

# **SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)**

## **I. GENERAL INFORMATION**

Device Generic Name: Prosthesis, Total Hip System, Semi-constrained, Metal/Ceramic/Ceramic/Metal, Cemented or Uncemented

Device Trade Name: R3™ delta Ceramic Acetabular System

Device Procode: MRA

Applicant's Name and Address: Smith & Nephew, Inc.  
Advanced Surgical Devices Division  
7135 Goodlett Farms Parkway  
Cordova, TN 38016 U.S.A.

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150030

Date of FDA Notice of Approval: 10/17/2016

## **II. INDICATIONS FOR USE**

The R3 delta Ceramic Acetabular System is indicated for use in skeletally mature patients requiring primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis.

## **III. CONTRAINDICATIONS**

The R3 delta Ceramic Acetabular System is contraindicated in individuals exhibiting any of the following:

- Insufficient quantity or quality of bone support; metabolic bone disease; osteoporosis
- Neurological or muscular conditions that would place an extreme load upon the hip joint or cause joint instability
- Active joint infections or chronic systemic infection
- Obese patients where obesity is defined as a BMI > 40
- Skeletal immaturity
- Known allergy to any of the implant materials

#### **IV. WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the R3 delta Ceramic Acetabular System labeling.

#### **V. DEVICE DESCRIPTION**

The R3 delta Ceramic Acetabular System consists of a ceramic on ceramic acetabular bearing couple combined with a compatible metal shell and one of four commercially available Smith & Nephew femoral stems. All implantable devices are supplied sterile and are for single use.

The bearing surfaces consist of zirconia toughened alumina ceramic acetabular liners and zirconia toughened alumina ceramic femoral heads; both are manufactured from BIOLOX<sup>®</sup> delta Zirconia Toughened Aluminum Oxide.

##### R3 delta Acetabular Liner

The ceramic acetabular liners feature a pre-assembled titanium band (ASTM F1472 and ISO 5832-3) and the male taper of the titanium band is designed for mechanical assembly to the internal female taper of the mating acetabular shell. The ceramic liners are available in ten sizes with two internal diameters, i.e., 32mm and 36mm. The 32mm liners are offered with two outer diameters of 48mm and 50mm, and the 36mm liners are offered with eight outer diameters of 48-66mm in 2mm increments.

##### Femoral Head

The ceramic ball heads are available in two diameter sizes: 32mm and 36mm. Each diameter head size has three different neck lengths, short (+0), medium (+4), and long (+8) for proper anatomic and musculature fit. All ball heads have an internal bore with an angle designed for conformity with the 12/14 cone taper of the femoral stems.

##### R3 Acetabular Shell and Ancillary Components

The R3 delta Ceramic Liners are intended to be used in conjunction with Smith & Nephew's R3 Acetabular Shells for cementless use. The R3 acetabular shells are manufactured from Ti-6Al-4V (ASTM F1472 and ISO5832-3). The outer shell geometry is hemispherical and has a sintered asymmetric porous coating from commercially pure titanium (ASTM F67 and ISO5832-2). The interior of the R3 Acetabular Shell features a female taper which is designed for mechanical assembly to the male taper of the outer titanium band of the mating R3 delta Ceramic Liner. There are eleven sizes of acetabular shells available, ranging from 48mm through 68mm outer diameter in 2mm increments. Each shell features an apex hole to accept the cup positioner / impactor instruments. Shells have either no screw holes or three screw holes arranged about the apex hole. These holes are for optional, adjunctive screw fixation to the superior acetabulum with Spherical Head Screws, which have a diameter of 6.35mm and lengths of 15-70mm. Hole covers are available to cover the shell holes if desired. Screws and hole covers are manufactured from Ti-6Al-4V ELI (ASTM F136).

### Femoral Stems

The ceramic femoral heads of the R3 delta Ceramic Acetabular System are intended to be used in conjunction with one of the following four, legally marketed femoral stems from Smith & Nephew (all featuring a 12/14 Taper):

- Titanium alloy (Ti-6Al-4V per ASTM F1472), cementless SYNERGY™ femoral stems (Standard and High Offset versions),
- Titanium alloy (Ti-6Al-4V per ASTM F1472), cementless POLARSTEM™ femoral stems (Standard and Lateral versions) \*,
- Titanium alloy (Ti-6Al-7Nb per ASTM F1295), cementless SL-PLUS™ femoral stems (Standard and Lateral versions),
- Titanium alloy (Ti-6Al-4V per ASTM F1472), cementless ANTHOLOGY™ femoral stems (Standard and High Offset versions),

The SYNERGY and ANTHOLOGY stems have a sintered, beaded porous coating made from commercially pure titanium (ASTM F67) on the proximal surface. The POLARSTEM femoral stems have a plasma sprayed titanium and hydroxyapatite (Ti/HA) dual coating on the surface\*.

*\* Note that the POLARSTEM stems legally marketed in the US have identical materials, design, dimensions, and sizes, as well as a similar coating thickness as the POLARSTEM stems used in the clinical trial (not available in the US) except that they were coated by Smith & Nephew while the POLARSTEM stems used in the clinical trial were coated by a supplier; see Section IX Summary of Nonclinical Studies for safety and effectiveness justification.*

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are several other alternative treatments of non-inflammatory arthritis of the hip including:

- The use of other commercially available total hip replacement implants which may include alternative bearing surfaces;
- Non-surgical treatment such as reduced activity, weight loss, physical therapy, and/or pain medication; and
- Other surgical treatments that do not involve the use of an implant, such as hip joint fusion.

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 the patient's expectations and lifestyle.

## **VII. MARKETING HISTORY**

The R3 delta Ceramic Acetabular System has been commercially available outside the United States (OUS) since 2008 with use in Australia, Austria, Belgium, Canada, China, Finland, Germany, Hong Kong, Italy, Japan, the Middle East, Netherlands, New Zealand, Norway, Poland, Portugal, South Africa, South Korea, Spain, Switzerland, and the United Kingdom. The product has not been withdrawn from any market due to safety and effectiveness reasons.

## **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.

### Potential Complications Associated with Any Total Hip Arthroplasty surgery

- Excessive wear of the implant components secondary to impingement of components or damage of articular surfaces
- Fracture, migration, loosening, subluxation, or dislocation of the prosthesis or any of its components; any of which may require a second surgical intervention or revision;
- Increased hip pain and/or reduced hip function
- Bone fractures
- Osteolysis and/or other peri-prosthetic bone loss
- Metal sensitivity reactions or other allergic/histological reactions to implant material
- Vascular damage resulting in significant blood loss, or
- Neurologic injury resulting in transient or permanent functional and/or sensory deficits
- Leg length change/discrepancy
- Deep venous thrombosis
- Pulmonary or vascular embolism
- Superficial or deep infection, delayed wound healing
- Periarticular calcification
- Myocardial infarction
- Gastrointestinal complications
- Genitourinary complications
- Decreased range of motion
- Aggravation of other joint or back conditions (due to positioning during surgery, postoperative leg length discrepancy, muscular deficiencies, etc.)
- Death

### Potential Complications Associated with Ceramic on Ceramic Hip Systems

Due to the materials of the device, these may include, but are not limited to, femoral head breakage, acetabular insert (liner) fracture, and device related noise such as

squeaking. Other adverse events, common to other hip systems may also occur but at different frequencies.

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

**IX. SUMMARY OF NONCLINICAL STUDIES**

**A. Laboratory Studies**

A battery of preclinical laboratory tests were conducted on the alumina composite matrix ceramic material used to manufacture the ceramic components. The metal components that comprise the rest of this system are made from materials that have been used for many years in total hip replacement (THR) surgery.

Non-clinical laboratory testing was provided in support of the R3 delta Ceramic Acetabular System including:

- Acetabular Shell-Liner Locking Mechanism Testing (push-out, lever-out, and torque to failure)
- Pre-fatigue Burst Testing of Acetabular Liner
- Pre- and Post-fatigue Burst Testing of Femoral Head and Acetabular Liner after Hydrothermal Aging
- Pre- and Post-Fatigue Burst Testing of Femoral Head
- Hip Simulator Wear Testing (pristine conditions, third-body (abrasive) conditions, and subluxation conditions)
- Stress Induced Zirconia Phase Transformation Testing
- Impact Load Testing
- Porous Coating Testing
- Ti/HA Dual Coating Testing
- Range of Motion (ROM) Analysis

Test	Purpose and Methods	Acceptance Criteria	Results
Acetabular Shell-Liner Locking Mechanism Testing (push-out, lever-out, and torque to failure)	The purpose of this test was to evaluate the locking mechanism of the BIOLOX <sup>®</sup> delta liners in the R3 shells.  Push-out, lever-out, and torque to failure testing was performed using 32mm ID BIOLOX <sup>®</sup> delta liners in 48mm OD R3 shells which represents the worst-case (the	<u>Push-out:</u> The push-out loads were greater or comparable to previously tested metal/UHMWPE constructs of legally marketed devices.  <u>Lever-out:</u> The lever-out moments	<u>Push-out:</u> The average ( $\pm$ std. dev.) push-out load of six R3 delta liners from R3 shells was $1006\pm 384$ N. Push-out loads of the R3 delta liners did not display a statistically significant difference compared to previously tested metal/UHMWPE

Test	Purpose and Methods	Acceptance Criteria	Results
	<p>smallest and thinnest liner and the least liner-shell contact area). Shell and liner constructs were assembled using the drop weight assembly method in ASTM F2009-00 (2011) using 3 impacts. Testing was performed per ASTM F1820-13 and a total of six shell-liner constructs were tested for each test.</p>	<p>were greater or comparable to previously tested metal/ Ultra-high-molecular-weight polyethylene (UHMWPE) constructs of legally marketed devices.</p> <p><u>Torque to Failure:</u> The acceptance criterion required the torque-to-failure moment to exceed the reported 2.4 N-m torque due to friction at the ball-liner interface [1] by a safety factor of five (e.g., 12 N-m).</p>	<p>constructs used for comparison.</p> <p><u>Lever-out:</u> The average (<math>\pm</math> std. dev.) lever-out moment of six R3 delta liners from R3 shells was <math>14.4 \pm 6.2</math> N-m. Lever-out moments of R3 delta ceramic liners did not display a statistically significant difference compared to the lever-out moments of previously tested metal/UHMWPE constructs used for comparison.</p> <p><u>Torque to Failure:</u> The average (<math>\pm</math> std. dev.) torque-to-failure moment of six R3 delta liners from R3 shells was <math>12.6 \pm 3.8</math> N-m. Torque-to-failure moments of R3 delta ceramic liners met the acceptance criterion.</p>
<p>Pre-fatigue Burst Testing of Acetabular Liner</p>	<p>The purpose of this test was to determine the axial compressive burst strength of the R3 delta ceramic acetabular liners through mechanical testing.</p> <p>The testing was conducted using the method specified in the FDA “Guidance Document for the Preparation of Premarket Notifications for Ceramic Ball Head System” [*]. Seven 32/39G</p>	<p>The acceptance criteria were an average burst strength exceeding an average failure load of 46 kN, with no component failing at less than 20 kN.</p>	<p>The average (<math>\pm</math> std. dev.) burst load of the seven R3 delta ceramic acetabular liners was <math>101 \text{ kN} \pm 12 \text{ kN}</math> and the minimum burst load was 87.0 kN.</p> <p>Burst strengths of R3 delta ceramic acetabular liners met the acceptance criteria.</p>

Test	Purpose and Methods	Acceptance Criteria	Results
	<p>BIOLOX<sup>®</sup> delta liners in combination with R3 shells were tested, which represents the worst case.</p>		
<p>Pre- and Post-fatigue Burst Testing of Femoral Head and Acetabular Liner after Hydrothermal Aging</p>	<p>The purpose of this study was to determine the pre- and post-fatigue static burst strength of R3 delta 32mm ceramic liners and heads after autoclaving.</p> <p>Twelve couples of R3 delta heads and liners were autoclaved for 10 cycles with a cumulative exposure time of 20 hours to simulate hydrothermal aging and resultant phase transformation of yttria-stabilized zirconia in the matrix of delta liners and heads. Six couples were burst tested using the method specified in the FDA “Guidance Document for the Preparation of Premarket Notifications for Ceramic Ball Head System” [*]. The other six couples were fatigue tested using a compressive load of 1.4/14 kN at 15 Hz and subsequently burst tested.</p>	<p><u>Pre-fatigue Burst Strength:</u> The acceptance criteria were an average burst strength exceeding an average failure load of 46 kN, with no component failing at less than 20 kN.</p> <p><u>Post-fatigue Burst Strength:</u> The acceptance criteria required the couples to pass 10 million cycles at 14kN with no macroscopically visible component failure and have no post-fatigue burst strength below 20 kN.</p>	<p><u>Pre-fatigue Burst Strength:</u> The couples had an average (<math>\pm</math> std. dev.) pre-fatigue burst strength of 94.2<math>\pm</math>17.9 kN with a minimum pre-fatigue burst strength of 69.6 kN.</p> <p><u>Post-fatigue Burst Strength:</u> All six couples completed 10 million cycles of fatigue without failure. The couple had an average (<math>\pm</math> std. dev.) post-fatigue burst strength of 111.6<math>\pm</math>10.2 kN with a minimum post-fatigue burst strength of 100.4 kN.</p> <p>All test results met the acceptance criteria.</p>
<p>Pre- and Post-Fatigue Burst Testing of Femoral Head</p>	<p>The purpose of this test was to determine the axial compressive burst strength of the delta ceramic femoral heads before and after fatigue testing.</p> <p>Axial compressive burst strength testing was conducted on five 28mm</p>	<p><u>Pre-fatigue Burst Strength:</u> The acceptance criteria were an average burst strength exceeding an average failure load of 46 kN, with no component failing at less than 20 kN.</p>	<p><u>Pre-fatigue Burst Strength:</u> The average burst load of the five BIOLOX<sup>®</sup> delta Ceramic femoral heads was 57.5 kN (minimum burst load of 41.4 kN).</p> <p><u>Post-fatigue Burst Strength:</u> All three</p>

