ORTHOPEDIC AND REHABILITATION DEVICES PANEL

Gaithersburg, Maryland

February 22, 2007

PMA P050016 Cormet 2000 Hip Resurfacing System

EXECUTIVE SUMMARY

Device Description

The Cormet 2000 Hip Resurfacing System is a metal-on-metal hip resurfacing system, and consists of two components - a resurfacing head and a monobloc acetabular component. The femoral head articulates in a multi-directional fashion within the acetabular component. Both femoral and acetabular components are manufactured from cast cobalt-chromium-molybdenum (Co-Cr-Mo) alloy complying with the requirements of ASTM F75 and ISO 5832-4. The castings undergo a double heat treatment comprising of hot isostatic pressing followed by solution annealing to reduce microporosity and promote homogeneity of the material. The heads, which are intended for cemented use, have a central stem polished distally to avoid distal fixation, and three internal splines to provide anti-rotational stability. The acetabular component, which is intended for use without bone cement, has the external surface finished with a bi-coating consisting of hydroxylapatite over plasma sprayed unalloyed titanium to facilitate bone on-growth onto the component and has two sets of external splines to provide anti-rotational stability.

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Executive Summary of the Clinical Results

This executive summary provides a review of the information submitted by Corin USA for its PMA P050016 for the Cormet 2000 Hip Resurfacing System.

The Cormet 2000 Hip Resurfacing PMA is the first hip resurfacing device to be reviewed by the FDA Advisory Panel that is supported by safety and effectiveness clinical data from a prospective controlled multi-center, U.S. based Investigational Device Exemption [redacted] clinical

trial. The purpose of this PMA is to demonstrate the safety and effectiveness of the Cormet 2000 Hip Resurfacing System.

The clinical trial compares the Cormet 2000 to the Osteonics ABC (Alumina Bearing Couple) ceramic-on-ceramic total hip arthroplasty system approved via PMA P000013 on February 3, 2003. Both groups have a hard-on-hard bearing surface without the issues associated with polyethylene debris. In addition, excellent results have been reported for the control device both in the PMA[i] and in the literature[ii,iii], making the control a formidable total hip arthroplasty challenge for the Cormet 2000 Hip Resurfacing System.

The primary efficacy objective of this study was to demonstrate non-inferiority of the Cormet 2000 implant system with regard to the likelihood of clinical success at Month 24+ relative to the control group. The patient success is based upon the composite clinical success as measured by Harris Hip Scores, occurrence of adverse events, radiographic failure, and revisions or pending revisions. The non-inferiority delta was specified to be equal to 0.08. Thus, the study was designed to reject the null hypothesis that the proportion of patients achieving composite clinical success with the Cormet 2000 resurfacing investigational device is at least 0.08 less than the proportion of patients achieving composite clinical success with the ABC ceramic-on-ceramic total hip replacement control device. Safety was determined by the incidence of peri-operative and postoperative complications.

A total of 337 patients were implanted with the Cormet 2000 Hip Resurfacing System in the Pivotal Study Unilateral group of patients at 12 investigational sites compared to the ceramic-on-ceramic control group (the Osteonics ABC System I and Osteonics ABC System II combined) with a total of 266 unilateral patients at 13 investigational sites. Overall, the Cormet 2000 Study includes a total of 1,148 procedures in the all enrolled group performed at latest analysis.

The statistical analysis demonstrated non-inferiority of the Cormet 2000 Hip Resurfacing system compared to the ceramic-on-ceramic total hip system based upon the composite clinical success criteria. Analysis also examined the comparison of each component of the criteria between the Cormet investigational group and the ceramic control group. Detailed analysis of study failures was completed to fully understand the effect of site variability and patient selection criteria on successful outcomes.

Analysis of the Cormet 2000 study data identified the importance of certain risk factors for revision. Small component size (highly correlated with sex/gender), a diagnosis other than osteoarthritis, a preoperative leg length discrepancy of greater than or equal to 1cm, and a low baseline Harris Hip Score (lower quartile defined as <43 points) emerged as significant risk factors for revisions among pivotal study procedures.

Further analysis quantified the additive effect on revision risk for a patient having multiple significant risk factors. The more risk factors a patient has, the greater the risk of procedure failure requiring a revision to the hip. For both the pivotal unilateral study group and the all enrolled study group including all sites, the number of preoperative risk factors is significantly related to risk of revision (test for linear association among percentages $p < 0.0001$). In the pivotal unilateral group including all sites, one of 120 patients (0.8%) with no preoperative risk factors was revised, 5 of 106 patients (4.7%) with 1 preoperative risk factor were revised, 12 of 60 patients (20.0%) with 2 preoperative risk factors were revised, and 6 of 16 patients (37.5%) with 3 preoperative risk factors were revised. The identified risk factors for revision and the cumulative effect of multiple risk factors is consistent with findings reported in the literature.

In summary, the Cormet 2000 Hip Resurfacing PMA presents prospective data on over 1,000 procedures performed at numerous investigational sites. The results of the Cormet 2000 PMA more accurately reflect the US surgeon experience with a new medical device than a single surgeon series since it incorporates the expected variability resulting from multiple centers, surgeon experience and patient populations. The analysis identifies specific patient risk factors, which are comparable to the literature, and demonstrates that the success of total hip resurfacing

is dependent upon surgeon training and proper patient selection. In addition, the analysis estimates the relative additive effect of risk factors on the potential for procedure failure. For patients with no preoperative risk factors, the risk of failure is low and the potential for success is high. For patients with multiple preoperative risk factors, the risk of failure is high and the potential for success is low. Most importantly, the Cormet 2000 Hip Resurfacing PMA demonstrates non-inferiority to the ceramic-on-ceramic control group based upon composite clinical success criteria that includes function, radiographs, adverse events and revisions.

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[i] Food and Drug Administration (FDA) Center for Device and Radiological Health (CDRH) Osteonics® ABC System; Trident™ System - P000013. Issued February 3, 2003. [web site] http://www.fda.gov/cdrh/pdf/p000013.html. (reference available upon request)

[ii] D'Antonio J, Capello W, Manley M, Naughton M, Sutton K. Alumina ceramic bearings for total hip arthroplasty: five-year results of a prospective randomized study. *Clinical Orthopaedics and Related Research*. 2005; 436:164-71.

[iii] D'Antonio J, Capello W, Manley M, Bierbaum B. New experience with alumina-on-alumina ceramic bearings for total hip arthroplasty. *Journal of Arthroplasty*. 2002;17: 390-7.

Clinical Summary

Table of Contents

1 DEVICE DESCRIPTION 8

1.1 General Overview 8
1.2 Femoral Component 8
1.3 Acetabular Component 8
1.4 Component Matching 8

2 INDICATIONS FOR USE / CONTRAINDICATIONS FOR USE 9

2.1 Indications for Use 9
2.2 Contraindications for Use 9

3 PRE-CLINICAL INFORMATION 11

3.1 General Overview 11
3.2 Sterilization Validation 11
3.3 Wear 11
3.4 Fatigue Strength Testing 12
3.5 Frictional Torque 12
3.6 Circulating Metal Ions 13
3.7 Surface Coating Validation 13
3.8 Range of Motion 14
3.9 Luxation Wear 14

4 STUDY DESIGN 15

4.1 Purpose of the Investigation 15
4.2 Evolution of the Study Design 15
4.2.1 Control Group 16
4.2.2 Composite Clinical Success 17
4.2.3 Radiographic Endpoints 18
4.3 Clinical Trial Design to Demonstrate Safety and Effectiveness 20
4.3.1 Control Group 20
4.3.2 Composite Clinical Success 21

5 CLINICAL STUDY RESULTS 23

5.1 Pivotal Study Unilateral Patients 23
5.1.1 Number of Subjects Enrolled 23
5.1.2 Patient Accounting 24
5.1.3 Protocol Deviations 29
5.1.4 Demographic Information 29
5.1.5 Surgical Details 31
5.1.6 Safety and Effectiveness Data 33
5.1.6.1 HHS 33
5.1.6.2 Radiographic Success 41

5.1.6.3 Absence of Revision or Pending Revision 43
5.1.6.4 Absence of Device Related Events 43
5.1.7 Secondary Endpoint 44
5.1.7.1 Short Musculoskeletal Function Assessment (SMFA) Dysfunction and Bother Scores 44
5.1.8 Safety 44
5.1.8.1 Adverse Events 44
5.1.8.2 Systemic Adverse Events 46
5.1.8.3 Hip Related Events 49
5.1.8.4 Device Related Events 53
5.1.8.5 Revisions / Removals Overview 55
5.1.8.6 Deaths 56
5.1.9 Potential Lost to Follow-up 56
5.1.10 Composite Clinical Success 57
5.1.10.1 Propensity Score Analysis of Patient Success 62
5.1.10.2 Imputations of Patient Success 63
5.1.10.3 Missing Data as Failures 63
5.1.10.4 Missing Data as Success 64
5.1.10.5 Stepwise Imputation 64
5.1.10.6 Multiple Imputation 64
5.2 Pivotal Study Bilateral Procedures 65
5.2.1 Number of Subjects Enrolled 65
5.2.2 Patient Accounting 67
5.2.3 Description of Deviations from Investigational Plan 70
5.2.4 Demographic Information 70
5.2.5 Surgical Details 72
5.2.6 Safety and Effectiveness Data 74
5.2.6.1 Harris Hip Score 74
5.2.6.2 Radiographic Success 76
5.2.6.3 Absence of Revision or Pending Revision 78
5.2.6.4 Absence of Device Related Events 78
5.2.7 Safety 78
5.2.7.1 Adverse Events 78
5.2.7.2 Systemic Adverse Events 80
5.2.7.3 Hip Related Events 82
5.2.7.4 Device Related Events 84
5.2.7.5 Revisions/Removals Overview 86
5.2.7.6 Deaths 86
5.2.8 Potential Lost to Follow-up 87
5.2.9 Composite Clinical Success 87
5.3 Continued Access 88
5.3.1 Number of Subjects Enrolled 88
5.3.2 Patient Accounting 89
5.3.3 Description of Deviations from Investigational Plan 91
5.3.4 Demographic Information 92
5.3.5 Surgical Details 93
5.3.6 Safety and Effectiveness Data 96

5.3.6.1 HHS 96
5.3.6.2 Radiographic Success 96
5.3.6.3 Absence of Revision or Pending Revision 96
5.3.6.4 Absence of Device Related Events 96
5.3.7 Safety 96
5.3.7.1 Adverse Events 96
5.3.7.2 Systemic Adverse Events 98
5.3.7.3 Hip Related Events 99
5.3.7.4 Device Related Events 101
5.3.7.5 Revisions / Removals Overview 103
5.3.7.6 Deaths 103
5.3.8 Potential Lost to Follow-up 103
5.3.9 Composite Clinical Success 104
5.4 All Enrolled 105
5.4.1 Safety 105
5.4.1.1 Adverse Events 105
5.4.1.2 Systemic Adverse Events 106
5.4.1.3 Hip Related Events 108
5.4.1.4 Device Related Events 112
5.4.1.5 Revisions / Removals Overview 113
5.4.1.6 Deaths 114

6 ADDITIONAL REVISION ANALYSIS 115

6.1 Overall device survival 115
6.2 Site Effect 119
6.3 Significant Patient Selection Criteria 119
6.4 Effect of Risk Factors 122
6.5 Multivariable Model 127
6.6 Additive Effect of Risk Factors 129
6.7 Summary for Revision Analysis 131

7 RISK/BENEFIT ANALYSIS 133

7.1 Risks 133
7.1.1 Femoral neck fracture 133
7.1.2 Femoral loosening 133
7.1.3 Increased circulating metal ions 134
7.2 Benefits 134
7.2.1 Reduced risk of dislocation 134
7.2.2 Higher function at 6 and 12 months post-operative 134
7.2.3 Advantages of hip resurfacing procedure in contrast to THA 135
7.3 Overall risk benefit profile 135

8 REFERENCES 137

TABLES

TABLE 1.4 FEMORAL COMPONENT/ACETABULAR COMPONENT COMPATIBILITY 8
TABLE 3.5 SUMMARY TABLE 'WORST-CASE' FRICTIONAL TORQUE STUDY (DECEMBER 2005)..... 13
TABLE 3.8 SUMMARY OF THE RANGE OF ANGULAR MOVEMENT OF EACH BEARING COUPLE IN THE CORMET 2000 HIP RESURFACING SYSTEM SIZE RANGE AND THE MINIMUM REQUIREMENTS AS SPECIFIED IN ISO 21535:2002 14
TABLE 4.2(1) COMPARISON OF STUDY DESIGN AND CLINICAL ENDPOINTS..... 16
TABLE 4.2(2) COMPARISON OF COMPOSITE CLINICAL SUCCESS ENDPOINTS..... 17
TABLE 4.2(3) COMPARISON OF RADIOGRAPHIC SUCCESS CRITERIA..... 18
TABLE 4.2(4) COMPARISON OF MEASUREMENT TECHNIQUES..... 19
TABLE 4.3(1) FOLLOW-UP INTERVAL COMPARISON 20
TABLE 4.3(2) INCLUSION/EXCLUSION COMPARISON 21
TABLE 5.1.1(1) PATIENT ENROLLMENT PIVOTAL STUDY UNILATERAL GROUP BY SITE – INVESTIGATIONAL 23
TABLE 5.1.1(2) PATIENT ENROLLMENT PIVOTAL STUDY UNILATERAL GROUP BY SITE – CONTROL..... 24
TABLE 5.1.2(1) PIVOTAL STUDY UNILATERAL PATIENT ACCOUNTABILITY - INVESTIGATIONAL GROUP 25
TABLE 5.1.2(2) DEFINITION OF TERMS FOR PATIENT ACCOUNTABILITY 25
TABLE 4.1 PROCEDURE ACCOUNTING AND FOLLOW-UP COMPLIANCE TABLE – PIVOTAL STUDY UNILATERAL PATIENTS AND UNILATERAL CONTROLS 27
TABLE 5.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS PIVOTAL STUDY UNILATERAL PATIENTS VS. UNILATERAL CONTROLS 30
TABLE 6.1 SURGICAL DETAILS PIVOTAL STUDY UNILATERAL PATIENTS VS. UNILATERAL CONTROLS 32
TABLE 7.1(1) PIVOTAL STUDY UNILATERAL PATIENTS AND UNILATERAL CONTROLS –MEAN HARRIS HIP TOTAL AND ROM SCORES 34
TABLE 7.1(2) PIVOTAL STUDY UNILATERAL PATIENTS VS. UNILATERAL CONTROLS –HARRIS HIP PAIN CATEGORY 35
TABLE 7.1(3) PIVOTAL STUDY UNILATERAL PATIENTS AND UNILATERAL CONTROLS HARRIS HIP FUNCTION SCORE CATEGORY 36
TABLE 7.1(4) PIVOTAL STUDY UNILATERAL PATIENTS AND UNILATERAL CONTROLS – HARRIS HIP TOTAL SCORE CATEGORY 37
TABLE 7.1(4)B PIVOTAL STUDY UNILATERAL PATIENTS AND UNILATERAL CONTROLS – HARRIS HIP TOTAL SCORE CATEGORY IN 10-POINT INCREMENTS 38
TABLE 7.1(5) PIVOTAL STUDY UNILATERAL PATIENTS AND UNILATERAL CONTROLS –HARRIS HIP TOTAL SCORE GREATER THAN OR EQUAL TO 80..... 39
TABLE 7.1(6) PIVOTAL STUDY UNILATERAL PATIENTS AND UNILATERAL CONTROLS INCREASE FROM BASELINE IN HARRIS HIP TOTAL SCORE GREATER THAN OR EQUAL TO 20..... 40
TABLE 8.1(B) RADIOGRAPHIC CLINICAL SUCCESS AMONG ORIGINAL PROTOCOL AND MODIFIED PROTOCOL COMBINED 42
TABLE 9.1(1) SUMMARY OF COMPLICATION COMPARISONS BETWEEN PIVOTAL STUDY UNILATERAL PATIENTS AND UNILATERAL CONTROLS - SUMMARY 45
TABLE 9.1(2) COMPLICATION COMPARISONS WITH CONTROLS – SYSTEMIC COMPLICATIONS 47
TABLE 9.1(3) COUNTS OF SYSTEMIC COMPLICATIONS BY TIME OF OCCURRENCE 48
TABLE 9.1(4) COMPLICATION COMPARISONS WITH CONTROLS – HIP RELATED COMPLICATIONS 50
TABLE 9.1(5) COUNTS OF HIP RELATED COMPLICATIONS BY TIME OF OCCURRENCE..... 52
TABLE 9.1(6) COMPLICATION COMPARISONS WITH CONTROLS – DEVICE RELATED EVENTS 53
(NUMBERED HERE AS IT APPEARED IN AMENDMENT 13) 53
TABLE 9.1(7) COUNTS OF DEVICE RELATED EVENTS BY TIME OF OCCURRENCE 54
TABLE 10.1 POTENTIAL LOST TO FOLLOW-UP - PIVOTAL STUDY UNILATERAL PATIENTS – (INVESTIGATIONAL VS. CONTROL)..... 57

TABLE 10.2. POTENTIAL LOST TO FOLLOW UP VS. TOTAL ENROLMENT – PIVOTAL STUDY UNILATERAL GROUP 57
TABLE 11.1 (1) MONTH 24 COMPOSITE CLINICAL SUCCESS (CCS) USING ORIGINAL HHS DEFINITION AND MODIFIED RADIOGRAPHIC ASSESSMENT 59
TABLE 11.1 (2) MONTH 24 COMPOSITE CLINICAL SUCCESS (CCS) USING MODIFIED HHS AND RADIOGRAPHIC DEFINITIONS 61
TABLE 11.1(3) ADJUSTED COVARIATE BETWEEN GROUP COMPARISONS 62
TABLE 11.1(4) 63
TABLE 11.1(4) MONTH 24 COMPOSITE CLINICAL SUCCESS (CCS) WITH PROPENSITY SCORE ADJUSTMENTS 63
TABLE 11.1(5) MULTIPLE IMPUTATION RESULTS FOR CCS RATES 65
TABLE 3.2(1) PATIENT ENROLLMENT PIVOTAL STUDY BILATERAL PROCEDURES BY SITE INVESTIGATIONAL GROUP 66
TABLE 3.2(2) PATIENT ENROLLMENT PIVOTAL STUDY BILATERAL PROCEDURES BY SITE CONTROL GROUP 67
TABLE 4.2 PROCEDURE ACCOUNTING AND FOLLOW-UP COMPLIANCE TABLE -PIVOTAL STUDY BILATERAL 68
TABLE 5.2 BASELINE AND DEMOGRAPHIC CHARACTERISTICS PIVOTAL STUDY BILATERAL PROCEDURES VS. BILATERAL CONTROLS 71
TABLE 6.2 SURGICAL DETAILS PIVOTAL STUDY BILATERAL PROCEDURES VS. BILATERAL CONTROL 73
TABLE 7.2(1) PIVOTAL STUDY UNILATERAL PATIENTS VS. PIVOTAL STUDY BILATERAL PROCEDURES – HARRIS HIP TOTAL SCORE > 80 POINTS 75
TABLE 7.2(2) PIVOTAL STUDY UNILATERAL PATIENTS VS. PIVOTAL STUDY BILATERAL PROCEDURES – HIP PAIN NO MORE THAN SLIGHT 76
TABLE 8.2 RADIOGRAPHIC CLINICAL SUCCESS AMONG ORIGINAL PROTOCOL AND MODIFIED PROTOCOL COMBINED PIVOTAL STUDY BILATERAL PROCEDURES 77
TABLE 9.2(1) SUMMARY OF COMPLICATION COMPARISONS BETWEEN PIVOTAL STUDY BILATERAL PATIENTS AND BILATERAL CONTROLS – SUMMARY 79
TABLE 9.2(2) COMPLICATION COMPARISONS WITH CONTROLS – SYSTEMIC COMPLICATIONS 81
TABLE 9.2(3) COUNTS OF SYSTEMIC COMPLICATIONS BY TIME OF OCCURRENCE 82
TABLE 9.2(4) COMPLICATION COMPARISONS WITH CONTROLS – HIP RELATED COMPLICATIONS (NUMBERED HERE AS IT APPEARED IN AMENDMENT 8) 83
TABLE 9.2(5) COUNTS OF HIP RELATED COMPLICATIONS BY TIME OF OCCURRENCE 84
TABLE 9.2(6) COMPLICATION COMPARISONS WITH CONTROLS – DEVICE RELATED COMPLICATIONS 85
TABLE 9.2(7) COUNTS OF DEVICE RELATED COMPLICATIONS BY TIME OF OCCURRENCE 86
TABLE 10.2 LOST TO FOLLOW-UP - PIVOTAL STUDY BILATERAL PROCEDURES (INVESTIGATIONAL VS. CONTROL) 87
TABLE 11.2(1) PIVOTAL STUDY UNILATERAL PATIENTS VS. PIVOTAL STUDY BILATERAL PROCEDURES – COMPOSITE CLINICAL SUCCESS (CCS) 88
TABLE 3.3(1) PATIENT ENROLLMENT CONTINUED ACCESS INVESTIGATIONAL GROUP[1] BY SITE 89
TABLE 4.3 PROCEDURE ACCOUNTING AND FOLLOW-UP COMPLIANCE TABLE INVESTIGATIONAL DEVICE CONTINUED ACCESS COHORT 90
TABLE 5.3 BASELINE AND DEMOGRAPHIC CHARACTERISTICS - INVESTIGATIONAL CONTINUED ACCESS COHORT 93
TABLE 6.3 SURGICAL DETAILS - INVESTIGATIONAL CONTINUED ACCESS COHORT 95
TABLE 9.3(1) SUMMARY OF COMPLICATIONS - CONTINUED ACCESS COHORT 97
TABLE 9.3(2) SPECIFIC COMPLICATIONS CONTINUED ACCESS COHORT 98
TABLE 9.3(3) COUNTS OF SPECIFIC COMPLICATIONS BY TIME OF OCCURRENCE - CONTINUED ACCESS COHORT 99
TABLE 9.3(4) SPECIFIC COMPLICATIONS - CONTINUED ACCESS COHORT 100

TABLE 9.3(5) COUNTS OF SPECIFIC COMPLICATIONS BY TIME OF OCCURRENCE - CONTINUED ACCESS COHORT 101
TABLE 9.3(6) SPECIFIC COMPLICATIONS - CONTINUED ACCESS COHORT 102
TABLE 9.3(7) COUNTS OF SPECIFIC COMPLICATION BY TIME OF OCCURRENCE 103
TABLE 10.3 POTENTIAL LOST TO FOLLOW-UP – CORMET 2000 IDE CONTINUED ACCESS COHORT 104
TABLE 9.4(1) SUMMARY OF COMPLICATION COMPARISONS BETWEEN ALL ENROLLED INVESTIGATIONAL AND CONTROL DEVICES – SUMMARY 105
TABLE 9.4(2) COMPLICATION COMPARISONS WITH CONTROLS – SPECIFIC COMPLICATIONS - ALL ENROLLED INVESTIGATIONAL AND CONTROL DEVICES 107
TABLE 9.4(3) SYSTEMIC COMPLICATIONS BY TIME OF OCCURRENCE – ALL ENROLLED PROCEDURES 108
TABLE 9.4(4) HIP RELATED COMPLICATION COMPARISONS WITH CONTROLS 109
TABLE 9.4(5) HIP RELATED COMPLICATIONS BY TIME OF OCCURRENCE 111
TABLE 9.4(6) DEVICE RELATED COMPLICATION COMPARISONS WITH CONTROLS 112
TABLE 9.4(7) DEVICE RELATED COMPLICATIONS BY TIME OF OCCURRENCE 113
TABLE 12.4(A) LIFE TABLE ANALYSIS 116
TABLE 2 REVISIONS BY CLINICAL SITE 119
TABLE 3 RISK OF REVISION IN PIVOTAL UNILATERAL COHORT AND ALL ENROLLED PROCEDURES: 120
ALL PROCEDURES AND PROCEDURES WITH AT LEAST 24 MONTHS FOLLOW-UP 120
TABLE 4 PREVALENCE OF RISK FACTORS FOR PIVOTAL UNILATERAL AND ALL ENROLLED PROCEDURES WITH AND WITHOUT EXCLUDING SITE 5 121
TABLE 5 STATISTICAL SIGNIFICANCE OF RELATIONSHIP OF REVISIONS TO BASELINE RISK FACTORS IN SURVIVAL ANALYSIS ASSESSING EACH RISK FACTOR ALONE 122
TABLE 6 COX REGRESSION HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR EACH POTENTIAL RISK FACTOR EVALUATED ONE-AT-A-TIME PIVOTAL UNILATERAL, PIVOTAL UNILATERA EXCLUDING SITE 5, AND BY SITE 125
TABLE 7 COX REGRESSION HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR EACH POTENTIAL RISK FACTOR EVALUATED ONE-AT-A-TIME ALL ENROLLED PROCEDURES, ALL ENROLLED PROCEDURES EXCLUDING SITE 5, AND BY SITE 126
TABLE 8 HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FROM FINAL MULTIVARIABLE COX REGRESSION MODELS FOR PIVOTAL UNILATERAL AND ALL ENROLLED PROCEDURES WITH AND WITHOUT EXCLUDING SITE 5 129
TABLE 9 ADDITIVE EFFECT OF RISK FACTORS 130
TABLE 10 ADDITIVE EFFECT OF MULTIPLE RISK FACTORS ON REVISIONS (SUM OF: SMALL COMPONENT SIZE, DIAGNOSIS OTHER THAN OSTEOARTHRITIS, LEG LENGTH DISCREPANCY ≥1CM, LOW BASELINE HHS) FOLLOW-UP TO MONTH 24 131

FIGURES

FIGURE 12.4(1) KAPLAN-MEIR SURVIVAL CURVES FOR ALL ENROLLED INVESTIGATIONAL AND CONTROL DEVICES 117

1 Device Description

1.1 General Overview

The Cormet 2000 Hip Resurfacing System is a metal-on-metal hip resurfacing system, and consists of two components – a resurfacing head and a monobloc acetabular component. The femoral head articulates in a multi-directional fashion within the acetabular component.

