.009	0.06*
Radiographic Success at 22+ Months % (n/N)	98.2% (108/110)	93.5% (202/216)	4.7% (-Inf., 8.3%)	8%	0.06	0.1*
KSSA Score at 22+ Months μ ± Std Dev, (n/N)	95.5 +/- 7.0 (112/132)	95.6 +/- 8.3 (208/246)	-0.05 (-Inf., 1.5)	6.4	<0.0001	<0.0001$
KSSF Score at 22+ Months μ ± Std, (n/N)	89.7 +/- 13.7 (117/132)	89.3 +/- 14.6 (210/246)	0.4 (-Inf., 3.1)	9.2	<0.0001	<0.0001$
Unilateral						
Revision/Removal/UADE Success % (n/N)	98.7% (74/75)	95.0% (151/159)	3.7% (-Inf., 8.0%)	10%	0.008	0.27*
Radiographic Success at 22+ Months % (n/N)	98.6% (69/70)	95.0% (152/160)	3.6% (-Inf., 7.6%)	8%	0.03	0.28*
KSSA Score at 22+ Months μ ± Std Dev, (n/N)	95.6 +/- 7.3 (72/86)	95.5 +/- 8.0 (153/179)	0.06 (-Inf., 1.9)	6.4	<0.0001	<0.0001$
KSSF Score at 22+ Months μ ± Std, (n/N)	88.3 +/- 15.1 (75/86)	90.1 +/- 14.6 (154/179)	-1.8 (-Inf., 1.6)	9.2	<0.0001	<0.0001$
Bilateral						
Revision/Removal/UADE Success % (n/N)	97.6% (41/42)	90.3% (56/62)	7.3% (-Inf., 14.9%)	10%	0.28	0.24*
Radiographic Success at 22+ Months % (n/N)	97.5% (39/40)	89.3% (50/56)	8.2% (-Inf., 16.1%)	8%	0.52	0.23*
KSSA Score at 22+ Months μ ± Std Dev, (n/N)	95.4 +/- 6.6 (40/46)	95.7 +/- 9.0 (55/67)	-0.3 (-Inf., 2.4)	6.4	<0.0001	<0.0001$
KSSF Score at 22+ Months μ ± Std, (n/N)	92.4 +/- 10.5 (42/46)	87.3 +/- 14.5 (56/67)	5.1 (-Inf., 9.3)	9.2	0.052	0.07$

Legend: μ = Mean. Std Standard Deviation. ^ One Sided 95% C.I. unless otherwise noted. #Two-sided 95% C.I.
*Indicates Fishers Exact Test. $Indicates T-test.

The data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical percentages for success in both the PP (97.4% versus 93.8%) and ITT (98.2% versus 93.5%) populations for the Radiographic Success at 22+ months – Effectiveness Co-Primary Endpoint. Additionally, the Control Group compared to the Investigational Group for each knee has higher numerical percentages for success in both the PP (97.5% versus 94.0%) and ITT (98.3% versus 93.7%) populations for the Revision/Removal/UADE Success Effectiveness Co-Primary Endpoint.

For the Radiographic Success at 22+ months the ITT (p=0.06) population did not meet the 8% margin for non-inferiority that was established for the Investigational Group in which 202 of 216 subjects (93.5%) compared to Control Group in which 108/110 subjects (98.2%) were a success. For the Radiographic Success at 22+ months the PP (p=0.03) population met the non-inferiority margin that was established for the Investigational Group in which 198 of 211 subjects (93.8%) compared to Control Group in which 112/115 subjects (97.4%) were a success.

Utilizing only safety and effectiveness data of the PP instead of also using the ITT population results in substantial uncertainty as subjects were originally randomized to receive the investigational device but were implanted with the control cemented subject device, because of concerns of inadequate device to bone fixation, but then went on to experiences AEs and Subject Device Revisions/Removal at higher rates. Because of the substantial number of AEs, their degree of seriousness and one case of Subject Device Revisions/Removal and conversion to TKA in these five subjects that were originally randomized to the subject device (ITT population) but due to an intraoperative protocol deviation had the control device implanted (PP population), the FDA contends that this non-inferiority study design should only claim success when both the ITT and PP analyses provide concordant results and this is consistent with the FDA Guidance Document entitled "E9 Statistical Principles for Clinical Trials".[3] Accordingly, CONSORT (Consolidated Standards for reporting trials) guidelines strongly recommend providing details of both estimates in clinical trials, because when ITT and PP provide identical conclusions, the confidence level of the investigator for the study results is augmented.[4]

In summary, that the primary effectiveness endpoint for this non-inferiority study was not met for the ITT population and there is not a reasonable assurance of effectiveness for all patients (e.g., unilateral and bilateral) knees). All the device revisions/removals would require a secondary surgical intervention. A portion of the patients will experience complications that may result in disability or permanent damage. When the full analysis dataset of the ITT and the PP populations led to different conclusions, confidence in the trial results is decreased to use the proposed PP population as the basis of approval for the subject device for its proposed Intended Use.