Test	Purpose and Methods	Acceptance Criteria	Results
	<p>long (+8) BIOLOX<sup>®</sup> delta ceramic on 12/14 taper cobalt chrome (CoCr) trunnions using the method specified in the FDA “Guidance Document for the Preparation of Premarket Notifications for Ceramic Ball Head System” [*]. The test construct of a 28mm long (+8) femoral head on a CoCr trunnion was chosen because it represents worst case; the tapers were manufactured from CoCrMo which has the highest elastic modulus of any Smith &amp; Nephew hip stem material and therefore transfers the greatest stress to the femoral head.</p> <p>A total of three 28 mm +8 mm offset (Long) femoral heads were fatigue tested and subsequently burst-tested.</p>	<p><u>Post-fatigue Burst Strength</u>: The acceptance criteria required the ceramic head to pass 10 million cycles at 14kN with no macroscopically visible component failure and have no post-fatigue burst strength below 20 kN.</p>	<p>constructs completed 10 million cycles of fatigue at a maximum load of 14 kN without failure, and had an average post-fatigue burst load of 66.6 kN (minimum post-fatigue burst load of 64 kN).</p> <p>All testing results met the acceptance criteria.</p>
Femoral Head Pull-off testing	<p>The purpose of this study was to determine the static pull-off strength of BIOLOX<sup>®</sup> delta ceramic femoral heads on trunnions with 12/14 tapers.</p> <p>Six 32mm +8mm femoral heads were impacted onto Ti-6Al-4V and Ti-6Al-7Nb trunnions, respectively using the drop weight method described in ASTM F2009-00(2011), which utilizes a 2.0 lbf (907 g) weight dropped from 10 in. (25.4 cm) height. Each head was impacted 3 times per trunnion. Pull-off</p>	<p>The pull-off loads were greater or comparable to CoCrMo heads on CoCrMo tapers used on legally marketed devices.</p>	<p>The average pull-off load for six (6) BIOLOX<sup>®</sup> delta femoral heads was 3,602±366 N and 3,275±428 N for the Ti-6Al-4V trunnions and Ti-6Al-7Nb trunnions, respectively. Pull-off loads for delta heads on Ti-6Al-4V and Ti-6Al-7Nb trunnions were 49% and 35% higher when compared to 32 mm +8 mm offset 12/14 taper CoCrMo heads on CoCrMo tapers used</p>

Test	Purpose and Methods	Acceptance Criteria	Results
	testing was performed, and the maximum pull-off load was recorded.		for comparison.
Hip Simulator Wear testing – Benign (Pristine) Conditions	<p>The purpose of this testing was to determine the wear and durability characteristics of the R3 delta device under standard ‘pristine’ conditions.</p> <p>Three (3) R3 delta liners (32/48mm) and 32mm delta heads were subjected to 5.0 million cycles (Mc) of hip joint simulation as per ISO 14242-1 using an AMTI machine. Tests were performed in bovine serum (20 g/L) at 1 Hz, with a peak load of 3.0 kN, and a cup inclination of 35°. Wear was measured gravimetrically.</p> <p>The wear results were compared to alumina (BIOLOX® forte) couples tested previously under similar conditions.</p> <p>Wear particles were collected and analysis as per ASTM F1877-05.</p>	Test was performed for characterization only.	<p>The average wear rate for the R3 delta specimens to 5.0 Mc was <math>0.08 \pm 0.05</math> mm<sup>3</sup>/Mc. The weighted average wear particle size under pristine testing was 0.2 micron. The wear behavior and surface features were comparable to that of alumina (BIOLOX® forte) couples tested previously.</p> <p>These results demonstrated that the ceramic-on-ceramic articulation surfaces used for the R3 delta system produced no significant wear after 5.0 Mc of pristine wear testing.</p>
Hip Simulator Wear Testing with titanium transfer on Biolox delta heads– Third-Body (Abrasive) Conditions	<p>The purpose of this testing was to determine the wear and durability characteristics of the R3 delta device under abrasive conditions simulating titanium contamination.</p> <p>Six R3 delta couples (32mm) were subjected to 3.0 Mc of hip simulation. The delta</p>	Lower volumetric wear rates compared to the control MoM bearing couples.	Under third-body abrasive conditions, the average wear rate for the R3 delta couples remained low at $0.02 \pm 0.01$ mm <sup>3</sup> /Mc. In contrast, the control MoM couples produced a wear rate of ~45 mm <sup>3</sup> /Mc. All ceramic surfaces

Test	Purpose and Methods	Acceptance Criteria	Results
	<p>heads were purposely (heavily) smeared with titanium, covering the entire articular surfaces. All other experimental methods were identical as described above (as per ISO 14242-1).</p> <p>These results were compared to metal-on-metal (MoM) couples (n=2) tested under similar conditions.</p> <p>Wear particles were collected and analyzed as per ASTM F1877-05.</p>		<p>appeared visually unaltered after testing, although there were areas of grain-pullout observed. This grain-pullout was less extensive than that observed under sublucation conditions. The weighted average wear particle size under third-body abrasive testing was 0.09 micron.</p> <p>These results demonstrated that the R3 delta system produced no significant wear after 3.0 Mc of third-body wear testing.</p>
<p>Hip Simulator Wear Testing – Bone cement Third-Body (Abrasive) Conditions</p>	<p>To determine the wear and durability characteristics of the R3 delta device under abrasive conditions simulating bone cement contamination.</p> <p>Three R3 delta specimens (32mm) were subjected to 2.0 Mc of hip simulation (AMTI) using a bovine serum lubricant that was contaminated with 10 g/L of Versabond™ bone cement powder (PMMA). All other experimental methods were identical as described above (as per ISO 14242-1). This test was carried out after the pristine (benign) wear testing using the same couples.</p>	<p>Test was performed for characterization only.</p>	<p>The average wear rate for the R3 delta specimens under bone cement contamination was <math>-0.01 \pm 0.02</math> mm<sup>3</sup>/Mc. Overall, this adverse wear test using PMMA powder was unable to cause increases in wear rates or cause notable damage for ceramic-on-ceramic couples.</p> <p>These results demonstrated that the R3 delta system produced no significant wear after 2.0 Mc of bone cement third-body wear testing.</p>

Test	Purpose and Methods	Acceptance Criteria	Results
	<p>No control couples were tested. No wear particle analysis was performed.</p>		
<p>Hip Simulator Wear Testing – Subluxation (Micro-separation) Conditions</p>	<p>To determine the wear and durability characteristics of the R3 delta device under repeated subluxation events, commonly known as micro-separation (MSX) testing.</p> <p>Three R3 delta specimens (32mm) were subjected to 3.0 Mc of MSX hip simulations that introduced 1.0 mm of joint separation (subluxation) during the swing phase of loading. This subluxation method was developed to produce stripe wear and grain-pullout on alumina implants. All other experimental methods were identical as described above (as per ISO 14242-1). The bovine serum lubricant did not contain PMMA or titanium particles. This test was carried out after the bone cement abrasive phase described above using the same couples.</p> <p>The wear results were compared to alumina (BIOLOX® forte) couples tested previously under similar methods.</p> <p>Wear particles were collected and analysis as per ASTM F1877-05.</p>	<p>The volumetric wear rates were lower or comparable to the control BIOLOX® forte couples.</p>	<p>Under subluxation conditions (MSX), the average wear rate for the R3 ZTA-Delta couples remained low at <math>0.28 \pm 0.06</math> mm<sup>3</sup>/Mc. Subluxation created stripe features, characterized by inter-granular fracture and grain-pullout, on heads and liners. The wear behavior and surface features were comparable to that of alumina (BIOLOX® forte) couples tested previously. The weighted average wear particle size under subluxation testing was 0.16 micron.</p> <p>These results demonstrated that the R3 delta system produced no significant wear after 3.0 Mc of subluxation wear testing.</p>

Test	Purpose and Methods	Acceptance Criteria	Results
Stress Induced Zirconia Phase Transformation Testing	<p>The purpose of this analysis was to measure the monoclinic zirconia phase content after micro separation hip simulator wear testing.</p> <p>Samples analyzed were tested on the hip simulator for 10 million cycles, 3 million of which were under sublaxation conditions. Monoclinic phase content was measured on the area of severe contact and a polished reference area utilizing X-ray diffraction.</p>	<p>Acceptance criterion is based on comparable investigation report that monoclinic content after very severe conditions can be increased to values up to ~50% without loss of residual strength.</p>	<p>The monoclinic content on the femoral head increased from 6% of the total zirconia phase content on the reference area to 12% on the severe wear area. The monoclinic content on the acetabular liner increased from 6% on the reference area to 7% on the severe wear area.</p> <p>The small amount of phase transformation from tetragonal to monoclinic in the delta ceramic should not deteriorate the long-term safety of these devices.</p>
Impact Load Testing	<p>The purpose of this test was to evaluate the impact strength of R3 delta ceramic liner and head couples. Acetabular shells were assembled by cementing them into wood blocks, and ceramic liners (32 mm ID, 48 mm OD R3 delta Ceramic Acetabular Liners, BIOLOX<sup>®</sup> delta) were assembled into the shells using the drop weight method in ASTM F2009-00(2011) which specifies a 2.0 lbf (907 g) drop weight and a drop height of 10.0 inches (25.4 cm). Ceramic femoral heads (32 mm +8, 12/14 taper BIOLOX<sup>®</sup> delta femoral</p>	<p>The acceptance load of 900 lbf (4 kN) was specified based on <i>in vivo</i> loading [2]. The impact loads were greater or comparable to REFLECTION<sup>™</sup> ceramic couples.</p>	<p>Six delta ceramic couples completed one million cycles of impact loading at 8,000 lbf (35.6 kN).</p> <p>This impact load represents approximately 8.9 times the acceptance loads. This load is also greater than the run-out load of REFLECTION ceramic couples.</p>

Test	Purpose and Methods	Acceptance Criteria	Results
	<p>heads) were assembled onto the stem taper using the drop weight method. Components were placed in a computer-controlled test frame and impact tested for 1 million cycles using 0.5 mm of separation and an impact force of 8,000 lbf (35.6 kN) (impact ramp time is 0.25 s).</p> <p>The approved REFLECTION ceramic couples were tested under identical conditions as control.</p>		
<p>Porous Coating Testing</p>	<p>The purpose of this testing was to characterize the STIKTITE™ porous coating of the R3 Acetabular Shells.</p> <p>Metallurgical, microstructural and mechanical characterization testing of the porous coating was provided in accordance with the FDA’s “Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement”, dated 4/28/94 [**].</p>	<p>In accordance with Guidance document [**] and standards.</p>	<p>Smith &amp; Nephew presented all testing in accordance with the Guidance document. The STIKTITE porous coating is sintered from asymmetric CP-titanium particles (ASTM F67) and has an average coating thickness of 941.3 µm, an average mean void intercept length of 148.8 µm or 144.5 µm (at two different thickness levels), an average volume percent of voids of 56.8%, an average static tensile strength of 48.2 MPa, and an average static shear strength of 38.4 MPa.</p> <p>The testing results met the requirements in Guidance document and standards.</p>

Test	Purpose and Methods	Acceptance Criteria	Results
Ti/HA Dual Coating Testing	<p>The purpose of this testing was to characterize the plasma sprayed titanium and hydroxyapatite (Ti/HA) dual coating on the POLARSTEM stems with regard to chemical / crystallographic, physical and mechanical requirements in accordance with the FDA’s “Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement”, dated 4/28/94 [**], and “510(K) Information Needed for Hydroxyapatite Coated Orthopedic Implants” dated March 10, 1995 (revised 2/20/97) [**].</p> <p>Testing to characterize both the Ti/HA coating applied by the supplier on the POLARSTEM stems used in the clinical study and the Ti/HA coating applied by Smith &amp; Nephew on the POLARSTEM stems cleared by the FDA was presented in order to demonstrate that the difference in coating supplier does not impact the safety and performance of the POLARSTEM stems.</p>	The acceptance criteria are in accordance with the Guidance documents [**, **] and the voluntary consensus standards.	<p>The testing results met the requirements in Guidance documents and standards.</p> <p>It can be concluded from the coating testing data as well as the stem testing referenced or provided in this PMA (i.e., fatigue testing, pull-off testing, and range of motion analysis) that the minor difference in characteristics of the Ti-HA coatings on the POLARSTEM stems will not impact the safety and performance of the POLARSTEM stems and the R3 delta Ceramic Acetabular System.</p>
Range of Motion (ROM) Analysis	<p>The purpose of this analysis was to evaluate the range of motion of the R3 delta Ceramic Acetabular System.</p> <p>A computer aided design</p>	The acceptance criteria were specified per ISO 21535:2007(E) and the minimum values for each	The minimum values for each motion obtained across all combinations analyzed are (per each of the four stems):

Test	Purpose and Methods	Acceptance Criteria	Results
	(CAD) analysis was performed in accordance with ISO 21535:2007(E) to evaluate the range of motion of the worst case constructs including R3 acetabular shell, R3 delta liner, delta head, and each of the four femoral stems intended for use with the R3 delta Ceramic Acetabular System.	motion are: 100° in flexion/extension (Delta); 60° in abduction/adduction (Epsilon); and 90° in internal/external rotation (Gamma).	<p><u>SYNERGY:</u> 148° (Delta)/ 134° (Epsilon)/222° (Gamma)</p> <p><u>POLARSTEM:</u> 140° (Delta)/ 130° (Epsilon)/220° (Gamma)</p> <p><u>SL-PLUS:</u> 142° (Delta)/ 112° (Epsilon)/170° (Gamma)</p> <p><u>ANTHOLOGY:</u> 148° (Delta)/ 132° (Epsilon)/220° (Gamma)</p> <p>All ROM results exceeded the minimum criteria.</p>

\*Guidance Document for the Preparation of Premarket Notifications for Ceramic Ball Hip Systems, available at:  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080786.pdf>

\*\* Guidance Document for Testing Orthopedic Implants With Modified Metallic Surfaces Apposing Bone Or Bone Cement (April 28, 1994), available at:  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081247.pdf>

\*\*\* 510(K) Information Needed for Hydroxyapatite Coated Orthopedic Implants March 10, 1995 (revised 2/20/97), available at:  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080225.pdf>

**B. Animal Studies**

No animal studies have been performed. Animal studies were not deemed necessary to determine the safety and effectiveness of the R3 delta Ceramic Acetabular System.

