FDA EXECUTIVE SUMMARY

Introduction

The subject of this Executive Summary is Corin U.S.A.'s Cormet 2000 Hip Resurfacing System premarket approval (PMA, P050016) application, a metal-on-metal hip resurfacing system comprised of two components – a short stemmed resurfacing femoral head and a monoblock acetabular component. The device has been reviewed by the Orthopedic Joint Devices Branch of the Division of General, Restorative, and Neurological Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application is greatly appreciated.

This summary includes five sections:

The first section describes the issues facing the FDA with respect to the interpretation of the clinical data and also presents our rationale for presenting this PMA to the advisory panel.

The second section describes the device and Indications for Use proposed by the applicant. The third section describes the preclinical data and prior clinical investigations which were provided by the applicant to support the device's safety and effectiveness.

The fourth section describes the clinical study protocol, patient outcomes using the revised endpoints, and statistical analyses for the data as presented in the PMA submission from the applicant to support the safety and effectiveness of the device.

The final section summarizes FDA's issues related to this PMA submission which generated the questions to the advisory panel.

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I. Rationale for Presentation to the Panel

This section describes the rationale for presentation of this PMA to the Orthopedic and Rehabilitation Devices Advisory Panel. This PMA application for the Cormet 2000 Hip Resurfacing System (HRS) is the second-of-a-kind metal-on-metal resurfacing hip system the FDA has reviewed. The first-of-a-kind was the Birmingham Hip Resurfacing System, which was presented to the Orthopedic and Rehabilitation Devices Panel on September 8, 2005 and approved by the FDA on May 9, 2006.

In general, our issues which we feel require Panel input include the following:

1) There have been multiple revisions to the proposed study primary safety and effectiveness endpoints during the course of the IDE study and during the review process of the PMA;

2) The approved IDE study proposed to enroll concurrent control subjects. The PMA is based upon a proposed historical control, after multiple attempts to replace the concurrent control group. This historical control population allows the applicant access to individual patient data having similar clinical and radiographic evaluation data; and

3) The PMA reports differences in the percentage of subjects requiring revision surgery for this device, the control device, and similar devices, and types of devices as presented in the literature and expected in common practice.

A. Study Design Issues

The applicant has presented data from a study designed to be a prospective, non-randomized (yet concurrently controlled) clinical study used to evaluate the Cormet 2000 Hip Resurfacing Implant System. The study was designed to be a non-inferiority trial comparing the proportion of patients that met the four patient success criteria (HHS, revisions, radiographic, and device-related adverse events) between the investigational and control groups.

1. ***Multiple revisions to the study protocol during the course of the IDE study***

   The original study compared the investigational device group, Group I, and two non-concurrent control groups, Group II and Group III. Group I was the investigational group treated with the Cormet 2000 HRS. Patients were to be sequentially enrolled. Group II was the control group treated with the Biomet M2a™ metal-on-metal total hip replacement. Group III was the control group treated with any FDA approved metal-on-polyethylene total hip replacement. Each investigational site was to generate data for Groups I and II, or data for Groups I and III. However, as enrollment into the study progressed, no control patients were actually enrolled for utilization in the analysis of data for this study. To address the absence of a control group, the applicant proposed and explored multiple historical control alternatives (metal-on-metal then ceramic-on-ceramic) as they began to analyze their data. Because of these changes to the originally-proposed control and introduction of an alternative historical control after completion of the study and the outcomes of the investigational group were already known to the applicant after comparison to the metal-on-metal historical control, we will be asking questions regarding the impact of these potential biases, if any, on the analysis of the outcomes of the study.

2. ***Multiple revisions of the study protocol at the time of PMA***
The original PMA was submitted on March 30, 2005 with fewer patient success criteria and a different control population (metal-on-metal hip data without having access to patient level data) than outlined in the approved IDE protocol. Table 4 on page 9 includes a summary of the study success endpoints used in the original PMA in comparison to the IDE approved protocol. Because of these changes to the originally-proposed study success endpoints, we will be asking questions regarding the impact of these potential biases on the analysis of the outcomes of the study.

3. ***Multiple revisions of the study protocol following analysis of the data in amendments to the PMA***
In response to a request for clarification of the data presented in the original application and additional information, the applicant submitted Amendment 8 to the PMA, proposing and using the clinical data from a ceramic-on-ceramic hip system, Osteonics ABC System (Alumina Bearing Couple, PMA P000013 approved on February 3, 2003), as the historical control. The applicant had access to patient level data for this historical control. The composite clinical success analysis included all of the originally approved and proposed study endpoints; however, the radiographic endpoint success criterion was different and appeared to be less stringent. Because of these changes to the originally-proposed study success endpoints, we will be asking questions regarding the impact of these potential biases on the analysis of the outcomes of the study.

A request was made for an analysis of the safety and effectiveness of the Cormet 2000 HRS according to the approved IDE protocol or to identify pre-specified radiographic endpoints that were applicable to a resurfacing hip system (such as any resurfacing systems previously discussed by the Orthopedic and Rehabilitation Devices Panel). The applicant responded with the data that is also presented in this Executive Summary. Please refer to Reference Tab 10 of this Panel Pack for a copy of the IDE Approved Protocol versus the Implemented IDE Study Protocol.

4. ***Other changes to the study design***
This section discusses the specific changes to the study design throughout the course of the IDE study and PMA review process. Please see Table 4 on Page 9 for an overview of the study success criteria used to evaluate the clinical data utilized in major submissions to the Agency.

    a. *Changes to data collection (radiographic) techniques*
    The IDE approved protocol included a radiographic measurement technique as outlined in Table 1.

Table 1: Comparison of Measurement Techniques

Comparison of Measurement Techniques			
Radiographic Analysis	**Original PMA Submission March 30, 2005**	**Original IDE Protocol dated March 20, 2003**	**Current Technique PMA Amendments 8 and 13**
Acetabular Migration vertical/ horizontal	Reference bottom of pelvis	Reference inferior teardrops	SAME
Acetabular Migration varus/valgus	Angle between a line joining edges of the cup and a line joining bottom of pelvis	Angle between a line joining edges of the cup and a line joining tear drops	SAME
Acetabular Radiolucencies	SAME	Serial	SAME
Femoral Subsidence Axis Femoral Canal	SAME	Line to lateral femoral cortex	Line from head center to top of greater trochanter
Femoral Tilt Varus/Valgus	SAME	Lines through femur midpoint and stem	SAME
Femoral Radiolucencies	SAME	Serial	SAME

b. Changes to radiographic analyses

In the current analysis, the applicant used a revised measurement technique and then applied revised success criteria to evaluate radiographic success. Please see Table 2 for a summary of the radiographic success criteria. The applicant has combined the femoral subsidence and femoral tilt endpoint into one. Therefore, the femoral component need only meet one of its endpoints to be a success. In addition, the original criteria indicated a radiolucency in any zone was considered a failure, as is common in hip prosthesis studies. However, the final proposed analysis indicated radiolucencies not in all zones to be a success, a possibly less stringent criterion for success than reported in the literature.

Table 2: Comparison of Radiographic Success Criteria

Comparison of Radiographic Success Criteria			
Radiographic Success Criteria	**Original PMA Submission**	**Original IDE Protocol**	**Current Criteria**
Acetabular Migration vertical/ horizontal	SAME	< 5mm	SAME
Acetabular migration varus/valgus	SAME	< 5 degrees	SAME
Acetabular Radiolucencies	Not Evaluated	None in any zone	Not in all zones
Femoral subsidence axis femoral canal	SAME	< 5mm	Combined (must have both for failure)
Femoral tilt varus/valgus	SAME	< 1 degree	
Femoral Radiolucencies	Not Evaluated	None in any zone	Not in all zones

FDA acknowledges that metal-on-metal hip resurfacing devices are relatively new to the US orthopaedic community and that the radiographic evaluation criteria of these devices have not been uniformly accepted. Because of the changes to the radiographic evaluation criteria and the success/failure endpoints after the first data analysis, we will be asking questions regarding the impact of these potential biases on the analysis of the outcomes of the study.

c. *Proposed primary effectiveness and safety endpoints definitions*

This section outlines the composite clinical success outcomes used in each submission to the Agency. The key changes for each endpoint are also described.

Approved IDE Protocol

The original IDE success definition was outlined as "…at 24 months a patient is defined as a success, if all four of the following are met:

1. Harris Hip Score (HHS) ≥ 20 point improvement
2. Has not had and is not planning a revision surgery.
3. Radiographic Success:
    a. Acetabular component
        - Migration <5mm vertical or horizontal
        - Migration <5°in varus/valgus
        - No new or progressive radiolucencies >1mm in **any** zones
    b. Femoral component
        - Subsidence <5mm
        - Tilting <1° in varus/valgus
        - No new or progressive radiolucencies >2mm in **any** zones
4. No device related complications—an AE due to the design and/or material composition of the implant and/or implant instrumentation; the relationship to the device will be determined by the investigator.

Any patient who does not meet all of the above criteria during any evaluation time point out to two years will be considered a failure."

Original PMA Submission

In the original PMA submission (P050016), the applicant modified the primary efficacy endpoint, which was proposed and defined in terms of a Month 24 Composite Clinical Success (CCS) criterion that required:

- No revision, removal, or replacement of any component of the study device during the 24 months post surgery; and
- Achieving a good clinical outcome as determined by having a Harris Hip Total score that was greater than or equal to 80 points at Month 24 or later.

The radiographs were evaluated only as part of a secondary analysis.

Amendments 8 and 13 of the PMA

In Amendment 8, the applicant changed all of the endpoints with the exception of "Absence of revision or pending revision." In Amendment 13, the applicant clarified several points and provided some additional analyses; however, the composite clinical success criteria were the same as those used in Amendment 8 of the PMA as summarized below.

1. Harris Hip Score (HHS) ≥ 80
2. Absence of revision or pending revision.
3. Radiographic Success:
    a. Acetabular component
        - Migration <5mm vertical or horizontal
        - Migration <5^{o} in varus/valgus
        - No new complete radiolucencies >1mm in **all three** zones
    b. Femoral component
        - Subsidence < 5mm **and** tilting < 1° in varus/valgus
        - No new complete radiolucencies >2mm in **all three** zones
4. Absence of device related events

This summary outlines the changes in study design and analysis that have been implemented throughout the course of the study and PMA review. It is important to consider these events and any potential biases they may introduce when evaluating the summary of clinical data presented in Section IV of this Executive Summary. We will be asking the Panel to comment on the impact of the multiple changes and timing of the changes to the protocol and the impact on the Agency's ability to interpret the data as presented in the PMA to characterize the safety and effectiveness of the Cormet 2000 HRS.

B. Revision Rate

In addition to the study design issues, the FDA is requesting Panel input regarding the percentage of patients requiring revision surgery within 2 years of the procedure.

Twenty-four revisions were noted in the pivotal, unilateral group and 44 revisions were observed in the entire investigational group. If one is to consider as the denominator the entire pivotal group of 337 procedures, the revision rate would be 7.1%. However, by the applicant's

accounting, only 302 of the pivotal group procedures had a 24+ month follow-up making the revision rate for the pivotal, unilateral group actually 7.9% (24/302). For all enrolled procedures, the revision rate is 8.3% (44/532) if only the procedures with 24+ month follow-up are taken into consideration.

Since resurfacing procedures require a different surgical technique than traditional total hip replacement surgery, the applicant expected a learning curve to develop as surgeons implanted more of the devices. The applicant considered the initial 25 procedures per investigator to determine whether a learning curve was present. Table 3 summarizes these risk factors and the revision rates associated with each risk factor in the pivotal and all enrolled groups.

Table 3: Significant risk factors affecting revision rates (as determined by applicant)

		Pivotal Unilateral	**Pivotal Unilateral 24+ Month Follow-up**	**All Enrolled**	**All Enrolled 24+ Month Follow-up**
	Revisions	**24**	**24**	**44**	**44**
	N	**337**	**302**	**1148**	**532**
	%	**7.1%**	**7.9%**	**3.8%**	**8.3%**
Gender	Female	11.9% (13/109)	12.8% (13/102)	6.5% (21/323)	12.4% (21/170)
	Male	4.8% (11/228)	5.5% (11/200)	2.8% (23/825)	6.4% (23/362)
Small Component Size	40/44mm	16.7% (13/78)	17.3% (13/75)	7.4% (22/296)	15.2% (22/145)
	>40/44mm	4.3%(11/259)	4.9% (11/227)	2.6% (22/843)	5.7% (22/387)
Non Osteoarthritis Diagnosis	AVN/RA	14.6% (7/48)	16.7% (7/42)	7.2% (9/125)	12.9% (9/70)
	Osteoarthritis	5.9% (17/289)	6.5% (17/260)	3.4% (35/1023)	7.6% (35/462)
Leg length discrepancy greater than or equal to 1 cm	≥ 1 cm	13.0% (12/92)	14.5% (12/83)	6.1% (18/296)	14.0% (18/129)
	< 1 cm	4.9% (12/245)	5.5% (12/219)	3.1% (26/849)	6.5% (26/403)
Baseline lowest quartile of function (HHS)	< 42.58	17.7% (15/85)	20.3% (15/74)	6.4% (18/283)	13.1% (18/137)
	≥ 42.58	3.6% (9/252)	4.0% (9/228)	3.1% (26/846)	6.7% (26/391)
Among 1st 25 procedures within a specific site	First 25	8.2% (12/147)	8.9% (12/135)	6.8% (16/234)	8.3% (16/192)
	After 1st 25	6.3% (12/190)	7.2% (12/167)	3.1% (28/914)	8.2% (28/340)

C. Summary

Therefore, the Agency is requesting the Panel's input to determine whether the clinical data collected in this study and presented in this PMA demonstrate the safety and effectiveness of the Cormet 2000 Hip Resurfacing System. The Panel questions in Section V outline our specific issues discussed here as well as the overall safety and effectiveness of the submitted clinical data.