Isolated Data (Unilateral and Bilateral Knees)
The unilateral knee data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical percentages for success in both the PP (97.3% versus 95.5%) and ITT (98.6% versus 95.0%) populations for the Radiographic Success at 22+ months – Effectiveness Co-Primary Endpoint (Tables 33 and 34). The data demonstrates that the Control Group compared to the Investigational Group for each knee has equivalent or higher numerical percentages for success in both the PP (97.5% versus 95.5%) and ITT (98.7% versus 95.0%) populations for the Revision/Removal/UADE Success Effectiveness Co-Primary Endpoint. In summary, the Unilateral knees when compared to the All Knees dataset showed numerical improvement in all four of the co-primary endpoints and all of them met their non-inferiority margins for both the PP and ITT populations.

The bilateral knee data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical percentages for success in both the PP (97.6% versus 89.1%) and ITT (97.5% versus 89.3%) populations for the Radiographic Success at 22+ months – Effectiveness Co-Primary Endpoint

(Tables 33 and 34). The data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical percentages for success in both the PP (97.7% versus 90.2%) and ITT (97.5% versus 89.3%) populations for the Revision/Removal/UADE Success Effectiveness Co-Primary Endpoint. In summary, the Bilateral Knees when compared to the All Knees dataset showed numerical decreases in three of the four co-primary endpoints. The data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical values for the KSSF score in both the PP (92.6 versus 87.1) and ITT (92.4 versus 87.3) populations. The bilateral knee data did not meet the non-inferiority margins for both the PP and ITT populations for the co-primary effectiveness endpoints of Revision/Removal/UADE Success p=0.29 and p=0.27, respectively); Radiographic Success at 22+ Months (p 0.54 and p=0.52, respectively); and KSSF Score at 22+ Months (p=0.07 and p=0.052, respectively).

When the full analysis dataset ITT and PP for the unilateral and bilateral knee dataset lead to essentially the same conclusions, confidence in the trial results is increased, and in this study confirms that the Investigational compared to the Control Group did not meet the non-inferiority criteria analysis for the bilateral knee subgroup study population for its proposed intended use in this patient population.[3,4]

Surgical Treatment Details

A summary of key findings of the 24-month Safety Data concerning the surgical time in minutes for the Investigational and Control groups by whether the surgery was a unilateral or simultaneous procedure is provided in Table 35. For unilateral knee procedures, the surgical time for the Investigational cementless device of 54.3 minutes when compared to the Control cemented device of 57.5 minutes was shorter though this was not statistically significant.

Table 35: Comparison of Surgical Treatment Details for the Investigational and Control Groups for Unilateral and Simultaneous Bilateral Knees

	Investigational (N=241)		Control (N=127)		
Surgical Time (minutes)	**Mean**	**95% CI**	**Mean**	**95% CI**	**p-value**
Unilateral, (N=378)	54.3 (n=225)	52.2, 56.3	57.5 (n=123)	54.3, 60.6	0.08
Simultaneous Bilateral, (N=20)	63.0 (n=16)	54.0, 72.0	58.9 (n=14)	45.1, 72.6	0.58

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: the type of surgical procedure (e.g., unilateral, bilateral). Subjects receiving a single implant were classified as a unilateral case. Subjects receiving two study devices (staged or simultaneously) were considered as bilateral cases from the start of the first knee being implanted, such that all case data was considered and analyzed as a bilateral case. Subjects

implanted with a single study device and later receiving a non-study device in the contralateral knee were also considered bilateral cases.

Regarding safety outcomes, a subgroup analysis was performed for both the unilateral and bilateral knees for the Investigational and Control Groups in Section X.D.1. Safety Results. The following relevant subsections and the associated tables contain a detailed report and analysis of the safety data outcomes for unilateral and bilateral knees.