### **C. Additional Studies**

#### **Biocompatibility**

The materials for use in the R3 delta Ceramic Acetabular System are standard materials used in permanently implanted orthopedic implants, including titanium alloy (ASTM F1472, ASTM F1295, and ASTM F136) and zirconia toughened alumina (ZTA) ceramic material (BIOLOX<sup>®</sup> delta).

#### **Sterilization**

The Smith & Nephew R3 delta Ceramic femoral heads and acetabular liners are sterilized by gamma radiation sterilization (Cobalt 60 Source) at a minimum dose of 25 kGy (2.5 Mrad). The process is validated using Method VDmax per the requirements of ISO 11137 to yield a minimum Sterility Assurance Level (SAL) of  $10^{-6}$ . The products are not labeled “pyrogen free.” The components are packaged in PETG trays sealed with Tyvek lids to maintain sterility.

#### **Shelf Life**

Shelf life testing was performed to verify sterile packaging integrity equivalent to 10 years for the R3 delta Ceramic Acetabular System.

## **X. SUMMARY OF PRIMARY CLINICAL STUDY**

The applicant performed a clinical study outside of the United States (“European Post-Market Study”) to establish a reasonable assurance of safety and effectiveness of hip arthroplasty with the R3 delta Ceramic Acetabular System for use in skeletally mature patients requiring primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis in the United States. Data from this clinical study was the basis for the PMA approval decision. A summary of the clinical study is presented below.

### **A. Study Design**

Patients were treated between June 1, 2009 and September 1, 2014. The database for the European Post-Market Study, from which the PMA data were abstracted, reflected data collected through October 31, 2014 and included 505 patients. There were 8 investigational sites, which included the countries of Germany, Finland, Denmark, the Netherlands, the United Kingdom, Belgium, and Spain.

The European Post-market Study was a prospective, consecutive, concurrently controlled, non-randomized, multi-center, clinical outcome study designed to collect safety and effectiveness data of the R3 acetabular cup with all bearing options

marketed in Europe. The subject selection process was predefined in the study protocol. The treatment option for patients requiring total hip arthroplasty was chosen by the surgeon during a preoperative visit. All available bearing options for the R3 acetabular cup were used in subjects enrolled in the study: BIOLOX<sup>®</sup> forte ceramic-on-ceramic, BIOLOX<sup>®</sup> delta ceramic-on ceramic (DOD), ceramic-on-crosslinked polyethylene (XLPE) (CoXLPE), Oxidized zirconium-on-XLPE (OxZr/XLPE), metal-on-XLPE (MoXLPE), and metal-on-metal (MoM).

In order to demonstrate the safety and effectiveness of the R3 delta Ceramic Acetabular System, a control group from the European Post-market Study was defined whose data had been collected concurrently according to the same study protocol. Per the applicant, “To serve as an effective control for the DOD, the control group must have been implanted with a head and liner articulation couple that is cleared or approved in the US, has a good performance record, and represents state of the art technology. The oxidized zirconium-on-XLPE (OxZr/XLPE) articulation coupling met the requirements for a suitable control group and had enrolled a comparable number of subjects to the DOD group; therefore, it was selected as the control device.” The control treatment was a legally marketed alternative with similar indications for use.

Data were abstracted for all subjects implanted with either a DOD or OxZr/XLPE articulation. The two treatment groups contained a combined total of 268 subjects from 7 sites and included all countries identified above except Germany. 131 subjects were implanted with the R3 acetabular cup combined with an OxZr/XLPE articulation couple and one of five femoral stems (SYNERGY, ANTHOLOGY, POLARSTEM, SL-PLUS, and SPECTRON stems) while 137 subjects were implanted with the R3 acetabular cup combined with a DOD articulation couple and one of four femoral stems (all above stems except SPECTRON).

The primary endpoint for the analysis was an overall success outcome determination at a minimum of 3 years post-surgery, which included implant survivorship, a modified Harris Hip Score (mHHS), and radiographic evaluation. In order to meet overall success, a subject must have demonstrated all of the following at the 3-year time point:

- No component revision; and
- mHHS of at least 80 points; and
- Radiographic success, defined as:
  - o No radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones; and
  - o No femoral or acetabular subsidence greater than or equal to 5mm from baseline; and
  - o No acetabular cup inclination changes greater than 4 degrees (4°)

Secondary safety and effectiveness measures included the individual subcomponents of overall success as well as the Western Ontario and McMaster Universities Arthritis

Index (WOMAC), as part of the Hip disability and Osteoarthritis Outcomes Score (HOOS), and the UCLA Activity Level Rating (UCLA).

In addition, safety evaluations included adverse events monitored over the course of the study. Adverse events were captured from the time of surgery until subjects completed the study or their data were abstracted from the study database, whichever came sooner. Adverse event adjudication was performed by an independent Clinical Events Committee (CEC) composed of three board-certified orthopedic surgeons.

Study success was defined as establishing non-inferiority of the DOD cohort compared to the OxZr/XLPE cohort based upon the 3-year clinical composite success (CCS) rates with a non-inferiority delta of 10%. The following hypothesis was tested to establish clinical non-inferiority of DOD relative to OxZr/XLPE:

$$\begin{aligned} H_0: \pi_{\text{DOD}} - \pi_{\text{OxZr/XLPE}} &\leq \delta \\ H_a: \pi_{\text{DOD}} - \pi_{\text{OxZr/XLPE}} &> \delta \end{aligned}$$

where  $\pi_{\text{DOD}}$  and  $\pi_{\text{OxZr/XLPE}}$  are the 3-year clinical composite success (CCS) rates of the investigational and control device, respectively.

#### 1. Clinical Inclusion and Exclusion Criteria

Enrollment in the European Post-market was limited to patients who met the following inclusion criteria:

- Patient is 18-75 years old and he/she is skeletally mature
- Patient requires primary total hip arthroplasty due to non-inflammatory degenerative joint disease (e.g. osteoarthritis, post-traumatic arthritis, avascular necrosis, dysplasia/ developmental dysplasia of the hip) or inflammatory joint disease (e.g. rheumatoid arthritis)
- Patient has met an acceptable preoperative medical clearance and is free from or treated for cardiac, pulmonary, hematological, etc., conditions that would pose excessive operative risk
- The patient is willing to comply to the follow-up schedule

Patients were not permitted to enroll in the European Post-market Study if they met any of the following exclusion criteria:

- Patient has active infection or sepsis (treated or untreated)
- Patient is a prisoner or has an emotional or neurological condition that would pre-empt their ability or unwillingness to participate in the study including mental illness, mental retardation, linguistic insufficiencies (i.e. immigrants), or drug/alcohol abuse
- Patients with acute hip trauma (femoral neck fracture)

Further, enrollment in the R3 delta Ceramic Acetabular System study was limited to patients who met the following inclusion criteria:

- Subject of the European Post-market Study
- Must have a signed informed consent

- Must have been implanted with a DOD or OxZr/XLPE articulation couple
- Must have all device labels available to allow confirmation of devices implanted

and

Patients were not permitted to enroll in the R3 delta Ceramic Acetabular System study if they met any of the following exclusion criteria:

- Any subject in the OxZr/XLPE arm who was implanted with any hip system component that is not 510(k) cleared for use in the US with the OxZr femoral head and XLPE acetabular liner\*
- Any subject in the DOD arm who was implanted with any hip system component (other than the ceramic acetabular liner) that is not 510(k) cleared for use with the ceramic head

*\* Note that the POLARSTEM stems legally marketed in the US have identical materials, design, dimensions, and sizes, as well as a similar coating thickness as the POLARSTEM stems used in the clinical trial (not available in the US) except that they were coated by Smith & Nephew while the POLARSTEM stems used in the clinical trial were coated by a supplier; see Section IX Summary of Nonclinical Studies for safety and effectiveness justification.*

## 2. Follow-up Schedule

All subjects were scheduled to return for post-operative follow-up examinations at 3 months ( $\pm 2$  weeks), 1 year ( $\pm 2$  months), and 3 years ( $\pm 2$  months) in the R3 delta Ceramic Hip System study. The European Post-market Study also included post-operative follow-up examinations at 5, 7, and 10 years postoperatively (Table 1).

**Table 1: Visit Schedule with Date Ranges**

Window	Description	In-window Relative Day		Continuous Visit Window Relative Date	
		Min	Max	Min	Max
Pre-op	Pre-operative	-28	-1/0	N/A	-1/0
Day 0	Operative	0	0	0	0
Discharge	Discharge	N/A	N/A	N/A	N/A
Day 90	3 Month Visit	76	104	1	227
Day 365	1 Year Visit	305	425	228	730
Day 1095	3 Year Visit	1005	1185	731	1460
Day 1825	5 Year Visit (1)	1645	2005	1461	2190
Day 2555	7 Year Visit (1)	2375	2735	2191	3102
Day 3650	10 Year Visit (1)	3470	3830	3103	N/A

(1) Not included in PMA analyses.

**Note:** Table includes “In-Window” follow-up time frames to allow for classification of in-window and out-of-window visits as well as SAP defined “Continuous Visit Windows” to “maximize the

data included and to pre-specify how the data collected outside of the “In-Window” follow-up ranges would be included in the analyses”.

Evaluations were performed according to the visit schedule below. Adverse events and complications were recorded at all visits (Table 2).

**Table 2: Assessments by Visit**

Data	Visit				
	Pre-op	Discharge	3 Months	1 Year	3 Years
Informed Consent	X				
Demographics/Medical History	X				
mHHS	X		X	X	X
UCLA	X		X	X	X
HOOS	X		X	X	X
Radiographic Evaluation		X		X	X
Adverse Events		On occurrence			

3. Clinical Endpoints

With regards to safety, the following data were collected: adverse events, device survivorship (revisions), and radiographic success/failure.

With regards to effectiveness, the following data were collected: mHHS, WOMAC scores, and UCLA scores.

With regard to success/failure criteria, the primary composite endpoint used to determine individual success was:

- No component revision; and
- mHHS of at least 80 points; and
- Radiographic success, defined as:
  - o No radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones; and
  - o No femoral or acetabular subsidence greater than or equal to 5mm from baseline; and
  - o No acetabular cup inclination changes greater than 4 degrees (4°)

Study success was defined as establishing non-inferiority of the DOD cohort compared to the OxZr/XLPE cohort based upon the 3-year clinical composite success (CCS) rates with a non-inferiority delta of 10%. The following hypothesis was tested to establish clinical non-inferiority of DOD relative to OxZr/XLPE:

$$H_0: \pi_{\text{DOD}} - \pi_{\text{OxZr/XLPE}} \leq \delta$$

$$H_a: \pi_{\text{DOD}} - \pi_{\text{OxZr/XLPE}} > \delta$$

where  $\pi_{\text{DOD}}$  and  $\pi_{\text{OxZr/XLPE}}$  are the 3-year clinical composite success (CCS) rates of the investigational and control device, respectively.

Revision was defined as reoperation where any component (acetabular cup, acetabular liner, femoral head, or femoral stem) was replaced.

#### Modified Harris Hip Score (mHHS)

The mHHS is a clinician-based outcome measure used to assess patient pain, function, deformity, and range of motion. Scoring assessment ranges from 0 (worst) to 100 (best). The mHHS is a modified version of the HHS, which has been found to be reliable and valid in measuring outcomes following total hip arthroplasty, and was collected pre-operatively as well as at each post-operative follow-up visit.

#### Western Ontario and McMaster Universities Arthritis Index (WOMAC)

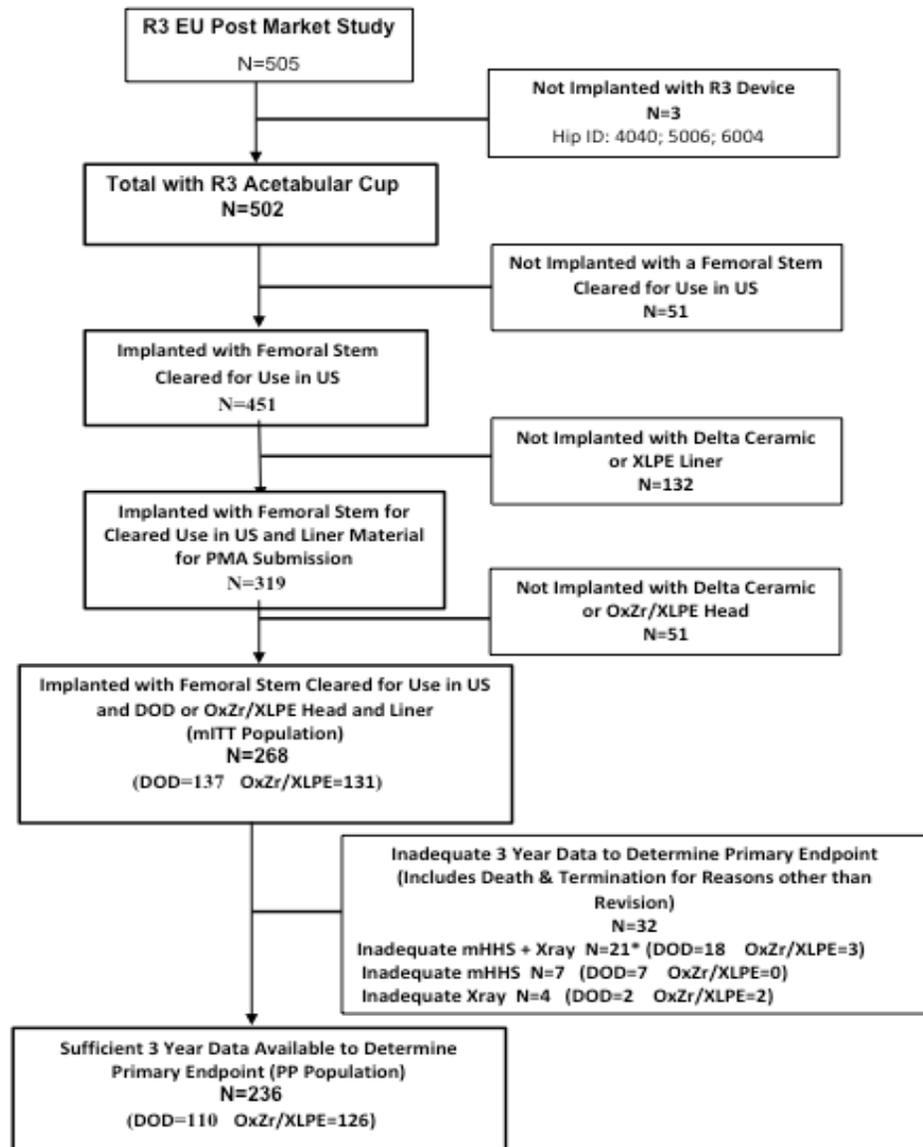
The WOMAC is a self-administered health status measure for osteoarthritis of the hip and is used to evaluate a patient's pain, stiffness, and physical function. It has been validated for evaluating outcomes following total hip arthroplasty. The WOMAC was collected using the Hip disability and Osteoarthritis Outcome Score (HOOS), which includes the WOMAC in its complete and original format. Only the WOMAC portion of the HOOS was collected in the European Post-market Study. The WOMAC scoring assessment ranges from 0 (worst) to 96 (best). The WOMAC score was collected at the preoperative, 3-month, 1-year, and 3-year follow-up visits.