Table 4: Study success criteria in each submission

	Original IDE [redacted]	Original P050016	P050016 Amendments 8 & 13
Control	Metal-on-Metal System or Metal-on-Polyethylene System	Metal-on-Metal Historical Control	ABC Ceramic-on-Ceramic System (P000013) Data
HHS Endpoint	Proposed >80 or an improvement of >20 points with inclusion criteria <70; Revised to >20 point improvement	>80	>80
Radiographic Endpoints:			
Acetabular Migration	• migration <5mm in vertical or horizontal direction; • migration <5º in varus/valgus direction	SAME	migration <5mm OR <5º
Acetabular Radiolucency	new or progressive complete radiolucencies ≤1mm or greater in any OR all zones	Not evaluated	not in ALL zones
Femoral Migration	• subsidence (lateral movement of the resurfacing head) <5mm; • tilting <1º in varus/valgus direction	SAME	migration <5mm OR <1º
Femoral Radiolucency	new or progressive complete radiolucencies ≤ 2mm in any OR all zones	Not evaluated	not in ALL zones
Radiographic Measurement Techniques:			
Acetabular Migration vertical/horizontal	Reference inferior teardrops	Stated "Reference inferior teardrops"; Later applicant said it actually was bottom of pelvis.	Reference inferior teardrops
Acetabular Migration varus/valgus	Mid tear drop and center of head	Stated "Reference inferior teardrops"; Later applicant said it actually was bottom of pelvis.	Mid tear drop and center of head
Acetabular Radioluencies	Serial	SAME	SAME
Femoral subsidence axis femoral canal	Line to lateral femoral cortex	SAME	Line from head center to top of greater trochanter
Femoral tilt varus/valgus	Lines through femur midpoint and stem	SAME	SAME
Femoral Radiolucencies	Serial	SAME	SAME
Revision	Revision surgery or planned revision surgery	SAME	SAME
Adverse Events	Not specified	Inconsistencies	Redefined - Device related include component breakage; femoral neck fracture; collapse or AVN of the femoral head; femoral loosening; acetabular loosening; dislocation

II. Background Information

Applicant and Address:
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A. Indications for Use

The applicant proposes the following Indications for Use:

The Cormet 2000 Hip Resurfacing System is intended for use in resurfacing hip arthroplasty for reduction or relief of pain and/or improved hip function in skeletally mature patients having the following conditions:

1. Non-inflammatory degenerative arthritis such as osteoarthritis, and avascular necrosis (AVN);
2. Inflammatory arthritis such as rheumatoid arthritis.

Hip resurfacing arthroplasty is intended as a primary joint replacement for patients who are at risk of requiring more than one hip joint replacement over their lifetime. While it is not possible to predict if a patient will require a future hip joint revision, several factors such as gender, age, weight, and activity level may increase the risk of the need for revision.

Contraindications:

1. Active or suspected infection in or around the hip joint;
2. Patients with bone stock inadequate to support the device. There must be sufficient bone to support the femoral resurfacing component after debridement of all damaged or weak bone;
3. Skeletal immaturity;
4. Distant foci of infection, which may cause hematogenous spread to the implant site;
5. Any mental or neuromuscular disorder, which would create an unacceptable risk of prosthesis instability, prosthesis fixation failure, or complications in postoperative care;
6. Obesity. An overweight or obese patient can produce loads on the prosthesis, which can lead to failure of the fixation of the device or to failure of the device itself;
7. Women of child bearing age due to unknown effects of the fetus of metal ion release;
8. Patients with known moderate or severe renal insufficiency;
9. Patients with known or suspected metal sensitivity (e.g., jewelry).

B. Device Description

The Cormet 2000 Hip Resurfacing System (HRS), a metal-on-metal hip resurfacing system, is comprised of two components – a resurfacing femoral head with a short stem and a monoblock acetabular component.

Femoral Component:
The substrate material for both the femoral and acetabular components is cast cobalt-chromium-molybdenum (Co-Cr-Mo) alloy that conforms to ASTM F75 "Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants." The femoral component is finished with a shotblast (Alumina grit) on its internal portion and approximately halfway down the short stem. The mode of primary fixation with the Cormet head component is bone cement. The secondary mode of fixation with the Cormet head is achieved by incorporation of three anti-rotation fins located adjacent to the internal chamfer.

Acetabular Component:
Both the femoral and acetabular components are composed of cast Co-Cr-Mo alloy that conforms to ASTM F75. The acetabular component is finished with a bi-coat comprised of hydroxyapatite (HA) on plasma sprayed unalloyed titanium. The cup is also plasma sprayed by shotblasting with Alumina grit. The characterization of the coatings is provided in the "Pre-Clinical Testing" section of the Executive Summary. The mode of primary fixation with the Cormet cup is an interference fit between the external surface and the prepared acetabular bone in which the cup is equatorially expanded to obtain a press-fit. The mode of secondary fixation with the Cormet cup is ingrowth/ongrowth of the bone to the cup. Both primary and secondary stability is aided by two sets of anti-rotation fins that wedge-fit into the ischium and pubis.

System:
A listing of the matching of femoral and acetabular components is included in Table 5.

Table 5: Cormet 2000 Hip Resurfacing System Sizes

	Femoral Component	**Acetabular Component**
Size 2	40mm	46 or 48mm
Size 4	44mm	50 or 52mm
Size 6	48mm	54 or 56mm
Size 8	52mm	58 or 60mm
Size 10	56mm	62mm

Radial Clearance:
Radial clearance, the difference in the radii of the head and articulating surface of the cup at the equator, determines how much synovial fluid can lubricate the bearing, without which seizing would occur. The radial clearance of the Cormet 2000 HRS for all sizes is controlled to be between 75 and 200 microns. Therefore, the diametrical clearance can range from 150 to 400 microns.

Sphericity:
Sphericity refers to the extent to which the bearing surface of the head and cup components approximate a perfect sphere. The sphericity, quantified as radial separation, is defined as the largest radial deviation of the points measured from the average radius. The radial separation is controlled to less than or equal to 10 microns, which meets with the ISO standard for conventional total hip replacements.

Surface Roughness:

Surface roughness (Ra value) refers to the irregularities on the articulating surface of the head and cup components as a result of machining operations. The Ra value is less than or equal to [redacted] which meets with the ISO standard for conventional total hip replacements.

III. Pre-Clinical Data and Prior Investigations

A. Pre-Clinical Testing

The following bench tests were performed on the Cormet 2000 HRS: Wear, Frictional Torque, Fatigue Strength, Surface Coating Characterization, Range of Motion (ROM), and Luxation Wear.

Wear Testing:

Worst Case Design:
The applicant performed wear testing on both extremes of the range (40mm and 56mm) in order to explore the potential worst case scenarios.

Acceptance Criteria:
The amount of wear particles produced was compared to the wear generated by a 28mm bearing couple (control), which is the standard size for a total hip replacement.

Methods:
Three wear testing studies were completed.

1. Three variables were tested to investigate which parameters had the most effect on wear: Sphericity, Diametrical Clearance and Metallurgy. The test compared the 'heat-treated' (Hot Isostatically Pressed and Solution Annealed) Cormet device to the previously manufactured 'as-cast' type device. Tests were carried out on a Stanmore MK3 simulator at AEA Technology, Harwell. Two 48mm diameter Cormet devices a type device were run to at maximum load (establishing steady-state conditions with diametrical bearing c respectively. These diametrical clearances span the rang

2. Another wear study evaluated the effect of metallurgy ('as cast' vs. 'heat-treated' high carbon 40mm diameter Co-Cr-Mo bearings) on wear. An 8-station MTS System hip joint simulator was used to investigate four and four diameter 'double heat-treated' (hot isostatically pressed and solution annealed) metal-on-metal bearings to under normal gait conditions. Radial biaxial-rocking motion was used to represent flexion/extension and abduction/adduction movements of the femur during ambulation. The loading cycle was based on the 'Paul' cycle applying between and

3. The final study investigated the effects of heat treatment on wear rates in metal-on-metal bearings. An 8-station MTS Sys ulator was used to investigate fou 'as-cast' and four 'heat-treated' metal-on-metal bearings under standard and 'severe' ga conditions up to cycles. Diametrical clearances were a mean of in the 'heat-treate d in the 'as cast' group and sphericity wa lled to in all the . biaxial-rocking motion was used to represent the flexion/extension and abduction/adduction movements of the femur during ambulation. All components were subject to of 'normal walking' (standard gait)

with a maximum load of [redacted] at 1Hz. Then 'fast-jogging' and additional normal walking tests were performed.

Results:

1. The applicant's report concludes there is no difference between the 'heat-treated' Cormet and 'as cast' devices. However, the Cormet devices, with improved sphericity, did show improved wear performance over versions of previously manufactured devices.

2. The 28mm diameter bearings indicated the highest steady-state wear rate with the largest running-in wear occurring in the 56mm bearings. The 40mm group had lower running-in and steady-state wear compared to the 28mm coupling. The 56mm bearings produced the lowest steady-state wear of all the groups.

3. The steady-state wear rates ($0.4mm^3/10^6$ cycles) found during 'normal walking' were similar to those for 36mm diameter metal-on-metal bearings reported in the literature. When 'normal walking' was resumed after the 'severe' wear, then the steady state wear rates returned to the level found prior to the 'severe' test regime.

Frictional Torque Testing:

Worst Case Design:
Size 56mm bearing samples were assumed 'worst-case' since torque is proportional to head diameter. Additionally, the five 56mm samples used for testing had the minimal diametrical clearances of [redacted] which provides the maximum initial contact area that leads to the highest frictional tor

Acceptance Criteria:
Andersson *et al.*[1] s [redacted] the torque required to remove a well cemented acetabular cup from a cadaveric socket is [redacted]

Methods:

1. In December 2005, five 56mm heads were paired with five 62mm cups to give the specified diametrical clearance [redacted]). The frictional torque of each bearing pair was recorded independently in flexion-extension and internal-external rotation under a joint load of [redacted]

2. In the first test performed in 1998, refer to test report entitled "Wear Simulation of the CORMET 2000 Resurfacing Prosthesis", three 48mm diameter Cormet heads were studied with diametrical clearances of [redacted]

3. In February 2005, more comprehensive testing was performed. New and worn components from previous wear studies were tested (40mm and 56mm head size representing the smallest and largest in the range for completeness). Flexion-extension and rotational torques were measured. Tests were performed at normal walking loads [redacted] and at extreme load cycles [redacted]

[1] Anderson GBJ, Freeman, MAR, Swanson, SAV. Loosening of the cemented acetabular cup in total hip replacement. *Journal of Bone and Joint Surgery.* 1972; 54B: 590-599.

Results:

1. imum absolute (modulus) torque was recorded at an average of and under a test load of respectively. The maxim olute r internal-external rotation was found to be an average of under a test load of respectively.

2. The exhibited maximum torques (during the initial running-in period) of reducing to averages of respectively, during stea

3. The maximum torque was found to occur during flexion-extension motion. The maximum absolute (modulus) torque was recorded in the 'as-new' condition for the 56mm bearings at an average of for the loads of respectively.

Fatigue Strength:

Worst case:
The distance from the center of rotation of the spherical head to the point of contact between the stem and the pre-drilled hole is the maximum for the 56mm head. The force that is transmitted through the center of the resurfacing head, therefore, creates a maximum bending moment in the 56mm device.

Acceptance Criteria:
ISO 7206-8 "Implants for Surgery - Partial and Total Hip Joint Prostheses - Part 8: Endurance Performance of Stemmed Femoral Components with Application of Torsion" for total hip replacements.

Methods:
The test method was configured to simulate the fault condition of the resurfacing head similar to ISO 7206-4 "Implants for Surgery - Partial and Total Hip Joint Prostheses - Part 4: Determination of Endurance Properties of Stemmed Femoral Components." The short stem was fixed by a metal jig at to the vertical and in of anteversion. The stem of the resurfacing head was held by epoxy resin on the distal section at a distance of below the underside of the head. This simulated the stem only being 'held' by the lower portion with no bony fixation on the upper stem and no load carrying by the underside of the resurfacing head. Five static tests were performed. The failure point was identified as the point on the load/extension graphs where the elastic region ended (became non-linear).

Five samples were then dynamically tested at (approximately 50% of the mean static failure load) at to

Results:
The mean static failure load was All samples went on to survive higher loads without catastrophic failure albeit with permanent deformation of the femoral stem. Five samples were then dynamically tested at (approximately 50% of the mean static failure load) at to without failure in the same test configuration.

Surface Coating Characterization:
The acetabular component is coated with a plasma sprayed unalloyed titanium and hydroxyapatite (HA) coating.

Plasma Spray

Acceptance Criteria:
The static shear strength of surface/substrate interface should exceed 20 MPa for porous surface coatings as tested per ASTM F1044 "Standard Test Method for Shear Testing of Calcium Phosphate Coatings and Metallic Coatings." The static tensile strength of the surface/substrate shall exceed 20 MPa for porous surface coatings. Shear fatigue strength testing per ASTM F1160 "Standard Test Method for Shear and Bending, Fatigue of Calcium Phosphate and Metallic Medical and Composite Calcium Phosphate/Metallic Coatings" should exceed 10 million cycles at a stress of 10MPa.

Methods:
The static shear strength of surface/substrate was tested per ASTM F1044. The static tensile strength of the surface/substrate was evaluated per ASTM F1147 "Standard Test Method for Tension Testing of Calcium Phosphate and Metal Coatings" and the shear fatigue strength was evaluated per ASTM F1160.

Results:
Table 6 summarizes the results of the plasma spray coating testing.

Table 6: Plasma Spray Coating Test Results

Test	N	Results	S.D.
Static Shear (ASTM F1044)	5	20.9 MPa	4.1
Static Tension (ASTM F1147)	3	35.9 MPa	2.8
Abrasion Strength	6	54.1mg weight loss	6.4
Surface Roughness	6	Ra 25.7 microns	7.2

Shear fatigue strength testing per ASTM F1160 was completed on six samples for 10 million cycles at a stress of 10MPa with no failures.

Hydroxyapatite (HA) Coating

Acceptance Criteria:
The acceptance criteria are described in "FDA"s 510(k) Information needed for Hydroxyapatite Coated Orthopaedic Implants dated March 10, 1995 (revised 2/20/97)."

Methods:
The HA coating was characterized with regard to density, particle size, porosity thickness, Ca/P ratio, solubility/dissolution, bonding strength and crystallinity.

Results:
Table 7 summarizes the results of the HA characterization.