- Unilateral Knees Safety Data – 24 Months: Refer to the subsections associated with Tables 20-24.
- Bilateral Knees Safety Data – 24 Months: Refer to the subsections associated with Tables 25-27.
- Unilateral and Bilateral Knees Safety Data – Over the Course of the Study: Refer to the subsections associated with Table 28-31.

Regarding effectiveness outcomes, a subgroup analysis was performed for both the unilateral and bilateral knees for the Investigational and Control Groups in Section X.D.2 Effectiveness Results. The following relevant subsections and the associated tables contain a detailed report and analysis of the safety data outcomes for unilateral and bilateral knees.

- Unilateral and Bilateral Knees Co-Primary Effectiveness Endpoints by Knee at 24 Months: Refer to the subsections associated with Tables 33-34.
- Unilateral and Simultaneous Bilateral Knees Surgical Treatment Details; Table 35.

The study was not specifically powered for unilateral and bilateral knee subgroups.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators of which none were full-time or part-time employees of the sponsor and seven (7) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 7
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

With regards to effectiveness, the primary objective of the clinical study was to show that the Oxford™ Cementless Partial Knee System is non-inferior to the Oxford™ Cemented Partial Knee System regarding each of the four co-primary effectiveness endpoints: Absence of Revision/Removal/UADE, Radiographic Success, Knee Society Score Assessment, and Knee Society Function Score. Study success required that the Cementless Group successfully demonstrated non-inferiority when compared to the Control Group for all four of the individual primary endpoints.

Combined Data (All Knees)

The primary effectiveness endpoint for this non-inferiority study of the complete data set (all knees) was met for the PP population. However, it was not met for the Radiographic Success endpoint in the ITT population ($p = 0.06$) and for overall study success. For the Radiographic Success endpoint, the data demonstrates that the Control Group had 108 of 110 knees classified as a success compared to the Investigational Group which had 202 of 216 knees classified as a success resulting in higher numerical success percentages in the ITT population (98.2% versus 93.5%). Additionally, the Control Group compared to the Investigational Group had a substantially higher percentage for success in the ITT population for the Revision/Removal/UADE Success effectiveness endpoint (98.3% versus 93.7%) although this did meet the non-inferiority criteria $p=0.009$). When the full analysis dataset of the ITT and the PP populations led to different conclusions, confidence in the trial results is decreased to use the proposed PP population as the basis of approval for the subject device for its proposed Intended Use.

Therefore, there was not reasonable assurance of effectiveness for all patients (e.g., unilateral and bilateral knees) based on the data.

Unilateral Knees

The unilateral knee data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical percentages for success in both the PP (97.3% versus 95.5%) and ITT (98.6% versus 95.0%) populations for the Radiographic Success at 22+ months – Effectiveness Co-Primary Endpoint. The data demonstrates that the Control Group compared to the Investigational Group for each knee has equivalent or higher numerical percentages for success in both the PP (97.5% versus 95.5%) and ITT (98.7% versus 95.0%) populations for the Revision/Removal/UADE Success Effectiveness Co-Primary Endpoint. In summary, the Unilateral Knees when compared to the All Knees dataset showed equivalent or numerical improvement in all four of the co-primary endpoints and all of them met their noninferiority margins for both the PP and ITT populations.

Bilateral Knees

The bilateral knee data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical percentages for success in both the PP (97.6% versus 89.1%) and ITT (97.5% versus 89.3%) populations for the Radiographic Success at 22+ months – Effectiveness Co-Primary Endpoint. The data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical percentages for success in both the PP (97.7% versus 90.2%) and ITT (97.6% versus 90.3%) populations for the Revision/Removal/UADE Success Effectiveness Co-Primary Endpoint. The data demonstrates that the Control Group compared to the Investigational Group for each knee has higher numerical values for the KSSF score in both the PP (92.6 versus 87.1) and ITT (92.4 versus 87.3) populations. In summary, the Bilateral Knees when compared to the All Knees dataset showed numerical decreases in three of the four co-primary endpoints. The bilateral knee data did not meet the non-inferiority margins for both the PP and ITT populations for the co-primary effectiveness endpoints of Revision/Removal/UADE Success (p=0.29 and p=0.28, respectively); Radiographic Success at 22+ Months (p=0.54 and p=0.52, respectively); and KSSF Score at 22+ Months (p=0.07 and p=0.052, respectively).