#### UCLA Activity Level Rating (UCLA)

The UCLA Activity Level Rating scale is a self-assessment of a person's activity level that ranges from wholly inactive (level 1) to regular participation in impact sports (level 10). The UCLA Activity Level Rating is a valid instrument for routine activity assessment in subjects undergoing total joint arthroplasty. The UCLA score was collected at the preoperative, 3-month, 1-year, and 3-year follow-up visits.

### **B. Accountability of PMA Cohort**

Data for the subjects of the PMA study were abstracted from the European Post-market study. The population of subjects ultimately analyzed was determined according to the following flowchart (Figure 1):



\*Includes 1 Death (DOD) and 8 Other Termination (7 DOD and 1 OxZr/XLPE)

**Figure 1: Flowchart of PMA Cohort Accountability**

A total of 268 subjects (137 DOD and 131 OxZr/XLPE) were enrolled in the study at 7 sites. At the time of database lock, 121/135 expected DOD subjects (89.6%) and 121/124 expected OxZr/XLPE (97.6%) subjects had any 3 year primary endpoint data available for analysis. Complete 3 year overall success (primary endpoint) data were available for 109/135 expected DOD subjects (80.7 %) and 119/124 (96.0 %) expected OxZr/XLPE subjects (Table 3). A success/failure determination based upon the primary endpoint, which included revisions, was able to be made for 110/137 (80.3%) of the DOD cohort and 126/131 (96.1%) of the OxZr/XLPE cohort.

**Table 3: Subject Accounting, mITT Population**

Summary	Pre-Op		3 Months		1 Year		3 Years	
	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE
Theoretical [1]	137	131	137	131	137	131	137	131
Deaths [2]	0	0	0	0	1	0	1	0
Failures [3]	0	0	1	4	1	5	1	7
Expected [4]	137	131	136	127	135	126	135	124
ActualA	NA	NA	NA	NA	123	122	109	119
% Follow-up [5]	NA	NA	NA	NA	91.1%	96.8%	80.7%	96.0%
ActualB	137	131	133	125	127	122	121	121
% Follow-up [6]	100.0%	100.0%	97.8%	98.4%	94.1%	96.8%	89.6%	97.6%

NA: Not applicable  
ActualA: Subjects with complete data for the primary endpoint (modified Harris Hip Score, radiographic evaluation and safety assessments), evaluated per protocol, in the window time frame  
ActualB: Subjects with any follow-up data reviewed or evaluated by investigator (“all evaluated” accounting).  
[1] Number of subjects that would have reached the beginning of the study window associated with each visit if all subjects returned.  
[2] Cumulative number of subjects that died during or prior to the study visit.  
[3] Cumulative number of subjects that failed (revision) during or prior to the study visit.  
[4] Theoretical subjects minus the number of deaths and revisions.  
[5] ActualA/Expected\*100  
[6] ActualB/Expected\*100

The modified intention to treat (mITT) population is defined as all subjects who consented to study participation and received the R3 Acetabular Cup System with the BIOLOX<sup>®</sup> delta ceramic on BIOLOX<sup>®</sup> delta ceramic or the OxZr/XLPE articulation couple. The per-protocol (PP) population is defined as all mITT subjects with complete 3 year primary endpoint data and no deviations to the inclusion and exclusion criteria. In the analyses completed, aside from the sensitivity analyses and tipping point analysis, no data were imputed for the missing data, and therefore the mITT population and PP populations were identical as there were no deviations to the inclusion and exclusion criteria.

**C. Study Population Demographics and Baseline Parameters**

The available population demographics and baseline parameters of the study population and individual study cohorts are provided in Table 4 and Table 5. The available demographics and baseline characteristics are typical of the patient

population in the US undergoing total hip arthroplasty. The study cohorts had no statistically significant difference in demographics or baseline parameters.

**Table 4: Demographics, mITT Population**

Outcomes	Treatment		P-value [1]
	DOD	OxZr/XLPE	
	N = 137	N = 131	
Age (years)			
Mean (SD)	61.8 (9.12)	62.9 (9.01)	0.3495
Median	63.2	64.8	
Min, Max	27, 75	32, 76 [2]	
Gender			
Female	90 (65.7%)	73 (55.7%)	0.1046
Male	47 (34.3%)	58 (44.3%)	
BMI (kg/m <sup>2</sup> )			
Mean (SD)	27.7 (4.74)	28.2 (5.38)	0.3803
Median	27.4	27.5	
Min, Max	19.1, 44.4	17.9, 43.0	
[1] P-value from Fisher's exact test for categorical variables and two-sample t-test for continuous variables.			
[2] Subject 6041 was aged 75.7 years at surgery and subject 3028 75.8 years, rounding leads to maximum age 76 years			

**Table 5: Baseline Characteristics, mITT Population**

Outcomes	Treatment		P-value [1]
	DOD	OxZr/XLPE	
	137	131	
Diagnosis			
Primary Osteoarthritis	116 (84.7%)	123 (93.9%)	0.1122
Dysplasia	4 (2.9%)	3 (2.3%)	
Posttraumatic Osteoarthritis	1 (0.7%)	0	
Osteonecrosis (AVN)	13 (9.5%)	4 (3.1%)	
Rheumatoid Arthritis	2 (1.5%)	1 (0.8%)	
Ankylosing Spondyloarthritis	1 (0.7%)	0	
Surgical History on the Study Hip			
None	135 (98.5%)	126 (96.2%)	0.2365
Internal Fixation	1 (0.7%)	3 (2.3%)	
Proximal Femoral Osteotomy	0	1 (0.8%)	
Acetabular Osteotomy	0	1 (0.8%)	
Other	1 (0.7%)	0	
Charnley Classification			
Only Ipsilateral Hip Involved	79 (57.7%)	71 (54.2%)	0.8584
Both Hips Involved	51 (37.2%)	53 (40.5%)	
Other Factors Affecting Locomotion	7 (5.1%)	7 (5.3%)	

[1] P-value from Fisher's exact test for categorical variables and two-sample t-test for continuous variables.

No data on racial demographics of those enrolled were collected to allow for assessment of the potential for differing outcomes or success rates amongst subjects of differing races. It is not expected racial differences would result in different

outcomes or success rates based upon use of the delta ceramic on delta ceramic bearing surface, which was the focus of this PMA. Racial demographic information will be collected as part of the new enrollment US PAS to further assess any impact of race on patient outcomes.

#### **D. Safety and Effectiveness Results**

##### **1. Safety Results**

The analysis of safety was based on the mITT cohort of patients (268 total subjects) defined as all subjects who consented to study participation and received the R3 Acetabular Cup System with the BIOLOX<sup>®</sup> delta ceramic on BIOLOX<sup>®</sup> delta ceramic or the OxZr/XLPE articulation couple. The key safety outcomes for this study, adverse events, device survivorship (revisions), and radiographic failure, are presented below in Table 6 to Table 15.

##### **Adverse Events:**

A summary of the total number of adverse events (AE), events adjudicated as serious, events adjudicated as related (device-related, procedure-related: operative site, procedure-related: systemic, and systemic), deaths, and removals or revisions are shown in Table 6 and Table 7. The AE seriousness and relatedness to the device and/or procedure were adjudicated by a CEC which consisted of three independent board-certified orthopedic surgeons. The AE data, including a narrative for each AE, were also reviewed by the FDA and the adjudication was modified for multiple AEs with agreement by the applicant.

A total of 487 events were reported in both treatment groups. There was no statistically significant difference in the number of hips reported as experiencing an AE between the DOD and OxZr/XLPE treatment groups, but there was a statistically significant difference in the total number of AEs reported between the groups. This difference in overall AEs was accounted for by a greater number of non-serious and non-device or procedure related AEs. Overall, the higher number of non-serious and non-device or procedure related AEs does not appear clinically meaningful based upon the lack of relationship to the device or procedure.

In the DOD group, 296 AEs were reported in 105 hips (76.6 %). Of those, 168 events in 71 hips (51.8%) were assessed as non-serious and 128 events in 73 hips (53.3%) were assessed as serious (SAEs). In the OxZr/XLPE group, 191 events were reported in 89 hips (67.9%). Of those, 68 events in 46 hips (35.1%) were assessed as non-serious and 123 events in 66 hips (50.4%) were assessed as serious. The treatment group difference in non-serious AEs was statistically significant by the number of hips and the number of events ( $p=0.0068$  and  $p<0.0001$  respectively) while the difference in SAEs was not statistically significant by the number of hips or the number of events ( $p=0.7138$  and  $p=0.9123$  respectively) (Table 6).

In the DOD group, 33 events in 31 (22.6%) hips were assessed as device-related, 50 events in 41 (29.9%) hips were assessed as procedure-related: operative site, 13 events in 10 (7.3%) hips were assessed as procedure-related: systemic, and 232 events in 89 (65.0%) hips were assessed as systemic (not related to the device or procedure). In the OxZr/XLPE group, 38 events in 26 (19.8%) hips were assessed as device-related, 46 events in 32 (24.4%) hips were assessed as procedure-related: operative site, 3 events in 3 (2.3%) hips were assessed as procedure-related: systemic, and 142 events in 71 (54.2%) hips were assessed as systemic. NOTE: some adverse events were assessed as both device and procedure-related (operative site or systemic); thus, the total of device-related, procedure-related: operative site, procedure-related: systemic, and systemic adverse events exceeds the total number of AEs. There were no statistically significant differences in AEs between the treatment groups by the number of hips or the number of events in terms of device or procedure relationship (Table 6). Further, there were no statistically significant differences in AEs between the treatment groups by the number of hips or the number of events in terms of device or procedure relationship when additionally classified by seriousness (Note: statistical significance could not be calculated for the number of serious procedure-related: systemic AEs) (Table 7)..

In the DOD group, 1 (0.7%) subject died from a head injury, which was believed to be unrelated to the device or procedure. In the OxZr/XLPE group, no subjects died.

**Table 6: Adverse Events, mITT Population**

Type of AE or Outcome	Treatment Group		Fisher's Exact Test P-value	Negative Binomial P-value [2]
	DOD N = 137 No. of Hips (%)	OxZr/XLPE N = 131 No. of Hips (%)		
<b>Event Classification</b>				
All AE/SAE	105 (76.6%)	89 (67.9%)	0.1329	
All AE/SAE Events	296	191		0.0016
<b>Outcomes, Death and Revision</b>				
Death	1 (0.7%)	0	1.0000	
Removal or Revision	1 (0.7%)	7 (5.3%)	0.0329	
<b>Seriousness per CEC [1]</b>				
Non-serious AE	71 (51.8%)	46 (35.1%)	0.0068	
Non-serious AE Events	168	68		<0.0001
SAE	73 (53.3%)	66 (50.4%)	0.7138	
SAE Events	128	123		0.9123
<b>Relationship per CEC [1]</b>				
Device related	31 (22.6%)	26 (19.8%)	0.6547	
Number of Device related	33	38		0.5555
Procedure-related Operative Site	41 (29.9%)	32 (24.4%)	0.3386	

Type of AE or Outcome	Treatment Group		Fisher's Exact Test P-value	Negative Binomial P-value [2]
	DOD N = 137 No. of Hips (%)	OxZr/XLPE N = 131 No. of Hips (%)		
Number of Procedure-related: Operative Site	50	46		0.8133
Procedure-related Systemic	10 (7.3%)	3 (2.3%)	0.0855	
Number of Procedure-related: Systemic	13	3		NE
Systemic (Not related to device or procedure)	89 (65.0%)	71 (54.2%)	0.0817	
Number of Systemic Events	232	142		0.0015

[1] Includes definitely and possibly related.  
[2] Analysis is based on a negative binomial model with number of events as the dependent variable, treatment as the factor, and log of time of study as the offset.  
Note: NE: Not Estimable due to lack of model convergence  
Note: Procedure-related: Operative Site is defined as an adverse event associated with the operative site i.e., involves the index hip or hip implants and surrounding area, or may involve a symptom known or suspected to originate from the index hip or hip implant, or involves the surgical access to the index hip.  
Note: Procedure-related: Systemic is defined as an adverse event of a systemic nature with no known causal association with orthopedic implants in general or total hip implants in particular, and are general-surgery related (not specifically related to THR surgery), or events that are not proximate to the index hip or index operative site.