1.2 Femoral Component

The femoral component is manufactured from cast cobalt-chromium-molybdenum (Co-Cr-Mo) alloy complying with the requirements of ASTM F75 and ISO 5832-4. The castings undergo a double heat treatment comprising of hot isostatic pressing followed by solution annealing to reduce microporosity and promote the homogeneity of the material. The component is intended for use with bone cement and is available in five sizes (external diameters): 40, 44, 48, 52 and 56mm. The heads have a central stem that increases in size through the range. The stem is polished distally to avoid fixation in this area. Three internal splines provide anti-rotational stability.

1.3 Acetabular Component

The acetabular component is manufactured from cast Co-Cr-Mo alloy as detailed in ASTM F75 and ISO 5832-4. The castings are double heat treated as described above. The external surface of the acetabular component is finished with a bi-coating comprised of hydroxylapatite over plasma sprayed unalloyed titanium, to facilitate bone on-growth onto the component. The component is intended for use without bone cement and is available in nine sizes (diameters): 46, 48, 50, 52, 54, 56, 58, 60 and 62mm. Two sets of external splines provide anti-rotational stability.

1.4 Component Matching

The matching of femoral and acetabular components is described in Table 1.4.

Table 1.4 Femoral Component/Acetabular Component Compatibility

Femoral Component Sizes	Mating Acetabular Component Sizes
40mm	46 or 48mm
44mm	50 or 52mm
48mm	54 or 56mm
52mm	58 or 60mm
56mm	62mm only

2 Indications for Use / Contraindications for Use

2.1 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.

2.2 Contraindications for Use

Contraindications, warnings and precautions for the use of the Cormet 2000 Hip Resurfacing System:

Contraindications

1. Active or suspected infection in or about 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 who are pregnant or are planning on becoming pregnant due to unknown effects on 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).

Warnings

1. Patients on medications (such as high-dose or chronic aminoglycoside treatment) or with co-morbidities (such as diabetes) that increase the risk of future, significant renal impairment should be advised of the possibility of increase in systemic metal ion concentration. Preoperative and postoperative monitoring of renal function (such cretinine, GFR, BUN) will be necessary.
2. Do not scratch the femoral or acetabular components' articulating surfaces.
3. Do not use another manufacturer's device in place of components of the Cormet 2000 Resurfacing Hip System. Design differences between manufacturers can lead to device failure.
4. Do not use these components for patients undergoing revision total hip replacement surgery.
5. Single use only. Never reuse an implant even if it appears undamaged.
6. Avoid notching the femoral neck, as this may lead to femoral neck fracture.
7. Avoid placing the femoral component in varus. Varus placement of femoral component has been associated with femoral neck fracture.
8. Do not handle the HA treated regions as it may compromise the sterility or cause failure under load.
9. Do not contour or bend an implant as it may compromise its fatigue strength and cause failure under load.

Precautions

1. Before clinical use, the surgeon should thoroughly understand all aspects of the surgical procedure and limitations of the device. Patients must be instructed in the limitations of the prosthesis, including, but not limited to, the impact of excessive loading through patient weight or activity, and be taught to govern their activities accordingly. If the patient is involved in an occupation or activity that includes substantial walking, running, lifting, or muscle strain, the resultant forces can cause failure of the fixation, the device, or both. The prosthesis will not restore function to the level expected with normal healthy bone, and the surgeon should advise the patient against having unrealistic functional expectations.
2. Surgeons should review the Cormet 2000 Hip Resurfacing System operative technique prior to implanting.
3. Clean articulating surfaces of debris prior to final reduction of the joint.
4. Avoid overly abducting the acetabular component, which can accelerate wear.
5. Ensure that the head outer diameter and acetabular inner diameter match prior to implanting.
6. Handle porous surfaces carefully so that particles are not dislodged from the component surface.
7. Routine postoperative follow-up is recommended to monitor implant position and patient well-being over time.
8. Appropriate selection, placement and fixation of the resurfacing hip components are critical factors, which affect implant service life. As in the case of all prosthetic implants, the durability of these components is affected by numerous biologic, biomechanic and other extrinsic factors, which limit their service life. Accordingly, strict adherence to the indications, contraindications, precautions and warnings for this product is essential to potentially maximize service life.

3 PRE-CLINICAL INFORMATION

3.1 General Overview

The following preclinical studies were carried out on the Cormet 2000 Hip Resurfacing System: sterilization validation, wear, fatigue strength testing, frictional torque, circulating metal ions, surface coating validations, range of motion (ROM), and luxation wear. The preclinical tests that have been performed and given as part of this PMA Submission show that the Cormet 2000 Hip Resurfacing System should function as intended when used in accordance with the directions for use.

3.2 Sterilization Validation

Femoral head and acetabular components of the Cormet 2000 Hip Resurfacing System are manufactured in a manufacturing facility complying with the requirements of ISO 13485:2003, Medical devices -- Quality management systems -- Requirements for regulatory purposes. The devices are sterilized by gamma irradiation delivered from a $cobalt_{60}$ source.

The sterilization process has been validated to achieve a routine sterility assurance level of 10^{-6} at a minimum dose of 25kGy in compliance with the requirements of BS EN 556:1995 *Sterilization of medical devices – Requirements for terminally sterilized devices to be labeled as "sterile."* The process is validated in accordance with the requirements of ISO 11137-1:2006, Sterilization of health care products -- Radiation -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices and ISO 11137-2:2006, Sterilization of health care products -- Radiation -- Part 2: Establishing the sterilization dose.

3.3 Wear

Three studies are reported relating to wear testing. All the tests used the same component bearing material, that is Co-Cr-Mo alloy to ASTM F75.

The initial study was commissioned in 1998 on the Cormet 2000 Hip Resurfacing System. The aim was to determine the impact of improved manufacturing tolerances and metallurgy on wear and investigated sphericity, diametrical clearance and metallurgy. The test compared the 'heat-treated' (hot isostatically pressed and solution annealed) Cormet 2000 Hip Resurfacing System to an 'as-cast' type device also commercially available. Tests were carried out on a Stanmore MkIII simulator at AEA Technology, Harwell. Two Cormet 2000 Hip Resurfacing Systems and one type device were run to cycles at maximum load establishing s te conditions with diametric bearing clearan respectively. The report concluded that there was no difference between the 'heat-treated' Cormet 2000 Hip Resurfacing System and 'as-cast' devices but showed a major wear improvement over previously manufactured devices due to the improved sphericity control. It reported lower wear rates than other metal-on-metal devices measured by AEA and reported in the literature.

A second, more comprehensive study investigated different bearing sizes and was carried out by the Interdisciplinary Research Centre at Queen Mary, University of London as a contract test report. An 8-station MTS System hip joint simulator was used to investigate four and four 'double heat-treated' (hot isostatically pressed and solution annealed as per Cormet 2000 H ystem specification) metal-on-metal bearings to under normal gait conditions. The results were then compared to diameter bearing data that was being researched for a different study.

The prostheses were factured to production specifications with regard to radial clearance, sphericity and surface finish. A biaxial-rocking motion was used to represent the flexion/extension and abduction/adduction movements of the femur during ambulation. The loading cycle was based on the 'Paul'

cycle (see report) applying between [redacted] and [redacted] at [redacted]. Newborn calf serum was used as the lubricant. Heads and cups were measured ev [redacted]

The [redacted] earings indicated the highest steady-state wear rate with the largest running-in wear occurring in the [redacted] bearings. The [redacted] group had lower running-in and steady-state wear compared to the [redacted] coupling. The [redacted] bearings, however, produced the lowest steady-state wear of all the groups. Be meter had no ce on observed wear patterns and wear mechanisms.

The final study investigated the effects of heat treatment on wear rates in metal-on-metal bearings and was carried out by the Interdisciplinary Research Centre at Queen Mary, University of London. An 8-station MTS int simulator was used to investigate four [redacted] as-cast' and four [redacted] (Cormet 2000 Hip Resurfacing Systems) earings under sta e' gait (fast-jogging) conditions up to [redacted] cycles.

The prostheses were manufactured to production specifications with regard to radial clearance, sphericity and surface finish. A [redacted] biaxial-rocking motion was used to represent the flexion/extension and abduction/adduction ents of the femur during ambulation. All co s were subject to three million cycles of 'normal walking' (standard gait) with a maximum load of [redacted] at [redacted]. Then 'fast-jogging' and additional 'normal walking' tests were performed. Heads and cups were measured every [redacted] million cycles.

The results concluded that the running-in, steady-state and total wear rates were similar for both material groups demonstrating that c ostructure do not appear to influence the wear behavior. The steady-state wear rates [redacted] found during 'normal walking' were similar to those reported for [redacted] diameter bearings ature. 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. There was no long-term detrimental effect from the 'severe test' regime.

To summarize, the long-term steady-state wear for the Cormet 2000 Hip Resurfacing System is similar to the results found in other metal-on-metal bearings. All the wear tests indicate a higher running-in wear rate compared to the minimal steady-state wear; evidence of fluid film type lubrication, as reported in the literature.

3.4 Fatigue Strength Testing

Strength testing was performed on five static and five dynamic (fatigue) [redacted] resurfacing heads that were identified as 'worst-case.'

The static test method was configured to simulate the fault condition of the resurfacing head similar to the ISO 7206-4 Implants for surgery - Partial and total hip joint prostheses – Part 4 – Determination of endurance properties of stemmed femoral components whereby the t simulates the loss o imal bone fixation. A jig fixed the resurfacing head at [redacted] to the vertical and in [redacted] of anteversion. The [redacted] value was determined by using the [redacted] stem-to-neck e (mean stem-shaft angle reported by Beaule et al.) plus a valgus angle of [redacted]. The stem of the resurfacing head was held on the distal section at a distance of [redacted] below the underside of the head. Five static tests were performed with the failure point identified as the point on the load/extension graphs where the elastic region ended. The mean static failure load was in excess of [redacted]. All samples went on to survive higher loads without catastrophic failure albeit with permanent deformation of the femoral stem.

3.5 Frictional Torque

Three independent frictional torque tests have been performed on the Cormet 2000 Hip Resurfacing System. In the latest study, [redacted] samples (head diameter) with the minimum specified radial clearanc (identified as 'worst-case' since torque is proportional to head diameter) were uniquely paired with five [redacted] The frictional torque of each bearing pair was recorded independently in flexion/extension and

internal/external rotation under a joint load of [redacted] The experimental protocol was the same as that previously reported in the February 2005 study. The maximum torque was found to occur duri[redacted] flexion/extension motion. The m[redacted] odulus) torque was recorded at an average of [redacted] and [redacted] under a test load of [redacted] respectively.

To conclude, the studies indicate torques significantly less than the torques to failure reported by Andersson et al.[2] (100Nm being suggested by Andersson et al as being the torque required to remove a 'well'-cemented acetabular cup from a cadaveric socket). Such torques reported are thought unlikely to, therefore, be of relevance *in vivo*. Table 3.5 summarizes the results of the 'worst-case' frictional torque study at 2.45kN.

Table 3.5 Summary Table 'Worst-Case' Frictional Torque Study (December 2005)

	Load, N	Bearing Diameter, mm	Maximum Torque, Nm	Radial Clearance, µm
Test 3 (Dec 2005) Flexion-extension	[redacted]	[redacted]	[redacted]	[redacted]
			Mean = [redacted]	*Me* [redacted]

3.6 Circulating Metal Ions

A series of [redacted] p[redacted] underwent a unilateral metal-on-metal hip resurfacing were prospectively followed ov[redacted] a [redacted] period. All patients underwent the procedure by the [redacted] urgeon[redacted] ho did not participate in the IDE study, but who has extensive experience with resurfacing. [redacted] of the [redacted] patients underwent a metal-on-metal hip resurfacing procedure on the second hip during the course of [redacted]e study. These [redacted] patients along with [redacted] other patients who had a previous hip resurfacing on the other hip had their cobalt and chromium metal ion levels assessed over time to determine the effect of bilateral hip resurfacing on metal ion levels.

Measurements were taken from [redacted] patients [redacted]h [redacted] of those having bilateral resurfacings. Preoperative metal ion levels were available for [redacted] of the [redacted] patients. Metal ion levels were available on all [redacted] bilateral patients. For patients with one resurfacing [redacted]ice, results of the study indicate that metal ion levels for cobalt and chromium initially increase following a metal-on-metal hip resurfacing, but plateau and start to decrease between [redacted] and [redacted] years post-implantation. The levels remained below their peak but did not [redacted]o preopera[redacted]evel[redacted]oughout the [redacted] follow-up reported in this study. Implantation of a [redacted] metal-on-metal resurfacing raised th[redacted] 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 [redacted] years. Chromium levels following bilateral surgery did not return to normal but were only slightly higher when compared to levels of a unilateral resurfacing.

3.7 Surface Coating Validation

The acetabular component coating, consisting of plasma sprayed unalloyed titanium and HA, was validated. The titanium coating was tested for static and dynamic shear, static tension and abrasion. Surface roughness was also calculated.

A [redacted] ples were tested in static shear according to ASTM F1044, resulting in an average strength of [redacted] ± [redacted] Shear fatigue strength testing was performed per ASTM F1160 *Standard test method for shear and bending fatigue of* [redacted] *phate and metallic medical and composite cal* [redacted] *phosphate/metallic coatings*. [redacted] were tested to [redacted] cycles at a stress of [redacted] with no failures. Three samples were tested in static tension accordance with ASTM F1147, resulting in an average strength of [redacted] with a standard deviation of [redacted] For abrasion, six samples were tested for an average of 54.1 ± 6.4mg of weight loss. Surface roughness measured from six sections of prepared material resulted

in an average Ra of ± The HA was validated across a wide range of variables, including density, particle size , dissolution, and bonding strength.

These validations showed appropriate levels of control over the coatings process in accordance with applicable guidelines.

3.8 Range of Motion

A study was conducted using a 3D CAD ROM investigation of the Cormet 2000 Hip Resurfacing System size range. The esurfacing head and cup/ cup combination has been shown to represent the 'worst-case' system in the size rang ovides the lowest range of angular motion in internal/external rotation, flexion/extension and abduction/adduction. Using a 'worst-case' femoral neck model, the results show that the Cormet 2000 Hip Resurfacing System, for all sizes, complies with ISO 21535:2002 *Evaluation of Relative Angular Motion of Components*. The results are presented below in Table 3.8.

Table 3.8 Summary of the Range of Angular Movement of each Bearing Couple in the Cormet 2000 Hip Resurfacing System Size Range and the Minimum Requirements as specified in ISO 21535:2002

Head-cup combination, mm	Internal/external rotation, deg	Flexion/extension, deg	Abduction/adduction, deg
ISO 21535	*90 (min)*	*80 (min)*	*60 (min)*

3.9 Luxation Wear

Luxation testing has been performed on five and five Cormet 2000 Hip Resurfacing System bearings. The procedure described in *Determination of Res to Luxations and Repositions of Total Hip Joint Prostheses* by Kaddick et al.[3], in *Bioceramics in Orthopedics*, edited by Wofart Phuhl, 1998 was used. These bearing couples represent the lower and upper ends of the Cormet 2000 Hip Resurfacing System size range. Bearing clearances were controlled to the maximum specified in the manufacturing tolerances to represent 'worst-case'. The forces required to cause luxation of the bearings during the first cycle were recorded and the displacement noted. The cups were examined and then repeated luxations were performed (a further ycles per bearing couple). A displacement of was pre-set since this was greater than the displacement required to cause luxation in the diameter bearings found during the first luxation.

After the first luxation cycle a small decrease in luxation force occurred for all bearing couples thought 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 for both the and bearings. Visual surface analysis of the bearings showed scratching at the end of s and is documented.

Literature is presented discussing the increased resistance to dislocation of large diameter metal-on-metal bearings and the effects of subluxation are presented.

4 Study Design

4.1 Purpose of the Investigation

The purpose of was to test the hypothesis that the Cormet 2000 Hip Resurfacing System is as effective as con arthroplasty. The Cormet 2000 Hip Resurfacing System was the investigational treatment and a conventional total hip arthroplasty system served as the control group. The primary efficacy objective of this study was to demonstrate non-inferiority of the Cormet 2000 implant system relative to control with regard to the likelihood of clinical success at Month 24+. The use of clinical success at the Month 24+ endpoint was based upon FDA's statement that Month 24+ and Month 36 follow-up points could be used to evaluate success rates and clinical results. Safety was determined by the incidence of peri-operative and postoperative complications.

4.2 Evolution of the Study Design

The original protocol proposed a sequentially enrolled, non-randomized control group of a total hip arthroplasty cohort. Discussion concerning the control group continued with FDA and is summarized below.

A brief recounting of the major event timelines for this investigation, provides an overview of the chronology of events with discuss of the key issues provided below:

- May 17, 2001 Cormet 2000 Hip Resurfacing System enrolled first patient;
- August 5, 2003 Pivotal IDE Study completed enrollment;
- August 21, 2003 Continued Access study began;
- March 26, 2005 PMA P050016 submitted to FDA;
- July 7, 2005 PMA Deficiency received by Sponsor;
- January 31, 2006 submission of PMA Amendment 8 to address deficiencies.
    - Deficiency response by item;
    - Updated Section III Summary of Preclinical and Clinical Studies;
    - Updated Section VI Clinical Study Results.
- May 18, 2006 2nd PMA Deficiency received by Sponsor
- August 11, 2006 submission of PMA Amendment 13 to address deficiencies
    - Deficiency response by item
    - Updated Section III Summary of Preclinical and Clinical Studies;
    - Updated Section VI Clinical Study Results; section 3.1 Pivotal Study Unilateral Patients; 3.4.8 Safety Data

The July 7, 2005 PMA deficiency highlighted two major clinical issues within the PMA, (1) the applicability of the historical control group and (2) the composite clinical success endpoints presented in the PMA in comparison to those identified in the original, approved study protocol. The Sponsor agreed that the clinical endpoints presented in the March 2005 PMA submission were inadequate in that they did not include the radiographic and device related adverse event success/failure criteria in assessing the composite clinical success (CCS). Amendment 8 provided a history of changes to the study analysis, justification for applicability of the current ceramic-on-ceramic control, and clinical and radiographic data to support the composite clinical success in alignment with the original study protocol. Clinical issues raised in the 2nd PMA deficiency (May 18, 2006) were addressed in Amendment 13 by providing additional justification for the radiographic success criteria and patient accountability for 85% follow-up to demonstrate CCS at the Month 24+ endpoint. FDA expressed concern at the July 13, 2006 meeting with the Sponsor that there have been several changes in study design and clinical endpoints during the IDE Study and in the PMA submission of the Cormet 2000 Hip Resurfacing System. While there have been inconsistencies in the conduct of this investigation with regard to adherence to explicit pre-defined study protocol, the Sponsor with the study investigators have conducted a prospective, multi-center IDE study through which they collected safety and

effectiveness clinical data on over 1,100 subjects implanted with the investigational hip resurfacing system. The clinical data submitted in this PMA is sufficient to support the safety and effectiveness of the Cormet 2000 Hip Resurfacing System. The Sponsor further believes that the changes to the study design have been an improvement and have increased FDA's ability to make a determination based on meaningful clinical evidence compared to an established control.

Provided below is a brief history of changes to and justification for applicability of the current control group, and clinical and radiographic data to support the composite clinical success endpoints.

4.2.1 Control Group

The Sponsor acknowledges that the Control group identified in Amendment 8 was the third control group proposed by the Sponsor, and by itself could be a cause for concern to FDA. The control group proposed in the PMA of March 2005 (OSMA Sponsored metal-on-metal reclassification petition) was found deficient by FDA as no line-by-line comparison of the datasets could be achieved. Therefore, the third control of the ABC ceramic-on-ceramic PMA approved control was thought to be the best option for addressing the deficiency noted by FDA. The Sponsor believes that the rationale provided to FDA for the use of the current ABC Ceramic-on-Ceramic control is robust and adequately addressed the control issues presented by FDA in the July 2005 PMA deficiency. It was the Sponsor's understanding that it was acceptable to submit the PMA update in Amendment 8 using the ABC Ceramic-on-Ceramic as an historical control group based upon communications with the FDA. The FDA's acceptance of the ABC control group was reinforced by the fact that there were no deficiencies associated with the use of this control group in the May 8, 2006 letter.

The Cormet 2000 and ABC IDE studies show similar designs and clinical endpoints as described in Table 4.2(1).