Table 7: HA Characterization

Chemical Composition	$2(Ca_5(PO_4)_3OH)$
Trace Elements	As <1 ppm Cd <1 ppm Hg <1 ppm Pb <1 ppm Total Heavy Metals <50
Ca/P ratio	Powder 1.697 (1.667± 0.03) Coating 1.655 (1.667± 0.02)
Crystallinity	Coating: 62%
Crystalline Phases	%HAP Powder: >97% Coating: >70%
	% Alpha TCP Powder: 0 Coating: <4%
	% Beta TCP Powder: 0 Coating: <6%
	%TCPM Powder: 0 Coating: <7%
	%CaO Powder: 0.7% Coating: <1%

Density	3.096 g/cm^3
Grain Size	10% <17 µm 90% <83 µm
Porosity	Global porosity: 27% Pore medium size: 38.92 µm Standard deviation: 31.71 µm
Thickness	119 µm
Solubility	$2x10^{-56}$
Tensile Strength	33.31 MPa (S.D. 6.5 MPa)
Adhesive Strength	14.9 MPa

Range of Motion:

Worst Case Design:

A cylindrical "femoral neck" results in the smallest angles of articulation than those found in-vivo with a natural oval femoral neck. Therefore, a cylindrical "femoral neck" was utilized to detect impingement between the acetabular cup and femoral neck. The 56mm diameter Cormet resurfacing head bearing surface subtends the smallest angle in the size range. The 62mm and 64mm acetabular cups' bearing surfaces subtend the largest angle in the size range (64mm not available in US). Therefore, the 56mm diameter head paired with the 62/64mm cup coupling produced the smallest articular angle before impingement. Impingement may lead to neck fracture or loosening of the acetabular cup. Therefore, range of motion is evaluated for a new hip system to identify a "typical" range of motion as identified by an ISO standard.

Acceptance Criteria:

As outlined in ISO 21535:2002 "Specific requirements for hip-joint replacement implants" the minimum allowable angle of flexion/extension is 80^o, abduction/adduction is 60^o and internal/external rotation is 90^o.

Methods:

Range of motion was evaluated per ISO 21535, which is intended for stemmed total hip replacements with diaphyseal fixation. The test protocol was modified to consider the proximal bone preserving nature of hip resurfacing, by molding a cylindrical femoral neck around the stemmed component. This modification is acceptable since the stemmed component is cemented into the shaft of the femur. Flexion/extension, abduction/adduction and internal/external rotation were measured by identifying the angle at which impingement occurs.

Results:
The flexion/extension angle at which impingement occurred with the worst case components was 83°, the abduction/adduction angle at which impingement occurred was 70° and the internal/external degree of rotation at which impingement occurred was 111°.

Luxation Wear:

Worst Case Design:
Five 40mm and five 56mm bearings were tested. Bearing clearances were controlled to 400µm, the maximum specified in the manufacturing tolerances. This is the 'worst-case' condition since initial laxity in the bearing is increased compared to lower clearances.

Acceptance Criteria:
Komistek *et al.*[2] used fluoroscopy to demonstrate that small diameter total hip replacement devices (metal-on-polyethylene) subluxed several millimeters during each gait cycle. With metal-on-metal bearings they were not able to detect any subluxation up to the resolution of the fluoroscope, which is 750 microns.

Methods:
Five 40mm and five 56mm bearings were tested in Ringers solution at 37º according to the procedure 'Determination of Resistance to Luxations and Repositions of Total Hip Joint Prostheses' by Kaddick *et al.*[3] A horizontal preload of 1kN was used. The forces required to cause luxation of the bearings during the first cycle were then recorded and the displacement noted. The cups were examined and then repeated luxations were performed (a further 999 cycles per bearing couple). A displacement of 10mm was pre-set since this was greater than the displacement required to cause luxation in the 40mm and 56mm diameter bearings found during the first luxation.

Results:
After the first luxation cycle, a small decrease in luxation force occurred for all bearing couples, which was thought to be due to rounding of the cup rim. Thereafter, a steady increase in maximum luxation force was noted until steady-state was achieved. This increase was consistent with increased surface roughening of both the head and cup bearing surfaces. Forces to cause luxation were in excess of 2kN for both the 40mm and 56mm bearings.

Visual surface analysis of the bearings showed scratching at the end of the tests. The applicant concluded that subluxation is unlikely to occur in large diameter metal-on-metal bearings.

B. Metal Ion Testing

Description of Study Population
A metal ion study was conducted at Coventry & Warwickshire Hospital, United Kingdom outside of the applicant's US IDE study. A series of 29 patients who underwent a unilateral metal-on-metal hip resurfacing procedure were prospectively followed over a seven-year period. Seven of the 29 patients underwent a metal-on-metal hip resurfacing procedure on the contralateral hip

[2] Komistek RD,. In vivo comparison of the hip separation after metal-on-metal or metal-on-polyethylene total hip arthroplasty. *Journal of Bone and Joint Surgery.* 2002; 84-A: 1836-1841.
[3] Kaddick, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH. Determination of resistance to luxations and repositions of total hip joint prostheses. In: Phuhl, W, editor. *Bioceramics in Orthopedics,* 1998.

during the course of the study. These seven patients along with four other patients who had a previous hip resurfacing on the other hip had their metal ion levels assessed over time to determine the effect of bilateral hip resurfacing on metal ion levels.

Implant Identification
Both the Corin-McMinn device and the Cormet device (the subject device) used in this study have cups with a HA coated back on a plasma sprayed titanium layer over the CoCr substrate with a supero-medial peg. Heads are similar in both devices, for use with cement and uncoated in the cement/implant contact areas. The significant differences between the Corin-McMinn and the Cormet are that the former has a splined supero-medial cup peg (Cormet is parallel and non-splined), two bearing surface integral introducer holes (Cormet has no holes) and two opposing stippled pads on the cup back (Cormet has low profile locating splines and no pads).

Measurement Techniques
Blood samples were taken from each patient. A plastic intravenous cannula was inserted, the metal needle removed and 5 mls of blood withdrawn and discarded. Samples were then taken and placed in 2 ml Heparin tubes, which had been tested for cobalt and chromium contamination. The blood was centrifuged and the plasma transferred into trace-metal free polycarbonate tubes. Cobalt and chromium levels were determined.

Metal Ion Levels
Metal ion levels are raised and remain elevated following metal-on-metal hip resurfacing; however, it is unclear if the levels to which they are raised are of any clinical significance.

Summary of Data
For patients with one resurfacing device, results of the study indicate that metal ion levels for cobalt and chromium initially increased following a metal-on-metal hip resurfacing but plateaued and started to decrease between one and two years post-implantation. The levels remained below their peak, but did not return to preoperative levels throughout the seven-year follow-up reported in this study. Implantation of a contralateral metal-on-metal resurfacing system further raised the metal ion levels, more notably cobalt ions compared to chromium ions. The cobalt levels did not return to normal following bilateral hip resurfacing and remained higher than patients with unilateral hip resurfacing over four years. Chromium levels following bilateral surgery do not return to normal, but are only slightly higher when compared to levels of a unilateral resurfacing.

C. Sterilization Validation

The implants are sterilized using a gamma irradiation dose in the range of 25 to 42 kGy. The applicant has agreed to a six-month shelf life, until complete sterilization and packaging validation testing for a 5-year shelf life has been completed.

D. Data from Explants

The applicant has not provided any explant data in the PMA submission.

E. Summary

The applicant has performed Wear, Frictional Torque, Fatigue Strength, Surface Coating Characterization, Range of Motion (ROM), and Luxation Wear Testing on the Cormet 2000 Hip Resurfacing Device. All of these test results are similar to those seen for traditional total hip replacement systems and do not raise any new questions. As the Panel has previously discussed, it is unknown what affect metal ions have on the body. At this time, patient labeling have been used to advise patients of any potential risks associated with metal ions.

IV. Clinical Data

A. Study Description

The applicant has presented data from a study originally designed to be a prospective, non-randomized, concurrently controlled clinical study used to evaluate the Cormet 2000 Hip Resurfacing Implant System. The study was designed to be a non-inferiority study to test the hypothesis that the Cormet 2000 Hip Resurfacing System (HRS) is as effective as conventional metal-on-metal or metal-on-polyethylene total hip arthroplasty. However, no patients were enrolled in the control arm of the study. Consequently, the study conducted was a non-randomized, historically controlled single arm study at twelve investigational sites.

1. IDE Approved Protocol

In G010047, the sponsor proposed to conduct a prospective, multicenter, non-randomized, concurrently controlled clinical study consisting of 395 patients with non-inflammatory degenerative joint disease of the hip. The study was conditionally approved on May 11, 2001 for 11 institutions with 200 subjects. The original study design compared the proportion of patients that met the four patient success criteria (HHS, revisions, radiographic, and device-related AE) between the investigational and control groups. A copy of the IDE protocol approved in March 2003 is included under Tab 10 of the Panel Pack.

a. Control Group

The original study was designed to compare the investigational device group, Group I, with two non-concurrent control groups, Group II and Group III. Group I was the investigational group treated with the Cormet 2000 HRS. Patients were to be sequentially enrolled. Group II patients in the control group were to be treated with the Biomet M2a™ metal-on-metal total hip replacement and Group III patients in the control group were to be treated with any FDA approved metal-on-poly total hip replacement. Each investigational site was supposed to collect data for Group I and Group II patients, or data for Group I and Group III patients. According to the protocol, sites which had not already treated control group patients were to recruit Group I patients first and then additional control group patients. The sites that had already treated control group patients were to continue to recruit all the control group patients and then the Group I patients. Control patients who were already implanted were not required to complete the Musculoskeletal Function Assessment (MFA), but those control patients who had not been implanted were required to follow the entire protocol, including the MFA. Analyses were to be performed at each follow-up interval (6 weeks ± 2 weeks, 6 months ± 1 month, 1 year ± 2 months and 2 years ± 2 months) for overall outcomes with the final evaluation and primary endpoint occurring at 24 months.

b. Original IDE Approved Study Definitions

Patient success definition: At 24 months, a patient is defined as a success if all four of the following are met:

1. Harris Hip Score (HHS) ≥ 20 point improvement
2. Has not had and is not planning a revision surgery.
3. Radiographic Success:
   i. Acetabular component
      - Migration < 5mm vertical or horizontal
      - Migration < 5°in varus/valgus
      - No new or progressive radiolucencies >1mm in **any** zones
   ii. Femoral component

- Subsidence < 5mm
- Tilting < 1° in varus/valgus
- No new or progressive radiolucencies >2mm in **any** zones

4. No device related complications—an AE due to the design and/or material composition of the implant and/or implant instrumentation; the relationship to the device will be determined by the investigator.

Any patient who did not meet all of the above criteria during any evaluation time point would be considered a failure.

2. Current PMA Amendment Study Definitions

For this PMA submission, the applicant's current analysis compares the data collected on the Cormet 2000 HRS to the ABC Ceramic-on-Ceramic total hip replacement (THR). The ABC Ceramic-on Ceramic THR data (patient level data acquired from Stryker Howmedica Osteonics) is being used as an historical control group. For this analysis, the study design compares the proportion of patients that meet the four patient success criteria (HHS, revisions, radiographic, and device-related AE) between the investigational and historical control groups. A copy of the latest version of the protocol is included under Tab 10 of the Panel Pack. It should be noted that this protocol was not reviewed or approved by the Agency, prior to submission of this PMA.

a. Control Group

The applicant uses the full data set of the Howmedica Osteonics ABC Ceramic-on-Ceramic system approved in PMA P000013 on February 3, 2003, as the historical control group. This is an alumina bearing total hip arthroplasty system. The data were collected in a prospective, randomized study at 16 investigational sites from 1996 to 1998. The outcome measures in this study included HHS, Adverse Events, Radiographs and Questionnaires.

b. Current Submission (Amendment 13) Success Criteria

Patient success definition: Month 24+ and 36 Month follow-up points were considered to evaluate success rates and clinical results.

1. Harris Hip Score (HHS) ≥ 80
2. Has not had and is not planning a revision surgery.
3. Radiographic Success:
   i. Acetabular component
      - Migration < 5mm vertical or horizontal
      - Migration < 5°in varus/valgus
      - No new complete radiolucencies >1mm in **all** three zones
   ii. Femoral component
      - Subsidence < 5mm **and** tilting < 1° in varus/valgus
      - No new complete radiolucencies > 2mm in **all** three zones
4. No device related complications including:
   - Bone breakage around the implanted components;
   - Aseptic loosening on the components, including complete radiolucency around the stem or evidence of the AVN under the femoral head;
   - Breakage of the device components (stem fracture, acetabular liner fracture, etc.);
   - Movement of the components in situ;
   - Dislocation of the hip.

Any patient who did not meet all of the above criteria during any evaluation time point would be considered a failure.

3. Statistical Considerations

a. Study Design and Analysis:
The applicant made changes to the control group and patient success criteria (HHS and radiographic criteria) which resulted in multiple analysis cohorts (e.g., 24 mo, 24+ mo, in and out of window, original and modified HHS definitions) throughout the duration of the study as well as after the data had already been analyzed by the applicant. It should be noted that every time a change in the protocol is made or an additional analysis is performed, the overall Type 1 error becomes inflated. This is because there are essentially more ways to reach statistical significance. Type 1 error may be defined as the probability of rejecting the null hypothesis when it is true, or in this case, inferring non-inferiority when one should not.

b. Margin of Non-inferiority (delta):
The non-inferiority margin, delta, is defined as the maximum clinically insignificant difference between the investigational device and the comparator. It follows that a difference greater than this (on the negative side) would render the new device clinically inferior. The margin of non-inferiority for the Cormet 2000 HRS was chosen to be 8% (i.e., -0.08) at the IDE stage and was based on a clinical decision. This means that as long as the Composite Clinical Success (CCS) rate for the Cormet 2000 HRS was not more that 8% worse than the control (i.e., diff > -.08), it would be considered non-inferior to it. A difference greater than 8% (i.e., diff ≤ -.08) would render the Cormet 2000 HRS clinically inferior to the control. It should be emphasized that this difference is not the observed difference (point estimate) between the Cormet 2000 HRS and the control population, but is based on the lower limit of the 95% confidence interval to account for variability in the study population. In general, to justify a slightly lower efficacy rate for a device, there must be some other advantage. In this case, the bone conserving feature of the Cormet 2000 HRS and its potential applicability to a younger population who may need a THR in the future is its presumed benefit.

4. Inclusion/Exclusion Criteria

A side by side comparison of the Inclusion/Exclusion Criteria between the investigational and control groups is made in Table 8.