**Table 7: Adverse Events by Relationship and Seriousness, mITT Population**

Relationship per CEC [1]	Treatment Group		Fisher's Exact Test P-value	Negative Binomial P-value [2]
	DOD N = 137 No. of Hips (%)	OxZr/XLPE N = 131 No. of Hips (%)		
<b>Device related</b>				
Serious	9 (6.6%)	13 (9.9%)	0.3765	
Number of Serious	9	19		0.1107
Non-Serious	22 (16.1%)	16 (12.2%)	0.3868	
Number of Non-Serious	24	19		0.4939
<b>Procedure-related: Operative Site</b>				
Serious	13 (9.5%)	17 (13.0%)	0.4395	
Number of Serious	14	24		0.1440
Non-Serious	32 (23.4%)	18 (13.7%)	0.0591	
Number of Non-Serious	36	22		0.0894
<b>Procedure-related: Systemic</b>				
Serious	4 (2.9%)	1 (0.8%)	0.3709	
Number of Serious	6	1		NE
Non-Serious	6 (4.4%)	2 (1.5%)	0.2826	
Number of Non-Serious	7	2		0.1344

Relationship per CEC [1]	Treatment Group		Fisher's Exact Test P-value	Negative Binomial P-value [2]
	DOD N = 137 No. of Hips (%)	OxZr/XLPE N = 131 No. of Hips (%)		
[1] Includes definitely and possibly related.				
[2] Analysis is based on a negative binomial model with number of events as the dependent variable, treatment as the factor, and log of time of study as the offset.				
Note: NE: Not Estimable due to lack of model convergence				

The severity of AEs was adjudicated by the investigators as mild, moderate, or severe as AE severity was unable to be determined by the CEC based on review of study records (Table 8)

There were greater numbers of hips and events in all three severity categories (mild, moderate, and severe) in the DOD cohort as expected by the overall greater number of AEs in the DOD cohort, but when assessed by device or procedure relatedness again almost all the greater numbers were accounted for by systemic (non-device or procedure related) AEs. The only statistically significant difference in AEs by severity was for severe systemic AEs (p=0.0010 for hips and p=0.0002 for events) (Table 8).

**Table 8: Adverse Events by Severity per Investigator and Relationship per CEC**

Severity Per Investigator	Treatment Group		Fisher's Exact Test P-value	Negative Binomial P-value [2]
	DOD N = 137 No. of Hips (%)	OxZr/XLPE N = 131 No. of Hips (%)		
<b>Mild</b>				
Mild	74 (54.0%)	66 (50.4%)	0.6248	
Number of Mild	144	104		0.0509
<b>Relationship per CEC [1]:</b>				
Device related	23 (16.8%)	18 (13.7%)	0.5028	
Number of Device related	25	27		0.7821
Procedure-related Operative Site	29 (21.2%)	22 (16.8%)	0.4368	
Number of Procedure-related Operative Site	34	31		0.7898
Procedure-related Systemic	7 ( 5.1%)	1 (0.8%)	0.0668	
Number of Procedure-related Systemic	9	1		NE
Systemic (Not related to device or procedure)	59 (43.1%)	51 (38.9%)	0.5353	
Number of Systemic (Not related to device or procedure)	100	72		0.0953
<b>Moderate</b>				
Moderate	48 (35.0%)	44 (33.6%)	0.8977	
Number of Moderate	89	62		0.0994

Severity Per Investigator	Treatment Group		Fisher's Exact Test P-value	Negative Binomial P-value [2]
	DOD N = 137 No. of Hips (%)	OxZr/XLPE N = 131 No. of Hips (%)		
<b>Relationship per CEC [1]:</b>				
Device related	6 (4.4%)	6 (4.6%)	1.0000	
Number of Device related	6	7		NE
Procedure-related Operative Site	9 (6.6%)	9 (6.9%)	1.0000	
Number of Procedure-related Operative Site	11	10		NE
Procedure-related Systemic	2 (1.5%)	1 (0.8%)	1.0000	
Number of Procedure-related Systemic	2	1		NE
Systemic (Not related to device or procedure)	42 (30.7%)	37 (28.2%)	0.6894	
Number of Systemic (Not related to device or procedure)	76	51		0.0912
<b>Severe</b>				
Severe	44 (32.1%)	22 (16.8%)	0.0044	
Number of Severe	63	25		0.0007
<b>Relationship per CEC [1]:</b>				
Device related	2 (1.5%)	4 (3.1%)	0.4386	
Number of Device related	2	4		NE
Procedure-related Operative Site	4 (2.9%)	5 (3.8%)	0.7449	
Number of Procedure-related Operative Site	5	5		NE
Procedure-related Systemic	2 (1.5%)	1 (0.8%)	1.0000	
Number of Procedure-related Systemic	2	1		NE
Systemic (Not related to device or procedure)	41 (29.9%)	17 (13.0%)	0.0010	
Number of Systemic (Not related to device or procedure)	56	19		0.0002
[1] Includes definitely and possibly related.				
[2] Analysis is based on a negative binomial model with number of events as the dependent variable, treatment as the factor, and log of time of study as the offset.				
Note: NE: Not Estimable due to lack of model convergence.				

Table 9 provides the AEs identified as device-related in both treatment cohorts by onset interval. The most common device related AEs were bone fracture femur/fissure/fracture subtrochanteric (DOD, 5; OxZr/XLPE, 5), dislocation (DOD, 0; OxZr/XLPE, 5), study sided groin pain (DOD, 3; OxZr/XLPE, 4), study sided hip pain (DOD, 5; OxZr/XLPE, 11), and trochanteritis (DOD, 4; OxZr/XLPE, 1).

**Table 9: Device-related Adverse Events by Onset Interval**

	Intraoperative (0 Days)		3 Months (1-227 Days)		1 Year (228-730 Days)		3 Years (731-1460 Days)		>3 Years (>1460 Days)		Total	
	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	DOD	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE
Number of Hips	137	131	137	131	133	129	126	127	4	6	137	131
Bone Fracture- Femur	0	1	2	3	0	0	0	0	0	0	2	4
Bursitis	0	0	0	2	2	0	0	0	0	0	2	2
Dislocation	0	0	0	3	0	1	0	1	0	0	0	5
Elevated Metal Ions	0	0	0	0	0	0	3	0	0	0	3	0
Femoral Component	0	0	0	3	0	0	0	0	0	0	0	3
Fissure	1	1	1	0	0	0	0	0	0	0	2	1
Fracture- Subtrochanteric	0	0	1	0	0	0	0	0	0	0	1	0
Groin pain, study hip side	0	0	2	0	1	1	0	3	0	0	3	4
Inflammation	0	0	0	0	1	0	0	0	0	0	1	0
Leg Length Change	1	0	0	0	1	0	0	0	0	0	2	0
Leg Pain	0	0	1	0	0	0	0	0	0	0	1	0
Limp, study hip side	0	0	1	0	1	0	0	0	0	0	2	0
Muscular/ Connective Tissue	0	0	0	0	0	1	0	0	0	0	0	1
Nervous	0	0	0	0	0	0	1	0	0	0	1	0
Operative side pain from other than study hip	0	0	0	0	1	0	0	0	0	0	1	0
Pain at Op site	0	0	0	0	0	1	0	1	0	0	0	2
Pain in study hip	0	0	2	4	2	2	1	4	0	1	5	11
Pain, unknown etiology	0	0	0	0	0	0	0	1	0	0	0	1
Skeletal	0	0	0	0	0	1	0	1	0	0	0	2
Subluxation, no component specified	0	0	0	0	0	0	1	0	0	0	1	0
Trendelenberg gait	0	0	1	1	0	0	0	0	0	0	1	1
Trochanteritis	0	0	2	0	2	0	0	1	0	0	4	1
Uncoded - Hip weakness	0	0	1	0	0	0	0	0	0	0	1	0
<b>Total</b>	<b>2</b>	<b>2</b>	<b>14</b>	<b>16</b>	<b>11</b>	<b>7</b>	<b>6</b>	<b>12</b>	<b>0</b>	<b>1</b>	<b>33</b>	<b>38</b>

	Intraoperative (0 Days)		3 Months (1-227 Days)		1 Year (228-730 Days)		3 Years (731-1460 Days)		>3 Years (>1460 Days)		Total	
	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	DOD	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE
Note: Number of Hips = Number of hips evaluated at that time period and overall.												
Note: Includes the number of occurrences for each type of event.												
Note: Three hips (#7019, 7073, and 7098) have a missing AE start date; therefore, date of readmission was used for determining the AE onset interval.												
Note: Hips with missing AE start date that could not be determined are excluded since AE onset is unknown.												

Table 10 provides the AEs identified as procedure-related: operative site in both treatment cohorts by onset interval. The most common procedure-related: operative site related AEs were bone fracture femur/fissure/fracture subtrochanteric (DOD, 7; OxZr/XLPE, 5), dislocation (DOD, 0; OxZr/XLPE, 5), study sided groin pain (DOD, 3; OxZr/XLPE, 4), study sided hip pain (DOD, 6; OxZr/XLPE, 11), trochanteritis (DOD, 4; OxZr/XLPE, 1), and superficial infection only (DOD, 1; OxZr/XLPE, 3).

**Table 10: Procedure-related: Operative Adverse Events by Onset Interval**

	Intraoperative (0 Days)		3 Months (1-227 Days)		1 Year (228-730 Days)		3 Years (731-1460 Days)		>3 Years (>1460 Days)		Total	
	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE
Number of Hips	137	131	137	131	133	129	126	127	4	6	137	131
Bone Fracture- Femur	1	1	2	3	0	0	1	0	0	0	4	4
Bursitis	0	0	0	2	2	0	0	0	0	0	2	2
Deep Infection > 6 weeks	0	0	0	1	0	0	0	0	0	0	0	1
Deep Vein Thrombosis	0	0	0	1	0	0	0	0	0	0	0	1
Delayed Wound Healing	1	0	1	0	0	0	0	0	0	0	2	0
Dislocation	0	0	0	3	0	1	0	1	0	0	0	5
Elevated Metal Ions	0	0	0	0	0	0	3	0	0	0	3	0
Femoral Component	0	0	0	3	0	0	0	0	0	0	0	3
Fissure	1	1	1	0	0	0	0	0	0	0	2	1
Fracture- Subtrochanteric	0	0	1	0	0	0	0	0	0	0	1	0
Groin pain, study hip side	0	0	2	0	1	1	0	3	0	0	3	4
Hematoma, Hemarthrosis	0	0	2	1	0	0	0	0	0	0	2	1
Heterotopic Ossification- Generic Reporting	0	0	0	0	1	0	0	0	0	0	1	0

	Intraoperative (0 Days)		3 Months (1-227 Days)		1 Year (228-730 Days)		3 Years (731-1460 Days)		>3 Years (>1460 Days)		Total	
	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE
Heterotopic Ossification: Grade I	0	0	1	0	0	0	0	0	0	0	1	0
Infection	0	0	0	1	0	0	0	0	0	0	0	1
Inflammation	0	0	2	0	1	0	0	0	0	0	3	0
Leg Length Change	1	0	0	0	2	0	0	0	0	0	3	0
Leg Pain	0	0	1	0	0	0	0	0	0	0	1	0
Limp, study hip side	0	0	1	0	1	0	0	0	0	0	2	0
Lymphatic	0	0	1	0	0	0	0	0	0	0	1	0
Muscular/ Connective Tissue	0	0	1	0	0	1	0	0	0	0	1	1
Nervous	0	0	1	0	0	0	1	0	0	0	2	0
Operative side pain from other than study hip	0	0	0	0	1	0	0	0	0	0	1	0
Pain at Op site	0	0	0	0	0	1	0	1	0	0	0	2
Pain in study hip	0	0	3	4	2	2	1	4	0	1	6	11
Pain, unknown etiology	0	0	0	0	0	0	0	1	0	0	0	1
Post-op swelling of study leg	0	0	1	1	0	0	0	0	0	0	1	1
Skeletal	0	0	0	0	0	1	0	1	0	0	0	2
Subluxation, no component specified	0	0	0	0	0	0	1	0	0	0	1	0
Superficial Infection Only	0	0	1	3	0	0	0	0	0	0	1	3
Trendelenberg gait	0	0	1	1	0	0	0	0	0	0	1	1
Trochanteritis	0	0	2	0	2	0	0	1	0	0	4	1
Uncoded - Hip weakness	0	0	1	0	0	0	0	0	0	0	1	0
<b>Total</b>	<b>4</b>	<b>2</b>	<b>26</b>	<b>24</b>	<b>13</b>	<b>7</b>	<b>7</b>	<b>12</b>	<b>0</b>	<b>1</b>	<b>50</b>	<b>46</b>

Note: Number of Hips = Number of hips evaluated at that time period and overall.

Note: Includes the number of occurrences for each type of event.

Note: Three hips (#7019, 7073, and 7098) have a missing AE start date; therefore, date of readmission was used for determining the AE onset interval.

Note: Hips with missing AE start date that could not be determined are excluded since AE onset is unknown.

Table 11 provides the AEs identified as procedure-related: systemic in both treatment cohorts by onset interval. The most common procedure-related: systemic related AEs were circulatory (DOD, 2; OxZr/XLPE, 0), digestive/GI (DOD, 2; OxZr/XLPE, 0), fever (DOD, 2; OxZr/XLPE, 0), nervous (DOD, 4; OxZr/XLPE, 0), and urinary (DOD, 1; OxZr/XLPE, 1), and superficial infection

only (DOD, 1; OxZr/XLPE, 3).

**Table 11: Procedure-related: Systemic Adverse Events by Onset Interval**

	Intraoperative (0 Days)		3 Months (1-227 Days)		1 Year (228-730 Days)		3 Years (731-1460 Days)		>3 Years (>1460 Days)		Total	
	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE
Number of Hips	137	131	137	131	133	129	126	127	4	6	137	131
Circulatory	1	0	1	0	0	0	0	0	0	0	2	0
Digestive/ Gastrointestinal	0	0	2	0	0	0	0	0	0	0	2	0
Fever	0	0	2	0	0	0	0	0	0	0	2	0
Hematologic/ Immune System	0	0	0	1	0	0	0	0	0	0	0	1
Mental/behavioral	0	0	0	1	0	0	0	0	0	0	0	1
Nervous	0	0	3	0	0	0	0	0	0	0	3	0
Perioperative Pulmonary Embolism	0	0	1	0	0	0	0	0	0	0	1	0
Post-op swelling of study leg	0	0	1	0	0	0	0	0	0	0	1	0
Respiratory	0	0	1	0	0	0	0	0	0	0	1	0
Urinary	0	0	1	1	0	0	0	0	0	0	1	1
Total	1	0	12	3	0	0	0	0	0	0	13	3

Note: Number of Hips = Number of hips evaluated at that time period and overall.  
 Note: Includes the number of occurrences for each type of event.  
 Note: Three hips (#7019, 7073, and 7098) have a missing AE start date; therefore, date of readmission was used for determining the AE onset interval.  
 Note: Hips with missing AE start date that could not be determined are excluded since AE onset is unknown.