In summary, the Unilateral Knees when compared to the All Knees dataset showed equivalent or numerical improvement in all four of the co-primary endpoints and met the non-inferiority margins for both the PP and ITT populations. The etiology of the differences in the Investigational and Control Group Modified Effectiveness Co-Primary Endpoints success rates based upon a unilateral compared to a bilateral knee patient subpopulation is unknown but may be related to the load and stresses placed upon the subject device when the contralateral knee is implanted with a contralateral subject device (e.g., simultaneous surgery, staged bilateral surgery) or when there is bilateral knee disease. The study was not specifically powered for unilateral and bilateral knee subgroups.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

Combined Data (All Knees)
For the complete dataset of All Knees, the relative risk of the Investigational compared to Control Group for device-related AEs of the index knees is 2.09 with a 95% CI of (1.05, 4.18) in the ITT and 1.55 with a 95% CI (0.83, 2.87) in the PP populations, showing that the risk of a device-related AE for the Investigational group is higher than the Control group. Additionally, the relative risk of the Investigational Group compared to the Control Group for AEs of the index knees is 1.44 with 95% CI (1.11, 1.88) in the ITT and 1.36 with 95% CI (1.06, 1.76) in the PP populations that is both clinically and statistically significant. In both the PP and ITT populations the percentage of device-related AEs in a knee was higher overall and for each severity subgroup in the Investigational group compared to the Control Group. In both the PP and ITT populations the percentage of device-related AE outcomes in a knee that were both Tolerated and Not Tolerated was higher overall in the Investigational group compared to the Control Group. In both the PP and ITT populations the percentage of device related AE outcomes in a knee that were both Resolved and Not Resolved was higher overall in the Investigational group compared to the Control Group. In the PP population, the Investigational group compared to the Control group had a clinically but not statistically significant over two-fold risk of sustaining a device revision or removal and over four-fold risk of being converted to a total TKA. Overall, in the All Knees dataset the Investigational compared to the Control Group had both clinically and statistically significant increased safety data concerns.

Unilateral Knees
For the Unilateral Knees, the relative risk of the Investigational compared to the Control Group for device-related AEs of the index knees is 1.50 with a 95% CI of (0.68, 3.31) in the ITT and 1.00 with a 95% CT (0.49, 2.00) in the PP populations, showing that the risk of a device-related AE for the Investigational Group is slightly higher than the Control Group in the ITT population and equal in the PP population. In the PP population, the Investigational Group compared to the Control Group had a clinically but not statistically significant increased risk of sustaining a device revision or removal (RR 1.66; 95% CI 0.35, 7.79) and over two-fold risk of being converted to a total TKA (RR 2.37; 95% CI 0.28, 19.92). In the ITT population, The Control Group of unilateral knees had one device revision/removal and no conversions to a TKA. The unilateral knees subpopulation had similar safety data regarding all device-relatedness and serious/non-serious adverse event reporting when comparing the 24-Month to the Over the Course of the Study safety data timepoint evaluations. Overall, the unilateral knee subpopulation when compared to the All Knees dataset had considerably improved safety data regarding device-relatedness and serious/non-serious adverse event reporting.

For the unilateral knees, in the PP population the percentage of device-related AEs in unilateral knees was equal and similar for each severity subgroup in the Investigational group (N 154) [Mild: n=15, (9.7%); Moderate: n=4 (2.6%); Severe: n=5 (3.2%)] compared to the Control Group (N=73 [Mild: n=8, (11%); Moderate: n=2 (2.7%); Severe: n=2 (2.7%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Tolerated and Not Tolerated was similar overall in the Investigational group [Tolerated: n=13, (8.4%)); Not Tolerated: n=8 (5.2%)] compared to the Control Group [Tolerated: n=7, (9.6%)); Not Tolerated: n=3 (4.1%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Resolved and Not Resolved was similar in the Investigational group [Resolved: n=2, (1.3%)); Not Resolved: n=19 (12%)] compared to the Control Group [Resolved: n=1, 1.4%)); Not Resolved: n=9 (12%)]. Slightly higher rates were reported in the Investigational compared to the Control Group of device-related AEs classification in the ITT population for mild and severe severity classification groups and AE outcomes that were Not Tolerated or Not Resolved. Overall, the unilateral knee subpopulation when compared to the All Knees dataset had improved safety data regarding device-related AE severity classification and device-related AE Outcomes adverse event reporting.