Table 4.2(1) Comparison of Study Design and Clinical Endpoints

Protocol Element	Cormet 2000 IDE Study	ABC IDE Study
Type of Study	IDE – Hip Resurfacing	IDE – Total Hip Arthroplasty
Bearing Type	Metal-on-Metal	Ceramic-on-Ceramic
Study Design	Prospective, non-randomized, historical control	Prospective, randomized
Number of centers	14	16
Numbers of procedures	1148	349
Intervals	Preoperative, 6 weeks, 6, 12, 24 and 24+ months	Preoperative, 6 weeks, 6, 12, 24 and 24+ months
Measures	HHS Adverse Events Radiographs Questionnaire	HHS Adverse Events Radiographs Questionnaire

The ABC control group meets the purpose of the study, which is to provide a recent series of total hip arthroplasty patients where there is adequate data available for comparison purposes. As the control group is ceramic-on-ceramic, both groups have a hard-on-hard bearing surface without the risk of issues associated with polyethylene debris. The historical control was enrolled in 1996 through 1998. In addition, excellent results have been reported for the control device both in the PMA[4] and in the literature[5,6], making the control a formidable total hip arthroplasty challenge for the Cormet 2000 Hip Resurfacing System. Total

hip arthroplasty of this design is currently the premier product line offered by many companies and is the current state of the art technology for total hip arthroplasty.

4.2.2 Composite Clinical Success

Table 4.2(2) provides a summary of the CCS from the original protocol, PMA P050016 and in this PMA amendments 8 and 13. In the March 2005 submission (PMA P050016), the Composite Clinical Success (CCS) was not presented in accordance with that described in the original, approved protocol.

Table 4.2(2) Comparison of Composite Clinical Success Endpoints

Composite Clinical Success Criteria	PMA Submission March 2005	Approved IDE Protocol	Current Criteria for PMA (Amendment 8 & 13)
HHS	≥ 80 points	20 point improvement	➔SAME (also presented as ≥ 80 as "modified CCS")
No revisions/ pending revisions	SAME ←	no revisions/ pending revisions	➔SAME
Radiographic Success	Not Included	Original definitions	Modified definitions
Device Related Adverse Events	Not Included	Not Specified	Specified

The following discussion provides justification for the current modifications in Composite Clinical Success endpoints.

Harris Hip Score (HHS) Assessment over time:

- In Amendment 8, the Sponsor presented the position that a dichotomization of the Harris Hip Total Score at the 80-point cutoff line is more widely used than a 20 point improvement as an indicator of patient success.[7,8] Design of the HHS was proposed with the predictor of future prosthesis success or failure as a goal. In the original article that introduced the HHS parameters and numeric values, Harris applied the categories of excellent (90 –100 points), good (80-90 points), fair (70-80 points), and poor (< 70 points). Clinical results of patients examined using the newly defined instrument showed that there was no significant deterioration of the good to excellent arthroplasty results with time. However, the Sponsor recognizes that the earliest protocol specified a clinical success criterion that included changes from baseline in HHS of at least 20 points.

Therefore, the HHS component of the Composite Clinical Success (CCS) was presented in two ways:

- According to the original protocol Harris Hip Score success was defined as at least 20 point increase at Month 24+ compared to the preoperative score
- Presented in Amendment 8, Harris Hip Score success was defined as having a total score of at least 80 points at Month 24+.

Using either definition, the percentages of patients achieving clinical success at Month 24+ on the basis of the HHS criterion alone are very similar between the investigational and control groups, with the investigational group having slightly better results. Among 283 investigational device patients 279 (98.5%) had changes from pre surgery baseline to Month 24+ that were at equal to 20 points. This compares to 230 of 240 (95.8%) control patients, the better performance of the investigational device nearly reaching statistical significance (Fisher's Exact test p=0.06). Analogously, 272 of 283 (96.1%) of patients in the investigational device group and 241 of 253 (95.3%) patients in the control device group achieved having a Month 24+ Harris Hip Total score of at least 80 points. The observed superior efficacy for the

investigational device was not statistically significant for this parameter (p=0.67). The smaller sample size among controls is a consequence of missing baseline scores among control devices. The reason for the apparent difference between the investigational and control devices for the ≥ 20-point improvement criterion is not clear, but could have been due to no preoperative upper limitation of HHS for the control study. One patient in the Cormet 2000 Study with a preoperative HHS of 17.25, a Month 24 HHS of 44 points, and pending revision for acetabular loosening, was not included as a HHS failure using this criterion because the patient had ≥ 20-point improvement in score. Since a patient can have ≥ 20 point improvement in score and still be a clinical failure, the Sponsor believes that the HHS Total score of ≥ 80 points at Month 24+ provides FDA with the most clinically relevant end point, even though this parameter does not favor the investigational device compared to results based on ≥ 20 point improvement in score outcomes. FDA is able to evaluate the performance of the devices using either criterion as it sees fit as all data and analyses are provided.

4.2.3 Radiographic Endpoints

Metal-on-metal hip resurfacing is new to the US market and the scientific community is still identifying methods to evaluate success clinically and radiographically. Based upon review of the hip resurfacing literature, other PMA submissions, and recommendation from clinicians and radiographic advisers, the Sponsor provided modifications and rationale to FDA to support clinically relevant radiographic endpoints. Table 4.2(3) provides comparison of radiographic endpoints.

Table 4.2(3) Comparison of radiographic success criteria

Radiographic Success Criteria	Original Submission	Original Protocol	Current Criteria for PMA (Amendment 8 & 13)
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	➔SAME } Combined (must have both for failure)
Femoral tilt varus/valgus	SAME ←	< 1 degree	➔SAME
Femoral Radiolucencies	Not Evaluated	None in any zone	Not in all zones

The justification for the two changes in radiographic success is as follows:

- New or progressive complete radiolucencies ≤1mm in **all three** zones
  Clinical Justification: It has been a standard practice to classify the acetabular cup or femoral stem as failure if radiolucencies are identified in all three zones of the components[9,15]. Amstutz[15] presented radiographic results of the first 400 hips treated with metal-on-metal hybrid surface arthroplasties at an average follow-up of 3.5 years. The author presented an incidence of 32% of the cases (122 hips) to have acetabular radiolucencies in one or two zones. These cases were not classified as failures. Only one cup with migration (score 9) was considered a failure in this study. In the PMA P040033, femoral radiolucencies were assessed based on a score of 0-9 points and score 8 and 9 (radiolucencies in all three zones) were classified as failures. In addition, radiolucencies in all three zones around the component as failure is consistent with the failure criteria for the control device approved by FDA in 2003[4].

- Femoral component subsidence (lateral movement of the resurfacing head) <5mm **and** tilting <1° in varus/valgus direction
  Clinical Justification: The radiographic failure endpoint of change in component tilt measured on sequential radiographs was identified in 2001 by FDA and the Sponsor and assigned an arbitrary value of 1 degree in response to FDA determination in that success would be defined by "no femoral tilt" (March 16, 2001). This success/failure measurement, change of 1 degree of femoral tilt as an indication of device failure, is unsubstantiated in the literature with the use of plain films and was not found to be an independent measurement of radiographic success for hip resurfacing arthroplasty as reported in the literature[10,11,12,15]. Further, employing the pre-defined endpoint of change of 1 degree femoral tilt as evidenced on serial plain radiographs is sensitive to minor changes in patient positioning on serial films, raising issues of accuracy and reliability of measurement and resulting in reporting of false positive results indicative of clinical failure in well-functioning hips. Femoral component tilting of <1 degree in the varus/valgus direction not relevant to the evaluation of safety and effectiveness of the investigational device under review and provides no scientific value. Therefore a femoral component was considered a failure if there was subsidence of the femoral component of ≥ 5mm and tilt of the femoral component of ≥ 1 degree.

In addition, an orthopaedic surgeon (Dr. Thomas Schmalzried) who participates in hip resurfacing IDE studies stated that [personal communication: conference call with Schmalz on June 27, 2006]:

> "Femoral component tilt that is clinically significant would not occur without other signs of failure. It is impossible to change the rotation of the femoral component without observing other signs of failure".

Thomas Gruen, a well-known radiographic reviewer, provided the following comment [personal communication: memo from Tom dated July 13, 2006]:

> "Regarding the success criteria of less than 1 degree change in femoral tilt angle would imply that a tilt of one degree or more would represent a radiographic and/or clinical failure…this tight angular change has, as far as I know, not been demonstrated for any surface replacement femoral component or for that matter any other type of femoral component or acetabular component".

Measurement techniques for acetabular component migration and tilt and femoral component subsidence were done in accordance with the original protocol as well as the modified version summarized below in Table 4.2(4).

Table 4.2(4) Comparison of Measurement Techniques

Radiographic Analysis	Original Submission dated March 26, 2005	Original Protocol dated March 20, 2003	Current Technique for PMA (Amendment 8 & 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

The justification for the two changes in radiographic measurements is as follows:

- Acetabular component migration and tilt
  Clinical Justification: Data presented in the PMA dated March 26 2005, were not based on the techniques defined above. Therefore, the review of the radiographs in accordance to the original protocol was done for the first time in PMA Amendment 8.
- Femoral component subsidence
  Clinical Justification: The bony landmark for this measurement was not clearly stated in the protocol. According to the technique defined in the protocol, a point on the lateral femoral cortex that intersects the longitudinal line through the midpoints of the femoral component is considered a bony landmark. This landmark cannot be identified consistently in serial radiographs. Therefore, the top of the greater trochanter has been identified as the best reference point for the measurement of downward migration of the femoral component (Biedermann et al.[10] and Beaule et al.[11]). A longitudinal line was drawn through the femur, ensuring that the line passed through the midpoint of the femur at each point. The distance between a horizontal line through the top of the greater trochanter and one through the center of the head (made at right angles to the vertical line through the mid point of the femur) was measured for evaluating the subsidence of the resurfacing head.

4.3 Clinical Trial Design to Demonstrate Safety and Effectiveness

A prospective, multi-center, IDE study was conducted utilizing components of the Cormet 2000 Hip Resurfacing System in the United States under [redacted] Safety and effectiveness is based upon comparison to an historical control group, a ceramic-on-ceramic total hip arthroplasty implant system.

4.3.1 Control Group

This control group was comprised of total hip arthroplasty patients with an Osteonics ABC (Alumina Bearing Couple) enrolled in [redacted] These ceramic bearings were approved via PMA P000013 on February 3, 2003.

The pivotal study has a subset of unilateral patients implanted under the IDE study of 337 patients, which is directly comparable to a set of 266 unilateral control patients. Table 4.2.1 above shows that the study design, clinical endpoints and core data collected for these studies was essentially the same. In addition, the follow-up time-points and the intervals around these time-points were very similar as illustrated in **Table 4.3(1)**.

Table 4.3(1) 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	±2months/+expanded	±2 months
2 years	±2 months	±2 months/+ expanded	±2 months
2+ years		Any evaluation 22+ months=24+ months	

The majority of the eligibility criteria (10 of 14) were consistent for both studies. A side-by-side comparison of the inclusion/exclusion criteria between the studies is presented in Table 4.3(2). There were four criteria that had no effect and were of no consequence to the study population comparison. The remaining four criteria were slightly different between the studies, yet comparisons of the populations enrolled found these parameters (age, diagnosis and preoperative HHS) to be similar between the populations.

Table 4.3(2) Inclusion/Exclusion Comparison

	Inclusion/Exclusion	Cormet 2000 Approved Protocol	Control Group Study
Well matched	Is skeletally mature	X	X
	Is mentally capable of follow-up	X	X
	Will be available for 2-year 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 Effect	No extensive deformity of femoral head	X*	Not relevant
	No known allergy 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
Differences	Has preoperative HHS <70 points	X	No limits
	No Congenital Dysplasia of the Hip (CDH)	X	Included in study
	Age	No limits	21-75 years
	Inflammatory arthritis	Included in study	X

*PI discretion

The ABC control group provides a recent series of total hip arthroplasty patients having adequate data available to serve as the control group for purposes of clinical trial to demonstrate safety and effectiveness of the Cormet Hip Resurfacing arthroplasty system.

4.3.2 Composite Clinical Success

The Cormet 2000 IDE Study identified "patient success" at Month 24 and Month 24+ postoperatively as a patient who achieved four distinct success criteria. They are as follows:

- HHS ≥ 20 point increase; HHS ≥ 80;
- Radiographic Success;
- Absence of Revision/Removal or Pending Revision/Removal;
- Absence of Device Related AE.

The following non-inferiority hypothesis was tested in primary efficacy analyses of Composite Clinical Success (CCS) comparing clinical outcomes between patients in the investigational Pivotal Study Unilateral cohort and patients in the Unilateral Control cohort.

The null and alternative non-inferiority hypotheses were formulated to be consistent with the Blackwelder approach[13] and are as follows:

H_o: $P_{Cormet2000} - P_{HCG} \leq -0.08$ (investigational clinically inferior to control)

H_a: $P_{Cormet2000} - P_{HCG} > -0.08$ (investigational not clinically inferior to control)

The revised study was designed to reject the null hypothesis that the Cormet 2000 resurfacing device (investigational device) is clinically inferior to the ABC ceramic-on-ceramic total hip replacement (control) in term of the proportion of patients achieving composite clinical success. The non-inferiority delta was

specified to be equal to 0.08. Thus, the study was designed to reject the null hypothesis that proportion of patients achieving composite clinical success with the investigational device is at least 0.08 less than the proportion of patients achieving composite clinical success with the control device.

A one-sided 95% non-inferiority confidence interval for the difference in proportions was determined in order to test this hypothesis. If the lower bound of this confidence interval exceeds -0.08 then the null hypothesis may be rejected and it can be concluded that in terms of composite clinical success, the investigational device is not clinically inferior to the control device.

The criteria for CCS are as follows:

- CCS at Month 24+ with at least good clinical results as defined by a Harris Hip Total score of at least 20 points higher at Month 24+ as compared to preoperative baseline score, absence of revision of any of the components of the investigational device, absence of device related AEs, and absence of radiographic failure;
- CCS at Month 24+ with at least good clinical results as defined by a Harris Hip Total score of at least 80 points at Month 24+, absence of revision of any of the components of the investigational device, absence of device related AEs, and absence of radiographic failure.

The test for non-inferiority of CCS is presented in two ways:

- According to the original Harris Hip Score criterion, absence of revision or pending revision, no device related Adverse Events (AEs) as defined, and modified radiographic assessment.
- According to the modified Harris Hip Score criterion, absence of revision or pending revision, no device related Adverse Events (AEs) as defined, and modified radiographic assessment.

5 Clinical Study Results

NOTE: Some Tables are numbered here in the Clinical Study Results summary as they appeared in Amendments 8 and 13. Headers and subheaders per topic are numbered consecutively throughout this section.

5.1 Pivotal Study Unilateral Patients

5.1.1 Number of Subjects Enrolled

Investigational

The first subject was enrolled into the Cormet 2000 IDE Study on May 17, 2001 and study enrolment was completed on August 5, 2003. A total of 337 patients represent the Pivotal Study Unilateral group of patients implanted with the Cormet 2000 Hip Resurfacing System.

See Table 5.1.1(1) for a summary of the number of patients enrolled by site in the Pivotal Study Unilateral group for the investigational device.

Table 5.1.1(1) Patient Enrollment Pivotal Study Unilateral Group by Site – Investigational

Investigators	Location	Total Number of Patients Enrolled
	Springfield, IL	31
	Mobile, AL	6
	Englewood, NJ	6
	Colombia, SC	134
	Rockledge, FL	21
	New York, NY	6
	Baltimore, MD	42
	Sarasota, FL	46
	Durham, NC	3
	Los Angeles, CA	2
	Galesburg, IL	38
	Cleveland, OH	2
TOTAL		337

Note: [1] The IDE Pivotal Study Unilateral group includes unilateral procedures excluding major protocol violations. Five patients who also received contralateral study devices after 730 days are included; their contralateral procedure was performed during the Continued Access portion of the study so are included in the Cormet 2000 IDE Continued Access group. Both procedures among patients in the IDE cohort receiving contralateral implants within 730 days are included in the Pivotal Study Bilateral group.

Control

The enrolment 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 Hip Resurfacing System. See Table 5.1.1(2) for a summary of the number of patients enrolled by site in the Pivotal Study Unilateral group for the control device.

Table 5.1.1(2) Patient Enrollment Pivotal Study Unilateral Group by Site – Control

Investigators	Location	Total Number of Patients Enrolled
	Boston, MA	28
	Indianapolis, IN	32
	La Jolla, CA	19
	Moontownship, PA	51
	Atlanta, GA	2
	Philadelphia, PA	6
	New York, NY	17
	Durham, NC	8
	Athens, GA	14
	Lansing, MI	19
	Atlanta, GA	18
	Toledo, OH	26
	Boca Raton, FL	26
TOTAL		266

5.1.2 Patient Accounting

Table 5.1.2(1) presents an overview of patient accountability for the Investigational Pivotal Study Unilateral group.

Table 5.1.2(1) Pivotal Study Unilateral Patient Accountability - Investigational Group

Status at Month 24+	Number of subjects
Pivotal study group enrolment	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

Table 5.1.2(2) provides definitions of terms for patient accountability.

Table 5.1.2(2) Definition of Terms for Patient Accountability

Term	Definition
Actual[A]	Patients contributing all endpoint data that were evaluated within the protocol defined window
Actual[B]	Patients contributing any data that were evaluated at a visit regardless of whether the visit was within the follow-up windows (not overlapping other protocol defined visit intervals)
Month 24 CCS Actual[A]	Patients contributing all endpoint data that were evaluated within the protocol defined window or were known failures up to exact 24 month surgical anniversary.
Month 24+ CCS Actual[A]	Patients contributing all endpoint data that were evaluated within the protocol defined window PLUS Rollback imputation based on next available value (e.g., Month 36) if within the protocol defined visit window or were known failures up to exact 24 month surgical anniversary.
Month 24 CCS Actual[B]	Patients contributing all endpoint data that were evaluated regardless of follow-up windows (not overlapping other protocol defined visit intervals) or were known failures up to exact 24 month surgical anniversary.
Month 24+ CCS Actual[B]	Patients contributing all endpoint data that were evaluated regardless of follow-up windows (not overlapping other protocol defined visit intervals) PLUS Rollback imputation of Month 36 data regardless of window or were known failures up to exact 24 month surgical anniversary.

The availability of follow-up evaluations for the investigational and control Pivotal Study Unilateral group is listed in Table 4.1 below. Maximum length of follow-up as of the date of database lock, July 26, 2006, was 1803 days. Data for patients with greater than Month 36 follow-up was captured in the Month 24+column.

Table 4.1 Procedure Accounting and Follow-up Compliance Table – Pivotal Study Unilateral Patients and Unilateral Controls

Table 4.1
Procedure Accounting and Follow-up Compliance Table
Pivotal Study Unilateral Patients and Unilateral 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%	98.1%	85.6%	97.7%	91.3%	98.5%	39.8%	73.2%
(9) Harris Hip Total Score[10]	337	252	328	245	288	238	285	245	263	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%

[Source: Tables_Followup_Accounting_v2.sas]

Row 8 - All Evaluated Visit Compliance (%) is calculated by dividing the Actual[B] patients with any data point available (not included in table above) by the expected due for clinic visit.
Line 11 Actual[B] includes patients with all data available regardless of window.

Notes for Procedure Accounting and Follow-up Accounting Tables
[1] The theoretical follow-up is the number of implants that would have been examined if all patients returned on the exact anniversary of their respective initial surgery dates.
[2] Cumulative deaths up to and including the current interval. Although the cumulative numbers of deaths are recorded on this row, only deaths among implants that are theoretically due for that interval are subtracted from theoretical due to determine the number expected due.
[3] This row records the cumulative number of failures that have taken place according by the exact anniversary of scheduled follow-up visit. Although the cumulative numbers of failures are recorded on this row, only failures among implants that are theoretically due for that interval are subtracted from theoretical due to determine the number expected due. The cumulative revisions in Month 36 includes a revision in Month 39.
[4] Patients in this category are those who are theoretically due because their exact visit anniversary for that interval is on or before the date of database closure, they are within the evaluation time window, but have not been evaluated yet.
[5] Some of the deaths and revisions listed in rows 2 and 3 may not be included among theoretical due. This row provides the total number of cumulative deaths and revisions among those listed as theoretically due in row 1. This count is subtracted from theoretical due to obtain expected due for clinical evaluations (i.e.,. for HHS and radiography).
[6] Expected due for clinic visit is equal to Theoretical due (row 1) minus Not yet over due (row 4) minus not Deaths and revisions among theoretical due (row 5). This row serves as denominator for clinical evaluation % follow up.
[7] Expected due plus theoretical due revisions is computed by adding row 6 to the number of cumulative revisions among theoretical procedures. This row serves as the denominator for composite clinical success outcomes since revisions are known to be CCS failures.
[8] All Evaluated Accounting (Actual^{B}) is based on the evaluations on-file among those expected due without regard to whether assessment was within the assessment window.
[9] All Evaluated Visit Compliance (%) is computed as the number on-file among those expected due divided by the expected number due (row 6) expressed as a percentage. All evaluated compliance is based on the presence of any clinical data, even if incomplete, and demonstrates that the procedure is actively followed at least up to the specific interval.
[10] Harris Hip Total (Actual^{B}). This is the count of Harris Hip Total scores available for the that interval including those both within and out of window.
[11] Radiographic evaluation (Actual^{B}). The number of radiographic evaluations on-file including those both within and out of window. For Month 24 and Month 24+, this includes procedures evaluable and non-evaluable for the new composite radiographic endpoint.
[12] CCS at Mos. 24, 24+ or HHS+radiographic, otherwise (Actual^{B}). For Months 24 and 24+ this row indicates the numbers of procedures with all components on-file that are necessary to evaluate composite clinical success with revisions included as CCS failures. For other time points, this row only indicates that both Harris Hip Total scores and radiographic evaluations are on-file.
[13] Actual^{B} % Follow-up. The denominator for % follow-up for this row is row 7 for Months 24 and 24+ and is row 6 for other time intervals. This is because the status of revisions is known for CCS. For Months 24 and 24+ this row indicates (Actual^{B}) % follow-up for the primary efficacy endpoint (CCS) only counting radiographic assessments in which the new composite radiographic endpoint is determined. For other time intervals, this is row is equal to the % of procedures with HHS and radiographic assessments divided by row 6.
[14] Actual^{A} intervals: 6 weeks ± 2 weeks, 6 months ± 1 month, 12 months ± 2 months, 24 months ± 2 months, annually ± 2 months.
[15] Actual^{A} accounting excludes Harris Hip Total scores and radiographic evaluations that are outside of the intervals indicated in note 14.
[16] Actual^{A} % Follow-up is computed as row 16 divided by 7, expressed as a percentage.

Investigational Group

A total of 243 (72.3%) patients in the "All Evaluated (Actual^{B}) Among Expected Due Procedures" group were evaluable for Month 24 composite clinical success (CCS). However, 292 patients (86.9%) were evaluable for Month 24+ CCS. Of 45 patients not evaluable for Month 24+ CCS, three patients died, nine patients had Harris Hip Scores only, five patients had radiographic data only, and 28 patients who did not return for their minimum Month 24+ follow-up visit had no clinical or radiographic data.

Control Group

A subset of the control cohort continues to be evaluated through a postmarket study for the ceramic-on-ceramic device. Therefore, in order to avoid extrapolating beyond the follow-up experience in the

investigational group, control follow-up was truncated at the maximum number of days encountered in the investigational group (1803 days). This guaranteed that the longest follow-up was identical in the investigational and control groups. A total of 250 (95%) Pivotal Study Unilateral Patients in the control group of the "All Evaluated (Actual[B]) Among Expected Due Procedures" completed Month 24 postoperative follow-up. However, 260 patients had at least some data available at Month 24+ and 256 (97.0%) were evaluable for Month 24+ CCS. Of the 10 patients not included in the CCS evaluation, one patient died, five patients had incomplete HHS scores and four patients were lost to follow-up.