Table 8: Inclusion/Exclusion Criteria Comparison

Inclusion/Exclusion	Cormet 2000 Approved Protocol	Control Group Study
Is skeletally mature	X	X
Is mentally capable of follow-up	X	X
Will be available for 2 yr follow-up	X	X
Deemed candidate by diagnosis of investigator	X	X
No active infection	X*	X
No severe osteoporosis	X*	X
Not a prisoner	X	X
Is not pregnant	X	X
Is not morbidly obese	X*	X*
No ipsilateral previous surgery	X	X
No extensive deformity of femoral head	X*	Not applicable
No known allergies to implants	X	None included in study
No neoplastic disease	X*	None included in study
No above the knee amputation either extremity	X	None included in study
No previous Girdlestone procedure	X	Information Not Available to Applicant
No previous hip fusion	X	Information Not Available to Applicant
No AKA of either extremity	X	Information Not Available to Applicant
Does not require structural bone graft	X	Information Not Available to Applicant
No previous ipsilateral hemi-resurfacing, total resurfacing, total bipolar, total unipolar, or total hip replacement	X	Information Not Available
No nonunion or malunion of the femur	X	Information Not Available
Has preoperative HHS < 70 points	X	No limits
No Congenital Dysplasia of the Hip (CDH)	X	Included in study
Age	No specified limits	21-75
Inflammatory Arthritis	Included in study	

*PI discretion

The applicant indicates the main inclusion/exclusion criteria were consistent for both studies and any significant differences are biased in favor of the control such as Inflammatory Arthritis not being included in the control, but in the Cormet 2000 study.

PANEL QUESTION: Please be advised that you will be asked to comment on the appropriateness of changing the controls during the study progression as well as after the original data analyses were performed and how this impacts our ability to interpret the data.

B. Patient Populations

Under the US IDE (G010047), the applicant collected data on 1,154 cases implanted with the Cormet 2000 HRS. Six procedures involved the use of a pegged acetabular component, which were not reported as part of the IDE study and were not included in the applicant's analysis for this PMA. Therefore, 1,148 patients were enrolled in the Cormet 2000 HRS study, eight of which were enrolled under the compassionate use provision. The study populations are identified as the following:

1. Pivotal Study Unilateral Patients

A total of 337 patients were enrolled in the pivotal study unilateral group of patients implanted with the Cormet 2000 HRS. These patients comprise the primary safety and effectiveness cohort for the PMA.

The IDE pivotal study group includes unilateral procedures, excluding major protocol violations. Five patients who also received contralateral study devices after 730 days are included in this cohort; their contralateral procedure was performed during the Continued Access portion of the study, so they are included in the Continued Access Group.

2. Pivotal Study Bilateral Patients

Both procedures for patients in the IDE cohort receiving contralateral implants within 730 days were included in the pivotal study bilateral group. Forty-nine (49) patients underwent two procedures for a total of 98 procedures. Another four (4) patients received a non-IDE study pegged acetabular component on one side so that procedure has been excluded from the analysis. Taking this into consideration, the pivotal study bilateral cohort consisted of 102 procedures in 53 patients.

3. Continued Access Patients

The continued access population is part of the all enrolled procedures and as such is part of the primary safety analysis cohort yet was not utilized by the applicant to assess effectiveness. Consequently, no comparisons were made between this population and the control. These patients were enrolled at the same IDE participating centers following the same protocol used to enroll subjects in the pivotal group. The continued access cohort consists of the following groups of procedures:

- Unilateral procedures with date of surgery after 8/5/2003 (date of closure of IDE study cohort);
- Both side bilateral procedures with date of surgery after or on 8/5/2003 (date of closure of IDE study cohort);
- Second side bilateral procedures if first surgery in IDE cohort was greater than 730 days prior to second surgery.

A total of 609 procedures in 562 patients represent the continued access cohort implanted with the Cormet 2000 HRS.

4. All Enrolled Cohort

The all enrolled cohort includes subjects from all three cohorts, as well as the eight compassionate use subjects for a total of 1,148 subjects. The data is compiled together for safety information.

5. Control Patients

The enrollment phase of the ABC Ceramic-on-Ceramic study began on October 29, 1996 and was completed on October 20, 1998. The Osteonics ABC System I and Osteonics ABC System II combined for a total of 266 unilateral patients and these data serve as the control for the Cormet 2000 HRS.

In the clinical results analysis, the unilateral pivotal cohort is evaluated for effectiveness and the all enrolled cohort is evaluated for safety.

C. Accounting

The follow-up time points for both the investigational and control studies are included in Table 9. All patients were to be evaluated annually, as defined below, until the last patient entered into the study had reached the two-year time point. The following outcome measures were to be taken at each prescribed interval: HHS, radiographs, Musculoskeletal Function Assessment (MFA) and Complications.

In the original PMA submission, follow-up rates did not consider the protocol-defined windows for each follow-up time. If you do consider the original protocol-defined time windows, patient follow-up was only 62% at two years. In order to improve follow-up rates, the Agency suggested the applicant bring patients back in for evaluation at a 24+ month (24 months or greater) time point. With any hip replacement procedure, once a subject is a failure, they are a failure for the remainder of the study. Therefore, the final time point used for the evaluation of Composite Clinical Success (CCS) was 24+ months.

Table 9: Follow-up Interval Comparison

	Cormet 2000 Approved Protocol	Cormet 2000 PMA Submission	ABC IDE Study
6 weeks	±2 weeks	±2 weeks + expanded	±3 weeks
6 months	±1 month	±1 month + expanded	±1 month
1 year	±2 months	±2 months + expanded	±2 months
2 years	±2 months	±2 months + expanded	±2 months
24+ months		Any evaluation 22+ months	

1. Patient Accounting

The following section describes the follow-up rates for each cohort.

a. Pivotal Study Unilateral Patient Accountability

Table 10 presents an overview of the data available for the pivotal study cohort.

Table 10: Pivotal Study Unilateral Patient Accountability

Status at Month 24+	Number of Subjects
Pivotal study group enrollment	337
Patients with complete CCS score	292
Patient died before Month 24+	1
Patients not evaluated for CCS	44
Died after 24 month interval	2
Complete HHS data only	9
Complete Radiographic data only	5
Patients with no Month 24+ data; Potential lost to follow-up	28

The availability of follow-up evaluations for the investigational and control Pivotal Study Unilateral group is provided in Table 11 below.

Table 11: Procedure Accounting and Follow-Up Compliance Table – Pivotal Study Unilateral Patients and Controls

As of Date of Database Closure	Pre-Op		Week 6		Month 6		Month 12		Month 24		Month 24+		Month 36	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
(1)Theoretical follow-up[1]	337	266	337	266	337	266	337	266	337	266	337	266	314	266
(2) Cumulative deaths including non-theoretically due[2]	0	0	0	0	0	0	0	1	1	2	1	2	4	2
(3) Cumulative revisions including non-theoretically due[3]	0	0	2	1	5	1	7	3	16	3	16	3	24	3
(4) - Not Yet Overdue[4]	0	0	0	0	0	0	0	0	0	0	0	0	32	0
(5) - Deaths+revisions among theoretical due[5]	0	0	2	1	5	1	7	4	17	5	17	5	26	5
(6) = Expected due for clinic visit[6]	337	266	335	265	332	265	330	262	320	261	320	261	256	261
(7) = Expected due+revisions among theoretical due[7]	337	266	337	266	337	266	337	265	336	264	336	264	280	264
All Evaluated Accounting (Actual[B]) Among Expected Due Procedures[8]														
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
(8) All Evaluated Visit Compliance (%)[9]	100.0%	100.0%	99.1%	99.2%	90.4%	94.0%	89.7%	96.1%	85.6%	97.7%	91.3%	96.5%	39.8%	73.2%
(9) Harris Hip Total Score[10]	337	252	328	245	288	238	285	245	283	246	283	252	77	186
(10) Radiographic evaluation[11]			313		232		234		259		291		53	
(11) CCS at Mos. 24, 24+ or HHS+radio. otherwise[12]			332	245	297	238	294	245	243	250	292	256	97	186
(12) Actual[B] % Follow-up for CCS or HHS+radio.CCS[13]			99.1%	92.5%	89.5%	89.8%	89.1%	93.5%	72.3%	94.7%	86.9%	97.0%	37.9%	71.3%
Within Window Accounting (Actual[A]) Among Expected Due[14]														
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
(13) Harris Hip Total Score[15]	337	252	277	221	161	183	192	215	200	206	281	251	22	156
(14) Radiographic evaluation[15]			277		161		192		202		283		22	
(15) CCS at Mos. 24, 24+ or HHS+radio otherwise[15]			277	221	161	183	192	215	202	209	285	254	22	156
(16) Actual[A] % Follow-up for CCS or HHS+radio.CCS[16]			82.7%	83.4%	48.5%	69.1%	58.2%	82.1%	60.1%	79.2%	84.8%	96.2%	8.6%	59.8%

Thus, the follow-up rate at 24+ Months for patients with complete information to determine safety and effectiveness was 84.8% (285/336). The control follow-up rate at 24+ Months was 254/264 or 96.2%.

b. All Enrolled Patient Accountability

At 24+ Months, the follow-up rate is 348/686 (50.7%) in comparison to 335/347 (96.5%) for the control 'all enrolled' cohort. In addition, although there have been 1,148 procedures completed to date, many of the patients have not yet reached the 24+ month endpoint in the continued access cohort.

2. Data Accounting

The following tables list the data accountability for the primary effectiveness endpoints for the unilateral pivotal study cohort. The All Enrolled Cohort is intended to be evaluated for safety; however, the applicant did provide some effectiveness data, so that data accountability has been included here.

a. Harris Hip Score

Harris Hip Scores (HHS) were collected at each follow-up point described in Table 9.

i. Pivotal Study Unilateral Cohort

Table 12 demonstrates the HHS follow-up at each time point. There were 337 subjects in the investigational (I) group and 266 in the control (C) group.

Table 12: Pivotal Study HHS Follow-Up

	I		C	
	N	**%**	**n**	**%**
Total Enrolled	337	-	266	-
Preoperative	337	-	252	-
Week 6	329	-	246	-
Month 6	288	-	239	-
Month 12	285	-	246	-
Month 24	263	78.0	247	92.9
Month 24+	283	84.0	253	95.1
Month 36	80	23.7	187	70.3

The HHS follow-up at 24+ Months is 283/337 or 84.0%. For the control group, the follow-up is 253/266 or 95.1%; however, it should be noted that the control group is missing some baseline scores.

ii. All Enrolled Cohort

The applicant has HHS data on 497/686 (72.4%) subjects that have reached 24+ months in the All Enrolled Cohort.

b. Radiographs

The applicant has only evaluated the final Month 24 or Month 24+ radiographs in comparison to the baseline radiographs, which is considered a worst-case scenario. The applicant does not provide any data regarding the control radiographic data, because there were no radiographic failures in the control group at 24 Months.

i. Pivotal Study Unilateral Cohort

Table 13 includes radiographic data accounting at Month 24 and 24+.

Table 13: Radiographic Data Accountability – Pivotal Study Unilateral Cohort

	Month 24		Month 24+	
	N	**%**	**N**	**%**
Total Radiographs Available	259		291	
Not available to the reviewer for evaluation	30		10	
Evaluable for radiographic success	229	68.0%	281	83.4%

The applicant has collected evaluable radiographs on 281/337 (83.4%) of subjects.

ii. All Enrolled Cohort

The applicant has evaluable radiographic data on 336/686 (49.0%) subjects that have reached 24+ months.

3. *Demographics*

a. *Baseline and Demographic Characteristics*

Baseline patient demographic and clinical characteristics between the Cormet 2000 HRS unilateral pivotal study patients and ABC Ceramic-on-Ceramic control patients are compared in Table 14. Table 15 includes the baseline and demographic characteristics of All Procedures. As noted in these tables, some of the information collected for the investigational group was not available in the control population.

Table 14: Baseline and Demographic Characteristics: Pivotal Study Unilateral Patients vs. Unilateral Controls

	Investigational				Control				p[&]
	N	%			N	%			
Number of procedures	337				266				–
Number of patients	337				266				
Males	228	67.7%			165	62.0%			0.150
Females	109	32.3%			101	38.0%			
Primary diagnosis	n	%			n	%			0.135
Osteoarthritis	289	85.8%			206	83.7%			
Rheumatoid Arthritis	4	1.2%			0	0.0%			
Avascular necrosis	44	13.1%			40	16.3%			
Other Diagnosis Present	7	2.1%			20	7.5%			0.001
Charnely Class	n	%			n	%			
Unilateral joint, no other disability	235	69.7%							
Bilateral joint, no other disability	86	25.5%							
Uni or bilateral plus conditions affecting function	16	4.7%							
Contralateral hip	n	%			n	%			
Symptomatic	37	11.0%							
Replaced/Fused	17	5.0%							
Asymptomatic	283	84.0%							
Knee status	n	%			n	%			
Symptomatic (either knee)	34	10.1%							
Replaced/Fused (either knee)	3	0.9%							
Both asymptomatic	300	89.0%							
Surgery within 12 months	36	10.7%							
Harris Pain Category	n	%			n	%			0.194
None/Ignores	0	0.0%			0	0.0%			
Slight	0	0.0%			2	0.8%			
Mild	2	0.6%			7	2.6%			
Moderate	154	45.7%			94	35.3%			
Marked	173	51.3%			160	60.2%			
Totally disabled	8	2.4%			3	1.1%			
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Age at surgery (yrs)	50.1	9.6	15.0	79.0	53.3	11.1	23.0	75.0	<0.001
Weight (lbs)	190.4	40.7	95.0	341.0	188.7	39.7	93.0	340.0	0.692
Duration of symptoms	47.6	49.1	3.0	374.0					
Harris Hip Total Score	50.1	11.6	12.2	72.0	49.7	11.3	24.5	90.1	0.233

Notes: [&] Wilcoxon rank sum tests for interval variables and ordinal variables (age, weight, HHS pain and total scores). Chi-square tests for all other variables.