Bilateral Knees

For the Bilateral Knees, the relative risk of the Investigational compared to the Control Group for device-related AEs of the index knees is 4.64 with a 95% CI of (1.11, 19.45) in the ITT and 4.85 with a 95% CI (1.16, 20.30) in the PP populations, showing that the risk of a device-related AE for the Investigational Group was clinically and statistically significantly increased compared to the Control Group. In the PP population, the Investigational Group compared to the Control Group had a clinically but not statistically significant over four-fold increased risk of sustaining a device revision or removal (RR 4.47; 95% CI 0.56, 35.73). Additionally, in the Investigational Group 3 patients (5.5%) compared to none in the Control Group were converted to a total TKA. The bilateral knees subpopulation had similar safety data regarding all device-relatedness and serious/non-serious adverse event reporting when comparing the 24-Month to the Over the Course of the Study safety data timepoint evaluations. Overall, the bilateral knee subpopulation when compared to the All Knees dataset had clinically and statistically significant increased safety data concerns regarding device-relatedness and serious/non-serious adverse event reporting.

For the bilateral knees, in the PP population the percentage of device-related AEs in bilateral knees was substantially increased for each severity subgroup in the Investigational group (N 55) [Mild: n=7, (13%); Moderate: n=4 7.3%); Severe: n=3 (5.5%)] compared to the Control Group (N=41) [Mild: n=1, (2.4%); Moderate: n=1 (2.4%); Severe: n=1 (2.4%)]. In the PP population the percentage of device-related AE outcomes in a knee that were both Tolerated and Not Tolerated was higher overall in the Investigational group [Tolerated: n=6, (11%)); Not Tolerated: n=7 (13%)] compared to the Control Group [Tolerated: n=1, (2.4%)); Not Tolerated: n 1 (2.4%)].

In the PP population the percentage of device-related AE outcomes in a knee that were both Resolved and Not Resolved was higher overall in the Investigational group [Resolved: n=4, (7.3%)); Not Resolved: n=9 (16%)] compared to the Control Group [Resolved: n=0, (0%)); Not Resolved: n=2 (4.9%)]. Similar findings were reported in the ITT population concerning device-related AEs classification by severity and AE outcomes. Overall, the bilateral knee subpopulation had clinically significant increased safety data concerns regarding device-related AE severity classification and device-related AE Outcomes adverse event reporting.

The Investigational compared to the Control Group demonstrated increased overall safety data adverse event reporting concerns for the bilateral compared to the unilateral knee patient subpopulation. The etiology of this difference in adverse event reporting between the two groups is unknown by may be related to the load and stresses placed upon the subject device when the contralateral knee is implanted with a contralateral subject device (e.g., simultaneous surgery, staged bilateral surgery) or when there is bilateral knee disease.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. There are probable benefits, including reduced pain and improved function, associated with the Oxford™ Cementless Partial Knee System (Investigational Group) for the unilateral knee patient subpopulation for the following modified Intended Use/Indications for Use statement: The Oxford™ Cementless Partial Knee System is indicated for use in unilateral knee procedures with osteoarthritis or avascular necrosis limited to the medial compartment of the knee. It is intended to be implanted without the application of bone cement for patients whose clinical condition would benefit from a shorter surgical time compared to the cemented implant.

Benefits:

1) The clinical study results at 2-years follow-up for both the PP and ITT populations demonstrates that the unilateral knee patients met the non-inferiority testing for the modified four co-primary effectiveness endpoints: (Radiographic Success, Knee Society Score Assessment, and Knee Society Function Score) at the 22+ Month time point and Absence of Revision/Removal/UADE at the 24-Month time point.

2) The clinical study reported a shorter surgical time of 3.2 minutes for unilateral knee patients using the Oxford™ Cementless Partial Knee System compared to the cemented device version (Control Group)

Risks:
The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval. In Unilateral Knee patients the majority of the

risks of the use of the Oxford™ Cementless Partial Knee System compared to the cemented device version (Control Group) were equivalent or slightly higher.

1) For the Unilateral Knees, the relative risk of the Investigational Group compared to the Control Group for device related AEs of the index knees is 1.50 with a 95% CI of (0.68, 3.31) in the ITT and 1.00 with a 95% CI (0.49, 2.00) in the PP populations, showing that the risk of a device-related AE for the Investigational Group is slightly but not statistically higher than the Control Group in the ITT population and equal in the PP population.

2) For Unilateral Knees, the Investigational Group compared to the Control Group had a clinically but not statistically significant increased risk of sustaining a device revision or removal (RR 1.66; 95% CI 0.35, 7.79) and over two-fold risk of being converted to a total TKA (RR 2.37; 95% CI 0.28, 19.92) in the PP population.