5.1.3 Protocol Deviations

There were a total of six major protocol deviations among all enrolled procedures (pegged acetabular components) of which only one occurred in the unilateral group. These procedures have been removed from the analysis. There were no other major protocol deviations reported for patients in the investigational Pivotal Study Unilateral group. There were no protocol deviations reported during a comparable time frame in the Unilateral Control cohort.

5.1.4 Demographic Information

There was complete demographic information available for analysis for all patients enrolled in both the investigational and control Pivotal Study Unilateral group.

See Table 5.1 for a demographic summary of the patients enrolled in investigational and control groups.

Table 5.1 Baseline and Demographic Characteristics Pivotal Study Unilateral Patients vs. Unilateral Controls

Table 5.1
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	0.000
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.

Source [Tables_BaselineDemo_v2.sas]

There were more males (228; 67.7%) than females (109; 32.3%) enrolled in the Pivotal Unilateral Study cohort. There were also more males (165; 62.0%) than females (101; 38.0%) enrolled in the Unilateral Control cohort. The mean age of patients in the Pivotal Unilateral Study cohort at surgery was 50.1 years (SD 9.6, 15-79). Patients were older in the Unilateral Control cohort (mean age 53.3 yrs.; SD 11.1; 23-75). Over 85% of the patients in the Pivotal Unilateral Study cohort had a diagnosis of OA. A very similar percentage of patients presented with a primary diagnosis of OA in the Unilateral Control cohort (83.7%)

There was a significant difference between the investigational and control groups in respect to age at the time of surgery with the investigational group having the younger mean age. However, the three-year difference in mean age does not appear to be clinically relevant. There were no significant differences between the two cohorts in the male/female ratio, primary diagnosis, preoperative mean HHS, and weight. Data were not collected for Charnley Class, contralateral hip or knee status, duration of symptoms, and surgery within 12 months for the control group.

5.1.5 Surgical Details

Surgical details have been received for all 337 patients enrolled in the Pivotal Study Unilateral group. Details for the 337 surgeries are listed in Table 6.1 along with the surgical details for 266 patients enrolled in the Unilateral Control cohort.

Table 6.1 Surgical Details Pivotal Study Unilateral Patients vs. Unilateral Controls

Table 6.1
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	%			0.000
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	%			0.000
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%			0.000

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.

[Source: Tables_Surgical_Details.sas]

5.1.6 Safety and Effectiveness Data

The safety and effectiveness endpoints are being reported for the 24+Month timeframe.

As noted above, criteria for evaluation of the CCS include:

- HHS ≥ 20 point increase; HHS ≥ 80;
- Radiographic Success;
- Absence of Revision/Removal or Pending Revision/Removal;
- Absence of Device Related AE.

5.1.6.1 HHS

Harris Hip Total scores were evaluated as supporting efficacy endpoints in two ways. The first success criterion was related to the individual patient composite HHS[7] results at Month 24+ postoperatively compared to the preoperative status. Specifically, an improvement of ≥20 points in HHS at Month 24+ postoperatively over baseline (preoperative) values demonstrated patient success. The Sponsor believes that presentation of the HHS clinical success criterion as a patient achieving an Harris Hip Total score of ≥80 points at Month 24+ postoperatively is more clinically relevant than the criterion based on an improvement of 20 points or more. The HHS clinical success is presented both ways in this document.

The mean values, standard deviations, and minimum and maximum values of the HHS (range 0-100) and Range of Motion (ROM) Score (range 0-5) are summarized in Table 7.1(1) for patients in the Pivotal Study Unilateral cohort and patients in the Unilateral Control cohort.

Table 7.1(1) Pivotal Study Unilateral Patients and Unilateral Controls –Mean Harris Hip Total and ROM Scores

Table 7.1(1)
Pivotal Study Unilateral Patients
and Unilateral Controls
Mean Harris Hip Total and ROM Scores
All Evaluated (Actual[B])

	Investigational Total Score					Controls Total Score					
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	p-value[1]
Pre-0p	337	50.1	11.6	12.2	72.0	252	49.7	11.3	24.5	90.1	0.233
Week 6	329	77.4	12.4	26.4	100.0	246	79.0	11.7	40.6	100.0	0.021
Month 6	288	95.7	7.9	49.7	100.0	239	93.7	9.0	36.4	100.0	0.002
Month 12	285	96.2	7.9	41.9	100.0	246	95.0	8.0	52.3	100.0	0.002
Month 24	263	96.7	7.5	43.8	100.0	247	96.2	7.6	48.0	100.0	0.810
Month 24+	283	96.7	7.5	43.8	100.0	253	96.2	7.7	48.0	100.0	0.519
Month 36	80	96.2	7.6	66.9	100.0	187	96.0	7.7	48.6	100.0	0.619

	Investigational ROM Score					Controls ROM Score					
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	p-value[1]
Pre-0p	337	4.37	0.57	0.83	5.00	262	4.33	0.50	2.08	5.00	0.133
Week 6	330	4.65	0.29	3.20	5.00	252	4.67	0.22	3.73	5.00	0.931
Month 6	289	4.83	0.17	4.25	5.00	243	4.86	0.16	3.40	5.00	0.242
Month 12	286	4.86	0.15	4.38	5.00	251	4.90	0.13	4.13	5.00	0.016
Month 24	263	4.86	0.17	3.85	5.00	251	4.91	0.13	3.90	5.00	0.000
Month 24+	283	4.86	0.16	3.85	5.00	254	4.91	0.13	3.90	5.00	0.000
Month 36	83	4.82	0.41	1.68	5.00	189	4.93	0.08	4.63	5.00	0.005

Notes: [1] Wilcoxon Rank Sum Test

Source [Tables_Clinical_Followup_PRIMEFF_v2.sas]

The mean HHS was in the excellent range (90-100 points) for both the investigational and control groups at the Month 24+ follow-up interval. Mean scores were 96.7 and 96.2, respectively, for the investigational and control groups (p=0.519).

ROM values were 4.86 for the investigational group and 4.91 (out of possible 5 points) for the control group at Month 24+. The scores represent a statistical difference (p<0.01). However, the actual values represent an arc of motion of 103.0 (SD 17.5) for the investigational group and 106.1 (SD 10.6) for the control group and do not appear to represent a clinically relevant difference in ROM.

The control group showed a slightly higher total HHS score at the Week 6 visit but this trend was reversed at the Month 6 and Month 12 visits where the investigational group had a higher total score. There was no significant difference between the groups at Week 6 and Month 6 visits with respect to ROM however the control group showed a slightly higher ROM score at the Month 12 visit.

Tables 7.1(2) and 7.1(3) present the Harris Hip major categories of pain (0-44 points) and function (0-47 points) preoperatively, at Week 6, and at Months 6, 12, 24, 24+ and 36 among Pivotal Study Unilateral cohort patients and Unilateral Control cohort patents.

Table 7.1(2) Pivotal Study Unilateral Patients vs. Unilateral Controls –Harris Hip Pain Category

Table 7.1(2)
Pivotal Study Unilateral Patients vs. Unilateral Controls
Harris Hip Pain Category
All Evaluated (Actual[B])

	Preoperative				Week 6				Month 6				Month 12			
	I		C		I		C		I		C		I		C	
Hip Pain	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
None	0	0.0%	0	0.0%	131	39.6%	145	55.1%	206	70.5%	166	66.4%	216	75.3%	185	71.4%
Slight	0	0.0%	2	0.8%	149	45.0%	61	23.2%	68	23.3%	53	21.2%	51	17.8%	48	18.5%
Mild	2	0.6%	7	2.6%	30	9.1%	41	15.6%	9	3.1%	24	9.6%	7	2.4%	18	6.9%
Moderate	154	45.7%	94	35.3%	18	5.4%	15	5.7%	9	3.1%	7	2.8%	10	3.5%	8	3.1%
Marked	173	51.3%	160	60.2%	3	0.9%	1	0.4%	0	0.0%	0	0.0%	3	1.0%	0	0.0%
Disabled	8	2.4%	3	1.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

	Month 24				Month 24+				Month 36				Wilcoxon Rank Sum p-values	
	I		C		I		C		I		C			
Hip Pain	n	%	n	%	n	%	n	%	n	%	n	%	**Interval**	**p-value**
None	212	80.6%	196	76.3%	229	80.9%	197	76.1%	68	80.0%	150	78.1%	Preoperative	0.194
Slight	39	14.8%	45	17.5%	41	14.5%	45	17.4%	12	14.1%	27	14.1%	Week 6	0.026
Mild	5	1.9%	8	3.1%	6	2.1%	9	3.5%	2	2.4%	8	4.2%	Month 6	0.174
Moderate	4	1.5%	7	2.7%	4	1.4%	7	2.7%	3	3.5%	6	3.1%	Month 12	0.290
Marked	3	1.1%	1	0.4%	3	1.1%	1	0.4%	0	0.0%	1	0.5%	Month 24	0.223
Disabled	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	Month 24+	0.162
[Source: Tables_Clinical_Followup_PRIMEFF_v2.sas]													Month 36	0.695

Table 7.1(3) Pivotal Study Unilateral Patients and Unilateral Controls Harris Hip Function Score Category

Table 7.1(3)
Pivotal Study Unilateral Patients and Unilateral Controls
Harris Hip Function Score Category
All Evaluated (Actual[B])

	Preoperative				Week 6				Month 6				Month 12			
	I		C		I		C		I		C		I		C	
Category	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Normal (40-47)	7	2.1%	9	3.6%	58	17.7%	41	16.7%	260	91.9%	201	85.2%	263	93.3%	215	88.5%
Mild Dysfunction (40-<40)	141	41.8%	96	38.1%	88	26.8%	92	37.4%	15	5.3%	28	11.9%	14	5.0%	25	10.3%
Moderate Dysfunction (20-<30)	138	40.9%	114	45.2%	141	43.0%	97	39.4%	8	2.8%	6	2.5%	5	1.8%	3	1.2%
Severe Dysfunction (10-<20)	42	12.5%	30	11.9%	40	12.2%	16	6.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Disabled (0-<10)	9	2.7%	3	1.2%	1	0.3%	0	0.0%	0	0.0%	1	0.4%	0	0.0%	0	0.0%

	Month 24				Month 24+				Month 36				Wilcoxon Rank Sum p-values	
	I		C		I		C		I		C			
Category	n	%	n	%	n	%	n	%	n	%	n	%	**Interval**	**p-value**
Normal (40-47)	246	93.5%	229	93.9%	264	93.3%	237	93.7%	70	88.6%	174	93.0%	Preoperative	0.981
Mild Dysfunction (40-<40)	13	4.9%	12	4.9%	14	4.9%	12	4.7%	5	6.3%	10	5.3%	Week 6	0.038
Moderate Dysfunction (20-<30)	4	1.5%	3	1.2%	5	1.8%	4	1.6%	4	5.1%	3	1.6%	Month 6	0.019
Severe Dysfunction (10-<20)	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	Month 12	0.062
Disabled (0-<10)	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	Month 24	0.879
[Source: Tables_Clinical_Followup_PRIMEFF_v2.sas]													Month 24+	0.853
													Month 36	0.214

The majority of patients in both the investigational and control groups experienced marked hip pain preoperatively. Pain scores improved over time for both groups and 81% (229 patients) of the investigational group reported having experienced no pain at the Month 24+ follow-up evaluation. This was compared to 76% (197 patients) of the control group having experienced no pain at the same postoperative interval (p=0.162).

Improvement in function was noted at Month 24+ postoperative in both investigational and control groups with 93.3% and 93.7% of the patients in each group, respectively, having normal function (score between 40 and 47 points) (p=0.853). No patients were reported to have severe dysfunction or disability in either group at the Month 24 or 24+ postoperative follow-up intervals.

The control group showed higher function at the Week 6 visit, but then the investigational group overtook the control group and had better HHS function scores at the Month 6 and marginally at the Month 12 visits. Regarding the Pain Score, the control group reported less pain at the Week 6 visit, but this group difference disappeared at the subsequent postoperative visits. A review of AEs at Week 6 to Month 6 demonstrated a higher number of hip related AEs for the investigational group (34 events for the investigational group vs. 13 events for the control group) with the majority of the AEs related to hip pain and muscle weakness which may have contributed to the score differential.

The frequency distributions of HHS by category over time are presented in Table 7.1(4) and Table 7.1(4) b. There was no significant difference (p=0.904) at Month 24+ in the distribution of Harris Score categories between the investigational and control cohorts.

Table 7.1(4) Pivotal Study Unilateral Patients and Unilateral Controls – Harris Hip Total Score Category

Table 7.1(4)
Pivotal Study Unilateral Patients and Unilateral Controls
Harris Hip Total Score Category
All Evaluated (Actual[B])

	Preoperative				Week 6				Month 6				Month 12			
	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%	56	17.0%	38	15.4%	261	90.6%	189	79.1%	256	89.8%	209	85.0%
80-89	0	0.0%	0	0.0%	72	21.9%	95	38.6%	11	3.8%	31	13.0%	14	4.9%	23	9.3%
70-79	1	0.3%	9	3.6%	126	38.3%	70	28.5%	10	3.5%	9	3.8%	9	3.2%	6	2.4%
<70	336	99.7%	242	96.0%	75	22.8%	43	17.5%	6	2.1%	10	4.2%	6	2.1%	8	3.3%

	Month 24				Month 24+				Month 36			
	I		C		I		C		I		C	
Category	n	%	n	%	n	%	n	%	n	%	n	%
90 -100	240	91.3%	225	91.1%	258	91.2%	230	90.9%	70	87.5%	166	88.8%
80-89	14	5.3%	11	4.5%	14	4.9%	11	4.3%	4	5.0%	12	6.4%
70-79	2	0.8%	5	2.0%	4	1.4%	6	2.4%	5	6.3%	4	2.1%
<70	7	2.7%	6	2.4%	7	2.5%	6	2.4%	1	1.3%	5	2.7%

[Source: Tables_Clinical_Followup_PRIMEFF_v2.sas]

Wilcoxon Rank Sum p-values	
Interval	p-value
Preoperative	0.001
Week 6	0.012
Month 6	0.000
Month 12	0.102
Month 24	0.933
Month 24+	0.904
Month 36	0.750

This presentation of the data shows that the investigational group preoperatively may have been more debilitated 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). This may have contributed to the slightly better score distribution at the early (Week 6) visit for the control group. By the Month 6 visit the investigational group then overtook the control group with better score distributions. The trend continued at Month 12 with no difference at Month 24 or Month 24+ for both groups.

Table 7.1(4)b, demonstrates the consistency of study results for the investigational and control groups at Month 24+. No patient in either group had a total score <40 points, and each had one patient in the 40 to 49 point range.

Table 7.1(4)b Pivotal Study Unilateral Patients and Unilateral Controls – Harris Hip Total Score Category in 10-point increments

Table 7.1(4)b
Pivotal Study Unilateral Patients and Unilateral Controls
Harris Hip Total Score Category
All Evaluated (Actual[B])

	Preoperative				Week 6				Month 6				Month 12			
	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%	56	17.0%	38	15.4%	261	90.6%	189	79.1%	256	89.8%	209	85.0%
80-89	0	0.0%	0	0.0%	72	21.9%	95	38.6%	11	3.8%	31	13.0%	14	4.9%	23	9.3%
70-79	1	0.3%	9	3.6%	126	38.3%	70	28.5%	10	3.5%	9	3.8%	9	3.2%	6	2.4%
60-69	71	21.1%	28	11.1%	50	15.2%	25	10.2%	1	0.3%	9	3.8%	2	0.7%	6	2.4%
50-59	106	31.5%	77	30.6%	15	4.6%	10	4.1%	3	1.0%	0	0.0%	3	1.1%	2	0.8%
40-49	94	27.9%	92	36.5%	7	2.1%	8	3.3%	2	0.7%	0	0.0%	1	0.4%	0	0.0%
30-39	50	14.8%	35	13.9%	1	0.3%	0	0.0%	0	0.0%	1	0.4%	0	0.0%	0	0.0%
20-29	9	2.7%	10	4.0%	2	0.6%	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%

	Month 24				Month 24+				Month 36			
	I		C		I		C		I		C	
Category	n	%	n	%	n	%	n	%	n	%	n	%
90 -100	240	91.3%	225	91.1%	258	91.2%	230	90.9%	70	87.5%	166	88.8%
80-89	14	5.3%	11	4.5%	14	4.9%	11	4.3%	4	5.0%	12	6.4%
70-79	2	0.8%	5	2.0%	4	1.4%	6	2.4%	5	6.3%	4	2.1%
60-69	5	1.9%	3	1.2%	5	1.8%	3	1.2%	1	1.3%	4	2.1%
50-59	1	0.4%	2	0.8%	1	0.4%	2	0.8%	0	0.0%	0	0.0%
40-49	1	0.4%	1	0.4%	1	0.4%	1	0.4%	0	0.0%	1	0.5%
30-39	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
20-29	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
10-19	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%

Wilcoxon Rank Sum p-values	
Interval	
Preoperative	0.196
Week 6	0.015
Month 6	0.000
Month 12	0.105
Month 24	0.929
Month 24+	0.901
Month 36	0.751

[Source: Tables_Clinical_Followup_PRIMEFF_v2.sas]

Tables 7.1(5) and 7.1(6) summarize the HHS criteria over time. Table 7.1(5) summarizes patients with a total HHS >80 points, considered a clinical success. Table 7.1(6) provides a comparison of preoperative HHS to Month 24 and Month 24+ to establish success based on ≥20-point improvement over baseline.

Table 7.1(5) Pivotal Study Unilateral Patients and Unilateral Controls –Harris Hip Total Score Greater Than or Equal to 80

Table 7.1(5)
Pivotal Study Unilateral Patients
and Unilateral Controls
Harris Hip Total Score Greater Than or Equal to 80
All Evaluated (Actual[B])

	Number and Percentage Meeting Criteria						
	Investigational			Controls			
	N	n	%	N	n	%	p-value[1]
Pre-op	337	0	0.0%	252	1	0.4%	0.428
Week 6	329	128	38.9%	246	133	54.1%	0.000
Month 6	288	272	94.4%	239	220	92.1%	0.295
Month 12	285	270	94.7%	246	232	94.3%	0.850
Month 24	263	254	96.6%	247	236	95.5%	0.650
Month 24+	283	272	96.1%	253	241	95.3%	0.673
Month 36	80	74	92.5%	187	178	95.2%	0.393

Notes: [1] Fisher's Exact test.

[Source: Tables_Clinical_Followup_PRIMEFF_v2.sas]

A total HHS of 80 or greater is considered good to excellent. The percentage of patients reaching this threshold was higher in the control group at Week 6 and the percentage of patients in both groups with good or excellent HHS were similar at later intervals. The Month 24+ comparisons showed that very similar percentages achieved good to excellent results (96.1% in the investigational group versus 95.3% in the control group). The difference in percentages was not statistically significant (p=0.673).

The original protocol used a 20-point increase at Month 24 from baseline as success criteria for HHS. Table 7.1(6) shows the percentages of patients that met this definition of success.

The percentages of patients achieving clinical success based on a 20-point improvement in HHS were similar in the investigational and control groups at the Month 24 (98.6% in the investigational group versus 95.8% in the control group; p=0.100) and at the Month 24+ (98.8% in the investigational group versus 96.6% in the control group; p=0.060) time points.

Table 7.1(6) Pivotal Study Unilateral Patients and Unilateral Controls Increase from Baseline in Harris Hip Total Score Greater Than or Equal to 20

Table 7.1(6)
Pivotal Study Unilateral Patients
and Unilateral Controls
Increase from Baseline in Harris Hip Total Score
Greater Than or Equal to 20 - All Evaluated (Actual[B])

	Number and Percentage Meeting Criteria						
	Investigational			Controls			
	N	n	%	N	n	%	p-value[1]
Week 6	329	219	66.6%	233	176	75.5%	0.025
Month 6	288	282	97.9%	225	216	96.0%	0.291
Month 12	285	280	98.2%	235	225	95.7%	0.115
Month 24	263	259	98.5%	234	224	95.7%	0.100
Month 24+	283	279	98.6%	240	230	95.8%	0.060
Month 36	80	79	98.8%	177	171	96.6%	0.441

Notes: [1] Fisher's Exact test.

[Source: Tables_Clinical_Followup_PRIMEFF_v2.sas]

There were four patients with <20 points improvement at Month 24+ compared to baseline values and eleven patients with a HHS <80 points at Month 24+ postoperatively in the Cormet 2000 Hip Resurfacing Study. This finding suggests that the dichotomization of the HHS at 80-points may be more conservative than the 20-point improvement presentation.

Presented either way, there was no statistically significant difference compared to the controls with over 95% of the patients in each device group having a HHS of ≥80 points at Month 24+ (96.1% investigational group compared to 95.3% control group) or greater than 20 point improvement in HHS at Month 24+ over the preoperative score (98.6% investigational group compared to 95.8% control group). In total, there were more patients in the control group (10 patients) with less than 20-point improvement in HHS than in the investigational group (four patients).

There were 11 patients with HHS of <80 points at Month 24+ postoperatively in the investigational group. Nine of these patients had a HHS <80 at Month 24 and two patients had a HHS <80 points at Month 24+. A summary of the patient demographics and reasons for the HHS Score <80 points at Month 24 and 24+ was provided in Amendment 13.

5.1.6.2 Radiographic Success

Radiographic results including both the original protocol and the modified protocol are presented in Table 8.1(b). The Sponsor and independent radiograph reviewer believe this radiographic assessment allowed an accurate assessment of clinical success based on review of available radiographs. It minimized the effect of patient positioning on measurement results and offered a radiographic assessment that can be compared to the total hip arthroplasty control.

Table 8.1(b) Radiographic Clinical Success Among Original Protocol and Modified Protocol Combined

Table 8.1(b)
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.

[Source: Tables_Radiography_Rama_Expected.sas]

As presented in Table 8.1(b) there were no patients with radiolucencies in all acetabular zones at Month 24+. There were no cup failures based on migration and tilt criteria at Month 24+. There were 10 stem failures at Month 24+ as defined by both subsidence of ≥5mm and tilt of ≥1degree. One stem failure also had three-zone radiolucency in addition to component subsidence and tilt. Based on composite radiographic endpoints used in constructing the CCS, there were a total of 10 (3.6%) radiographic failures at Month 24+.

5.1.6.3 Absence of Revision or Pending Revision

Investigational Group

Twenty-four revisions were reported among investigational Pivotal Study Unilateral devices at latest follow-up. Reasons for revision included: acetabular loosening (four patients), dislocation (one patient), femoral loosening (11 patients), and femoral neck fracture (eight patients). There were no pending revisions in this group. More detail is provided in 5.1.8.5 and a narrative of each revision was provided in Amendment 13.

Control

Five patients (1.9%) were reported to have revision of one or more components of the ABC Ceramic-on-Ceramic System. One was revised following a peri-prosthetic fracture following a fall, one for recurrent dislocation, one for deep joint infection, one for excessive hip pain and suspected sepsis, and one for subsidence and femoral component loosening following a traumatic event. These patients were among the 266 unilateral patients. Description of each revision was reported in Amendment 13.