Table 15: Baseline and Demographic Characteristics: All Investigational Procedures vs. All Controls (Unilateral and Bilateral)

	Investigational				Control				p[&]
	N	%			N	%			
Number of procedures	1148				349				--
Number of patients	1030				318				
Males	825	71.9%			227	65.0%			0.015
Females	323	28.1%			122	35.0%			
Primary diagnosis	n	%			n	%			0.001
Osteoarthritis	1023	89.1%			273	83.0%			
Rheumatoid Arthritis	9	0.8%			0	0.0%			
Avascular necrosis	116	10.1%			56	17.0%			
Other Diagnosis Present	52	4.5%			20	5.7%			0.358
Charnely Class	n	%			n	%			
Unilateral joint, no other disability	587	51.2%							
Bilateral joint, no other disability	433	37.8%							
Uni or bilateral plus conditions affecting function	127	11.1%							
Contralateral hip	n	%			n	%			
Symptomatic	229	19.9%							
Replaced/Fused	136	11.8%							
Asymptomatic	783	68.2%							
Knee status	n	%			n	%			
Symptomatic (either knee)	217	18.9%							
Replaced/Fused (either knee)	7	0.6%							
Both asymptomatic	924	80.5%							
Surgery within 12 months	214	18.6%							
Harris Pain Category	n	%			n	%			0.267
None/Ignores	2	0.2%			0	0.0%			
Slight	3	0.3%			4	1.1%			
Mild	12	1.1%			11	3.2%			
Moderate	425	37.2%			127	36.4%			
Marked	680	59.5%			203	58.2%			
Totally disabled	20	1.8%			4	1.1%			
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Age at surgery (yrs)	51.2	9.8	15.0	88.0	53.1	11.4	21.0	75.0	0.001
Weight (lbs)	193.8	41.9	95.0	375.0	189.8	39.3	93.0	340.0	0.290
Duration of symptoms	47.6	48.9	2.0	480.0					
Harris Hip Total Score	50.0	11.5	12.2	99.7	49.8	11.4	24.5	90.1	0.561

Notes: [&] Wilcoxon rank sum tests for interval variables and ordinal variables (age, weight, HHS pain and total scores). Chi-square tests for all other variables.

For the unilateral patients, there were more males (228; 67.7%) than females (109; 32.2%) enrolled in the investigational group. There were also more males (165; 62.0%) than females (101; 38.0%) enrolled in the control group. The mean age of patients in the investigational group at time of surgery was 50.1 years (SD 9.6, 15-79). Patients were older in the control group (mean age 53.3 yrs.; SD 11.1; 23-75). Over 85% of the patients in the investigational group and over 83% in the control group had a diagnosis of OA.

b. Statistical Comparison

Fisher's Exact Test and Wilcoxon Rank Sum Test:
The applicant used Fisher's Exact Test (categorical variables) and Wilcoxon Rank Sum Test (continuous variables) to compare baseline comparability between the Cormet 2000 HRS and the ABC control. There were no differences in gender, mean weight, percent OA, or preoperative HHS between the Cormet and ABC control. There was a statistically significant difference in mean age (50.0 Cormet vs 53.3 control). Complications and adverse events were compared between the Cormet 2000 HRS and the control using Fisher's Exact Test.

Propensity Score Analysis:
In a non-randomized study, and particularly with the use of historical controls that were treated at a different place and time, biases can result from imbalances of baseline characteristics. A propensity score analysis is one way of determining if the two treatment groups are comparable enough that they would have had approximately equal chances of receiving either treatment, had this been a randomized study. The applicant performed a propensity score analysis including the variables believed to potentially have a clinical impact on patient outcome: gender, age, weight marked pain at baseline, and HHS at baseline. These covariates then become the independent variables in a logistic regression with treatment assignment to the dependent variable. Each subject receives a propensity score and the distribution is categorized into quintiles. If there is much overlap between the two treatment groups, one can conclude that patient characteristics were not highly predictive of enrollment in one study or the other, and that selection bias was minimal. The mean propensity score for the Cormet group was 0.59 and was 0.55 for the ABC control. The discrimination index was 0.61, indicating that only 61% of the time would randomly selected Cormet patients have a higher probability of receiving the Cormet Hip compared to a randomly selected control.

Although the applicant's propensity score analysis showed little bias, a propensity score analysis with only 5 covariates may be limited. The applicant could not include many covariates in the model because there was not corresponding information available for the control group for other covariates.

D. Clinical Results

The clinical data the applicant collected to demonstrate the safety and effectiveness of the Cormet 2000 HRS is presented here.

1. Treatments

Tables 16 and 17 summarize the surgical details reported for the investigational pivotal study unilateral group and the all enrolled cohort, respectively.

Table 16: Surgical Details: Pivotal Study Unilateral Patients vs. Unilateral Controls

	Investigational		Control		p[1]
	N	%	N	%	
Number of procedures	337		266		--
Number of patients	337		266		
Surgical Approach	**n**	**%**	**n**	**%**	<0.001
Lateral	34	10.1%	0	0.0%	
Postero-lateral	261	77.4%	245	92.1%	
Anterior	41	12.2%	20	7.5%	
Trochanteric	0	0.0%	1	0.4%	
Unspecified[a]	1	0.3%	0	0.0%	
Femoral Implant Sizes	**n**	**%**	**n**	**%**	<0.001
28mm	0	0%	32	12.0%	
32mm	0	0%	234	88.0%	
40mm	20	5.9%	0	0.0%	
44mm	58	17.2%	0	0.0%	
48mm	126	37.4%	0	0.0%	
52mm	93	27.6%	0	0.0%	
56mm	40	11.9%	0	0.0%	
Cup Implant Sizes	**n**	**%**	**n**	**%**	0.360
46mm	13	3.9%	2	0.8%	
48mm	7	2.1%	10	3.8%	
50mm	43	12.8%	19	7.1%	
52mm	17	5.0%	51	19.2%	
54mm	99	29.4%	57	21.4%	
56mm	25	7.4%	44	16.5%	
58mm	79	23.4%	46	17.3%	
60mm	16	4.7%	22	8.3%	
62mm	38	11.3%	9	3.4%	
64mm	0	0.0%	6	2.3%	
Cup Fixation Method	**n**	**%**	**n**	**%**	
Cemented	2	0.6%	0	0.0%	
Press-Fit	335	99.4%	266	100.0%	
Intraoperative Complications[2]	**n**	**%**	**n**	**%**	
Femoral neck notched	4	1.2%	0	0.0%	0.134
Femoral fracture	0	0.0%	1	0.4%	0.441
Cardiovascular/Arrhythmia	3	0.9%	6	2.3%	0.193
Ceramic Insert Chip	0	0.0%	6	2.3%	0.007
Other[b]	6	1.8%	31	11.7%	<0.001

Notes:

[1] Kruskal-Wallis test for femoral and cup size, exact tests for other variables.

[2] Complications are not counted more than once per procedure.

[a] Unspecified refers to a field that was left unanswered and the answer was not obtained prior to database closure.

[b] There were 5 intraoperative complications designated as 'other' among 4 pivotal study unilateral patients. These included: rash, greater trochanter notching, hematoma, and two cases of other systemic complications.

Table 17: Surgical Details: Pivotal Study Unilateral Patients vs. Unilateral Controls

	Investigational		Control		p[1]
	N	%	N	%	
Number of procedures	1148		349		–
Number of patients	1030		318		
Surgical Approach	n	%	n	%	<0.001
Lateral	96	8.4%	0	0.0%	
Postero-lateral	902	78.6%	321	92.0%	
Anterior	135	11.8%	27	7.7%	
Trochanteric	1	0.1%	1	0.3%	
Unspecified[a]	14	1.2%	0	0.0%	
Femoral Implant Sizes[x]	n	%	n	%	<0.001
28mm	0	0%	35	10.0%	
32mm	0	0%	314	90.0%	
40mm	56	4.9%	0	0.0%	
44mm	240	21.1%	0	0.0%	
48mm	393	34.5%	0	0.0%	
52mm	359	31.5%	0	0.0%	
56mm	91	8.0%	0	0.0%	
Cup Implant Sizes[x]	n	%	n	%	0.150
46mm	36	3.2%	2	0.6%	
48mm	19	1.7%	12	3.4%	
50mm	190	16.7%	20	5.7%	
52mm	51	4.5%	58	16.6%	
54mm	320	28.1%	74	21.2%	
56mm	73	6.4%	61	17.5%	
58mm	331	29.1%	67	19.2%	
60mm	30	2.6%	33	9.5%	
62mm	89	7.8%	14	4.0%	
64mm	0	0.0%	8	2.3%	
Cup Fixation Method[x]	n	%	n	%	
Cemented	6	0.5%	0	0.0%	
Press-Fit	1131	99.5%	349	100.0%	
Intraoperative Complications[2]	n	%	n	%	
Femoral neck notched	6	0.5%	0	0.0%	0.346
Femoral fracture	0	0.0%	1	0.3%	0.233
Cardiovascular/Arrythmia	5	0.4%	7	2.0%	0.009
Ceramic Insert Chip	0	0.0%	8	2.3%	<0.001
Other[b]	20	1.7%	38	10.9%	<0.001

Notes:

[1] Kruskal-Wallis test for femoral and cup size, exact tests for other variables.

[2] Complications are not counted more than once per procedure.

[a] Unspecified refers to a field that was left unanswered and the answer was not obtained prior to database closure.

[b] There were 12 intraoperative complications designated as 'other' in 11 enrolled investigational device procedures. These included: rash, greater trochanter notching, hematoma, 2 cases of other systemic complications, 'loose body' leg length discrepancy, muscle weakness, nerve palsy, low hemoglobin/hematocrit, skin split, and broken drill bit.

The surgical details table reveals differences between the investigational and control groups in the type of surgical approaches used, in the femoral implant sizes and cup implant sizes. In addition, some of the intraoperative complications are specific to the devices used. For example, ceramic insert chipping would not be found with a metal-on-metal resurfacing system and femoral neck fracture would not be expected in the control group. These differences raise concerns over the suitability of the controls used in the present study.

2. *Effectiveness Evaluations*

The Composite Clinical Success (CCS) criteria demonstrating effectiveness include Harris Hip Score, Radiographic Evaluation, Revisions and Adverse Events. The Revisions and Adverse Events are described in the Safety Evaluation Section on page 44 of this Executive Summary.

a. Harris Hip Scores (HHS)

Individual patient composite HHS results at month 24 postoperatively were compared to the preoperative status.

i. Pivotal Study Unilateral Patients:

In Table 18, the distribution of total HHS scores collected over time is presented for the unilateral procedures in the investigational (I) and control (C) groups using time windows not approved in the IDE protocol.

Table 18: Pivotal Study Unilateral Patients and Unilateral Controls – Harris Hip Score

	Preoperative				Month 24				Month 24+				Month 36			
	I		C		I		C		I		C		I		C	
Category	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
90-100	0	0.0	1	0.4	240	91.3	225	91.1	258	91.2	230	90.9	70	87.5	166	88.8
80-89	0	0.0	0	0.0	14	5.3	11	4.5	14	4.9	11	4.3	4	5.0	12	6.4
70-79	1	0.3	9	3.6	2	0.8	5	2.0	4	1.4	6	2.4	5	6.3	4	2.1
60-69	71	21.1	28	11.1	5	1.9	3	1.2	5	1.8	3	1.2	1	1.3	4	2.1
50-59	106	31.5	77	30.6	1	0.4	2	0.8	1	0.4	2	0.8	0	0.0	0	0.0
40-49	94	27.9	92	36.5	1	0.4	1	0.4	1	0.4	1	0.4	0	0.0	1	0.5
30-39	50	14.8	35	13.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
20-29	9	2.7	10	4.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
10-19	6	1.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
0-9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	337		252		263		247		283		253		80		187	

Results:

This presentation of the data shows that the investigational group preoperatively may have started off with lower HHS scores with nearly all patients reporting scores less than 70 points (one patient in the investigational group had a preoperative HHS >70 compared to nine in the control group). There was no significant difference at Month 24 or Month 24+ for either groups.

As noted earlier, the applicant has changed the total HHS score success criteria since initiation of the study. The HHS clinical success/failure is presented both ways over time in Tables 19 and 20. Table 19 summarizes patients with a total HHS > 80 points, considered a clinical success in the current analysis. Table 20 provides a comparison of preoperative HHS to Month 24 and Month 24+ to establish success based on 20-point improvement over baseline (the original HHS endpoint per the agreed upon IDE protocol).

Table 19: Pivotal Study Unilateral Patients and Unilateral Controls Harris Hip Total Score Greater Than or Equal to 80 – All Evaluated

	Number and Percentage Meeting Criteria					
	Investigational			Controls		
	N	n	%	N	n	%
Pre-op	337	0	0.0	252	1	0.4
Week 6	329	128	38.9	246	133	54.1
Month 6	288	272	94.4	239	220	92.1
Month 12	285	270	94.7	246	232	94.3
Month 24	263	254	96.6	247	236	95.5
Month 24+	283	272	96.1	253	241	95.3
Month 36	80	74	92.5	187	178	95.2

Table 20: Pivotal Study Unilateral Patients and Unilateral Controls Increase from Baseline in Harris Hip Total Score Greater Than or Equal to 20 – All Evaluated

	Number and Percentage Meeting Criteria					
	Investigational			Controls		
	N	n	%	N	n	%
Week 6	329	219	66.6	233	176	75.5
Month 6	288	282	97.9	225	216	96.0
Month 12	285	280	98.2	235	225	95.7
Month 24	263	259	98.5	234	224	95.7
Month 24+	283	279	98.6	240	230	95.8
Month 36	80	79	98.8	177	171	96.6

Results:
The Month 24 and Month 24+ comparisons showed that the proportion meeting this definition of success was similar between the populations. Similarly, the dichotomization of the populations on the 20-point improvement line showed the populations were similar at the Month 24 and Month 24+ time points.

There were four patients with < 20 points improvement at Month 24 compared to baseline values and nine patients with a HHS < 80 points at Month 24 postoperatively in the Cormet 2000 Hip Resurfacing Study. Presented either way, there was not a significant difference compared to the control population with over 95% of the patients in each group having a HHS of > 80 points at Month 24 or greater than 20 point improvement in HHS at Month 24 over the preoperative score. There were 10 patients with HHS of < 80 points at minimum Month 24 postoperatively in the investigational group. Nine of these patients had a HHS < 80 at Month 24 and one patient had a HHS < 80 points at Month 24+.

ii. <u>All Enrolled Cohort:</u>
There was no significant difference at Month 24 in the distribution of Harris Score categories between the investigational and control All Enrolled Procedures cohorts.

The total HHS scores continued to improve throughout the study with the majority of patients in the investigational and control groups showing the total HHS scores > 80, which is considered to be a good to excellent clinical result. No appreciable differences were noted between the investigational and control populations regardless of what method was used.

b. Radiographic Evaluations:

Individual patient radiographs at Month 24+ postoperatively were compared to the immediate post-operative radiographs. The applicant has significantly changed the radiographic endpoints from the approved IDE protocol. The radiographic measurement technique and success criteria changes, instituted by the applicant, were outlined in Section I of the Executive Summary (pgs. 4-6).

i. Pivotal Study Unilateral Patients:

All radiographic results presented by the applicant are provided in Table 21.