Table 12 provides the AEs identified as systemic (not related to the device or procedure) in both treatment cohorts. The most common systemic AEs were skeletal (DOD, 92; OxZr/XLPE, 67), digestive/GI (DOD, 26; OxZr/XLPE, 8), endocrine/nutritional/ metabolic (DOD, 8; OxZr/XLPE, 4), nervous (DOD, 17; OxZr/XLPE, 9), eye/adnexa (DOD, 10; OxZr/XLPE, 6), respiratory (DOD, 14; OxZr/XLPE, 4), and urinary (DOD, 14; OxZr/XLPE, 3).

**Table 12: Systemic (Not Related to Device or Procedure) Adverse Events by Onset Interval**

	Intraoperative (0 Days)		3 Months (1-227 Days)		1 Year (228-730 Days)		3 Years (731-1460 Days)		>3 Years (>1460 Days)		Total	
	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE
Number of Hips	137	131	137	131	133	129	126	127	4	6	137	131
Cancer, known origin	0	0	1	0	2	0	3	2	0	2	6	4
Circulatory	0	0	1	0	4	10	5	8	0	0	10	18

	Intraoperative (0 Days)		3 Months (1-227 Days)		1 Year (228-730 Days)		3 Years (731-1460 Days)		>3 Years (>1460 Days)		Total	
	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE	DOD	OxZr/ XLPE
Death from unknown cause	0	0	0	0	1	0	0	0	0	0	1	0
Digestive/ Gastrointestinal (GI)	0	0	3	2	9	3	14	1	0	2	26	8
Ear/Mastoid Process	0	0	0	0	1	0	1	0	0	0	2	0
Elevated Metal Ions	0	0	0	0	1	0	0	0	0	0	1	0
Endocrine/ Nutritional/ Metabolic	0	0	1	3	5	1	2	0	0	0	8	4
Eye/Adnexa	0	0	0	0	2	1	7	5	1	0	10	6
Hematologic/Immune System	0	0	0	1	1	0	5	0	0	0	6	1
Infection	0	0	0	1	2	1	1	0	0	0	3	2
Lymphatic	0	0	1	0	0	2	1	0	0	0	2	2
Mental/behavioral	0	0	0	0	1	3	1	2	1	0	3	5
Muscular/Connective Tissue	0	0	0	0	1	3	4	0	0	0	5	3
Nervous	0	0	1	3	11	5	5	1	0	0	17	9
Pain, unknown etiology	0	0	1	0	0	0	0	0	0	0	1	0
Reproductive System	0	0	3	0	0	1	3	0	0	0	6	1
Respiratory	0	0	2	0	2	2	10	2	0	0	14	4
Skeletal	0	0	13	12	40	31	39	23	0	1	92	67
Skin/Subcutaneous Tissue	0	0	2	0	1	1	0	2	0	0	3	3
Urinary	0	0	3	2	5	1	6	0	0	0	14	3
<b>Total</b>	<b>0</b>	<b>0</b>	<b>32</b>	<b>24</b>	<b>89</b>	<b>65</b>	<b>107</b>	<b>46</b>	<b>2</b>	<b>5</b>	<b>230</b>	<b>140</b>

Note: Number of Hips = Number of hips evaluated at that time period and overall.

Note: Includes the number of occurrences for each type of event.

Note: Three hips (#7019, 7073, and 7098) have a missing AE start date; therefore, date of readmission was used for determining the AE onset interval.

Note: Hips with missing AE start date that could not be determined are excluded since AE onset is unknown.

#### Survivorship (Revision):

Revision was defined as reoperation where any component (acetabular cup, acetabular liner, femoral head, or femoral stem) was replaced. In the DOD group, 1 (0.7%) subject had a device revision. In the OxZr/XLPE group, 7 (5.3%) subjects had a device revision. The treatment group difference in the revision rate was nominally significant (p=0.0329). Despite a p-value less than 0.05, statistical significance is not ensured due to the potential for bias introduced by performing multiple analyses.

A Kaplan-Meier survival analysis was performed to determine the expected rate of revision for any reason for both treatment groups. The survival time was calculated using time from surgery to revision, regardless of the reason. Subjects

without revision had time calculated one of two ways: (1) time from surgery to last clinical or radiographic evaluation, or (2) time from surgery to death. Subjects without a revision had their time variable censored.

The Kaplan-Meier estimates for implant survivorship are presented over time in Table 13. When revision was defined as the endpoint for survivorship, the results at 3 years showed a 99.3% survivorship (95% CI: 97.4%-100.0%) for the DOD group and a 94.7% survivorship (95% CI: 89.5%-99.8%) for the OxZr/XLPE group. There was a nominally significant difference between the two treatment groups (log rank p-value = 0.0284).

**Table 13: Kaplan-Meier Estimates for Implant Survivorship, mITT Population**

Time (in Months)	Treatment Group								P-value [2]
	DOD				OxZr/XLPE				
	n. risk [1]	Cumulative Events	KM Estimate	95% CI	n. risk [1]	Cumulative Events	KM Estimate	95% CI	
3	137	1	0.993	(0.978, 1.000)	131	4	0.969	(0.940, 0.999)	0.0284
12	135	1	0.993	(0.978, 1.000)	127	6	0.954	(0.918, 0.990)	
24	133	1	0.993	(0.978, 1.000)	124	7	0.947	(0.908, 0.985)	
36	126	1	0.993	(0.974, 1.000)	123	7	0.947	(0.895, 0.998)	

[1] n. risk is the number of hips at risk at the beginning of the time interval.  
[2] Log-Rank test of equality over treatment groups.

Details regarding the device revisions including the treatment group involved, device/procedural relatedness, survival time of the implant, and reasons for the revision are provided in Table 14.

**Table 14: Device Revisions, mITT Population**

Study Group	Subject ID	Device(s) Revised	Device-Related	Procedure-Related	Survival Time [months]	Reason for Revision
DOD	6013	S	Possibly	Definitely, Operative Site	1.6	Heavy fall resulting in femoral fracture
OxZr/XLPE	4004	S, H	Possibly	Definitely, Operative Site	0.1	Subject tripped and fell resulting in a peri-prosthetic fracture femur
	3022	S, H	Possibly	Definitely, Operative Site	1.0	Femur fracture
	4007	S, H	Possibly	Definitely, Operative Site	11.2	Loosening of stem, femoral pain and shortening of leg

Study Group	Subject ID	Device(s) Revised	Device-Related	Procedure-Related	Survival Time [months]	Reason for Revision
	4023	S, H, T	Possibly	Definitely, Operative Site	12.9	More pain, loosening stem
	3049	S, H, C, T, L	Possibly	Definitely, Operative Site	0.7	Subsidence of the femur component
	7079	S, H, C, T, L	No	Definitely, Operative Site	1.9	Hip infection
	4024	C	Possibly	Definitely, Operative Site	6.2	More pain (acute)

Note: Revision Procedure (s): S=femoral stem; H= femoral head; C=acetabular cup; T=taper sleeve; L=acetabular liner

#### Radiographic Failure

The radiographic analysis was performed by an independent board-certified radiologist reviewer according to a pre-defined Radiographic Analysis Protocol. Radiographic failure was defined as evidence of radiolucencies greater than 2 mm in 50% or more of the cup or stem zones, a position change of the cup or stem (subsidence of the femoral or acetabular components of greater than or equal to 5 mm), or acetabular cup inclination changes greater than 4 degrees.

At the 3-year follow-up visit, no hips in either group met the definition of failure due to radiolucencies, 4 (3.4%) hips in the DOD group and 8 (6.7%) hips in the OxZr/XLPE group had evidence of cup or stem subsidence greater than or equal to 5 mm, and one hip in the OxZr/XLPE group had evidence of an inclination change in the acetabular cup greater than 4 degrees. There were no statistically significant differences in overall radiographic outcomes between the two treatment groups (Table 15).

**Table 15: Radiographic Failure at 3 years, mITT Population**

Independent Radiographic Evaluation	Treatment Group	
	DOD	OxZr/XLPE
Number of Hips Evaluated	116	119
Radiolucencies Failure	0 (0.0%)	0 (0.0%)
Subsidence $\geq$ 5 mm	4 (3.4%)	8 (6.7%)
Cup Inclination $\geq$ 4 degrees	0 (0.0%)	1 (0.8%)
P-value [1]	0.31	

[1] Fisher's exact test of difference between treatment group and overall radiographic failure

2. Effectiveness Results

The analyses of effectiveness were based on the mITT cohort of patients, defined as all subjects who consented to study participation and received the R3 Acetabular Cup System with the BIOLOX<sup>®</sup> delta ceramic on BIOLOX<sup>®</sup> delta ceramic or the OxZr/XLPE articulation couple, or the PP population which was defined as all mITT subjects with complete 3 year primary endpoint data and no deviations to the inclusion and exclusion criteria. In the analyses, aside from the sensitivity analyses and tipping point analysis, no data were imputed for the missing data, and therefore the mITT population and PP populations were identical as there were no deviations to the inclusion and exclusion criteria. The key effectiveness outcomes for this study, individual study success, mHHS, WOMAC score, and UCLA score, are presented below in Table 16 to Table 22 below.

The primary effectiveness assessment was based upon an overall success outcome determination of the composite primary endpoint at a minimum of 3 years post-surgery. The composite primary endpoint included implant survivorship, modified Harris Hip Score (mHHS), and radiographic evaluation. Study success was defined as establishing non-inferiority of the DOD cohort compared to the OxZr/XLPE cohort based upon the 3-year clinical composite success (CCS) rates with a non-inferiority delta of 10%. Secondary effectiveness measures included the mHHS subcomponents of overall success as well as the WOMAC and UCLA scores.

Table 16 summarizes overall success as well as individual components of success in both treatment groups of the PP population at 3 years. 86.4% of subjects in the DOD group and 80.2% of subjects in the OxZr/XLPE group attained overall success of the composite endpoint at 3 years. While non-inferiority was statistically significant, superiority was not significant; thus, the DOD treatment is non-inferior to the OxZr/XLPE treatment.

**Table 16: Clinical Composite Success at 3 Years, PP Population**

Outcomes	Treatment		Non-Inferiority P-value [1]	Superiority P-value [2]
	DOD	OxZr/XLPE		
Overall Success at 3 Years				
Yes	95 (86.4%)	101 (80.2%)	0.0004	0.2050
No	15 (13.6%)	25 (19.8%)		
Total	110	126		

Components of Success at 3 Years				
No component revision	121/122 (99.2%)	121/128 (94.5%)	NA	NA
mHHS of at least 80 points	101/111 (91.0%)	109/120 (90.8%)		
No radiographic failure [3]	112/116 (96.6%)	110/119 (92.4%)		

Note: NA = Not Applicable  
 [1] P-value from Blackwelder’s test of non-inferiority assessing the null hypothesis that the difference (DOD –OxZr/XLPE) in success percentages is less than or equal to -10%.  
 [2] P-value from two-sided Chi-square test.  
 [3] No radiographic failure indicates no radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones, no femoral or acetabular subsidence greater than or equal to 5 mm from baseline, and no acetabular cup inclination changes greater than 4 degrees. The radiolucency assessment was based on the AP and lateral view if both were available, though only one complete view was required to make the assessment.

Sensitivity analyses to account for missing 3 year data were conducted. In the sensitivity analyses, three scenarios were used to determine whether missing data would have made an impact on determining significance of non-inferiority and superiority based on overall success. In the first scenario, all missing data were included as successes. The non-inferiority of the DOD cohort to OxZr/XLPE cohort remained significant and superiority was not achieved, which is consistent with the PP population analyses where missing data were not imputed. In the second scenario, all missing data were considered to be failures. No significance was demonstrated in non-inferiority or superiority of the DOD cohort to the OxZr/XLPE cohort. In the third scenario, the last observation (data from the 1-year post-operative visit) was carried forward to replace missing or partially missing information at the 3-year post-operative visit. The resulting analyses demonstrated non-inferiority between the DOD and OxZr/XLPE cohorts but did not support superiority, which is consistent with PP population analyses where missing data were not imputed. The results of the first and second scenarios are not unexpected as there were significantly more subjects with missing data in the DOD cohort.

A tipping point analysis was performed to further assess the impact of the missing data. In the tipping point analysis all possible combinations for imputing success/failure for the missing Clinical Composite Success (CCS) outcomes at 3 Years in the DOD (n=27 missing outcomes) and OxZr/XLPE (n=5 missing outcomes) groups were assessed. A summary of the tipping point analysis is presented below in Table 17. For a significant finding of non-inferiority, the number of successes in the DOD group needed for each of the possible numbers of successes in the OxZr/XLPE group ranges from 33.3% to 51.9%. In a worst-case scenario for maintaining non-inferiority, where all 5 OxZr/XLPE subjects missing data were successes, then 14/27 DOD (51.9%) subjects with missing data

would need to be successes. Given an overall success rate of 86.4% in the DOD group in those with complete 3 year data, it is expected that the DOD group would maintain non-inferiority if all data was collected. Further review of the data available for those subjects lacking complete 3 year data was performed. Based upon the review of this available data, no change in the finding of non-inferiority would be anticipated.

**Table 17: Summary of Tipping Point Analysis, mITT Population**

<b>OxZr/XLPE Successes (n/N)</b>	5 / 5	4 / 5	3 / 5	2 / 5	1 / 5	0 / 5
<b># DOD Successes Needed (n/N) [1]</b>	14 / 27	13 / 27	12 / 27	11 / 27	10 / 27	9 / 27
<b>% DOD Successes Needed [1]</b>	51.9%	48.1%	44.4%	40.1%	37.0%	33.3%
Note: n = Number of success.						
Note: N = Number of missing success/failure outcomes.						
[1] To achieve a significant finding of non-inferiority.						