It is important to note that the ceramic-on-ceramic control device was implanted by a group of orthopaedic surgeons highly trained in the performance of total hip arthroplasty. The hip resurfacing procedure as well as use of the investigational devices was new to each of the investigators in the Cormet 2000 Hip Resurfacing Study since a hip resurfacing system had not been approved for the US market at that time. The factors associated with a higher revision rate included female gender, smaller component size and lower preoperative HHS score, which are typical of those found in the literature for hip resurfacing procedures. A leg length discrepancy of at least 1 cm was also found to increase revision risk. In addition, two of the investigators had a higher rate of revision in the study (11/24 revisions; 45.8%). These factors demonstrate the need for surgeon education and careful patient selection to assure successful outcomes for patients receiving this procedure.

5.1.6.4 Absence of Device Related Events

A device related event was defined as “an Adverse Event that occurs due to the design and/or material composition of the implant and/or implant instrumentation”. More specifically, a device related event is:

- Bone breakage around the implanted components;
- Aseptic loosening of the components, including complete radiolucency around the stem or evidence of 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.

Investigational

Thirty-three device related events in 32 patients (9.5%) were reported for the Pivotal Study Unilateral Patients in the investigational group at Month 24+ follow-up. Reasons for device related events included: acetabular loosening (five patients), avulsed lesser trochanter (one patient), dislocation (one patient),

femoral loosening (13 patients), femoral neck fracture (11 patients), femoral subsidence (one patient) and greater trochanter fracture (one patient). There were no pending revisions in this group.

In the investigational group there were no events of acetabular fractures, intraoperative femoral fractures, and postoperative femoral fractures.

Control

There were 24 device related events in 21 patients (7.9%) during a comparable time frame in the control group. Reasons for device related events included acetabular fracture (one patient), avulsed lesser trochanter (one patient), intraoperative ceramic insert chip (six patients), dislocation (seven patients), intraoperative femoral fracture (one patient), postoperative femoral fracture (six patients), and femoral subsidence (two patients). There were no pending revisions in this group.

5.1.7 Secondary Endpoint

5.1.7.1 Short Musculoskeletal Function Assessment (SMFA) Dysfunction and Bother Scores

The Short Musculoskeletal Function Assessment[14] is a 46 item patient self report questionnaire consisting of a dysfunctional improvement in health-related function index which has 34 items for the assessment of patient function and the bother index which has 12 items for how much patients are bothered by functional problems. The SMFA has been validated for use as a clinical assessment of the impact of treatment in groups of patients who have musculoskeletal disease or injury.

In short, the SMFA Function and Bother subscales were transformed to z-scores based on US reference population data. Smaller values reflect better health related quality of life. Among 272 patients with baseline and Month 24+ assessments, the mean (SD) SMFA Function z-score was 1.55 (0.77). At Month 24+ the mean (SD) was reduced to -0.34 (0.64). The mean (SD) change from baseline was -1.83 (0.84) reflecting very large improvements in health related quality of life for patient receiving the investigational device. Similar results were observed for the SMFA Bother subscale.

5.1.8 Safety

5.1.8.1 Adverse Events

Adverse events (AEs) were collected according to the ICH GCP definitions. Therefore, any untoward medical occurrence during the course of the investigation including any unintended sign, symptom, or disease was requested to be reported from the investigative sites. In addition, each site was visited by monitors who scanned the source data (medical charts, etc) for unreported AEs. The sites were then prompted to report them.

Table 9.1(1) provides a summary of the number of patients reporting adverse events of the various types.

Table 9.1(1) Summary of Complication Comparisons between Pivotal Study Unilateral Patients and Unilateral Controls - Summary

Table 9.1(1)
Summary of Complication Comparisons between
Pivotal Study Unilateral Patients and Unilateral Controls - Summary

	Investigational			Control			Exact
	n[8]	N[9]	%	n[8]	N[9]	%	p-value
Any complication	173	337	51.3%	173	266	65.0%	0.001
Any hip-related complication	83	337	24.6%	81	266	30.5%	0.118
Any device-related complication	32	337	9.5%	21	266	7.9%	0.563
Any operative complication[1]	13	337	3.9%	42	266	15.8%	0.000
Any post operative complication[2]	166	337	49.3%	164	266	61.7%	0.003
Any post operative hip-related complication[3]	79	337	23.4%	67	266	25.2%	0.633
Any post operative device-related complication[4]	32	337	9.5%	15	266	5.6%	0.093
Any post operative serious complication[5]	56	337	16.6%				
Any post operative serious hip-related complication[6]	10	337	3.0%				
Any post operative serious device-related complication[7]	28	337	8.3%				
Deaths	4	337	1.2%	3	266	1.1%	1.000

Notes:
[1] Complications occuring during implant procedure as reported on Complication Form.
[2] Complications occuring after implant procedure as reported on Complication Form.
[3] Includes any post operative hip-related complication.
[4] Includes any post operative complication.
[5] Includes any post operative complication meeting the criteria for a serious complication as assessed by the investigator.
[6] Includes any post operative complication hip-related complication assessed by the investigator as serious.
[7] Includes any post operative complication.
[8] Number of procedures w ith at least one of the specific types of complications.
[9] Total number of procedures in this cohort of patients.

[Source: Tables_Safety_vs_ABCcontrols_PRIMEFF.sas]

As seen in Table 9.1(1), 173 patients of the 337 patients in the Pivotal Study Unilateral investigational group (51.3%) reported a complication during the course of the study. In comparison, 173 of the 266 Pivotal Study Unilateral control patients (65.0%) reported a complication. The increase in adverse event reporting in the investigational group reflects the intensive study monitoring and site training, and while still lower in percentage than the control group, demonstrates a more consistent approach to IDE Study adverse event reporting. Still, the control population is a more mature database as the study occurred in 1996 and all patients have more years of follow-up. This difference is demonstrated by the average months of follow-up in the investigational group (31.2 months) versus the control group (42.8 months) even though control group follow-up was censored to be no longer than the longest follow-up among investigational devices (1803 days). Differences in physician reporting, and other factors can also contribute to this difference.

Hip related complications were defined as any AE related to the operative hip. Any AEs related to the contralateral hip were grouped with systemic AEs. There were 83 patients with hip related AEs in the Pivotal Study Unilateral group for a rate of 24.6%. The control patients showed a similar rate of hip-

related events (30.5%)(p=0.118). Refer to Table 9.1(4) for a complete listing of hip related Adverse Events.

As defined above, the following AEs could be generally regarded as device related events:

- Bone breakage around the implanted components;
- Aseptic loosening of the components, including complete radiolucency around the stem or evidence of 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.

Not included in these device-related AEs for the CCS criteria were other radiographic findings such as partial stem radiolucencies. These findings were evaluated by the independent radiographic reviewer and would contribute to the arm of the patient success criteria that relates to radiographic success. Only a subset of patients with radiographic findings had these findings reported as an AE and no attempt was made to prompt the sites for Complication forms for radiographic findings.

The rate of device related AEs in the Pivotal Study Unilateral Patients cohort was 9.5%. Confidence in the definition employed is gained by comparing the rate in the control unilateral group which was 7.9%. No statistical differences in rates were observed between the groups.

Operative complications in the Cormet 2000 Study were collected on the Operative Form. The control did not employ a separate form, so the timing of the events had to be used to classify events as “operative”. The difference in the rates (3.9% Pivotal Study Unilateral group versus 15.8% control unilaterals) may be related to this difference in collection.

On the case report form for AEs, the investigator was asked to determine if the AE was serious (yes, no), and anticipated (yes, no). The definition of seriousness (ICH GCP) includes any untoward medical occurrence which:

- Results in death;
- Is life threatening (at the severity experienced);
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability/ incapacity; OR
- Is a congenital anomaly/birth defect.

The historical control group data did not include an assessment of seriousness. Therefore, the comparison between the groups in rates of serious AEs cannot be made.

One UADE was reported to FDA as a result of a revision of an investigational acetabular component in April 2006. The subject had a history of operative hip bursitis, which was treated by injection; upon revision, the coating on the acetabular cup was found to have delaminated. The investigation found this to be an isolated incident with no root cause determined.

The following sections provide a further analysis by AE type between the Pivotal Study Unilateral Patients in the investigational and control, and an analysis of the time-course of AEs experienced by the two populations.

5.1.8.2 Systemic Adverse Events

Systemic AEs were those reported events that did not relate directly to the operation or the operative site/device. An analysis of the types of events reported and their time course distribution showed expected rates of other body system complications for this type of population.

Table 9.1(2) represents a breakdown of systemic AEs for the investigational and control groups. The first column (n^1) is the number of patients experiencing this type of complication. The second column (N^2) is the total population number, and the two are divided to provide the rate as a percentage in the third column. A complete listing of all adverse events including those listed as "other" is provided in Amendment 13 Attachment D.

Table 9.1(2) Complication Comparisons with Controls – Systemic Complications

Table 9.1(2)
Complication Comparisons with Controls - Specific Complications
Pivotal Study Unilateral Patients and Unilateral Controls

	Investigational			Control			Exact
	n^1	N^2	%	n^1	N^2	%	p-value[3]
Systemic							
Arrhythmia (operative)	1	337	0.3%	0	266	0.0%	1.000
Bronchopulmonary	1	337	0.3%	10	266	3.8%	0.003
Carcinoma	2	337	0.6%	13	266	4.9%	0.001
Cardiovascular	7	337	2.1%	24	266	9.0%	0.000
Death - unrelated to device	4	337	1.2%	3	266	1.1%	1.000
DVT	4	337	1.2%	0	266	0.0%	0.134
Gastrointestinal	5	337	1.5%	13	266	4.9%	0.017
Genitourinary	3	337	0.9%	15	266	5.6%	0.001
Infection remote location	1	337	0.3%	4	266	1.5%	0.175
Lack of nutrition	1	337	0.3%	0	266	0.0%	1.000
Low hemoglobin/hematocrit	1	337	0.3%	0	266	0.0%	1.000
Neuropathy	1	337	0.3%	0	266	0.0%	1.000
Neurosensory	8	337	2.4%	28	266	10.5%	0.000
Nosebleed	1	337	0.3%	0	266	0.0%	1.000
PE	2	337	0.6%	1	266	0.4%	1.000
Rash	4	337	1.2%	7	266	2.6%	0.228
Thrombophlebitis	0	337	0.0%	3	266	1.1%	0.085
Trauma (non-hip related)	7	337	2.1%	24	266	9.0%	0.000
Varicose veins	1	337	0.3%	0	266	0.0%	1.000
Other	84	337	24.9%	86	266	32.3%	0.055

[3] Two-sided Fisher's Exact tests. Comparisons were not performed for femoral neck notched (operative), greater trochanter notching (operative), ceramic insert chip (operative), and femoral neck fracture since both devices were not exposed to these types of events. Also, p-values are not reported when there were no events in either group.

The slightly higher rate of systemic AEs were reported in the Pivotal Study Unilateral control group. Both groups are demographically well matched, although the control group was statistically older by a few years. This may have had a slight impact on the amount of co-morbid conditions pre-existing in the control group and therefore a higher observed rate in this group. The rates of systemic events over time are presented in Table 9.1(3).

Table 9.1(3) Counts of Systemic Complications by Time of Occurrence

Table 9.1(3)
Specific Complications by Time of Occurrence - Pivotal Study Unilateral Patients and Unilateral Controls

	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
Systemic														
Arrhythmia (operative)	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Bronchopulmonary	0	1	1	2	0	2	0	0	0	1	0	4	1	10
Carcinoma	0	0	0	0	1	2	1	2	0	2	0	8	2	14
Cardiovascular	2	6	1	4	0	0	0	3	2	3	2	9	7	25
Death - unrelated to device	0	0	0	0	0	0	0	1	1	1	3	1	4	3
DVT	0	0	3	0	1	0	0	0	0	0	0	0	4	0
Gastrointestinal	0	1	3	3	0	1	0	2	0	2	2	7	5	16
Genitourinary	0	5	1	5	1	3	0	0	1	1	0	1	3	15
Infection remote location	0	0	0	0	1	1	0	0	0	1	0	2	1	4
Lack of nutrition	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Low hemoglobin/hematocrit	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Neuropathy	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Neurosensory	1	0	4	3	0	3	0	4	2	6	1	14	8	30
Nosebleed	0	0	1	0	0	0	0	0	0	0	0	0	1	0
PE	0	0	1	1	1	0	0	0	0	0	0	0	2	1
Rash	1	0	3	2	0	1	0	1	0	2	0	2	4	8
Thrombophlebitis	0	0	0	2	0	0	0	0	0	0	0	1	0	3
Trauma (non-hip related)	0	0	1	0	1	4	1	2	2	5	2	14	7	25
Varicose veins	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Other	3	3	15	12	18	9	15	12	29	20	27	50	107	106

5.1.8.3 Hip Related Events

Hip related events were the most reported postoperative AEs concerning the hip or operative site. Table 9.1(4) gives a breakdown of the rates of hip related AEs for the investigational group and the corresponding control group.

Reviewing these events as they occurred over time, the rates of hip related events seem to be higher in the control group in the immediate postoperative (up to Week 6) timeframe. However, there were more hip related AEs in the investigational group at Week 6 to Month 6. The majority of AEs seem to be related to postoperative hip pain (bursitis, tendonitis and muscle weakness) at the operative site.

Table 9.1(4) Complication Comparisons with Controls – Hip Related Complications

Table 9.1(4) Complication Comparisons with Controls - Specific Complications Pivotal Study Unilateral Patients and Unilateral Controls							
	Investigational			Control			Exact
	n[1]	N[2]	%	n[1]	N[2]	%	p-value[3]
Hip Related Events							
Acetabular Crack (operative)	0	337	0.0%	0	266	0.0%	
Acetabular malpositioned (operative)	2	337	0.6%	0	266	0.0%	0.506
Broken drill bit (operative)	0	337	0.0%	0	266	0.0%	
Bursitis	16	337	4.7%	16	266	6.0%	0.584
Deep infection	0	337	0.0%	1	266	0.4%	0.441
Elevated metal ion level	1	337	0.3%	0	266	0.0%	1.000
Femoral Crack (operative)	0	337	0.0%	10	266	3.8%	0.000
Femoral neck notched (operative)	4	337	1.2%	0	266	0.0%	0.134
Femoral radiolucency	9	337	2.7%	0	266	0.0%	0.006
Greater Trochanter Notching (operative)	1	337	0.3%	0	266	0.0%	1.000
Hematoma	4	337	1.2%	2	266	0.8%	0.699
Heterotopic Bone Formation	6	337	1.8%	8	266	3.0%	0.416
Hip Pain (operative side)	18	337	5.3%	8	266	3.0%	0.225
Leg Length discrepancy	10	337	3.0%	0	266	0.0%	0.003
Limp	3	337	0.9%	0	266	0.0%	0.259
Loose Body	0	337	0.0%	0	266	0.0%	
Muscle Weakness	2	337	0.6%	0	266	0.0%	0.506
Myositis ossificans	3	337	0.9%	0	266	0.0%	0.259
Nerve palsy	1	337	0.3%	4	266	1.5%	0.175
Skin split	0	337	0.0%	0	266	0.0%	
Soft Tissue Trauma	1	337	0.3%	13	266	4.9%	0.000
Squeaking implant/clicking	6	337	1.8%	2	266	0.8%	0.476
Subchondral cyst	1	337	0.3%	0	266	0.0%	1.000
Subluxation	4	337	1.2%	0	266	0.0%	0.134
Superficial infection	3	337	0.9%	3	266	1.1%	1.000
Tendonitis	8	337	2.4%	5	266	1.9%	0.782
Trochanteric Crack (operative)	0	337	0.0%	7	266	2.6%	0.003
Wound Related (non-infected)	3	337	0.9%	16	266	6.0%	0.001
Other	2	337	0.6%	5	266	1.9%	0.250

Table 9.1(5) presents the hip related AEs over time for both groups. The control group's higher rates of specific AEs common to both procedures continue in this presentation of hip-related events.

Femoral neck notching is only associated with the investigational resurfacing group as the femoral neck is removed as an early step in total hip replacement. Neck notching has been reported in the literature,[15] however, very few rates of this event have been published. One series did identify notching in 16 out of the 63 patients reported for a rate of 25%,[16] and another reported 26/50 (52%) cases that resulted in

femoral neck fracture had notching.[17] Femoral neck notching is known to be dependent on the surgical technique and might be expected to be higher in a multi-center trial such as this one. Neck notching is thought to be problematic as it may be a risk factor for future femoral neck fractures. However, none of the four cases with a reported intraoperative femoral neck notching went on to have a femoral neck fracture later in their treatment course.

Trochanter notching is also more associated with resurfacing as a factor of the instrumentation used to resurface the femoral head. Similarly, trochanteric and femoral cracking are associated more with total hip systems, as the resurfacing stem does not invade the shaft of the femur or the trochanter.

Postoperative leg length discrepancy was reported in ten patients in the investigational group and not at all in the unilateral control group. It is important to note, that resurfacing by design is less susceptible to iatrogenic leg length discrepancies than total hip arthroplasty. In resurfacing, the femoral component is mounted directly on the patient's natural femoral head. Also, any bone removed from the acetabulum is replaced in kind by the acetabular cup component. Unless the devices are not seated fully, the surgeon cannot change the length of the leg. In total hip arthroplasty the femoral head and neck are removed and replaced by metal components. The surgeon can choose a femoral stem with varying neck angles and femoral heads with different head offsets to change the patient's leg length. The question remains as to why leg length discrepancy was reported more often in the Cormet 2000 Hip Resurfacing System group than the historical control group (total hip replacement). The first explanation is one of surgeon expectations. In total hip arthroplasty, a certain amount of leg length change is expected and tolerated without concern. In resurfacing arthroplasty, the surgeons expect no leg length discrepancy after the surgery. This expectation is distorted by two factors: the patient's natural leg length discrepancy, and the effects of the underlying arthritis in leg shortening. Therefore, if a patient had a leg length discrepancy preoperatively, they would maintain that leg length discrepancy after resurfacing. Also, if a patient naturally had a 1cm leg length discrepancy at birth, and then developed arthritis on the longer side, that leg length could shorten to be more even with the contralateral side. When resurfacing occurred, the leg would then be lengthened to their native state of +1cm. In this study, an assessment of preoperative leg length discrepancy other than as reported in preoperative HHS was not undertaken and so is not available for reference.

Reports of leg length discrepancy have been noted in the literature for hip resurfacing. Amstutz et al.[15] reported a rate of leg length discrepancy of 25/355=7%. The authors explained that all cases had LLD preoperatively.

Table 9.1(5) Counts of Hip Related Complications by Time of Occurrence

Table 9.1(5)
Specific Complications by Time of Occurrence - Pivotal Study Unilateral Patients and Unilateral Controls

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

5.1.8.4 Device Related Events

The protocol definition of device related AE was "an AE that occurs due to the design and/or material composition of the implant and/or implant instrumentation". From this definition, we have further refined the category to include:

- Bone breakage around the implanted components;
- Aseptic loosening of the components, including complete radiolucency around the stem or evidence of 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.

Table 9.1(6) gives a breakdown of the rates of device related AEs for the investigational group and the corresponding control group.

Table 9.1(6) Complication Comparisons with Controls – Device Related Events (Numbered here as it appeared in Amendment 13)

Table 9.1(6)
Complication Comparisons with Controls - Specific Complications
Pivotal Study Unilateral Patients and Unilateral Controls

	Investigational			Control			Exact
	n[1]	N[2]	%	n[1]	N[2]	%	p-value[3]
Device Related Events							
Acetabular Fracture	0	337	0.0%	1	266	0.4%	0.441
Acetabular loosening	5	337	1.5%	0	266	0.0%	0.070
Avulsed lesser trochanter	1	337	0.3%	1	266	0.4%	1.000
Ceramic Insert Chip (operative)	0	337	0.0%	6	266	2.3%	0.007
Dislocation	1	337	0.3%	7	266	2.6%	0.025
Femoral Fracture (operative)	0	337	0.0%	1	266	0.4%	0.441
Femoral Fracture (post-op)	0	337	0.0%	6	266	2.3%	0.007
Femoral loosening	13	337	3.9%	0	266	0.0%	0.001
Femoral neck fx	11	337	3.3%	0	266	0.0%	0.002
Femoral subsidence	1	337	0.3%	2	266	0.8%	0.586
Trochanter (greater) fx	1	337	0.3%	0	266	0.0%	1.000

Notes:

[1] Number of procedures with at least one of the specific types of complications. The total number of procedures with at least one complications is smaller than the sum, since procedures can have more than one type of complication.

[2] Total number of procedures in this cohort of patients.

[3] Two-sided Fisher's Exact tests. Comparisons were not performed for femoral neck notched (operative), greater Trochanter Notching (operative), ceramic insert chip (operative), and femoral neck fracture since both devices were not exposed to these types of events. Also, p-values are not reported when there were no events in either group.

[Source: Tables_Safety_vs_ABCcontrols_PRIMEFF.sas]

Table 9.1(7) presents the device related adverse events over time for both groups.

Table 9.1(7) Counts of Device Related Events by Time of Occurrence

Table 9.1(7)
Specific Complications by Time of Occurrence - Pivotal Study Unilateral Patients and Unilateral Controls

	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	0	0	1	0	0	0	2	0	2	0	5	0
Avulsed lesser trochanter	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Ceramic Insert Chip (operative)	0	6	0	0	0	0	0	0	0	0	0	0	0	6
Dislocation	0	0	1	7	0	0	0	0	0	0	0	0	1	7
Femoral Fracture (operative)	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Femoral Fracture (post-op)	0	0	0	3	0	2	0	0	0	0	0	1	0	6
Femoral loosening	0	0	0	0	0	0	1	0	7	0	5	0	13	0
Femoral neck fx	0	0	0	0	3	0	5	0	3	0	0	0	11	0
Femoral subsidence	0	0	0	0	1	0	0	1	0	1	0	0	1	2
Trochanter (greater) fx	0	0	0	0	0	0	0	0	0	0	1	0	1	0

[Source: Tables_Safety_vs_ABCcontrols_PRIMEFF.sas]

Acetabular fracture is a rare event in both groups, as expected. Acetabular fracture can happen both at the time of surgery due to cup impaction, or in the postoperative period due to trauma. In this control case, the fracture happened intraoperatively.

Acetabular loosening occurs when the acetabular cup is not seated fully in the surrounding bone during implant or when osteolysis or bone resorption occurs around the cup after implant. There were five cases of acetabular loosening in the investigational group for which three were revised to a total hip replacement system and one was revised to a pegged cup but retained the femoral resurfacing component.

Chipping and breakage of the ceramic insert at surgical impaction is a known risk of devices using this bearing couple. The devices are usually replaced intraoperatively with no known clinical sequelae. There were six cases reported in the control group.

The rate of dislocation of the pivotal unilateral group was significantly lower than that reported in the control group. This difference highlights the benefits of a large diameter head, which is one of the common features of resurfacing devices such as the Cormet 2000. The control group used ceramic heads that ranged from 28 to 32mm. In contrast, the investigational group had head sizes that ranged from 40 to 56mm. It is well established that an increase in head size decreases dislocation by increasing the ROM available prior to impingement which leads to the torquing out of the head from the cup.[18,19,20] Two other publications reported dislocation in resurfacing at 0.75% which is similar to the results achieved in this study.[15,21]

Peri-prosthetic femoral fracture is more common in total hip arthroplasty than in resurfacing arthroplasty and that difference is illustrated by the comparison of these two groups. The control group reported a rate of femoral fracture (intraoperatively and postoperatively) of 2.3% while none were reported in the investigational Pivotal Study Unilateral group. This difference can be attributed to the nature of the implant design. Total hip resurfacing relies on a large metal femoral component which cannulates the femur and extends into the diaphysis. Resurfacing, however, has a small femoral component that extends only into the femoral neck. Femoral fracture is a serious device related AE that must be corrected surgically with additional fixation and/or the revision of the component to a longer stem which by passes the break. This risk is naturally avoided by the design of the resurfacing femoral component.