Table 21: Radiographic Clinical Success Among Expected Due Original Protocol and Modified Protocol Combined – Pivotal Study Unilateral Patients

	Month 24		Month 24+	
	N		N	
Total radiographs (Actual[B]) in Table 4.1[1]	259		291	
Not available to the reviewer for evaluation[2]	30		10	
Evaluable for radiographic success	229		281	
	n/N	%	n/N	%
Radiolucency Acetabular Component				
I	0 /228	0.0%	0 /279	0.0%
II	0 /228	0.0%	0 /279	0.0%
III	2 /228	0.9%	2 /279	0.7%
All[3]	0 /228	0.0%	0 /279	0.0%
Radiolucency Femoral Component				
Superior	0 /229	0.0%	1 /279	0.4%
Tip	1 /229	0.4%	2 /279	0.7%
Inferior	0 /229	0.0%	1 /279	0.4%
All[3]	0 /229	0.0%	1 /279	0.4%
Cup migration and tilt[4]				
Superior/Inferior migration >= 5 mm[3]	0 /228	0.0%	0 /278	0.0%
Medial/Lateral migration >= 5 mm[3]	0 /228	0.0%	0 /278	0.0%
Varus/Valgus Tilt >= 5 degrees[3]	0 /228	0.0%	0 /278	0.0%
Stem migration and tilt[4]				
Subsidence of the femoral component >= 5 mm	7 /224	3.1%	10 /274	3.6%
Stem Tilting >= 1 degree	172 /226	76.1%	205 /276	74.3%
Subsidence of the femoral component >= 5 mm and Stem tilting>= 1 degree[3]	7 /226	3.1%	10 /276	3.6%
Other assessments				
Anteroversion of the head >= 5 mm	49 /223	22.0%	55 /267	20.6%
Retroversion of the head >= 5 mm	69 /223	30.9%	89 /267	33.3%
Hypertrophy in any zone	0 /229	0.0%	0 /279	0.0%
Resorption in any zone	0 /229	0.0%	0 /279	0.0%
Lysis in any zone	10 /229	4.4%	12 /279	4.3%
Composite radiographic failure	**7 /228**	**3.1%**	**10 /279**	**3.6%**

Notes:
[1] Total radiographic evaluations performed for Month 24 or Month 24+ among procedures expected due. The procedures in this table were used in comparisons with control devices.
[2] Not available to the independent medical reviewer for evaluation.
[3] Required for composite radiographic endpoint used in constructing the Composite Clinical Success.
[4] Complete component migration and tilt could not be measured for 5 cases. However, in the absence of any other indicators of failure for the component and absence of qualitative indicators of failure of the component in a serial review, these cases were not considered failure.

Results:
At Month 24+, two cases of acetabular radiolucencies were noted in zone III. However, none of the cases had radiolucencies in all three zones. In the femoral component, four cases had radiolucencies in various zones, but of those only one patient had lucencies in all three zones. There were no reports of cup migration and tilt. However, 10 procedures showed subsidence of the femoral component ≥ 5 mm (3.6%).

At Month 24+, a significant number (205/276 = 74.3%) of procedures revealed stem tilting ≥1 degree, which would have been considered a radiographic failure according to the original IDE protocol. Other reported radiographic assessments included

anteroversion of the head ≥ 5mm (55/267 = 20.6%), retroversion of the head ≥ 5 mm (89/267 = 33.3%) and evidence of lysis in any zone (12/279 = 4.3%).
The applicant does not provide any data regarding the control radiographic data, because there were no radiographic failures in the control group at 24 Months.

ii. All Enrolled Cohort:
Based on the revised radiographic success criteria there was no significant difference at Month 24 in the distribution of Radiographic Successes between the pivotal study unilateral and all enrolled cohorts. However, the follow-up data for the All Enrolled Cohort is only 49.0% at 24+ months.

Radiographic data for all enrolled surgical participants involving the investigational device is presented in Table 22.

Table 22: Radiographic Clinical Success Among Onfile Procedures Original Protocol and Modified Protocol Combined All Enrolled Investigational Devices

	Month 24		Month 24+	
	N		N	
Total radiographs (Actual[B]) in Table 4.4[1]	336		369	
Not available to the reviewer for evaluation[2]	61		33	
Evaluable for radiographic success	275		336	
	n/N	%	n/N	%
Radiolucency Acetabular Component				
I	0 /272	0.0%	0 /332	0.0%
II	0 /272	0.0%	0 /332	0.0%
III	4 /272	1.5%	4 /332	1.2%
All[3]	0 /272	0.0%	0 /332	0.0%
Radiolucency Femoral Component				
Superior	0 /274	0.0%	2 /332	0.6%
Tip	2 /274	0.7%	4 /332	1.2%
Inferior	0 /274	0.0%	2 /332	0.6%
All[3]	0 /274	0.0%	2 /332	0.6%
Cup migration and tilt[4]				
Superior/Inferior migration >= 5 mm[3]	1 /270	0.4%	2 /328	0.6%
Medial/Lateral migration >= 5 mm[3]	0 /270	0.0%	1 /328	0.3%
Varus/Valgus Tilt >= 5 degrees[3]	0 /270	0.0%	0 /328	0.0%
Stem migration and tilt[4]				
Subsidence of the femoral component >= 5 mm	8 /267	3.0%	12 /325	3.7%
Stem Tilting >= 1 degree	203 /270	75.2%	242 /328	73.8%
Subsidence of the femoral component >= 5 mm and Stem tilting>= 1 degree[3]	8 /270	3.0%	12 /328	3.7%
Other assessments				
Anteroversion of the head >= 5 mm	60 /269	22.3%	68 /320	21.3%
Retroversion of the head >= 5 mm	86 /269	32.0%	108 /320	33.8%
Hypertrophy in any zone	0 /275	0.0%	0 /332	0.0%
Resorption in any zone	0 /275	0.0%	0 /332	0.0%
Lysis in any zone	13 /275	4.7%	15 /332	4.5%
Composite radiographic failure	**9 /272**	**3.3%**	**13 /332**	**3.9%**

Notes:

[1] Total radiographic evaluations performed for Month 24 or Month 24+ among procedures expected due. The procedures in this table were used in comparisons with control devices.

[2] Not available to the independent medical reviewer for evaluation.

[3] Required for composite radiographic endpoint used in constructing the Composite Clinical Success.

[4] Component migration and tilt could not be measured for 8 cases. However, in the absence of any other indicators of failure for the component and absence of qualitative indicators of failure of the component in a serial review, these cases were not considered failure.

Results:
At 24+ months, the composite radiographic failure rate with the revised definitions as defined by the applicant, for the unilateral pivotal group was 10/279 = 3.6% and 13/332 = 3.9% for all enrolled patients. Thus, the data presented for all procedures did not show any significant difference from the radiographic data available for the pivotal study patients. It is important to note that the applicant only has radiographic data on 332 out of 668 (49.7%) investigational subjects that have reached 24+ months. However, the all enrolled cohort is intended to be evaluated for safety, not effectiveness.

Metal-on-metal hip resurfacing is a relatively new procedure and methods of radiographic evaluation have not been adequately standardized as to methodology (such as patient positioning, appropriate anatomic views, x-ray beam angles, etc.) or to interpretation of radiographic data. Clinical significance of some pre-defined endpoints used to measure success/failure is open to discussion. Minimal stem tilting of ≥ 1 degree may be a questionable success/failure predictor while subsidence of the femoral component ≥ 5 mm may be more significant. The significance of lysis in any one or in all zones is also open to discussion.

PANEL QUESTION: Please be advised that you will be asked to comment on the appropriateness of changes in radiographic evaluations, changes in radiographic success criteria, and the appropriateness of the sponsor's final proposal.

c. Composite Clinical Success:
The applicant has presented the composite clinical success (CCS) data using several methods as noted in Tables 23 and 24. N is the number of patients with complete CCS endpoints and n is the number of patients who are a success according to CCS criteria.

Table 23: Month 24 Composite Clinical Success (CCS)[1] Using Original Definition For Different Assumptions Regarding Interval Definitions and Imputations – Pivotal Study Unilateral Patients versus Unilateral Controls

	Investigational			Controls			Non-Inferiority Test	
	n	N	Prop.	n	N	Prop.	Diff.	95% CI LB[4]
Month 24+[2] CCS (Actual[B])	256	291	0.880	213	243	0.877	0.003	-0.044
Month 24+ CCS (Actual[A])[3]	251	284	0.884	212	241	0.880	0.004	-0.042
Month 24 CCS (Actual[B])	210	242	0.868	207	237	0.873	-0.006	-0.056
Month 24 CCS (Actual[A])	173	202	0.856	174	196	0.888	-0.031	-0.086

1 The original composite clinical success (CCS) criterion requires no revision of device and no device-related adverse event prior to the exact Month 24 anniversary (i.e., relative day 730), an increase from pre-treatment in Harris Hip Total score ≥ 20 points at Month 24 or later, and radiographic composite success at Month 24 or later. The sample sizes are lower in controls for this endpoint due to missing pre-treatment HHS Total scores.

2 Month 24+ outcomes are based on rollback imputations for missing Month 24 Harris Hip Scores and Month 24 Radiographic Success. If either of these is missing, the next available value is used (e.g., Month 36) is used to impute the missing value.

3 Actual^A intervals: Analyses using Actual^A intervals only include evaluations as follows: Pre-Op ≤ 0 days post surgery; Immed. interval 1-45 days; 6 Mo. Interval (6 ±1 mo.); 1 Yr Interval (12 ±2 mo.); 2 Yr Interval (24 ±2 mo.). Actual^A Month 24+ outcomes use the rollback imputation for Harris Hip Total scores and Radiographic Success. Actual^B analyses include all evaluated assessments for that interval.

4 Lower bounds of 1-sided 95% confidence intervals for differences between proportions with composite clinical successes (Investigational minus Control). The study w as designed to demonstrate clinical non-inferiority defined as a success rate no more than 0.08 smaller than control. The null hypothesis that the Investigational device is inferior to the Control device is rejected if the lower bound of the confidence interval is larger than -0.08.

Table 24: Month 24 Composite Clinical Success (CCS)[1] Using Modified Definition for Different Assumptions Regarding Interval Definitions and Imputations – Pivotal Study Unilateral Patients versus Unilateral Controls

	Investigational			Controls			Non-Inferiority Test	
	n	N	Prop.	n	N	Prop.	Diff.	95% CI LB[4]
Month 24+[2] CCS (Actual[B])	251	292	0.860	224	256	0.875	-0.015	-0.063
Month 24+ CCS (Actual[A])[3]	246	285	0.863	223	254	0.878	-0.015	-0.062
Month 24 CCS (Actual[B])	207	243	0.852	219	250	0.876	-0.024	-0.075
Month 24 CCS (Actual[A])	171	202	0.847	187	209	0.895	-0.048	-0.103

1 The modified composite clinical success (CCS) criterion requires no revision of device and no device-related adverse event prior to the exact Month 24 anniversary (i.e., relative day 730), a Harris Hip Total score ≥80 at Month 24 or later, and radiographic composite success at Month 24 or later.

2 Month 24+ outcomes are based on rollback imputations for missing Month 24 Harris Hip Scores. If the Month 24 Harris Hip Score is missing, the next available value is used (e.g., Month 36) is used to impute the missing value.

3 Actual^A intervals: Analyses using Actual^A intervals only include evaluations as follows: Pre-Op ≤ 0 days post surgery; Immed. interval 1-45 days; 6 Mo. Interval (6 ±1 mo.); 1 Yr Interval (12 ±2 mo.); 2 Yr Interval (24 ±2 mo.). Actual^A Month 24+ outcomes use the rollback imputation for Harris Hip Total scores and Radiographic Success. Actual^B analyses include all evaluated assessments for that interval.

4 Lower bounds of 1-sided 95% confidence intervals for differences between proportions with composite clinical successes (Investigational minus Control). The study w as designed to demonstrate clinical non-inferiority defined as a success rate no more than 0.08 smaller than control. The null hypothesis

that the Investigational device is inferior to the Control device is rejected if the lower bound of the confidence interval is larger than -0.08.

Results:
Data based on the approved protocol HHS criteria and modified HHS success criteria demonstrate non-inferiority of the Cormet 2000 HRS to the ABC Ceramic-on-Ceramic control using either the evaluation at Month 24 or at Month 24+ with expanded windows for patient follow-up.

The primary efficacy objective of this study was to demonstrate clinical non-inferiority with regard to the likelihood of clinical success at Month 24 relative to the control. In order to provide as complete a summary description as possible for Month 24 CCS, Month 24+ CCS, "Actual "B" Pivotal Study Unilateral Patients" was defined by the applicant to be the primary comparison vehicle. Analyses were performed to demonstrate that the rollback imputation as well as the out of window procedures had no effect on the overall results. The applicant contends that post hip replacement surgery, maximum clinical improvement is achieved sometime between one and two years post-surgery and that the clinical trajectory immediately following the two-year anniversary is stable or negative.

d. Sensitivity Analyses

A patient success criterion is defined as the achievement of four distinct success criteria at 24 months postoperatively: HHS ≥ 80, absence of revision, absence of device related AE, and radiographic success. The non-inferiority margin of 8% was met for almost all comparisons as mentioned earlier. Rollback imputation was used for patients who were out of window for the 24 Month evaluation, but had a later visit (i.e., 24+ Months). In order to evaluate the impact of the missing data, the applicant used several other methods of imputation to perform sensitivity analyses: (1) including all missing patients as failures, (2) including all missing patients as successes, (3) stepwise imputation, and (4) multiple imputations.