Modified Harris Hip Score (mHHS):

The mean baseline mHHS was lower in the DOD group (47.9) than the OxZr/XLPE group (57.0), which was statistically significant ( $p < 0.0001$ ), while at 3 years there was no statistically significant difference between the mean mHHS for the DOD (92.0) and OxZr/XLPE (93.7) groups ( $p = 0.2262$ ) (Table 18). Consistent with these findings, as seen in Table 19, the difference in the mean change from baseline was statistically significant at 1 year (DOD 43.7 and OxZr 35.9 ( $p < 0.0001$ )) and at 3 years (DOD 43.7 and OxZr 36.2 ( $p < 0.0001$ )) with the DOD group demonstrating greater improvement. It should be noted that substantial improvements in pain, function, and ROM (i.e. components of the mHHS) are anticipated following total hip arthroplasty, and hence the statistically significant difference in mean change from baseline at 1 and 3 years may be attributable to the lower baseline mHHSs in the DOD cohort.

**Table 18: Comparison of Modified Harris Hip Score for DOD and XLPE at Baseline and 3 Years, mITT Population**

Statistic	Baseline		3 Years	
	DOD	OxZr/XLPE	DOD	OxZr/XLPE
N	130	131	111	120
Mean	47.9	57.0	92.0	93.7
Median	47.0	61.0	96.0	99.0
SD	11.94	12.91	11.42	10.80
Minimum	20	11	44	27
Maximum	88	87	100	100

Statistic	Baseline		3 Years	
	DOD	OxZr/XLPE	DOD	OxZr/XLPE
P-value[1]	<0.0001		0.2262	
[1] P- value from two-sample t-test to assess the null hypothesis that the mean difference between treatment groups is homogenous				

**Table 19: Modified Harris Hip Score, Change from Baseline, mITT Population**

Treatment Group	Visit	Change from Baseline				P-value [1]
		N	Mean (SD)	Median	Min, Max	
DOD	3 Months	125	34.6 (16.46)	35.0	-15, 67	0.1758
	1 Year	118	43.7 (13.46)	44.0	3, 71	<0.0001
	3 Years	107	43.7 (14.45)	45.0	1, 71	<0.0001
OxZr/XLPE	3 Months	125	32.1 (13.38)	33.0	-18, 63	
	1 Year	122	35.9 (13.42)	36.0	-22, 86	
	3 Years	120	36.2 (12.32)	36.0	-1, 72	
[1] P-value from two-sample t-test to assess the null hypothesis of homogeneity of the change from baseline results between the treatment groups.						

Due to the potential for bilateral hip involvement to confound the mHHS results, mHHSs data from subjects with unilateral hip involvement only were analyzed. Similar to the mITT population mHHSs, subjects with unilateral hip involvement in the DOD group had lower baseline mean mHHSs (DOD 49.0 and OxZr/XLPE 58.5) with similar mean mHHSs at 3 years (DOD 93.1 and OxZr/XLPE 93.4). The difference in mean change from baseline at 3 years for the DOD group (44.0) compared to the OxZr/XLPE group (33.8) remained statistically significant (p<0.0001).

**WOMAC:**

The observed WOMAC Scores by treatment group and visit are provided in Table 20. At baseline, the mean WOMAC Score was 37.8 for the DOD group and 40.0 for the OxZr/XLPE group. The difference between treatment groups at baseline was not statistically significant. At 3 years, the mean score was 87.3 for the DOD group and 92.2 for the OxZr/XLPE group. The difference between treatment groups at 3 years was statistically significant (p=0.0005). However, the WOMAC score for the DOD group was 2.2 points (out of a possible 96) less than the OxZr/XLPE group at baseline and 4.9 less at 3 years. Therefore, accounting for the baseline 2.2 point difference, the actual difference at 3 years is 2.7 points which is not clinically meaningful. Further, as demonstrated in Table 21, there was no statistically significant difference between the treatment groups based upon the mean change from baseline at 1 year (DOD, 51.1 and OxZr/XLPE, 50.9 (p=0.9554)) or 3 years (DOD, 50.2 and OxZr/XLPE, 51.2 (p=0.6719)).

**Table 20: WOMAC Score, Observed, mITT Population**

Treatment Group	Visit	Observed				P-value [1]
		N	Mean (SD)	Median	Min, Max	
DOD	Baseline	129	37.8 (14.09)	39.0	6, 74	0.2074
	3 Months	117	81.3 (10.84)	84.0	51, 96	< 0.0001
	1 Year	122	88.6 (10.07)	93.0	39, 96	0.0222
	3 Years	115	87.3 (11.53)	92.0	39, 96	0.0005
OxZr/XLPE	Baseline	122	40.0 (14.47)	39.0	8, 76	
	3 Months	114	89.8 (8.94)	93.5	45, 96	
	1 Year	110	91.7 (10.18)	96.0	38, 96	
	3 Years	114	92.2 (9.10)	96.0	35, 96	

[1] P-value from two-sample t-test to assess the null hypothesis of the homogeneity of the observed results between the treatment groups.

**Table 21: WOMAC Score, Change from Baseline, mITT Population**

Treatment Group	Visit	Change from Baseline				P-value [1]
		N	Mean (SD)	Median	Min, Max	
DOD	3 Months	112	43.5 (17.06)	44.0	8, 85	0.0203
	1 Year	115	51.1 (16.03)	52.0	4, 80	0.9554
	3 Years	108	50.2 (15.84)	51.0	4, 81	0.6719
OxZr/XLPE	3 Months	107	48.9 (17.32)	49.0	-7, 88	
	1 Year	104	50.9 (17.46)	50.5	-13, 88	
	3 Years	108	51.2 (16.24)	50.0	-2, 88	

[1] P-value from two-sample t-test to assess the null hypothesis of homogeneity of the change from baseline results between the treatment groups.

UCLA Activity Score:

The observed UCLA scores by treatment group and visit are provided in Table 22. At baseline the mean score is 3.6 for the DOD group and 3.4 for the OxZr/XLPE group. At 3 years, the mean score is 6.1 for the DOD group and 5.9 for the OxZr/XLPE group. The differences between the treatment groups at baseline and 3 years are not statistically significant.

**Table 22: UCLA Activity Rating Scale, Observed, mITT Population**

Treatment	Visit	Change from Baseline				P-value [1]
		N	Mean (SD)	Median	Min,	
DOD	Baseline	137	3.6 (1.39)	3.0	2, 8	0.3527 / 0.9186
	3 Months	133	5.5 (1.55)	6.0	2, 8	0.0003 / 0.0002
	1 Year	126	6.1 (1.37)	6.0	2, 8	0.5416 / 0.6089
	3 Years	120	6.1 (1.30)	6.0	2, 8	0.4568 / 0.5408
OxZr/XLPE	Baseline	131	3.4 (1.11)	3.0	2, 7	
	3 Months	125	4.9 (.33)	5.0	3, 8	
	1 Year	122	6.0 (1.50)	6.5	2, 10	
	3 Years	120	5.9 (1.46)	6.0	3, 9	

[1] P-value from two-sample t-test/Wilcoxon Rank Sum test to assess the null hypothesis of the homogeneity of the observed results between the treatment groups.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: baseline HHS, Site, Age, Sex, BMI, Diagnosis, Surgical History, Charnley Classification and baseline UCLA. See the likelihood ratio tests and parameter estimates below in Table 23 and Table 24.

Note that the majority of the covariates were not associated with the primary outcome of overall success. The effects of Site ( $p = 0.02$ ) and Sex ( $p = 0.04$ ) were nominally significant, but would not have been significant after adjustment for multiple comparisons. Note also that there was no sex-by-treatment-group interaction ( $p=0.90$ ). The overall interaction between Site and treatment could not be assessed as there were several sites, which enrolled only from one treatment group. However, considering the two sites, which enrolled enough numbers in both groups, there was no site-by-treatment interaction, with the Breslow-Day test for homogeneity of odds ratios being non-significant ( $p= 0.53$ ).

In this covariate analysis, the treatment difference was non-significant, indicating the treatment group success rates are not statistically different for superiority. Moreover, treatment group has a log-odds ratio of -0.51 for the log-odds of 0/1, indicating that the R3 BIOLOX® delta DOD treatment is less likely than the Control treatment to be an overall success failure (and therefore more likely to be a success). This compares favorably to the unadjusted analysis where the log-odds ratio was -0.22 and where non-inferiority was demonstrated. Therefore, the non-inferiority conclusion is supported by the covariate adjusted analysis.

**Table 23: Likelihood Ratio Chi-Square Values for Covariate-Adjusted Logistic Regression Model**

Source	Nparm	DF	L-R ChiSquare	Prob>ChiSq
TRTP	1	1	2.3880686	0.1223
Base_HHS	1	1	0.53645213	0.4639
SITEID	6	6	14.6209345	0.0234*
AGE	1	1	1.55118421	0.2130
SEX	1	1	4.10968833	0.0426*
BMIBL	1	1	1.1644184	0.2806
DIAG	4	4	4.47948608	0.3450
HIST1	1	1	1.00232253	0.3167
CHARN	2	2	1.13635569	0.5666
UCLA_BASE	1	1	1.10430859	0.2933
TRTP*SEX	1	1	0.01682784	0.8968

**Table 24: Parameter Estimates for Covariate-Adjusted Logistic Regression Model**

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	-3.8710153	1538.5323	0.00	0.9980
TRTP[R3 BIOLOX® delta COC]	-0.5068409	0.3269577	2.40	0.1211
Base_HHS	0.01485903	0.0203362	0.53	0.4650
SITEID[01]	-1.6068353	0.9564	2.82	0.0929
SITEID[02]	0.5257888	1.1148051	0.22	0.6372
SITEID[03]	-1.15793	0.6174016	3.52	0.0607
SITEID[04]	-0.2523816	0.7118541	0.13	0.7229
SITEID[06]	0.9399682	0.5134335	3.35	0.0671
SITEID[07]	0.04360446	0.5141524	0.01	0.9324
AGE	0.0323702	0.0266458	1.48	0.2244
SEX[Female]	0.46009964	0.2360893	3.80	0.0513
BMIBL	0.04370182	0.040469	1.17	0.2802
DIAG[Dysplasia]	0.31442853	1538.5308	0.00	0.9998
DIAG[Osteonecrosis (AVN)]	-0.6600293	1538.5308	0.00	0.9997
DIAG[Other] [1]	-16.711734	4485.549	0.00	0.9970
DIAG[Primary Osteoarthritis]	-0.8360386	1538.5307	0.00	0.9996
HIST1[0]	0.58801245	0.5699328	1.06	0.3022
CHARN[Both Hips Involved]	0.2946568	0.4011235	0.54	0.4626
CHARN[Only Ipsilateral Hip Involved]	0.37270113	0.3879292	0.92	0.3367
UCLA_BASE	-0.2129281	0.2087261	1.04	0.3077
TRTP[R3 BIOLOX® delta COC]*SEX[Female]	0.02905476	0.2243027	0.02	0.8969
[1] Parameter estimate is unstable due to sparse data for this category				

A subgroup analysis of the primary endpoint, Clinical Composite Success, by gender for the PP population is provided below in Table 25. In the DOD group, 62/73 (84.9%) of the female and 33/37 (89.2%) of the male subjects attained Clinical Composite Success at 3 years. In the OxZr/XLPE group, 54/72 (75.0%) of the female and 47/54 (87.0%) of the male subjects attained Clinical Composite Success at 3 years. The differences in results by gender between the treatment groups are statistically significant for non-inferiority, which is consistent with the non-inferiority finding in the total PP population.

**Table 25: Clinical Composite Success at 3 Years by Gender, PP Population**

Outcomes	Treatment				Non-Inferiority P-value [1]	Superiority P-value [2]
	DOD		OxZr/XLPE			
	Female N=79	Male N=43	Female N=72	Male N=56		
Overall Success at 3 Years						
Yes	62 (84.9%)	33 (89.2%)	54 (75.0%)	47 (87.0%)	0.0013 (females)	0.1350 (females)
No	11 (15.1%)	4 (10.8%)	18 (25.0%)	7 (13.0%)	0.0381 (males)	0.7571 (males)
Total	73		72	54		
Components of Success at 3 Years						
No component revision	79 / 79 (100.0%)	42 / 43 (97.7%)	67 / 72 (93.1%)	54 / 56 (96.4%)	NA	NA
mHHS of at least 80 points	65 / 73 (89.0%)	36 / 38 (94.7%)	58 / 66 (87.9%)	51 / 54 (94.4%)		
No radiographic failure [3]	74 / 77 (96.1%)	38 / 39 (97.4%)	61 / 67 (91.0%)	49 / 52 (94.2%)		

Note: NA = Not Applicable

[1] P-value from Blackwelder's test of non-inferiority assessing the null hypothesis that the difference (DOD –OxZr/XLPE) in success percentages is less than or equal to 10%.

[2] P-value from two-sided Chi-square test.

[3] No radiographic failure indicates no radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones, no femoral or acetabular subsidence greater than or equal to 5 mm from baseline, and no acetabular cup inclination changes greater than 4 degrees. The radiolucency assessment was based on the AP and lateral view if both were available, though only one complete view was required to make the assessment.

### **E. 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 7 investigators of which none were full-time or part-time employees of the applicant and one 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: no investigators
- Significant payment of other sorts: one investigator
- Proprietary interest in the product tested held by the investigator: no investigators
- Significant equity interest held by investigator in sponsor of covered study: no investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

#### **XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION**

None.

#### **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 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**

The effectiveness of the R3 delta Ceramic Acetabular System was assessed using data collected in the above described clinical trial. The effectiveness assessment was based upon the overall study success, mHHSs, WOMAC scores, and UCLA scores. The data from analysis of the overall study success showed a success rate of 86.4% for the DOD investigational cohort and 80.2% for the OxZr/XLPE cohort. This resulted in a finding of significance for non-inferiority of the DOD cohort to the OxZr/XLPE comparator based upon a 10% non-inferiority delta ( $p=0.0004$ ). A sensitivity analysis using the last observation carried forward and a tipping point analysis both suggested maintenance of non-inferiority when missing data were imputed.