Femoral neck fracture is a known failure mechanism of hip resurfacing devices. In this series, a 3.3% rate of postoperative femoral neck fracture was observed in this cohort. While this rate is higher than recently published in a review of 50 cases from the Australian registry,[22] the registry conclusions are relevant to the study results. This report indicates that older, overweight women had a higher risk of fracture. The authors also link femoral neck fracture to superior neck notching at implant and varus placement of the femoral component of more than 5 degrees. Thus, surgical technique as well as patient selection is important influencing factors for the rate of this complication. The surgeon's learning curve has also been published as a factor in the rate of femoral neck fracture.[23] Comparing the pivotal unilateral rate of 3.3% to that of the Continued Access Cohort of 1.9%, a decreasing trend may be emerging as the study matures.

Femoral loosening is also more prevalent in resurfacing than in total hip arthroplasty although it is observed only in a small percentage of patients undergoing hip resurfacing. The small and minimally penetrating femoral stem is seated on a resurfaced native femoral head and secured with bone cement. In total hip arthroplasty, the larger femoral component is wedged into the cortical bone of the metaphysis and extends down the diaphysis. This results in an inherently more stable construct. In this study, the Pivotal Study Unilateral group showed a 3.3% rate of femoral loosening while none of the total hip control patients exhibited femoral loosening in the early timeframe. However, there were no femoral loosenings identified in the 698 procedures enrolled in the Continued Access Cohort which supports the trend identified above indicating a decreasing number of specific adverse events such as femoral neck fracture and femoral loosening as the study matures.

Overall, the rates of device related AEs were similar between the investigational (9.5%) and control (7.9%) groups in this study. The type of AE differs between the groups, however, as the investigational group exhibited higher rates of femoral neck fracture and component loosening, while the control group had higher rates of femoral fracture and dislocation.

5.1.8.5 Revisions / Removals Overview

Investigational Group

Twenty-four revisions were reported for Pivotal Study Unilateral Patients. Reasons for revision included: acetabular loosening (four patients), dislocation (one patient), femoral loosening (11 patients), and femoral neck fracture (eight patients). There were no pending revisions in this group.

A detailed analysis of factors associated with increased revision risk was conducted. In short, a multivariable Cox regression model (hazard ratio; 95% CI) was estimated based on data from the Pivotal Unilateral cohort. The following factors were simultaneously associated with increased revision risk: 40mm or 44mm versus larger component size (hazard ratio=5.5; 95% CI 2.3 to 13.5), a non osteoarthritis diagnosis (hazard ratio; 95% CI 1.8 to 13.8), a leg length discrepancy ≥ 1 cm (hazard ratio; 95% confidence 1.0 to 5.0), and a baseline Harris Hip Total score in the lowest quartile (HHS<43) of our sample (hazard ratio=6.4; 95% 95% CI 2.6 to 15.7). When 0, 1, 2, or 3 of these risk factors were present, 1 of 136 (0.7%), 5 of 117 (4.3%), 12 of 66 (18.2%), and 3 of 18 (33.3%), respectively, required revision. Restricting attention to patients with at least 24 months followup (including all revisions) in order to account for unequal follow-up, revision risk for patients with 0, 1, 2, and 3 risk factors was 1 of 120 (0.8%), 5 of 106 (4.7%), 12 of 60 (20.0%), and 6 of 16 (37.5%). The linear trend in these percentages was statistically significant ($p<0.0001$). Female gender was also a significant risk factor in unadjusted analyses (hazard ratio=2.4, 95% CI 1.1 to 5.5), but was not significant after controlling for component size. In addition, one investigator accounted for 10 of 24 (41.7%) of the revisions but only 38 of 337 (11.3%) of the procedures in the Pivotal Study Unilateral cohort. These factors demonstrate the need for careful patient selection and standardization of procedures among surgeons in order to assure successful outcomes for patients receiving this procedure.

Control Group

Five patients (1.9%) were reported to have revision of one or more components of the ABC Ceramic-on-Ceramic System. These patients were among the 266 unilateral patients. Refer to Section 3.1.6.3, Amendment 13 for narratives for each reported revision.

The increased rate of early revision in the investigational group when compared to the controls can be related back to the types of AEs that are more prevalent in the investigational group than the control. Femoral neck fracture is an event that is unique to resurfacing and was the cause of eight revisions in the early time period. Although dislocation was higher in the control group than the investigational group, dislocation is often treated by closed reduction and bracing which does not require a revision of the components.

It should also be noted that at the time the control study was undertaken, the investigators in that study were already expert in the surgery of total hip arthroplasty as the technique had been long established. In contrast, the surgeons in the Cormet 2000 resurfacing study performed their first resurfacing surgeries as part of this trial. Therefore, learning curve is captured in the investigational study results whereas these same issues were not part of the historical control group experience

5.1.8.6 Deaths

Investigational

One death (0.29%) was reported by Month 24 for patients in the Investigational Pivotal Study Unilateral group. This death was a result of due to complications of lung cancer. There were an additional three deaths reported for patients in the Investigational Pivotal Study Unilateral group by Month 36. Two of these were a result of cardiac disease and one was a result of lung cancer that had metastisized to the brain. A description of these events is provided in Amendment 13.

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 a myocardial infarction.

5.1.9 Potential Lost to Follow-up

The following Table 10.1 demonstrates the potential lost to follow-up in the Pivotal Study Unilateral Patients population.

Table 10.1 Potential Lost to Follow-Up - Pivotal Study Unilateral Patients – (Investigational vs. Control)

Pivotal Study Unilateral Patients	Number of Patients	Number of Patients
	Investigational	Control
Pivotal Study Group	337	266
Patients with complete CCS at Month 24+	292	256
Patients died before Month 24+	1	2*
Patients not evaluated for CCS	44	9
Died after 24 Month interval	2	0
Complete HHS data only	9	5
Complete Radiographic data only	5	0
Patients with no 24+ Month follow-up; Potential lost-to follow-up	28	4

*One patient who died was a device related AE failure at Month 24+; therefore included in the CCS

A total of 28 cases in the Pivotal Study Unilateral group are considered potentially lost to follow up as of the date of database closure for this report. Potential lost to follow up is being defined as missing Harris Hip Score and Radiograph data at Month 24 and Month 24+ follow up. Of the 28 cases, 16 (57%) were enrolled at Site 3, four (14%) at Site 10, three (11%) at Site 1, two (7%) each at Site 9 and Site 5, and one (4%) at Site 12. Table 10.2 below illustrates the number of potential lost to follow up cases at each site with the corresponding total enrolment in the Pivotal Study Unilateral group.

Table 10.2. Potential Lost to Follow up vs. Total Enrolment – Pivotal Study Unilateral Group

Site	Potential Lost to Follow-up	Total Enrolled	Percent Lost to Follow-up
Site 3	16	134	12%
Site 10	4	21	19%
Site 1	3	42	7%
Site 5	2	38	5%
Site 9	2	3	67%
Site 12	1	31	3%

5.1.10 Composite Clinical Success

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 control.

The CCS is being reported for the Month 24+ timeframe based on FDA's Patient Accounting deficiency requiring a minimum 85% follow-up for CCS evaluation. FDA stated that while it is not possible to obtain

data from earlier time points, that the Month 24+ and Month 36 follow-up points could be used to evaluate success rates.

The following non-inferiority hypothesis was test in primary efficacy analyses of Composite Clinical Success (CCS) comparing clinical outcomes between patients in the investigational Pivotal Study Unilateral cohort and patient in the Unilateral Control cohort.

The null and alternative non-inferiority hypotheses were formulated to be consistent with the Blackwelder approach and are as follows:

H_o: $P_{Cormet2000} - P_{HCG} \leq -0.08$ (investigational device clinically inferior to control)

H_a: $P_{Cormet2000} - P_{HCG} > -0.08$ (investigational device not clinically inferior to control)

The study was designed to reject the null hypothesis that the Cormet 2000 resurfacing device (investigational device) is clinically inferior to the ABC ceramic-on-ceramic total hip replacement (control) in term of the proportion of patients achieving composite clinical success. The non-inferiority delta was specified to be equal to 0.08. Thus, the study was designed to reject the null hypothesis that the proportion of patients achieving composite clinical success with the investigational device is at least 0.08 less than the proportion of patients achieving composite clinical success with the control device.

A one-sided 95% non-inferiority confidence interval for the difference in proportions was determined in order to test this hypothesis. If the lower bound of this confidence interval exceeds -0.08 then the null hypothesis may be rejected and it can be concluded that in terms of composite clinical success, the investigational device is not clinically inferior to the control device.

Achievement of composite clinical success (CCS) required:

- At least good clinical results as defined by a Harris Hip Total score of at least 20 points higher (original Harris Hip Score criterion) at Month 24+ as compared to preoperative baseline score,
- Absence of revision of any device components,
- Absence of device related AEs, and
- Absence of radiographic failure;

Analyses were also performed replacing the HHS component with:

- At least good clinical results as defined by a Harris Hip Total score of at least 80 points at Month 24+ (modified Harris Hip Score criterion).

The CCS using the HHS endpoint of a Month 24 and a Month 24+ HHS of ≥20 points improvement over baseline preoperative score, absence of revision of any device component, absence of device related AEs, and absence of radiographic failure is presented in Table 11.1(1).

Table 11.1 (1) Month 24 Composite Clinical Success (CCS) Using Original HHS Definition and Modified Radiographic Assessment

Table 11.1(1)
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 was 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.

Source [Tables_Clinical_Followup_vs_controls_PRIMEFFxz.sas]

n = Number of patients who are a success according to CCS criteria
N = Number of patients with complete CCS endpoints

For the analysis using an increase in Harris Hip Total score of ≥20 points, 256 of 291 Pivotal Study Unilateral patients (proportion=0.880) achieved Month 24+ composite clinical success. Similarly, 213 of 243 (proportion=0.877) Unilateral Control patients achieved composite clinical success. The difference in proportions is equal to +0.003. The lower bound of the one-sided 95% non-inferiority confidence interval is -0.044. Since -0.044 exceeds -0.08, the null hypothesis of inferiority is rejected with $p<0.05$ and it is concluded that the investigational device is not clinically inferior to the control device on the basis of this CCS. Sensitivity analyses in the remaining three rows of this table provide non-inferiority results varying the procedures included in analyses. The primary analysis is the most inclusive.

Similarly, the first row of Table 11.1(2) summarizes the results of the primary non-inferiority test defining at least good clinical results as HHS≥80 rather than as a change from baseline of ≥20 points. The sample sizes are 1 larger for investigational devices and 13 larger for control devices when comparing the first row in Table 11.1(2) to the first row in Table 11.1(1). There was one investigational device patient with baseline and Month 24 HHS equal to 34.8 and 75.4, respectively, for a change of 40.6 points. This patient was defined as a CCS failure due to HHS<80 even though there was incomplete radiographic evaluation. Conversely, based on the original HHS criterion for CCS, even though the increase in HHS

was at least equal to 20 points, confirmation of CCS success could not be made since success required good outcomes for all CCS components. In contrast, CCS failure simply needs any one component indicating failure whether or not the other components are evaluable. For example, a patient with a revision at Month 6 is a CCS failure even though there is no HHS or radiography (naturally) at Month 24. Among Unilateral control patients, there were 13 missing baseline HHS. Thus, these 13 patients could not be evaluated using the original HHS criterion of change from baseline at least equal to 20 points. In contrast, all of the 13 patients had Harris Hip total score that were at least equal to 96 points and so were clearly clinical successes in terms of the intent of the Harris Hip Score assessment. As a consequence, the modified CCS includes 13 more controls patients than the original CCS. These examples serve to reinforce the notion that the CCS based on requiring a Month 24 or Month 24+ HHS ≥80 points is greater clinical and research utility than the original criterion of requiring a change from baseline of at least 20 points.

Table 11.1 (2) Month 24 Composite Clinical Success (CCS) Using Modified HHS and Radiographic Definitions

Table 11.1(2)
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 Total 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 was 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.

[Source: Tables_Clinical_Followup_vs_controls_PRIMEFFz.sas]

n = Number of patients who are a success according to CCS criteria
N = Number of patients with complete CCS endpoints

For the analysis using a Harris Hip Total score of ≥80, 251 of 292 Pivotal Study Unilateral patients (proportion=0.860) achieved Month 24+ composite clinical success. Similarly, 224 of 256 (proportion=0.875) Unilateral Control patients achieved composite clinical success. The difference in proportions is -0.015. The lower bound of the one-sided 95% non-inferiority confidence interval is -0.063. Since -0.063 exceeds -0.08, the null hypothesis of inferiority is rejected with $p<0.05$ and it is concluded that the investigational device is not clinically inferior to the control device on the basis of this CCS. Sensitivity analyses in the remaining three rows of this table provide non-inferiority results varying the procedures included in analyses. The primary analysis is the most inclusive.

Primary analyses of the CCS based on the approved protocol HHS criteria and or the modified HHS criteria demonstrates non-inferiority of the Cormet 2000 Hip Resurfacing System to the ABC Ceramic-on-Ceramic control regardless of Month 24 evaluation or Month 24+ with expanded windows for patient follow-up.

The Sponsor proposes the Month 24+ Actual^{B} analysis as the most relevant presentation of the data. Clinically, patients post hip replacement have a stable course in the Month 24 to Month 36 postoperative timeframe. Therefore, including data after Month 24 (730 days) is not expected to improve the clinical results and the rollback imputation providing support for the rollback imputation. Furthermore, Bland-Altman agreement analyses of 85 procedures with both Month 24 and Month 36 HHS evaluations demonstrated no significant bias when imputing Month 24 values with Month 36 values (mean difference = -0.30; p=0.59; 95% CI for bias = -1.37 to 0.78). In only 2 of 85 cases (2.4%) was the Month 36 value more than 10 point larger than the corresponding Month 24 value. The 5th and 95th percentile values were -8.5 and 6.1 indicating that 90% of the differences were between -8.5 and 6.1 points. Similarly, the 10th and 90th percentile values were -5.9 and 3.1 points, respectively, indicating that in less than 10% of the cases was Month 36 more than 3.1 points larger than the corresponding Month 24 values.

Additionally, only 11 Actual^{B} patients (seven investigational; four control) had their Month 24 visit before the start of the visit window (i.e., before 670 days), and only three of these patients (one investigational patient at three days out of window; two control patients at four and 45 days out of window, respectively) had data available for CCS, all of which were considered to be successes. Therefore, the control device is favored by including all Month 24 visits out of window.

5.1.10.1 Propensity Score Analysis of Patient Success

A propensity score analysis was performed to assess and control for any selection bias in the results due to the non-randomized nature of the study. The propensity score analysis allows for simultaneously controlling for a number of covariates. Table 11.1(3) shows the differences in the covariates of gender, age, weight, marked pain at baseline and Harris Hip Score at baseline that were used in the propensity score analysis. All covariates included in the model were selected based on the factors believed to potentially have a clinical impact on a patient's outcome.

As shown in Table 11.1(3), the majority of covariates were not significantly different at baseline between treatment groups. A logistic regression was fit with the treatment group (*i.e.,* investigational or control) as the dependent variable and the covariates of gender, age, weight, marked pain at baseline and Harris Hip Score at baseline were included as the independent variables. The predicted values from this model (or the probability of being assigned to the investigational device given that patient's covariates) were then ranked and divided into quintiles. In order to assess the bias removed by use of the quintiles, as determined by the propensity scores, an analysis of variance linear model (if the variable is continuous) or a logistic regression was fit for each of the covariates as the dependent variables, with group and quintile as the independent variables. The statistical significance of group differences with and without controlling for propensity score quintile are given in Table 11.1(3). In all cases, the p-values increased when controlling for propensity score quintile, and in the case of age, went from being significant (p<0.001) to not significant (p=0.342). This demonstrates that the propensity score is a balancing score and group differences controlling for the propensity remove the influence of any imbalance between groups in these variables.

Table 11.1(3) Adjusted Covariate Between Group Comparisons

Variable	Unadjusted p-value	Adjusted p-value
Marked Pain at Baseline	0.150	0.823
Gender	0.135	0.982
Weight	0.692	0.756
Baseline HHS	0.233	0.859
Age	<0.001	0.342

Table 11.1(4) contains the treatment group odds ratio for CCS outcome based on the four different patient populations (Month 24 Actual[A], Month 24 Actual [B], Month 24+ Actual[A] and Month 24+ Actual[B]) and the two definitions of CCS (modified and original). As shown in this table, and as anticipated, there is some variability in success rates across quintiles. When adjusting for the propensity scores through use of the propensity score or quintiles of the propensity score, the overall study conclusions do not change. In most cases the propensity score adjustment results in a treatment group odds ratios for CCS outcome that is closer to 1.0.

Table 11.1(4) Month 24 Composite Clinical Success (CCS) with Propensity Score Adjustments

Table 11.1(4)

Month 24 Composite Clinical Success (CSS) with Propensity Scores Adjustments

	Unadjusted			Adjusted by Continuous Score			Adjusted by Quintile		
	Odds Ratio	**95% CI**	**p-value**	**Odds Ratio**	**95% CI**	**p-value**	**Odds Ratio**	**95% CI**	**p-value**
Modified Definition									
Month 24 Actual[A]	0.65	(0.36, 1.16)	0.147	0.72	(0.40, 1.31)	0.285	0.79	(0.43, 1.44)	0.441
Month 24 Actual[B]	0.81	(0.49, 1.36)	0.435	0.90	(0.54, 1.53)	0.703	0.96	(0.57, 1.63)	0.885
Month 24+ Actual[A]	0.88	(0.53, 1.45)	0.610	0.96	(0.58, 1.61)	0.890	1.03	(0.61,1.73)	0.916
Month 24+ Actual[B]	0.88	(0.53, 1.44)	0.597	0.96	(0.58, 1.59)	0.882	1.03	(0.62, 1.71)	0.907
Original Definition									
Month 24 Actual[A]	1.33	(0.73, 2.40)	0.351	1.32	(0.72, 2.43)	0.368	1.18	(0.64, 2.19)	0.591
Month 24 Actual[B]	0.95	(0.56, 1.62)	0.854	0.97	(0.56, 1.66)	0.903	1.04	(0.60, 1.80)	0.879
Month 24+ Actual[A]	1.04	(0.61, 1.77)	0.884	1.06	(0.62, 1.82)	0.832	1.13	(0.66, 1.95)	0.659
Month 24+ Actual[B]	1.03	(0.61, 1.73)	0.911	1.05	(0.62, 1.78)	0.852	1.12	(0.66, 1.91)	0.668

5.1.10.2 Imputations of Patient Success

As previously noted, patient success was defined at Month 24 postoperatively as a patient who achieved four distinct success criteria. They are as follows: good or excellent clinical results as reflect by the value of the Harris Hip Total score, absence of revision, absence of device related AE, and radiographic success. Non-inferiority with an 8% delta was shown for the primary comparison involving Month 24+ follow-up with expanded intervals as well as most other scenarios regarding inclusion of patients in the analysis. In order to assess the impact of missing data on the non-inferiority comparisons, results using several imputation methods were assessed. The following methods were used to impute the results for patients missing composite clinical success endpoints: (1) including all patients as failures; (2) including all patients as successes; (3) a stepwise imputation method; and (4) a multiple imputation method. Imputation methods (1), (2) and (4) were performed for CCS outcome based on all four of the patient populations (Month 24 Actual[A], Month 24 Actual[B], Month 24+ Actual[A] and Month 24+ Actual[B]) and the two definitions of CCS (modified and original). Imputation (3) (the stepwise imputation method) was only performed for the Month 24+ Actual B patient population because this patient population is the most representative patient population and meets FDA's requirement of ≥85% follow-up at Month 24+ to evaluate success rate.

5.1.10.3 Missing Data as Failures

Due to the imbalance of missing data between groups, imputing all missing data as failures results in a larger percentage of imputed failures in the investigational group than in the control group. Including all patients with missing data as failures yields differences in rates that are similar to the differences in the

percentages of missing data. For this reason, the 8% delta was not met. However, the addition of 54 patients to the Month 24+ CCS evaluation in Amendment 13 (85% follow-up) compared to Amendment 8 (70% follow-up) did not change the overall success rate [Table 11.1(2) 95% CI LB –0.062 in Amendment 8 and –0.063 in Amendment 13]. While 44 patients are missing CCS in the current analysis, 14 of those have either HHS or radiographs that would contribute to patient success. There is no reason to believe that all the remaining patients with missing data would be failures. Rather, based on the current update, the failure rate would be expected to remain constant.

5.1.10.4 Missing Data as Success

Similar to imputing all missing data as failures, the imbalance of missing data between groups results in imputing unequal percentages of successes in each treatment group. Including all patients with missing data as successes yields differences in rates that are similar to the differences in the percentages of missing data. Since the 8% delta was met in almost all cases for the observed data, the 8% delta was met when imputing all missing data as successes and in most cases the imputed success rates were higher in the investigational group than in the control group.

5.1.10.5 Stepwise Imputation

The stepwise imputation method first assumes a 'worst-case' scenario in which all patients missing data in the investigational group are included as failures and all patients missing data in the control group are included as successes. From this 'worst- case' scenario, at each step one control patient with missing data previously assumed to be a success was considered to be a failure and one investigational patient with missing data previously assumed to be a failure was assumed to be a success. Similar biases in imputations occur with this method due to the imbalance of missing data. The results of this imputation show that, for the original endpoint, if the underlying distribution of missing cases included up to 31 failures (success rate of 33%) in the treatment group and at least 15 failures (success rate of 35%) in the control group then the endpoint would still be met. For the modified endpoint, if the underlying distribution of missing cases included up to 22 failures in the treatment group and 10 failures in the control group then the endpoint would still be met.

5.1.10.6 Multiple Imputation

In addition, a multiple imputation method was performed using PROC MI (SAS). A monotone missing data pattern was first created to account for the 13 missing baseline HHS scores in the control group using the device specific means to replace the missing values. The imputation fit a logistic model based on the Month 24+ patient population with the modified CCS as the dependent variable and age at the time of surgery, gender, baseline HHS, weight and treatment group were included as covariates. The predicted values from this model were used to impute the missing data five times assuming a monotone missing pattern. The results from the five imputations are shown in Table 11.1 (5).

Table 11.1(5) Multiple Imputation Results for CCS Rates

	Investigational (N=337)	Control (N=266)	Difference	95% Lower Confidence Bound
Imputation 1	85.20%	86.80%	-1.7%*	-6.3%
Imputation 2	85.50%	88.00%	-2.5%	-7.1%
Imputation 3	86.10%	88.00%	-1.9%	-6.4%
Imputation 4	84.90%	87.20%	-2.4%*	-7.0%
Imputation 5	85.50%	87.20%	-1.8%*	-6.4%

*Differences may vary slightly from the difference in the presented rates due to rounding

PROC MIANALYZE was then used to assess the variability of these results. The results showed the variability among the imputations was insignificant (p=0.470). Therefore, the baseline characteristics of the patients with missing data do not indicate that significantly different results would be observed for these patients.