Including all missing patients as failures resulted in the 8% delta not being met due to the larger number missing CCS among the Cormet 2000 HRS as compared to the control (44 vs. 10, respectively). All patients being failures is an unlikely scenario as many of those missing CCS still had partial data indicating they would have been a success. Including all missing patients as successes did preserve the 8% delta; however, this is an unlikely scenario as well. Stepwise imputation starts with a "worst-case" scenario where all Cormet missing patients are assumed failures and all control missing patients are assumed successes. Then in a stepwise fashion, one Cormet failure is changed to a success and one control success is changed to a failure until the non-inferiority hypothesis is met. This type of imputation was performed only on the 24+ month (out of window) cohort because it met the FDA recommendation of greater than 85% follow-up. This required 15 patients to be crossed over in each treatment group under the original CCS and using the modified CCS criteria it required 23 Cormet patients to be changed to success and all 10 controls to failures (there were only 10 missing controls under the modified criteria). The original CCS criteria required only an improvement of ≥ 20 points in the HHS and the modified CCS required the post-operative HHS be ≥ 80.

In Multiple Imputation, the missing values are imputed via a logistic regression which uses device-specific means to replace missing values and adjusts for certain baseline

covariates. The predicted values are then used to impute the missing data and this process is repeated for several iterations until there is little change. With this method, the 8% delta was met for all 5 imputations. A statistical test on the variability of the imputations was insignificant, indicating that the patients with missing data would not be expected to have significantly different outcomes, given their baseline characteristics.

e. Effectiveness:

The data analyses based on the approved protocol HHS criteria and modified HHS success criteria demonstrate non-inferiority of the Cormet 2000 HRS to the ABC Ceramic-on-Ceramic control regardless of evaluation at Month 24 or at Month 24+ with expanded windows for patient follow-up. However, since the endpoints and control group were selected after data collection and analyses were initially performed, the potential for a significant amount of bias in the data analysis remains.

PANEL QUESTION: Please be advised that you will be asked to comment on the ability to adequately interpret the effectiveness data taking into consideration that the endpoints and control group were selected after data collection.

3. Safety Evaluation

The safety of the investigational device (Cormet 2000 HRS) was evaluated on the basis of adverse events which were defined as any untoward medical occurrence during the course of the investigation including any unintended sign, symptom, or disease related to the device use.

a. Deaths

i. Investigational Cohort

One death (0.29%) was reported by Month 24 for patients in the Investigational Pivotal Study Unilateral group. There were an additional three deaths reported for patients in the Investigational Pivotal Study Unilateral group by Month 36. The following is a description of the deaths of these study subjects.

- One patient death occurred 499 days following surgery due to complications of lung cancer.
- One patient death occurred 824 days following surgery due to cardiac disease.
- One patient death occurred 764 days following surgery due to lung cancer with metastases to the brain. Prior to this time, the site reported the subject's lung cancer as being in remission.
- One patient death occurred 883 days following surgery due to cardiac arrest following a two and a half mile hike. The site reported the subject as having no history of prior cardiac disease, with the exception of hypertension and hyperlipidemia for which he began receiving treatment three years prior to his death.

ii. Control

There were two deaths (0.8%) during a comparable time frame in the control group. One patient died of a carcinoma approximately 18 months postoperatively and the second patient died 11 months postoperatively due to myocardial infraction.

None of the deaths in either the investigational or control cohorts appear to be associated with the device.

b. Systemic Complications

Systemic adverse events are defined to include all events not directly related to the operation of the operative site and device. They are listed in Table 25.

Table 25: Complication Comparisons with Controls - Specific Complications – All Enrolled Investigational and Control Devices

	Investigational			Control			Exact
	n[1]	N[2]	%	n[1]	N[2]	%	p-value[3]
Systemic							
Arrhythmia (operative)	1	1148	0.1%	0	349	0.0%	1.000
Bronchopulmonary	2	1148	0.2%	12	349	3.4%	<0.001
Carcinoma	4	1148	0.3%	18	349	5.2%	<0.001
Cardiovascular	14	1148	1.2%	33	349	9.5%	<0.001
Death - unrelated to device	6	1148	0.5%	5	349	1.4%	0.142
DVT	9	1148	0.8%	0	349	0.0%	0.128
Gastrointestinal	8	1148	0.7%	19	349	5.4%	<0.001
Genitourinary	8	1148	0.7%	20	349	5.7%	<0.001
Infection remote location	10	1148	0.9%	4	349	1.1%	0.750
Lack of nutrition	1	1148	0.1%	0	349	0.0%	1.000
Low hemoglobin/hematocrit	3	1148	0.3%	0	349	0.0%	1.000
Neuropathy	1	1148	0.1%	0	349	0.0%	1.000
Neurosensory	8	1148	0.7%	32	349	9.2%	<0.001
Nosebleed	1	1148	0.1%	0	349	0.0%	1.000
PE	4	1148	0.3%	1	349	0.3%	1.000
Rash	8	1148	0.7%	10	349	2.9%	0.003
Thrombophlebitis	0	1148	0.0%	3	349	0.9%	0.013
Trauma (non-hip related)	10	1148	0.9%	30	349	8.6%	<0.001
Varicose veins	1	1148	0.1%	0	349	0.0%	1.000
Other	218	1148	19.0%	102	349	29.2%	<0.001

Results:

The systemic complications presented are related to major surgical procedures and do not necessarily indicate any particular association or predilection for the investigational or control surgical procedures. Although numerical differences are noted in certain categories between the investigational and the control population, one would have difficulty implicating any of the listed systemic complications with either surgical procedure.

Percentages of complications are provided with the denominator (N) composed of the entire investigational or control surgical population. However, not all surgical procedures have adequate follow-up data and thus an assumption is made that the procedures (patients) without follow-up did not have any complications. The percentages of complications are the best case scenario and may not represent the true rate of complications.

c. Hip Related Complications

Hip-related complications by time of occurrence are provided in Table 26.

Table 26: Specific Complications by Time of Occurrence – All Enrolled Procedures

	Intra-operative		Post Surgery to Week 6		Week 6 to Month 6		Month 6 to Month 12		Month 12 to Month 24		Post Month 24		Total	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Hip Related Events														
Acetabular Crack (operative)	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Acetabular malpositioned (operative)	0	0	0	0	1	0	0	0	3	0	0	0	4	0
Broken drill bit (operative)	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Bursitis	0	0	0	0	14	5	10	4	5	4	4	3	33	16
Deep infection	0	0	0	0	0	0	0	1	2	0	1	0	3	1
Elevated metal ion level	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Femoral Crack (operative)	0	12	0	0	0	0	0	0	0	0	0	0	0	12
Femoral neck notched (operative)	6	0	0	0	0	0	0	0	0	0	0	0	6	0
Femoral radiolucency	0	0	0	0	0	0	1	0	6	0	5	0	12	0
Greater Trochanter Notching (operative)	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Hematoma	1	0	3	3	2	0	1	0	1	0	0	0	8	3
Heterotopic Bone Formation	0	0	2	6	4	5	0	0	7	1	0	1	13	13
Hip Pain (operative side)	0	1	15	2	17	3	10	1	12	1	7	1	61	9
Leg Length discrepancy	1	0	7	0	8	0	1	0	3	0	2	0	22	0
Limp	0	0	7	0	5	0	1	0	0	0	0	0	13	0
Loose Body	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Muscle Weakness	2	0	2	0	5	1	0	0	1	0	0	0	10	1
Myositis ossificans	0	0	1	0	3	0	1	0	1	0	0	0	6	0
Nerve palsy	1	2	1	3	2	0	0	0	0	0	0	0	4	5
Skin split	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Soft Tissue Trauma	0	0	1	0	0	2	0	2	0	6	1	4	2	14
Squeaking implant/clicking	0	0	2	0	10	0	4	0	4	1	0	1	20	2
Subchondral cyst	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Subluxation	0	0	1	0	1	0	1	0	0	0	3	0	6	0
Superficial infection	0	0	4	5	2	0	1	0	0	0	0	0	7	5
Tendonitis	0	0	1	1	7	1	3	3	6	1	3	0	20	6
Trochanteric Crack (operative)	0	7	0	0	0	0	0	0	0	0	0	0	0	7
Wound Related (non-infected)	0	0	17	16	1	0	2	1	2	0	0	0	22	17
Other	0	4	0	1	2	0	2	1	1	1	0	1	5	8

Results:

Table 26 shows that some of the complications (i.e., femoral cracks/fractures) are intraoperative or in the near immediate post-operative period for both the investigational and control groups. Other complications (i.e., hip pain, bursitis, limp, etc.) were noted later in the post-operative course.

d. Implant Related Adverse Events

A time course comparison of various hip/device-related complications between the investigational and control populations is presented in Table 27.

Table 27: Specific Complications by Time of Occurrence - All Enrolled Procedures

	Intra-operative		Post Surgery to Week 6		Week 6 to Month 6		Month 6 to Month 12		Month 12 to Month 24		Post Month 24		Total	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Device Related Events														
Acetabular Fracture	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Acetabular loosening	0	0	3	0	3	0	0	0	3	0	2	0	11	0
Avulsed lesser trochanter	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Ceramic Insert Chip (operative)	0	8	0	0	0	0	0	0	0	0	0	0	0	8
Dislocation	0	0	1	8	0	2	0	0	1	0	0	0	2	10
Femoral Fracture (operative)	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Femoral Fracture (post-op)	0	0	0	4	0	2	0	0	0	0	0	1	0	7
Femoral loosening	0	0	0	0	0	0	1	0	7	0	6	0	14	0
Femoral neck fx	0	0	3	0	12	0	5	0	5	0	1	0	26	0
Femoral subsidence	0	0	0	0	1	0	1	1	1	1	1	0	4	2
Trochanter (greater) fx	0	0	0	0	0	0	0	0	0	0	1	0	1	0

Results:
The investigational group had a higher rate of acetabular and femoral loosening and femoral neck fractures while the control group had a higher rate of dislocations and femoral fractures.

Comparing hip-related adverse events between surgical procedures (investigational group vs. controls), which differ in several significant parameters, including materials and design, presents a challenge. For example, one would not expect ceramic insert chips with a metal-on-metal prosthesis. As noted previously, the denominator (N) used in calculations is composed of all surgical procedures (1,148 for the investigational group and 349 for the control group) although some of the procedures do not have complete follow-up. Another statistical and clinical difference in adverse event rates is that there were 26 femoral neck fractures in the investigational group (2.3%) and zero (0.0%) in the control group. Femoral neck fractures would also not be expected in the control group and may be seen as a potential risk of the investigational procedure. The rate of femoral neck fracture is reflected in the number of revisions in the study.

PANEL QUESTION: Please be advised that you will be asked to comment on the risk/benefit ratio for the proposed Cormet 2000 HRS.

e. Revisions:
Revisions are defined as adverse events necessitating removal or replacement of original surgical device. Revisions are considered to be the most severe adverse events as they indicate a total failure of the surgical procedure or device. Table 28 provides the number of revisions in the Pivotal Unilateral group and for All Enrolled patients who received the investigational device.

Table 28: Risk of Revision in Pivotal Unilateral Cohort and All Enrolled Procedures – All Procedures and Procedures with At Least 24 Month Follow-Up

		Pivotal Unilateral	Pivotal Unilateral 24+ Month Follow-up	All Enrolled	All Enrolled 24+ Month Follow-up
	Revisions	**24**	**24**	**44**	**44**
	N	**337**	**302**	**1148**	**532**
	%	**7.1%**	**7.9%**	**3.8%**	**8.3%**
Gender	Female	11.9% (13/109)	12.8% (13/102)	6.5% (21/323)	12.4% (21/170)
	Male	4.8% (11/228)	5.5% (11/200)	2.8% (23/825)	6.4% (23/362)
Small Component Size	40/44mm	16.7% (13/78)	17.3% (13/75)	7.4% (22/296)	15.2% (22/145)
	>40/44mm	4.3%(11/259)	4.9% (11/227)	2.6% (22/843)	5.7% (22/387)
Non Osteoarthritis Diagnosis	AVN/RA	14.6% (7/48)	16.7% (7/42)	7.2% (9/125)	12.9% (9/70)
	Osteoarthritis	5.9% (17/289)	6.5% (17/260)	3.4% (35/1023)	7.6% (35/462)
Leg length discrepancy greater than or equal to 1 cm	≥ 1 cm	13.0% (12/92)	14.5% (12/83)	6.1% (18/296)	14.0% (18/129)
	< 1 cm	4.9% (12/245)	5.5% (12/219)	3.1% (26/849)	6.5% (26/403)
Baseline lowest quartile of function (HHS)	< 42.58	17.7% (15/85)	20.3% (15/74)	6.4% (18/283)	13.1% (18/137)
	≥ 42.58	3.6% (9/252)	4.0% (9/228)	3.1% (26/846)	6.7% (26/391)
Among 1st 25 procedures within a specific site	First 25	8.2% (12/147)	8.9% (12/135)	6.8% (16/234)	8.3% (16/192)
	After 1st 25	6.3% (12/190)	7.2% (12/167)	3.1% (28/914)	8.2% (28/340)

Results:
Twenty-four (24) revisions were noted in the Pivotal Unilateral group and 44 revisions were observed in the entire investigational group. In the Pivotal Unilateral group, the reasons for revisions were acetabular loosening (four patients), dislocation (one patient), femoral loosening (eleven patients), and femoral neck fractures (eight patients). Within the Continued Access group, an additional 16 patients had revisions, which included eleven (11) femoral neck fractures, four (4) acetabular loosenings, and one (1) deep joint infection. Four (4) revisions were also noted in the Pivotal Bilateral study group [one (1) deep infection, two (2) femoral neck fractures, and one (1) femoral component subsidence] making a total of 44 revisions for all surgical procedures. If one is to consider as the denominator the entire pivotal group of 337 procedures, the revision rate would be 7.1%. However, apparently only 302 of the pivotal group procedures had 24+ month follow-up available, making the revision rate for the Pivotal Unilateral group actually 7.9% (24/302).

Considering all enrolled procedures, the revision rate is 8.3% (44/532) if only the procedures with 24+ month follow are taken into consideration. A subgroup analysis showed that within this patient cohort, males had a lower revision rate than females (6.5% vs. 12.9%). Further, patients in whom a smaller component was implanted,

patients with diagnosis other than OA, patients with significant leg length discrepancy and baseline HHS in the lowest quartile of function all had revision rates greater than the overall average of 7.9% for the Pivotal Unilateral group or 8.3% for the All Enrolled group with a 24+ month follow-up.

Five patients (1.9%, 5/266) were reported to have revision of one or more components of the ABC Ceramic-on-Ceramic System in the All Enrolled control group.