The mHHS data revealed the mean mHHSs to be lower at baseline in the DOD cohort (47.9) than the OxZr/XLPE cohort (57.0), which was statistically significant ( $p < 0.0001$ ), while at 3 years there was no statistically significant difference between the DOD (92.0) and OxZr/XLPE (93.7) cohorts ( $p = 0.2262$ ). In addition, the difference in mean change from baseline was statistically significant at 1 year (43.7 DOD cohort compared to 35.9 in the OxZr/XLPE cohort ( $p < 0.0001$ )) as well as at 3 years (43.7 DOD cohort compared to 36.2 in the OxZr/XLPE cohort ( $p < 0.0001$ )), demonstrating greater improvement in the DOD cohort. It should be noted that substantial improvements in pain, function, and ROM (i.e. components of the mHHS) are anticipated following total hip arthroplasty and hence the statistically significant difference in mean change from baseline at 1 and 3 years may be attributable to the lower baseline mHHSs in the DOD cohort.

The WOMAC score data revealed a mean baseline WOMAC Score of 37.8 for the DOD cohort and 40.0 for the OxZr/XLPE cohort. The difference between treatment groups at baseline was not statistically significant. At 3 years, the mean WOMAC score was 87.3 for the DOD group and 92.2 for the OxZr/XLPE group. The difference between treatment groups at 3 years was statistically significant ( $p = 0.0005$ ). However, the WOMAC score for the DOD was 2.2 points (out of a possible 96) less at baseline and 4.9 less at 3 years. Therefore, accounting for the initial 2.2 point difference, the actual difference at 3 years is 2.7 points which is not clinically meaningful. Further, as demonstrated in Table 25, there were no statistically significant differences between the treatment groups based upon the mean change from baseline at 1 year (DOD 51.1 and OxZr/XLPE 50.9 ( $p = 0.9554$ )) or 3 years (DOD 50.2 and OxZr/XLPE 51.2 ( $p = 0.6719$ )). Overall, the increase in WOMAC scores was comparable between the two cohorts.

The UCLA score data revealed a baseline mean score of 3.6 for the DOD cohort and 3.4 for the OxZr/XLPE cohort. At 3 years, the mean score was 6.1 for the DOD cohort and 5.9 for the OxZr/XLPE cohort. The increase in UCLA scores was comparable between the two cohorts.

In conclusion, the study data support that at 3 years post-operative, the R3 delta Ceramic Acetabular System, used in skeletally mature patients requiring primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis, is at least as effective as primary total arthroplasty when using the OxZr/XLPE bearing surface, the same R3 acetabular cup, and four femoral stems.

## **B. Safety Conclusions**

The risks of the R3 delta Ceramic Acetabular System are based on nonclinical laboratory data as well as data collected in the clinical study conducted to support PMA approval as described above.

Nonclinical testing performed on the device demonstrated that the R3 delta Ceramic Acetabular System should be as safe as other legally marketed total hip systems with same indications for use.

In the clinical study to support PMA approval of the R3 delta Ceramic Acetabular System, the risks of the investigational R3 delta Ceramic Acetabular System were assessed based upon AEs, device survivorship, and radiographic failure. The rates of R3 delta Ceramic Acetabular System subjects who experienced at least one adverse event classified as device and/or procedure related (including those also classified as severe) were comparable to the corresponding rates in subjects implanted with an OxZr/XLPE bearing surface used with the same R3 acetabular cup and four femoral stems. The rates of radiographic failure were also comparable between the two groups without statistical significance, although numerically lower in DOD group (3.4%) than the OxZr/XLPE group (7.5%). The rates of revision were 0.7% in the DOD group and 5.3% in the OxZr/XLPE group (5.3%), which was nominally significant ( $p=0.0329$ ). Despite a  $p$ -value less than 0.05, statistical significance is not ensured due to the potential for bias introduced by performing multiple analyses.

In conclusion, the study data indicates that, at 3 years post-operative, the R3 delta Ceramic Acetabular System, used in skeletally mature patients requiring primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis, is at least as safe as the OxZr/XLPE bearing surface used with the same R3 acetabular cup and four femoral stems.

### **C. Benefit-Risk Determination**

The probable benefits and risks of the R3 delta Ceramic Acetabular System used for the indications identified above are based upon the clinical study conducted to support PMA approval as previously described. The clinical study demonstrated several benefits and risks of the R3 delta Ceramic Acetabular System used for total hip arthroplasty over the 3 year time period studied as presented below.

#### **Benefits**

- Overall success - Overall study success was based upon a composite primary endpoint assessed at 3 years post-surgery. The composite primary endpoint was comprised of a component associated with benefit, the mHHS (which assesses function, pain, deformity, and hip ROM), and components associated with risk, device revision and radiographic failure. 86.4% of subjects in the DOD group and 80.2% of subjects in the OxZr/XLPE group attained overall success of the composite endpoint at 3 years. Non-inferiority of the DOD cohort was statistically significant.

- mHHS - The benefit of the R3 Biolox delta Ceramic Acetabular System in terms of improved function and hip ROM, diminished pain, and/or absence of deformity, as assessed using the mHHS, at 3 years was greater than that associated with use of an OxZr/XLPE bearing surface same R3 acetabular cup and one of four femoral stems. It should be noted that substantial improvements in pain, function, and ROM (i.e. components of the mHHS) are anticipated following total hip arthroplasty and hence the greater benefit, reflected in strong statistical significance, may be attributable to the lower baseline mHHSs in the DOD cohort.
  - When assessing the mHHS for mean change from baseline there was a statistically significant difference in the change from baseline at 1 year (43.7 in the DOD cohort compared to 35.9 in the OxZr/XLPE cohort) and 3 years (43.7 in the DOD cohort compared to 36.2 in the OxZr/XLPE cohort) in favor of the DOD cohort ( $p < 0.0001$  at both 1 and 3 years).
  - The difference in mean mHHS between the DOD and OxZr/XLPE cohorts was statistically significant at baseline ( $p < 0.0001$ ) with the DOD having lower baseline mHHSs (DOD 47.9 and OxZr/XLPE 57.0) while the difference was not statistically significant different at 3 years (DOD 92.0 and OxZr/XLPE 93.7 ( $p = 0.2262$ )). This mean data demonstrates that the DOD subjects had increased pain, reduced function, increased deformity, and/or decreased hip ROM at baseline compared to the OxZr/XLPE group but comparable pain, function, hip ROM, and deformity at 3 years post-operatively.
  - In addition, the DOD subjects on average had to experience greater improvement in the mHHS in order to reach the success threshold of 80 points with 101/111 (91.0%) of the DOD cohort and 109/120 (90.8%) OxZr/XLPE cohort achieving this threshold.
- WOMAC - The benefit of the R3 delta Ceramic Acetabular System in terms of improved function, diminished pain, and diminished stiffness, as measured using the WOMAC, at 3 years was comparable to that associated with use of an OxZr/XLPE bearing surface the same R3 acetabular cup and four femoral stems. The WOMAC score for the DOD was 2.2 points (out of a possible 96 points) less at baseline, which was not statistically significant, and 4.9 less at 3 years, which was statistically significant. Accounting for the initial 2.2 point difference the actual difference at 3 years was 2.7 points, which is not clinically meaningful. Further, there were no statistically significant differences between the treatment groups based upon the mean change from baseline at 1 year (DOD 51.1 and OxZr/XLPE 50.9 ( $p = 0.9554$ )) or 3 years (DOD 50.2 and OxZr/XLPE 51.2 ( $p = 0.6719$ )).
- UCLA Activity Rating Score - The benefit of the R3 delta Ceramic Acetabular System in terms of improved subject activity levels, as measured using the UCLA

Activity Rating score, at 3 years was comparable to that associated with use of an OxZr/XLPE bearing surface with the same R3 acetabular cup and 4 femoral stems. At baseline the mean score was 3.6 for the DOD group and 3.4 for the OxZr/XLPE group. At 3 years, the mean score was 6.1 for the DOD group and 5.9 for the OxZr/XLPE group.

## **Risks**

- Adverse Events - The AE data from this clinical trial demonstrates that the risks associated with use of the R3 delta Ceramic Acetabular System are comparable to those associated with use of an OxZr/XLPE bearing surface, the same R3 acetabular cup, and four approved femoral stems. There was no statistically significant difference in the number of hips suffering an AE but there was a statistically significant difference in the total number of AEs reported between the DOD and OxZr/XLPE treatment groups. This difference in overall AEs was almost solely accounted for by a greater number of non-serious and non-device or procedure related AEs (including AEs classified by severity and device and/or procedure relatedness).

Survivorship - In the DOD group 1 (0.7%) subject had a device revision due to a femoral fracture and involved only the femoral stem. In the OxZr/XLPE group 7 (5.3%) subjects had a device revision. The treatment group difference in the revision rate was nominally significant ( $p=0.0329$ ) in favor of a lower revision rate in the DOD cohort. Despite a p-value less than 0.05, statistical significance is not ensured due to the potential for bias introduced by performing multiple analyses.

- Radiographic Failure - In terms of radiographic failure which was defined as evidence of radiolucencies greater than 2 mm in 50% or more of the cup or stem zones, a position change of the cup or stem (subsidence of the femoral or acetabular components of greater than or equal to 5 mm), or acetabular cup inclination changes greater than 4 degrees, the DOD cohort risks are comparable to the OxZr/XLPE cohort. At the 3-year follow-up visit, no hips in either group met the definition of failure based upon radiolucencies, four (3.4%) hips in the DOD group and eight (6.7%) hips in the OxZr/XLPE group had evidence of subsidence greater than or equal to 5 mm, and one hip in the OxZr/XLPE group had evidence of an inclination change in the acetabular cup greater than 4 degrees. Overall 4 DOD and 9 OxZr/XLPE subjects met the definition for radiographic failure which did not result in a statistically significant difference.

### **Additionally Considered in R/B:**

Several other factors were considered in determination of the probable benefits and risks for the R3 delta Ceramic Acetabular System. Limitations of the clinical study included lack of subject randomization, lack of subject blinding to their treatment group, lack of collection of racial/ethnic demographic data, and the inability of the CEC to adequately adjudicate AE severity. In addition, the impact

of missing data and the robustness of the sensitivity and tipping point analyses provided to address the missing data, as well as the generalizability of the study results were also considered.

The submission did not include specific information on patient perspectives for this device.

In conclusion, the data support that, for use in skeletally mature patients requiring primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis, the probable benefits of the R3 delta Ceramic Acetabular System outweigh the probable risks through 3 years of follow-up.

#### **D. Overall Conclusions**

The nonclinical and clinical data presented in this application support the reasonable assurance of safety and effectiveness of the R3 delta Ceramic Acetabular System when used in accordance with the indications for use. Based on the clinical study results, it is reasonable to conclude that a significant portion of the indicated patient population will achieve clinically significant results and that the clinical benefits of the use of the R3 delta Ceramic Acetabular System in terms of improvement in pain and function, increased hip ROM, and /or diminished deformity outweigh the risks associated with the device and surgical procedure through 3 years of follow-up.

#### **XIV. CDRH DECISION**

CDRH issued an approval order on 10/17/2016. The final conditions of approval cited in the approval order are described below.

In addition to the conditions outlined above, the applicant has agreed to conduct two post-approval studies outlined below.

1. ODE Lead PMA Post-Approval Study (PAS) – Long-Term Follow-up of current EU patients PAS: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This is a single arm, prospective, multi-center, post-approval study, and will be conducted as per protocol dated September 26, 2016, Version 0.2 received in the applicant's email dated September 29, 2016. The study will consist of 135 subjects who were implanted with the R3 delta Ceramic Acetabular System in the pivotal study followed to 10 years post-operatively. The study will collect data on device survivorship, adverse events, and Modified Harris Hip Score (mHHS) as well as perform radiographic evaluations at clinic visits 5, 7, and 10 years post-operatively. In cases where subjects fail to return for clinic visits, telephone follow-up for determination of device survival and patient satisfaction will be conducted. The primary endpoint of the PAS is device survivorship at 10 years post-operatively. Adverse event data will include the onset date, description, severity, seriousness, duration, action taken, and outcome of each adverse event as well

as the relationship of the adverse event to the device and/or procedure. The radiographic data will include an assessment for radiographic success/failure based upon the criteria identified in the composite primary endpoint of the pivotal study. The applicant will submit reports to the US FDA every 6 months for the first two years of the study, and then annually to completion.

2. OSB Lead PMA Post-Approval Study (PAS) – Short to Mid-Term Follow-up of New US Patients PAS: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. This is a prospective cohort study, and will be conducted as per protocol dated October 03, 2016, Version 0.3 received in the applicant’s email dated October 5, 2016. The purpose of the study is to assess the performance of the device in the US population. The study population is comprised of US patients who receive the device in the postmarket environment. A total of 183 patients will be enrolled in the study. Patients will be followed for 3 years. The primary endpoint is overall study success at 3 years post procedure. Success is defined the same way it was in the premarket cohort, to allow comparison. Overall Success is defined as: no component revision, and Modified Harris Hip Score (mHHS) of at least 80 points, and no radiographic failure, defined as: no radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones, no femoral or acetabular subsidence greater than or equal to 5 mm from baseline, and no acetabular cup inclination changes greater than 4 degrees. Secondary endpoints include clinical assessments of pain and function using the modified Harris Hip Score, radiographic findings and implant survivorship. Results obtained by the US cohort will be directly compared with results obtained by the premarket cohort (OUS-Cohort). Additionally, demographic data including gender, age, height, weight, and race will be collected to allow for an assessment of differences and comparison of outcomes between the US and European populations. Study reports will be submitted every 6 months to FDA for the first two years of the study and then annually until completion of data collection. A Final Report will be submitted 3 months after the completion of data collection. An interim data release will occur at the midpoint of the study, 2.5 years after study initiation. The interim data release will be comprised of data regarding secondary endpoints.

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] Lambert, Richard D. "The Effect of Femoral Head Material on the Frictional Moment during Articulation". Smith & Nephew, Inc. Research Report OR-92-114, October 1992.

[2] Bergmann, G., et al. "Hip contact forces and gait patterns from routine activities." Journal of biomechanics 34.7 (2001): 859-871.