5.2 Pivotal Study Bilateral Procedures

The Pivotal Study Bilateral cohort is discussed in the following sections. The information presented here is taken from Amendment 8, submitted to FDA on January 31, 2006. The presentation of the data follows the order of the presentation for the Pivotal Study Unilateral Patients cohort for consistency. It should be noted that bilateral patients may have the confounding variable of the contralateral side procedure affecting function. The HHS data should then be interpreted with this bias in mind. Similarly, AEs were reported per procedure. Updated safety information is provided in the all enrolled section of this document (see section 5.4). It should be noted that despite the biasing factor of the opposite side procedure, the results throughout this section are highly consistent with those presented for the Pivotal Study Unilateral Patients cohort.

5.2.1 Number of Subjects Enrolled

Investigational Group

This group consists of procedures enrolled during the original IDE study with a second hip implanted with the Cormet 2000 Hip Resurfacing device within 730 days of the first side surgery. Forty-nine patients underwent two procedures for a total of 98 procedures. Another four patients received a non-IDE study pegged acetabular component on one side and that side is excluded from the analysis. This results in an additional four procedures. This cohort consists of 102 procedures in 53 patients.

See Table 3.2(1) for a summary of the number of procedures enrolled by site in the Pivotal Study Bilateral Procedures group for the investigational device.

Table 3.2(1) Patient Enrollment Pivotal Study Bilateral Procedures by Site Investigational Group

Investigators	Location	Number of Procedures	Number of Patients
	Springfield, IL	10	5
	Mobile, AL	4	2
	Colombia, SC	46	25
	Rockledge, FL	6	3
	Baltimore, MD	16	8
	Sarasota, FL	6	3
	Los Angeles, CA	2	1
	Galesburg, IL	8	4
	Cleveland, OH	4	2
TOTAL		102	53

Control Group

A summary of the number of patients and procedures enrolled by site in the Control ABC Ceramic-on-Ceramic System for bilateral procedures is presented in Table 3.2(2).

Table 3.2(2) Patient Enrollment Pivotal Study Bilateral Procedures by Site Control Group

Investigators	Location	Number of Procedures	Number of Patients
	Boston, MA	14 2	10 1
	Indianapolis, IN	14 5	8 3
	Moontownship, PA	11 2	6 1
	New York, NY	6	4
	Philadelphia, PA	1	1
	Durham, NC	1	1
	Athens, GA	6	4
	Atlanta, GA	8 4	5 2
	Toledo, OH	2	1
	Boca Raton, FL	7	5
TOTAL		83	52

5.2.2 Patient Accounting

The availability of follow-up evaluations for the investigational and control Pivotal Study Bilateral Procedures is listed in Table 4.2. Maximum length of follow-up as of the database lock, December 7, 2005, was Month 36.

Table 4.2
Procedure Accounting and Follow-up Compliance Table
Pivotal Study Bilateral Procedures and Bilateral Control Procedures
(Second Procedure within 24 Months of First Procedure)

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]	102	83	102	83	102	83	101	83	89	83	89	83	51	83
(2) Cumulative deaths including non-theoretically due[2]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(3) Cumulative revisions including non-theoretically due[3]	0	0	0	0	1	0	2	0	3	0	3	0	4	0
(4) - Not Yet Overdue[4]	0	0	0	0	0	0	1	0	1	0	1	0	8	0
(5) - Deaths+revisions among theoretical due[5]	0	0	0	0	1	0	2	0	3	0	3	0	2	0
(6) = Expected due for clinic visit[6]	102	83	102	83	101	83	98	83	85	83	85	83	41	83
(7) = Expected due+revisions among theoretical due[7]	102	83	102	83	102	83	100	83	88	83	88	83	43	83
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%	100%	98%	100%	89%	99%	89%	99%	79%	96%	79%	98%	41%	86%
(9) Harris Hip Total Score[10]	101	73	95	71	84	77	84	72	64	77	64	79	14	71
(10) Radiographic evaluation[11]			76		62		62		60		63		10	
(11) CCS at Mos. 24, 24+ or HHS+radio. otherwise[12]			72	71	56	77	59	72	46	77	55	79	7	71
(12) Actual[B] % Follow-up for CCS or HHS+radio.CCS[13]			71%	86%	55%	93%	60%	87%	52%	93%	63%	95%	17%	86%
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]	101	73	64	60	36	53	46	62	43	63	61	79	4	66
(14) Radiographic evaluation[15]			64		36		46		42		60		4	
(15) CCS at Mos. 24, 24+ or HHS+radio otherwise[15]			64	60	36	53	46	62	32	63	54	79	4	66
(16) Actual[A] % Follow-up for CCS or HHS+radio.CCS[16]			63%	72%	36%	64%	47%	75%	36%	76%	61%	95%	10%	80%

[Source: Tables_Followup_Accounting_v2.sas]

Table 4.2 Procedure Accounting and Follow-Up Compliance Table -Pivotal Study Bilateral

Note: Row 8 All Evaluated Visit Compliance (%) is calculated by dividing the Actual[B] patients with any data point available (not included in table above) by the expected due for clinic visit. Line 11 Actual[B] includes patients with all data available regardless of window.

Notes for Procedure Accounting and Follow-up Accounting Tables
[1] The theoretical follow-up is the number of implants that would have been examined if all patients returned on the exact anniversary of their respective initial surgery dates.
[2] Cumulative deaths up to and including the current interval. Although the cumulative numbers of deaths are recorded on this row, only deaths among implants that are theoretically due for that interval are subtracted from theoretical due to determine the number expected due.
[3] This row records the cumulative number of failures that have taken place according by the exact anniversary of scheduled follow-up visit. Although the cumulative numbers of failures are recorded on this row, only failures among implants that are theoretically due for that interval are subtracted from theoretical due to determine the number expected due. The cumulative revisions in Month 36 includes a revision in Month 39.
[4] Patients in this category are those who are theoretically due because their exact visit anniversary for that interval is on or before the date of database closure, they are within the evaluation time window, but have not been evaluated yet.
[5] Some of the deaths and revisions listed in rows 2 and 3 may not be included among theoretical due. This row provides the total number of cumulative deaths and revisions among those listed as theoretically due in row 1. This count is subtracted from theoretical due to obtain expected due for clinical evaluations (i.e.,. for HHS and radiography).
[6] Expected due for clinic visit is equal to Theoretical due (row 1) minus Not yet over due (row 4) minus not Deaths and revisions among theoretical due (row 5). This row serves as denominator for clinical evaluation % follow up.
[7] Expected due plus theoretical due revisions is computed by adding row 6 to the number of cumulative revisions among theoretical procedures. This row serves as the denominator for composite clinical success outcomes since revisions are known to be CCS failures.
[8] All Evaluated Accounting (Actual^{B}) is based on the evaluations on-file among those expected due without regard to whether assessment was within the assessment window.
[9] All Evaluated Visit Compliance (%) is computed as the number on-file among those expected due divided by the expected number due (row 6) expressed as a percentage. All evaluated compliance is based on the presence of any clinical data, even if incomplete, and demonstrates that the procedure is actively followed at least up to the specific interval.
[10] Harris Hip Total (Actual^{B}). This is the count of Harris Hip Total scores available for the that interval including those both within and out of window.
[11] Radiographic evaluation (Actual^{B}). The number of radiographic evaluations on-file including those both within and out of window. For Month 24 and Month 24+, this includes procedures evaluable and non-evaluable for the new composite radiographic endpoint.
[12] CCS at Mos. 24, 24+ or HHS+radiographic, otherwise (Actual^{B}). For Months 24 and 24+ this row indicates the numbers of procedures with all components on-file that are necessary to evaluate composite clinical success with revisions included as CCS failures. For other time points, this row only indicates that both Harris Hip Total scores and radiographic evaluations are on-file.
[13] Actual^{B} % Follow-up. The denominator for % follow-up for this row is row 7 for Months 24 and 24+ and is row 6 for other time intervals. This is because the status of revisions is known for CCS. For Months 24 and 24+ this row indicates (Actual^{B}) % follow-up for the primary efficacy endpoint (CCS) only counting radiographic assessments in which the new composite radiographic endpoint is determined. For other time intervals, this is row is equal to the % of procedures with HHS and radiographic assessments divided by row 6.
[14] Actual^{A} intervals: 6 weeks ± 2 weeks, 6 months ± 1 month, 12 months ± 2 months, 24 months ± 2 months, annually ± 2 months.
[15] Actual^{A} accounting excludes Harris Hip Total scores and radiographic evaluations that are outside of the intervals indicated in note 14.
[16] Actual^{A} % Follow-up is computed as row 16 divided by 7, expressed as a percentage.

Investigational Group

Of patients representing 64 procedures with a complete HHS, a total of 43 (52%) procedures in the "All Evaluated (Actual^{B}) Among Expected Due Procedures" group have complete clinical and radiographic Month 24 postoperative follow-up. Eighteen patients did not return for their minimum Month 24 follow-up visit and no clinical data are available for these patients. No patients died however three patients had revision of one or more components before the Month 24 postoperative follow-up interval and were therefore excluded from the study.

Control Group

As described earlier, a subset of the control cohort continues to be evaluated through a postmarket study for the ceramic-on-ceramic device so the length of follow-up for this group was derived based on the longest available follow-up of the Cormet 2000 pivotal study patients. For the 52 patients (83 procedures) in the bilateral ABC control group, 82 hips were evaluated (79 with complete HHS) at Month 24+. No

patients died or were revised. One patient was lost to follow-up. This patient was last seen at the Month 6 evaluation at which time a composite HHS of 97 points was reported.

5.2.3 Description of Deviations from Investigational Plan

As stated previously in Section 5.1.3, there were a total of six deviations in all enrolled procedures (pegged acetabular components) of which four occurred in the bilateral group. These procedures have been removed from the analysis. There were no other major protocol deviations reported for patients in the investigational Pivotal Study Bilateral group. There were no protocol deviations reported during a comparable time frame in the control Pivotal Study Bilateral group.

5.2.4 Demographic Information

There was complete demographic information available for analysis for all procedures enrolled in both the investigational and control Pivotal Study Bilateral Procedures Cohorts. See Table 5.2 for a demographic summary of the patients/procedures enrolled in the investigational and control cohorts.

Table 5.2 Baseline and Demographic Characteristics Pivotal Study Bilateral Procedures vs. Bilateral Controls

Table 5.2
Baseline and Demographic Characteristics
Pivotal Study Bilateral Procedures vs. Bilateral Controls

	Investigational				Control				p[&]
	N	**%**			**N**	**%**			
Number of procedures	102				83				--
Number of patients	53				52				
Males	72	70.6%			62	74.7%			0.534
Females	30	29.4%			21	25.3%			
Primary diagnosis	**n**	**%**			**n**	**%**			0.406
Osteoarthritis	83	81.4%			67	80.7%			
Rheumatoid Arthritis	2	2.0%			0	0.0%			
Avascular necrosis	17	16.7%			16	19.3%			
Other Diagnosis Present	6	5.9%			0	0.0%			0.025
Charnely Class	**n**	**%**			**n**	**%**			
Unilateral joint, no other disability	7	6.9%							
Bilateral joint, no other disability	88	86.3%							
Uni or bilateral plus conditions affecting function	7	6.9%							
Contralateral hip	**n**	**%**			**n**	**%**			
Symptomatic	27	26.5%							
Replaced/Fused	38	37.3%							
Asymptomatic	37	36.3%							
Knee status	**n**	**%**			**n**	**%**			
Symptomatic (either knee)	12	11.8%							
Replaced/Fused (either knee)	0	0.0%							
Both asymptomatic	90	88.2%							
Surgery within 12 months	45	44.1%							
Harris Pain Category	**n**	**%**			**n**	**%**			0.143
None/Ignores	0	0.0%			0	0.0%			
Slight	1	1.0%			2	2.4%			
Mild	1	1.0%			4	4.8%			
Moderate	37	36.6%			33	39.8%			
Marked	59	58.4%			43	51.8%			
Totally disabled	3	3.0%			1	1.2%			
	Mean	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	
Age at surgery (yrs)	48.0	11.6	19.0	68.0	52.4	12.1	21.0	75.0	0.026
Weight (lbs)	195.3	48.3	105.0	340.0	193.1	38.2	110.0	300.0	0.912
Duration of symptoms	35.4	37.2	2.0	240.0					
Harris Hip Total Score	48.6	12.0	15.4	85.0	50.3	12.1	26.7	74.0	0.348

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.

Source [Tables_BaselineDemo_v2.sas]

There were more procedures for males (72; 70.6%) than females (30; 29.4%) enrolled in the investigational bilateral group. The mean age of patients based on date of procedure in the investigational group at surgery was 48.0 years (SD 11.6, 19-68). Over 80% of the procedures had a diagnosis of OA.

There were more procedures for males (62; 74.7%) than females (21; 25.3%) enrolled in the control bilateral group. Patients were older in the control group 52.4 years (SD 12.1; 21-75). Over 80% of the procedures had a diagnosis of OA.

There was a significant difference between the investigational and control groups in respect to age at the time of surgery (Wilcoxon Rank Sum Test, p=0.026) with the investigational group having the younger mean age. However, the four year difference in mean age does not appear to be clinically relevant. There were no significant differences between the two cohorts in the male/female ratio, primary diagnosis, preoperative HHS, and weight. Data were not collected for Charnley Class, contralateral hip or knee status, duration of symptoms, and surgery within 12 months for the control group.

5.2.5 Surgical Details

Surgical details have been received for all 102 procedures enrolled in the investigational Pivotal Study Bilateral Procedures Cohort. Details for the 102 procedures are listed in Table 6.2 along with the surgical details for all procedures enrolled in the control Pivotal Study Bilateral Procedures Cohort.

Table 6.2 Surgical Details Pivotal Study Bilateral Procedures vs. Bilateral Control

Table 6.2
Surgical Details
Pivotal Study Bilateral Procedures vs. Bilateral Controls

	Investigational				Control				p[1]
	N	%			N	%			
Number of procedures	102				83				--
Number of patients	53				52				
Surgical Approach	n	%			n	%			0.000
Lateral	13	12.7%			0	0.0%			
Postero-lateral	73	71.6%			76	91.6%			
Anterior	16	15.7%			7	8.4%			
Trochanteric	0	0.0%			0	0.0%			
Unspecified[a]	0	0.0%			0	0.0%			
Femoral Implant Sizes	n	%			n	%			0.000
28mm	0	0%			3	3.6%			
32mm	0	0%			80	96.4%			
40mm	1	1.0%			0	0.0%			
44mm	33	32.4%			0	0.0%			
48mm	27	26.5%			0	0.0%			
52mm	32	31.4%			0	0.0%			
56mm	9	8.8%			0	0.0%			
Cup Implant Sizes	n	%			n	%			0.010
46mm	0	0.0%			0	0.0%			
48mm	1	1.0%			2	2.4%			
50mm	25	24.5%			1	1.2%			
52mm	8	7.8%			7	8.4%			
54mm	18	17.6%			17	20.5%			
56mm	9	8.8%			17	20.5%			
58mm	26	25.5%			21	25.3%			
60mm	6	5.9%			11	13.3%			
62mm	9	8.8%			5	6.0%			
64mm	0	0.0%			2	2.4%			
Cup Fixation Method	n	%			n	%			
Cemented	3	2.9%			0	0.0%			
Press-Fit	99	97.1%			83	100.0%			
Intraoperative Complications[2]	n	%			n	%			
Femoral neck notched	0	0.0%			0	0.0%			0.135
Femoral fracture	0	0.0%			0	0.0%			0.440
Cardiovascular/Arrhythmia	0	0.0%			1	1.2%			0.449
Ceramic Insert Chip	0	0.0%			2	2.4%			0.200
Other[b]	1	1.0%			7	8.4%			0.023

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 was 1 intraoperative complication designated as 'other' among pivotal study bilateral procedures. This was a 'loose body' complication.

[Source: Tables_Surgical_Details.sas]

The one intraoperative complication that occurred in the investigational group was a loose body in the acetabulum that was recognized on x-ray and subsequently was removed. A comparison of intraoperative complications between the investigational and control cohorts is located in Section 3.2.7.1 Adverse Events.

5.2.6 Safety and Effectiveness Data

Data for bilateral procedures are included in the all enrolled group safety analysis. Harris Hip Scores were computed and compared to the Pivotal Study Unilateral Patients.

5.2.6.1 Harris Hip Score

As described in Section 4.2, the first success criterion was related to the individual patient composite HHS[7] results at Month 24 postoperatively compared to the preoperative status. Specifically, the HHS $\geq$ 20 points at two years postoperatively over baseline (preoperative) values demonstrated patient success. In the PMA submission of March 26, 2005 (PMA P050016) the HHS clinical success criterion was presented as a patient achieving a composite HHS of $\geq$ 80 points at Month 24.

Table 7.2(1) summarizes patients with a total HHS $\geq$ 80 points with over 95% of the procedures demonstrating HHS $\geq$ 80 points from Month 12 through Month 36. There were no patients with a HHS < 80 in the bilateral investigational group at Month 24 and Month 24+. Similarly, there were no bilateral procedures in the control group with a HHS <80 at Month 24 and Month 24+. There was no statistical difference in HHS >80 points at Month 24 (two sided Fisher's exact test; p=0.213) or Month 24+ (two sided Fisher's exact test; p=0.220) comparing the investigational Pivotal Study Unilateral with the investigational Pivotal Study Bilateral groups.

Table 7.2(1) Pivotal Study Unilateral Patients vs. Pivotal Study Bilateral Procedures – Harris Hip Total Score ≥ 80 Points

Table 7.2(1)
Pivotal Study Unilateral Patients vs. Pivotal Study Bilateral Procedures
Harris Hip Total Score >=80 Points

	Pivotal Study Unilateral Patients			Pivotal Study Bilateral Procedures			Unilateral vs. Bilateral	
	n	N	%	n	N	%	Diff.	p-value[2]
6 Weeks	129	331	39.0%	43	95	45.3%	-6.3%	0.287
6 Months	272	287	94.8%	79	85	92.9%	1.8%	0.592
12 Months	268	282	95.0%	82	84	97.6%	-2.6%	0.542
24 Months	245	254	96.5%	64	64	100.0%	-3.5%	0.213
24+ Months [1]	253	263	96.2%	64	64	100.0%	-3.8%	0.220
36 Months	37	38	97.4%	14	14	100.0%	-2.6%	1.000

Notes:

[1] Month 24+ is equal to Month 24 if non-missing. If not, missing values were replaced by evaluations at later dates if available (i.e., rollback imputation).

[2] P-values are from two-sided Fisher's exact tests.

[Source: Tables_Clinical_Followup_UnivBilat.sas]

Table 7.2(2) compares the bilateral procedures with no more than slight hip pain to the pivotal study unilateral patient group. There was no difference in scores at any postoperative time frame (Week 6 – Month 6) with both groups demonstrating no or slight pain in over 95 % of the patients at minimum Month 24. Again, there was no statistically significant difference in results compared to the Pivotal Study Unilateral group.

Table 7.2(2) Pivotal Study Unilateral Patients vs. Pivotal Study Bilateral Procedures – Hip Pain No More Than Slight

Table 7.2(2)
Pivotal Study Unilateral Patients vs. Pivotal Study Bilateral Procedures
Hip Pain No More Than Slight

	Pivotal Study Unilateral Patients			Pivotal Study Bilateral Procedures			Unilateral vs. Bilateral	
	n	N	%	n	N	%	Diff.	p-value[2]
6 Weeks	281	332	84.6%	78	96	81.3%	3.4%	0.433
6 Months	273	291	93.8%	80	85	94.1%	-0.3%	1.000
12 Months	265	284	93.3%	82	84	97.6%	-4.3%	0.182
24 Months	242	254	95.3%	64	65	98.5%	-3.2%	0.479
24+ Months [1]	250	263	95.1%	64	65	98.5%	-3.4%	0.318
36 Months	38	39	97.4%	13	14	92.9%	4.6%	0.462

Notes:

[1] Month 24+ is equal to Month 24 if non-missing. If not, missing values were replaced by evaluations at later dates if available (i.e., rollback imputation).

[2] P-values are from two-sided Fisher's exact tests.

[Source: Tables_Clinical_Followup_UnivBilat.sas]

5.2.6.2 Radiographic Success

The radiographic information for the investigational Pivotal Study Bilateral Procedures group was collected in the same manner as was done for the investigational Pivotal Study Unilateral group. Refer to Section 4.2 for a complete description of the Radiographic Success criteria.

A presentation of radiographic results for the investigational Pivotal Study Bilateral Procedures combining the original and the modified protocol is presented in Table 8.2

Table 8.2 Radiographic Clinical Success Among Original Protocol and Modified Protocol Combined Pivotal Study Bilateral Procedures

Table 8.2
Radiographic Clinical Success Among Onfile Procedures
Original Protocol and Modified Protocol Combined
Pivotal Study Bilateral Procedures

	Month 24		Month 24+	
	N		**N**	
Total radiographs (Actual[B])	60		63	
Non-evaluable for radiographic success[2]	16		10	
Evaluable for radiographic success	44		53	
	n/N	**%**	**n/N**	**%**
Radiolucency Acetabular Component				
I	0 /44	0.0%	0 /53	0.0%
II	0 /44	0.0%	0 /53	0.0%
III	2 /44	4.5%	2 /53	3.8%
All[3]	0 /44	0.0%	0 /53	0.0%
Radiolucency Femoral Component				
Superior	0 /45	0.0%	1 /53	1.9%
Tip	1 /45	2.2%	2 /53	3.8%
Inferior	0 /45	0.0%	1 /53	1.9%
All[3]	0 /45	0.0%	1 /53	1.9%
Cup migration and tilt[4]				
Superior/Inferior migration >= 5 mm[3]	1 /42	2.4%	2 /49	4.1%
Medial/Lateral migration >= 5 mm[3]	0 /42	0.0%	1 /49	2.0%
Varus/Valgus Tilt >= 5 degrees[3]	0 /41	0.0%	0 /48	0.0%
Stem migration and tilt[4]				
Subsidence of the femoral component >= 5 mm and Stem tilting>= 1 degree[3]	1 /44	2.3%	2 /52	3.8%
Other assessments				
Stem Tilting >= 1 degree	30 /43	69.8%	36 /51	70.6%
Anteroversion of the head >= 5 mm	11 /46	23.9%	13 /53	24.5%
Retroversion of the head >= 5 mm	17 /46	37.0%	19 /53	35.8%
Hypertrophy in any zone	0 /46	0.0%	0 /53	0.0%
Resorption in any zone	0 /46	0.0%	0 /53	0.0%
Lysis in any zone	3 /46	6.5%	3 /53	5.7%
Composite radiographic failure	**2 /44**	**4.5%**	**3 /53**	**5.7%**

Notes:
[1] Total radiographic evaluations performed for Month 24 or Month 24+ including those not expected due.
[2] Did not meet criteria for re-evaluation for new composite radiographic endpoint.
[3] Required for composite radiographic endpoint used in constructing the Composite Clinical Success.
[4] Component migration and tilt could not be measured for 3 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.

[Source: Tables_Radiography_Rama.sas]

As presented in Table 8.2, there were no components with radiolucency in all zones at Month 24 and Month 24+. There was one (2.4%) cup failure based on migration and tilt criteria at Month 24. and an additional cup failure (4.1%) at Month 24+ based on these same criteria. There was one (2.3%) stem failure at Month 24 defined by both subsidence of ≥ 5mm and tilt of ≥ 1 degree and one (3.8%) additional stem failure at Month 24+. Based on composite radiographic endpoints used in constructing the CCS, there were a total of two (4.5%) radiographic failures at Month 24 in the bilateral investigational groups and a total of three (5.7%) radiographic failures at Month 24+ in this same group. Complete description provided in Amendment 13.