As a post-hoc analysis, the applicant considered the initial 25 procedures at each center to evaluate whether a learning curve could explain the number of revisions noted in the study. However, evaluation of procedures with adequate follow-up data did not reveal revision rates to be significantly affected by a learning curve. The applicant has noted that one surgical center (Site 5) had a greater revision rate than other surgical sites. Table 29 compares the types of patients who had surgery at Site 5. Site 5 had a higher percentage of patients who required a small component size, had a greater leg discrepancy, and the lowest function HHS scores. Site 5 also had a lower percentage of surgical patients with diagnosis other than osteoarthritis.

Table 29: Prevalence of Risk Factors for Pivotal Unilateral and All Enrolled Procedures with and without Excluding Site 5

		Pivotal Unilateral	Pivotal Unilateral Excluding Site 5	Pivotal Unilateral Site 5	All Enrolled	All Enrolled Excluding Site 5	All Enrolled Site 5
Small Component Size	%	23.1%	22.7%	26.3%	26.0%	24.0%	35.6%
	n	78	68	10	296	227	69
	N	337	299	38	1139	945	194
Non Osteoarthritis Diagnosis	%	14.2%	15.7%	2.6%	10.9%	12.2%	4.6%
	n	48	47	1	125	116	9
	N	337	299	38	1148	954	194
Leg length discrepancy greater than or equal to 1 cm	%	27.3%	19.7%	86.8%	25.9%	13.8%	85.1%
	n	92	59	33	296	131	165
	N	337	299	38	1145	951	194
Baseline lowest quartile of function (HHS)	%	25.2%	21.4%	55.3%	25.1%	24.8%	26.3%
	n	85	64	21	283	233	50
	N	337	299	38	1129	939	190
Among 1st 25 procedures within a specific site	%	43.6%	41.8%	57.9%	20.4%	21.9%	12.9%
	n	147	125	22	234	209	25
	N	337	299	38	1148	954	194

Kaplan-Meier Analysis:
Time-to-failure analysis was performed using Kaplan-Meier survival curves on the All Enrolled Cohort (n=1148; however the denominator at 24 months was based on n=498). A patient remains in the survival curve until they either experience the event in question (e.g., a revision) or become "censored". If they become lost to follow-up, or die, they are considered censored, and exit the "pool at risk" (denominator). A Kaplan-Meier survival

analysis was performed comparing the Cormet 2000 HRS to the ABC control, for any mode of failure including femoral fracture. At 24 months, the applicant determined implant survival was 95.8% for Cormet versus 99.1% for control. This was statistically significant in favor of the control ($p<0.01$). A survival curve on the 337 subjects in the Pivotal Study unilateral cohort showed that the survival at 24 months was 95%, virtually identically to that of the All-Enrolled Cohort. Because the number of patients at risk diminishes over time, Peto's method was appropriately used to determine standard errors for estimates of survival at the key timepoints (months 6, 12, and 24).

Cox Regression:
The applicant used Cox Proportional hazards regression to determine what covariates were related to revision. Cox regression is a type of survival analysis that can measure the effect of covariates on the variable of interest (i.e., failure). The significant covariates were gender, component size, and pre-operative HHS. However, the effect of gender on revision was actually due to fact that females received smaller component sizes, and it is component size that has more effect. Diagnostic indication was not found to be related to revision.

Cox regression was also used to evaluate the learning curve and the high revision rate at Site 5 (10/38 patients were revised at Site 5 including 7 of the first 25 patients). There were 24 revisions total in the Pivotal Unilateral study cohort. Cox regression indicated that a patient among the first 25 procedures at Site 5 had twice the risk of being revised compared to a patient not among the first 25 (hazard ratio= 2.0). For all investigative sites except Site 5, the learning curve (defined as the first 25 procedures), was not a significant predictor of revision, and disappeared if Site 5 was excluded from the analysis. When baseline HHS was added to the model, the effect of the learning curve at Site 5 diminished but did not disappear. An analysis of baseline risk factors showed that the high prevalence of leg length discrepancies ≥ 1 cm and low baseline HHS at Site 5 suggests that different patient selection criteria may have been used at Site 5.

The data from Site 5 contributes to the apparent heterogeneity of patients across sites.

Literature Review:
The applicant has provided a compilation of literature dealing with hip resurfacing devices in Table 30. Most of these publications show revision rates < 3%, but in some cases the published revision rates are as high as 6.3% to 7%. The literature does not specifically address the rates in males vs. females or in patients requiring smaller devices or having greater leg discrepancy and lower function HHS scores.

The reported rates of femoral neck fractures in the literature range from 1.3% to 3% using as the denominator the number of procedures performed without knowledge on how many of those procedures actually had adequate follow-up at 24+ months. The literature also indicates that a high percentage of hip revisions are associated with femoral neck fractures.

In addition, please note the Birmingham Hip Resurfacing System is the only metal–on-metal resurfacing system approved for sale in the U.S.

Table 30: Literature Summary of Contemporary Metal-on-metal Total Hip Resurfacing Revision Rates

Citation	Number of Subjects	Revision Rate	Femoral Neck Fracture	Comments
Australian Orthopaedic Association National Joint Replacement Registry. Annual Report. Adelaide: AOA; 2005.	5379 (BHR, Conserve, Conserve Plus, ASR, Cormet 2000, Durom, Icon, Recap)	118/5379=2.2% Male: 63/3792=1.7% Female 55/1587=3.55	70/118=59.3%	Significant factors: Female gender; male > 65 years Rate is significantly affected by gender, age, diagnosis
Australian Orthopaedic Association National Joint Replacement Registry. Annual Report. Adelaide: AOA; 2006.	7,205 ((BHR, Conserve, Conserve Plus, ASR, Cormet 2000, Durom, Icon, Recap)	177/7205=2.5% Male: 86/4846=1.8% Female 62/1866=3.3%	Not evaluated	Resurfacing more frequently undertaken in younger males (72.8% in 2005 vs 70.5% reported in 2004) and 90.4% < 65 years.
Shimmin AJ, Back D. Femoral neck fracture following Birmingham hip resurfacing. *JBJS [Br]* 2005; 87-B 463-4.	3429 (BHR)	Did not report	50/3429=1.46%	Patient factors included gender and proximal femoral bone quality Did not report revisions for other reasons
Little CP, Ruiz AL, Harding IJ, et al. Osteonecrosis in retrieved femoral heads after failed resurfacing arthroplasty of the hip. *JBJS[Br]* 2005 ; 87-B : 320-3.	377 (358 BHR, 19 Cormet 2000)	15/377=4.0% [Total including 2 acetabular revisions =17/377=4.5%] Mean time to failure: nine weeks for femoral neck fracture; 1.5 years for other causes.	8/15=53.3%	Reasons for revision: 8 fem neck fx; 5 femoral loosening, 1 for inflammation, 1 persistent pain 2 acetabular revisions not included in series
Pollard TCB, Baker RP, Eastaugh-Waring SJ et al. *JBJS[Br]* May 2006.	54 BHR (of 63) vs 54 hybrid THA Single surgeon [includes learning curve for BHR]	4/63=6.3%	3 / 4=75%	BHR: 6% revised and additional 8% femoral migration THR: 8% intent to revise secondary to osteolysis
Mont M. Ragland P, Bezwada H, et al. The results of metal-on-metal resurfacing hip arthroplasty: learning curve stratification of results. AAOS, Washington DC Feb 27, 2005.	200 Conserve Plus IDE– single new surgeon	14/200=7%	12/14=86% 12/200=6.0% (11 of first 50; 1 of next 150)	Demonstrates effect of learning curve for individual IDE surgeon.
Amstutz HC, Beaule PE, Dorey FJ, et al. Metal-on-metal hybrid surface arthroplasty: two to six-year follow-up study. *JBJS[Am]* 2004; 86-A (1): 28-39.	400 Conserve Plus IDE study; single surgeon Mean 3.5 yr follow-up	12/400=3.0% 7 loose fem 3 fem neck fx 1 recurrent subluxations 1 late DJI	3/12=25%	Overall survivorship =94.4% at 4 years Femoral component fixation score > 7 -Females -Smaller component (males)

Siebel T Maubach S, Morlock MM. Lessons learned from early clinical experience and results of 300 ASR hip resurfacing implants. Proc ImechE Vol 220 J eng in Medicine.	300 ASR 2 surgeons mean 202 days follow-up	8/300 revised (2.7%) (5 neck fracture, 3 cup revision)	5/8=62.5%	A learning curve was evident from the reduction in revision from 5 in the first 100 to 2 in the next 100 to 1 in the last 100. Optimal indications: large head-to-neck diameter ratio (> 1.2) Implies large head with relatively narrow neck
Cormet 2000 IDE Study	1148 multicenter All Enrolled	At 24+ Month Follow-up 44/532 (8.3%) All Enrolled 44/1148 (3.8%)	20/44=45%	Multicenter US IDE Risk factors for revision: female gender, small component size, low preoperative HHS Risk factors for revision: female gender, small component size, diagnosis of AVN or RA

PANEL QUESTION: Please be advised that you will be asked to discuss questions related to the impact and interpretation of safety and effectiveness data provided for this PMA because the endpoints and control group were selected after data collection, including specific questions related to revision rates and potential risk to the patient.

E. Discussion

Overall Statistical Issues

The validity of drawing inferences from statistical hypothesis testing is all based on the integrity of the study design, conduct and analysis. The changes that were made to the protocol, the selection of a control group knowing the results in the investigational group, the multiple analyses performed, the issue of a learning curve and heterogeneous patient selection criteria at one of the sites, all are limitations of this study. In addition, there is the revision rate, which was not addressed by the learning curve analyses. The procedure follow-up makes establishment of actual complication rates, including the femoral neck fracture rate and the revision rate, difficult to evaluate.

VI. Summary and Panel Questions

In conclusion, the applicant has provided a PMA which includes clinical data which the applicant believes supports the safety and effectiveness of the Cormet 2000 Hip Resurfacing System (HRS). Although the data analyses provided suggests the non-inferiority of the Cormet 2000 HRS in comparison to the Osteonics ABC Ceramic-on-Ceramic System, due to the changes in study design and proposed controls, the Agency will be asking questions regarding the impact of potential biases that may have been introduced into the data analysis and presentation of outcomes. It should also be noted that this analysis does consider the higher revision rate exhibited by patients in both the pivotal study group, as well as the 'All Enrolled' cohort with 24+ month follow-up data. Due to the revision rate, the applicant considered the significant risk factors that may affect revision rates. The applicant identified female patients, with smaller component sizes, with non-osteoarthritis diagnoses and leg length discrepancies greater than 1cm to be at the highest risk for revision, which may already be consistent with current experience and thinking about total hip arthroplasty. All of the issues outlined in this Executive Summary have generated the following questions for the Panel members:

Panel Questions:

1. The applicant planned to conduct a prospective, non-randomized, concurrently controlled clinical study to evaluate the Cormet 2000 Hip Resurfacing System. The control subjects were to receive a cleared metal-on-metal or metal-on-polyethylene total hip replacement; however, no subjects were ever actually enrolled in the control arm of the study. In the original PMA submission, the applicant proposed and used metal-on-metal hip data as a historical control. In Amendments 8 and 13 of the PMA, the sponsor reanalyzed their clinical data using another device, Osteonics ABC Ceramic-on-Ceramic System (Alumina Bearing Couple, approved in PMA P000013 on February 3, 2003), as the historical control.

   Please discuss the appropriateness of changing the controls during the study progression as well as after the original data analyses were performed and how this impacts the ability to interpret the data. Please also comment on the relevance of using the Osteonics ABC System as an appropriate control for a clinical study using the Cormet 2000 Hip Resurfacing System as the investigational arm.

2. Various radiographic measurement techniques and criteria have been used to evaluate the success/failure of resurfacing hip devices. The original IDE approved protocol included the following radiographic success criteria:

   a. Acetabular component
      - Migration <5mm vertical or horizontal
      - Migration <5°in varus/valgus
      - No new or progressive radiolucencies >1mm in **any** zones

   b. Femoral component
      - Subsidence <5mm
      - Tilting <1° in varus/valgus
      - No new or progressive radiolucencies >2mm in **any** zones

In Amendments 8 and 13 of the PMA submission, the sponsor provided a new radiographic technique and then analyzed the radiographs according to the following revised endpoints:

a. Acetabular component
   - Migration <5mm vertical or horizontal
   - Migration <5^{o} in varus/valgus
   - No new complete radiolucencies >1mm in **all three** zones

b. Femoral component
   - Subsidence < 5mm **and** tilting < 1° in varus/valgus
   - No new complete radiolucencies >2mm in **all three** zones

Based on this information:

a. Please discuss the appropriateness of changing the study radiographic measurement techniques and success/failure criteria after the study completion.

b. Please comment on whether the final proposed endpoints are accurate to predict the success/failure of this resurfacing hip system.

3. The applicant provided additional analyses of the learning curve and explored risk factors that may help investigate the revision rates observed for the Cormet 2000 Hip Resurfacing System. For subjects in the Pivotal Unilateral Cohort with 24+ month follow-up data, there was a 7.9% (24/302) revision rate and for the All Enrolled Cohort with 24+ month follow-up there was an 8.3% (44/532) revision rate.

   a. Please discuss the significance of these revision rates and any safety concerns they raise. As part of this discussion, please also consider the observation that femoral neck fractures were present in 2.3% of the Cormet 2000 Hip Resurfacing System.

   b. The applicant's analysis of patient selection criteria demonstrates the device revision rate is higher than average for females, patients requiring use of smaller device components, patients with diagnoses other than osteoarthritis, patients with low function HHS scores and patients with leg length discrepancies $\geq$ 1 cm. Please comment on the significance of these risk factors, given the applicant's proposed indications for use:

      "The Cormet 2000 Hip Resurfacing System is intended for use in resurfacing hip arthroplasty for reduction or relief of pain and/or improved hip function in skeletally mature patients having the following conditions:

      1. Non-inflammatory degenerative arthritis such as osteoarthritis, and avascular necrosis (AVN);
      2. Inflammatory arthritis such as rheumatoid arthritis.

      Hip resurfacing arthroplasty is intended as a primary joint replacement for patients who are at risk of requiring more than one hip joint replacement over their lifetime. While it is not possible to predict if a patient will require a

future hip joint revision, several factors such as gender, age, weight, and activity level may increase the risk of the need for revision."

4. Under CFR 860.7(e)(1) effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. Considering the study design and endpoints discussed today, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is effective.

5. Under CFR 860.7(d)(1) , safety is defined as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of the intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks. Considering the revision rates and femoral neck fractures for the subject device, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is safe.