3) For the Unilateral Knees, the percentage of device-related AEs for each severity subgroup for the Investigational Group compared to the Control Group was similar for the PP population and similar but slightly higher for the ITT population except for the moderate severity subgroup.

4) The percentage of the AE outcomes in the unilateral knee subjects categorized as both Tolerated and Not Tolerated as well as Resolved versus Not Resolved for the Investigational Group compared to the Control Group was similar for the PP population. Slightly higher rates were reported in the Investigational compared to the Control Group of device-related AEs outcomes in the ITT population for mild and severe severity classification groups and AE outcomes that were Not Tolerated or Not Resolved.

Additional factors to be considered in determining probable risks and benefits for the Oxford™ Cementless Partial Knee System device include the following:

1) Using the modified four co-primary effectiveness endpoints there was an overall compliance rate of 87.3% with 316 of 362 subjects at the 22+ month follow-up for Radiographic Success, Knee Society Score Assessment, and Knee Society Function Score endpoints and 24-month follow-up for Revision/Removal/UADE Success endpoint.

2) The clinical study results at 2-years follow-up for both the PP and ITT populations demonstrates that the bilateral knee patients did not meet the non-inferiority testing for three of the four modified co-primary effectiveness endpoints for both the PP and ITT populations: Radiographic Success and Knee Society Function Score at the 22+ Month time point and Absence of Revision/Removal/UADE at the 24-Month time point.

3) For the Bilateral Knees, the relative risk of the Oxford™ cementless compared to the Oxford™ cemented group for device-related AEs of the index knees is 4.64 with a 95% CI of (1.11, 19.45) in the ITT and 4.85 with a 95% CI (1.16, 20.30) in the PP populations which is both clinically and statistically significant.

4) Both the unilateral and bilateral knee subpopulations had similar safety data regarding all device-relatedness and serious/non-serious adverse event reporting when comparing the 24-Month to the Over the Course of the Study safety data timepoint evaluations.

5) For the Bilateral Knees, the Investigational group compared to the Control group had a clinically but not statistically significant over four-fold increased risk of sustaining a device revision or removal (RR 4.47; 95% CI 0.56, 35.73) in the PP population.

6) For the Bilateral Knees, the percentage of device-related AEs for each severity subgroup for the Investigational Group compared to the Control Group was substantially increased for both the PP and ITT populations.

7) The percentage of the AE outcomes in the bilateral knee subjects categorized as both Tolerated and Not Tolerated as well as Resolved and Not Resolved for the Investigational Group compared to the Control Group was substantially increased for both the PP and ITT populations.

8) Based upon the clinical data, when a simultaneous bilateral surgery or planned staged bilateral procedures are considered for a patient the Oxford™ Cemented Partial Knee System should be used.

1. Patient Perspective
   Patients choose to undergo partial knee replacement to reduce pain and improve function. The KSSA and KSSF scores, which measures improvement in pain and function of the knee joint, showed for unilateral patients that the Oxford™ Cementless Partial Knee System was non-inferior compared to the Cemented version.

In conclusion, given the available information above, the data support that for use in unilateral knee procedures with osteoarthritis or avascular necrosis limited to the medial compartment of the knee in those patients whose clinical condition would benefit from a shorter surgical time compared to the cemented implant that the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Oxford™ Cementless Partial Knee System when used in accordance with the indications for use statement.

This study demonstrated that the Oxford™ Cementless Partial Knee System is non-inferior to the Oxford™ Meniscal Unicompartmental Knee System with respect to the study's four modified co-primary effectiveness endpoints and the two devices have equivalent or slightly higher safety profiles for the unilateral patient subpopulations.

The pre-clinical and clinical data in this PMA application support the reasonable assurance of safety and effectiveness of the Oxford™ Cementless Partial Knee System for use in unilateral knee procedures with osteoarthritis or avascular necrosis limited to the medial compartment of the knee. It is intended to be implanted without the application of bone cement for patients whose clinical condition would benefit from a shorter surgical time compared to the cemented implant.

XIV. CDRH DECISION

CDRH issued an approval order on November 22, 2024.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Guidance for Industry and FDA Staff. Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications. August 30, 2019.
2. U.S. Food & Drug Administration. What is a Serious Adverse Event (see: https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event.
3. Guidance for Industry. E9 Statistical Principles for Clinical Trials. September, 1998.
4. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel randomized trials. PLoS Med. 2010;24(3):e1000251. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials | PLOS Medicine