5.2.6.3 Absence of Revision or Pending Revision

Investigational Group

Four revisions were performed for procedures in the investigational Pivotal Study Bilateral Procedures group at minimum Month 24+. Reasons for revision included: deep infection (one procedure), femoral neck fracture (two procedures), and femoral subsidence (one procedure) There were no pending revisions in this group.

Control Group

There were no device failures during a comparable time frame in the control Pivotal Study Bilateral Procedures group.

5.2.6.4 Absence of Device Related Events

Investigational

Four device related events (3.9%) were reported for the Pivotal Study Bilateral Procedures in the investigational group at Month 24+ follow-up. Reasons for device related events included: acetabular loosening (one patient, 1.0%), femoral neck fracture (two patients, 2.0%), and femoral subsidence (one patient, 1.0%).

There were no events of acetabular fractures, avulsed lesser trochanter, dislocation, intraoperative or postoperative femoral fractures, femoral loosening or greater trochanter fracture in the investigational group.

Control

There were six device related events (7.2%) during a comparable time frame for the Pivotal Study Bilateral Procedures in the control group. Reasons for device related events included two events of operative ceramic insert chip (2.4%), three events of dislocation (3.6%), and one event of postoperative femoral fracture (1.2%).

There were no events of acetabular fracture, acetabular loosening, avulsed lesser trochanter, operative femoral fracture, femoral loosening, femoral neck fracture, femoral subsidence, and greater trochanter fracture in the control group.

5.2.7 Safety

5.2.7.1 Adverse Events

Table 9.2(1) provides a summary of the number of patients reporting AEs of the various types in the bilateral investigational and control groups.

Table 9.2(1) Summary of Complication Comparisons Between Pivotal Study Bilateral Patients and Bilateral Controls – Summary

Table 9.2(1)
Summary of Complication Comparisons between
Pivotal Study Bilateral Patients and Bilateral Controls - Summary

	Investigational			Control			Exact
	n[8]	N[9]	%	n[8]	N[9]	%	p-value
Any complication	19	102	18.6%	54	83	65.1%	0.000
Any hip-related complication	11	102	10.8%	16	83	19.3%	0.142
Any device-related complication	4	102	3.9%	6	83	7.2%	0.348
Any operative complication[1]	1	102	1.0%	10	83	12.0%	0.003
Any post operative complication[2]	19	102	18.6%	46	83	55.4%	0.000
Any post operative hip-related complication[3]	11	102	10.8%	12	83	14.5%	0.506
Any post operative device-related complication[4]	4	102	3.9%	4	83	4.8%	1.000
Any post operative serious complication[5]	10	102	9.8%				
Any post operative serious hip-related complication[6]	3	102	2.9%				
Any post operative serious device-related complication[7]	3	102	2.9%				
Deaths	0	102	0.0%	0	83	0.0%	

Notes:
[1] Complications occuring during implant procedure as reported on Complication Form.
[2] Complications occuring after implant procedure as reported on Complication Form.
[3] Includes any post operative hip-related complication.
[4] Includes any post operative complication.
[5] Includes any post operative complication meeting the criteria for a serious complication as assessed by the investigator.
[6] Includes any post operative complication hip-related complication assessed by the investigator as serious.
[7] Includes any post operative complication.
[8] Number of procedures w ith at least one of the specific types of complications.
[9] Total number of procedures in this cohort of patients.

[Source: Tables_Safety_vs_ABCcontrols_IDEBILAT.sas]

Nineteen procedures of the 102 procedures in the investigational Pivotal Study Bilateral Procedures group reported a complication during the course of the study. In comparison, 54 of the 83 Pivotal Study Bilateral Control Group reported a complication. The lower rate of complications in the investigational group will be examined more closely as each type of complication is presented in the following tables. However, the control population is a more mature database as the study occurred in 1996 and all patients have more years of follow-up. This difference is demonstrated by the average months of follow-up in the investigational bilateral group (22.4 months) versus the control group (34.7 months). Differences in physician reporting, monitoring procedures, and other factors can also contribute to this basic difference.

Hip related complications were defined as any AE related to the operative hip. Any AEs related to the contralateral hip were grouped with systemic AEs. There were 11 procedures with hip related AEs in the pivotal study bilateral group for a rate of 10.8%. The control patients showed a higher rate of hip-related events (19.3%), which follows from the higher overall rate.

Refer to Section 5.1.6.4 for a complete description of device related AEs as described in the Cormet 2000 Hip Resurfacing System Protocol.

Not included in these device related AEs for the CCS criteria were other radiographic findings such as partial stem radiolucencies. These findings were evaluated by the independent radiographic reviewer

and contributed to the arm of the patient success criteria that relates to radiographic success. Only a subset of patients with radiographic findings had these findings reported as an AE and no attempt was made to prompt the sites for AE forms for radiographic findings.

The rate of device related AEs in the pivotal bilateral cohort was 3.9% compared to the rate in the control bilateral group, which was 7.2%. No statistical differences in rates were observed between the groups.

Operative complications in the Cormet 2000 study were collected on the Operative Form. The control did not employ a separate form, so the timing of the events had to be used to classify events as “operative”. The difference in the rates (1.0% investigational bilaterals versus 12.0% control bilaterals) may be related to this difference in collection.

The following sections provide a further analysis by AE type between the Pivotal Study Bilateral Procedures in the investigational and control, and an analysis of the time-course of AEs experienced by the two populations.

5.2.7.2 Systemic Adverse Events

Systemic AEs were those reported events that did not relate directly to the operation or the operative site/device. An analysis of the types of events reported and their time course shows expected rates of other body system complications for this type of population.

Table 9.2(2) represents a breakdown of systemic AEs for the investigational and control groups. The first column (n^1) is the number of procedures in which this type of complication occurred. The second column (N^2) is the total population number, and the two are divided to provide the rate as a percentage in the third column.

Table 9.2(2) Complication Comparisons with Controls – Systemic Complications

Table 9.2(2) Complication Comparisons with Controls - Specific Complications Pivotal Study Bilateral Patients and Bilateral Controls							
	Investigational			Control			Exact
	n[1]	N[2]	%	n[1]	N[2]	%	p-value[3]
Systemic							
Arrhythmia (operative)	0	102	0.0%	0	83	0.0%	
Bronchopulmonary	0	102	0.0%	2	83	2.4%	0.200
Carcinoma	0	102	0.0%	1	83	1.2%	0.449
Cardiovascular	0	102	0.0%	9	83	10.8%	0.001
Death - unrelated to device	0	102	0.0%	0	83	0.0%	
DVT	0	102	0.0%	0	83	0.0%	
Gastrointestinal	0	102	0.0%	6	83	7.2%	0.007
Genitourinary	0	102	0.0%	5	83	6.0%	0.017
Infection remote location	0	102	0.0%	0	83	0.0%	
Lack of nutrition	0	102	0.0%	0	83	0.0%	
Low hemoglobin/hematocrit	0	102	0.0%	0	83	0.0%	
Neuropathy	0	102	0.0%	0	83	0.0%	
Neurosensory	0	102	0.0%	3	83	3.6%	0.088
Nosebleed	0	102	0.0%	0	83	0.0%	
PE	0	102	0.0%	0	83	0.0%	
Rash	0	102	0.0%	3	83	3.6%	0.088
Thrombophlebitis	0	102	0.0%	0	83	0.0%	
Trauma (non-hip related)	0	102	0.0%	4	83	4.8%	0.039
Varicose veins	0	102	0.0%	0	83	0.0%	
Other	7	102	6.9%	16	83	19.3%	0.014

[3] Two-sided Fisher's Exact tests. Comparisons were not performed for femoral neck notched (operative), greater trochanter notching (operative), ceramic insert chip (operative), and femoral neck fracture since both devices were not exposed to these types of events. Also, p-values are not reported when there were no events in either group.

Again, a higher rate of many systemic AEs was reported in the control Pivotal Study Bilateral Procedures group than the investigational Pivotal Study Bilateral group. As discussed earlier, there is no medical reason why a higher rate of cardiovascular events, for example, would be observed for the control than the investigational group. Both groups are demographically well matched, although the control group was statistically older by a few years. This may have had a slight impact on the amount of co-morbid conditions pre-existing in the control group and therefore a higher observed rate in this group.

Reviewing these events as they occurred over time, the rate of systemic events seems to be higher in the control group both early (intraoperatively to Week 6) and late (Month 12 on). The higher rate of late AEs can be attributed to the increased maturity of the control dataset. The early difference may be explained by differences in reporting between centers/investigators or differences in surgical implantation techniques. The rates of these systemic events over time are presented in Table (9.2.3).

Table 9.2(3) Counts of Systemic Complications by Time of Occurrence

Table 9.2(3) Counts of Specific Complications by Time of Occurrence - Pivotal Study Bilateral Patients and Bilateral Controls														
	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
Systemic														
Arrhythmia (operative)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bronchopulmonary	0	0	0	0	0	2	0	0	0	0	0	0	0	2
Carcinoma	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Cardiovascular	0	1	0	4	0	1	0	0	0	0	0	3	0	9
Death - unrelated to device	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DVT	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal	0	1	0	3	0	0	0	0	0	0	0	2	0	6
Genitourinary	0	0	0	3	0	0	0	0	0	0	0	2	0	5
Infection remote location	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lack of nutrition	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Low hemoglobin/hematocrit	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Neuropathy	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Neurosensory	0	1	0	0	0	1	0	0	0	1	0	0	0	3
Nosebleed	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PE	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rash	0	0	0	0	0	0	0	0	0	3	0	0	0	3
Thrombophlebitis	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Trauma (non-hip related)	0	0	0	0	0	0	0	1	0	3	0	0	0	4
Varicose veins	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other	0	0	1	0	2	1	2	1	3	5	0	9	8	16

5.2.7.3 Hip Related Events

Hip related events were the most reported postoperatively AEs in the bilateral investigational and control groups concerning the hip or operative site. **Table 9.2.4** gives a breakdown of the rates of hip related AEs for the bilateral investigational group and the corresponding control group.

Table 9.2(4) Complication Comparisons with Controls – Hip Related Complications (Numbered here as it appeared in Amendment 8)

Table 9.2(4)
Complication Comparisons with Controls - Specific Complications
Pivotal Study Bilateral Patients and Bilateral Controls

	Investigational			Control			Exact
	n[1]	N[2]	%	n[1]	N[2]	%	p-value[3]
Hip Related Events							
Acetabular Crack (operative)	0	102	0.0%	1	83	1.2%	0.449
Acetabular malpositioned (operative)	0	102	0.0%	0	83	0.0%	
Broken drill bit (operative)	0	102	0.0%	0	83	0.0%	
Bursitis	2	102	2.0%	0	83	0.0%	0.503
Deep infection	2	102	2.0%	0	83	0.0%	0.503
Elevated metal ion level	0	102	0.0%	0	83	0.0%	
Femoral Crack (operative)	0	102	0.0%	2	83	2.4%	0.200
Femoral neck notched (operative)	0	102	0.0%				
Femoral radiolucency	1	102	1.0%	0	83	0.0%	1.000
Greater Trochanter Notching (operative)	0	102	0.0%				
Hematoma	0	102	0.0%	1	83	1.2%	0.449
Heterotopic Bone Formation	3	102	2.9%	5	83	6.0%	0.470
Hip Pain (operative side)	0	102	0.0%	0	83	0.0%	
Leg Length discrepancy	1	102	1.0%	0	83	0.0%	1.000
Limp	0	102	0.0%	0	83	0.0%	
Loose Body	1	102	1.0%	0	83	0.0%	1.000
Muscle Weakness	0	102	0.0%	1	83	1.2%	0.449
Myositis ossificans	0	102	0.0%	0	83	0.0%	
Nerve palsy	1	102	1.0%	1	83	1.2%	1.000
Skin split	0	102	0.0%	0	83	0.0%	
Soft Tissue Trauma	0	102	0.0%	1	83	1.2%	0.449
Squeaking implant/clicking	0	102	0.0%	0	83	0.0%	
Subchondral cyst	0	102	0.0%	0	83	0.0%	
Subluxation	1	102	1.0%	0	83	0.0%	1.000
Superficial infection	0	102	0.0%	2	83	2.4%	0.200
Tendonitis	1	102	1.0%	1	83	1.2%	1.000
Trochanteric Crack (operative)	0	102	0.0%	0	83	0.0%	
Wound Related (non-infected)	0	102	0.0%	1	83	1.2%	0.449
Other	0	102	0.0%	2	83	2.4%	0.200

Reviewing these events as they occurred over time, the rates of hip related events seems to be higher in the control group in the immediate postoperative (up to Week 6) timeframe. Heterotopic bone formation was reported the most frequently for both the investigational and control group from post surgery to Month 6. Table 9.2(5) presents the hip related AEs over time for both groups.

Table 9.2(5) Counts of Hip Related Complications by Time of Occurrence

Table 9.2(5) Counts of Specific Complications by Time of Occurrence - Pivotal Study Bilateral Patients and Bilateral Controls														
	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	0	0	0	0	0	0	0	0	0	0
Broken drill bit (operative)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bursitis	0	0	0	0	0	0	2	0	0	0	0	0	2	0
Deep infection	0	0	0	0	0	0	0	0	2	0	0	0	2	0
Elevated metal ion level	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Femoral Crack (operative)	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Femoral neck notched (operative)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Femoral radiolucency	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Greater Trochanter Notching (operative)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hematoma	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Heterotopic Bone Formation	0	0	1	2	1	3	0	0	1	0	0	0	3	5
Hip Pain (operative side)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Leg Length discrepancy	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Limp	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Loose Body	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Muscle Weakness	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Myositis ossificans	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nerve palsy	0	1	0	0	1	0	0	0	0	0	0	0	1	1
Skin split	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Soft Tissue Trauma	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Squeaking implant/clicking	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Subchondral cyst	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Subluxation	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Superficial infection	0	0	0	2	0	0	0	0	0	0	0	0	0	2
Tendonitis	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Trochanteric Crack (operative)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Wound Related (non-infected)	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Other	0	2	0	0	0	0	0	0	0	0	0	0	0	2

The control group's higher rates of specific AEs common to both procedures continue in this presentation of hip-related events.

Neck notching is thought to be problematic as it may be a risk factor for future femoral neck fracture. There were no reports in the investigational or control groups of femoral neck or greater trochanter notching.

Operative side hip pain was not reported in either group as well.

Leg length discrepancy was reported in one patient (1.0%) in the investigational group and not at all in the bilateral control group.

5.2.7.4 Device Related Events

The protocol definition of device related AE was "an AE that occurs due to the design and/or material composition of the implant and/or implant instrumentation". Table 9.2(6) gives a breakdown of the rates of device related AEs for the investigational group and the corresponding control group.

Table 9.2(6) Complication Comparisons with Controls – Device Related Complications

Table 9.2(6)
Complication Comparisons with Controls - Specific Complications
Pivotal Study Bilateral Patients and Bilateral Controls

	Investigation			Contro			
	n[1]	N[2]	%	n[1]	N[2]	%	p- [3]
Device Related Events							
Acetabular	0	102	0.0%	0	83	0.0%	
Acetabular	1	102	1.0%	0	83	0.0%	1.000
Avulsed lesser	0	102	0.0%	0	83	0.0%	
Ceramic Insert Chip				2	83	2.4%	
Dislocatio	0	102	0.0%	3	83	3.6%	0.088
Femoral Fracture	0	102	0.0%	0	83	0.0%	
Femoral Fracture	0	102	0.0%	1	83	1.2%	0.449
Femoral	0	102	0.0%	0	83	0.0%	
Femoral neck	2	102	2.0%				
Femoral	1	102	1.0%	0	83	0.0%	1.000
Trochanter	0	102	0.0%	0	83	0.0%	

Notes:

[1] Number of procedures with at least one of the specific types of complications. The total number of procedures at least one complications is smaller than the sum, since procedures can have more than one type of

[2] Total number of procedures in this cohort of

[3] Two-sided Fisher's Exact tests. Comparisons were not performed for femoral neck notched (operative), greater Notching (operative), ceramic insert chip (operative), and femoral neck fracture since both devices were not exposed these types of events. Also, p-values are not reported when there were no events in either

[Source:Tables_Safety_vs_ABCcontrols_IDEBILAT.sas]

Table 9.2(7) presents the device related AEs over time for both groups.

Table 9.2(7) Counts of Device Related Complications by Time of Occurrence

Table 9.2(7)
Counts of Specific Complications by Time of Occurrence - Pivotal Study Bilateral Patients and Bilateral Controls

	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	0	0	0	0	0	0	0	0	0	0	0	0	0
Acetabular loosening	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Avulsed lesser trochanter	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ceramic Insert Chip (operative)	0	2	0	0	0	0	0	0	0	0	0	0	0	2
Dislocation	0	0	0	1	0	2	0	0	0	0	0	0	0	3
Femoral Fracture (operative)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Femoral Fracture (post-op)	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Femoral loosening	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Femoral neck fx	0	0	0	0	1	0	0	0	0	0	1	0	2	0
Femoral subsidence	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Trochanter (greater) fx	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[Source: Tables_Safety_vs_ABCcontrols_IDEBILAT.sas]

Overall, the rates of device related AEs are similar between the bilateral investigational and bilateral control groups in this study (p=0.348). The type of AE differs between the groups, however, as the investigational group exhibited higher rates of component loosening, the control group had higher rates of femoral fracture and dislocation.

5.2.7.5 Revisions/Removals Overview

Investigational Group

Four revisions were reported for the investigational Pivotal Study Bilateral Procedures group at Month 24+ follow-up. Reasons for revision included: deep infection (one procedure), femoral neck fracture (two procedures), and femoral component subsidence (one procedure). There were no pending revisions in this group.

Control Group

There were no device failures during a comparable time frame in the control Pivotal Study Bilateral Procedures group.

5.2.7.6 Deaths

Investigational Group

There were no deaths reported for patients in the investigational Pivotal Study Bilateral Procedures group.

Control Group

There were no deaths reported for patients in the control Pivotal Study Bilateral group during a comparable time frame.

5.2.8 Potential Lost to Follow-up

The Table 10.2 demonstrates the potential lost to follow-up in the Pivotal Study Bilateral Procedures population.

Table 10.2 Lost to Follow-Up - Pivotal Study Bilateral Procedures (Investigational vs. Control)

Pivotal Study Bilateral Group	Number of Procedures	Number of Procedures
	Investigational	Control
Expected due at Month 24 follow-up	85	83
Returned for Month 24 follow-up	67	82
Missed Month 24 follow-up	18	1
Returned for Month 24+ follow-up	0	0
Potential Lost to follow-up	18	1

5.2.9 Composite Clinical Success

Pivotal Study Bilateral Procedures were not included in computation of the CCS for this study. However, it is relevant to note that the bilaterally implanted patients performed similarly to the Pivotal Study Unilateral group.

The CCS comparing the unilateral and bilateral pivotal study investigational group, using a Harris Hip Total score endpoint of at least 80 points at Month 24 and Month 24+, absence of revision of any of the components of the investigational device, absence of device related AEs, and absence of radiographic failure is presented in Table 11.2(1). As demonstrated, the CCS for the investigational bilateral group is 89.1% at Month 24 compared to 85.8% for the investigational unilateral group. There is no statistical significance for Month 24 (two sided Fisher's exact test, p=0.644) and Month 24+ (two sided Fisher's exact test, p=0.824).

Table 11.2(1) Pivotal Study Unilateral Patients vs. Pivotal Study Bilateral Procedures – Composite Clinical Success (CCS)

Table 11.2(1)
Pivotal Study Unilateral Patients vs. Pivotal Study Bilateral Procedures
Composite Clinical Success (CCS)[1]

	Pivotal Study Unilateral Patients			Pivotal Study Bilateral Procedures			Unilateral vs. Bilateral	
	n	N	%	n	N	%	Diff.	p-value[3]
24 Months	188	219	85.8%	41	46	89.1%	-3.3%	0.644
24+ Months[2]	206	238	86.6%	49	55	89.1%	-2.5%	0.824

[1] **Composite Clinical Success** - The 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+ is equal to Month 24 if non-missing. If not, missing values were replaced by evaluations at later dates if available (i.e., rollback imputation).

[3] P-values are from two-sided Fisher's exact tests.

[Source: Tables_Clinical_Followup_UnivBilat.sas]

5.3 Continued Access

The Continued Access Cohort is discussed in the following sections. The information presented here is taken from Amendment 8, submitted to FDA on January 31, 2006. The continued access population is part of the all enrolled procedures and as such is a part of the primary safety analysis cohort. Therefore, updated safety information is provided in the all enrolled section of this document (see Section 5.4). These patients were all enrolled at the same IDE participating centers following the same protocol as the IDE. No comparisons are made between this population and the control as a similar population cannot be discerned from the datasets.

5.3.1 Number of Subjects Enrolled

The Continued Access Cohort consists of the following groups of procedures:

- Unilateral procedures with date of surgery > 8/5/2003 (date of closure of the IDE study cohort);
- Both side bilateral procedures with date of surgery > 8/5/2003 (date of closure of the IDE study cohort);
- Second side bilateral procedure if first surgery in IDE cohort > 730 days prior to second surgery.

A total of 609 procedures in 562 patients represent the Continued Access group implanted with the Cormet 2000 Hip Resurfacing System.

See Table 3.3(1) for a summary of the number of procedures and patients enrolled by site in the IDE Continued Access Cohort. Two of the IDE study sites did not participate in the continued access portion of the study.

Table 3.3(1) Patient Enrollment Continued Access Investigational Group[1] by Site

Investigators	Location	Number of Procedures	Number of Patients
	Springfield, IL	41	37
	Mobile, AL	10	10
	Englewood, NJ	66	66
	Colombia, SC	185	167
	Rockledge, FL	25	22
	Baltimore, MD	38	37
	Sarasota, FL	106	101
	Los Angeles, CA	2	2
	Galesburg, IL	128	112
	Cleveland, OH	8	8
TOTAL		609	562

[1]Continued Access Cohort includes procedures implanted after August 6, 2003.

5.3.2 Patient Accounting

The availability of follow-up evaluations for the Continued Access Cohort is listed in Table 4.3. Maximum length of follow-up as of the date of database lock, December 7, 2005, was 795 days. The average days of follow-up in the Continued Access group was 253.9 days.

Table 4.3 Procedure Accounting and Follow-up Compliance Table Investigational Device Continued Access Cohort

Table 4.3
Procedure Accounting and Follow-up Compliance Table
Investigational Device Continued Access Cohort

As of Date of Database Closure	Pre-Op	Week 6	Month 6	Month 12	Month 24	Month 24+	Month 36
	I	I	I	I	I	I	I
(1)Theoretical follow-up[1]	609	606	538	403	94	94	0
(2) Cumulative deaths including non-theoretically due[2]	0	1	1	1	1	1	1
(3) Cumulative revisions including non-theoretically due[3]	0	4	10	11	13	13	13
(4) - Not Yet Overdue[4]	0	2	17	46	31	31	0
(5) - Deaths+revisions among theoretical due[5]	0	5	10	8	2	2	0
(6) = Expected due for clinic visit[6]	609	599	511	349	61	61	0
(7) = Expected due+revisions among theoretical due[7]	609	603	520	356	62	62	0
All Evaluated Accounting (Actual[B]) Among Expected Due Procedures[8]							
	I	I	I	I	I	I	I
(8) All Evaluated Visit Compliance (%)[9]	100%	95%	76%	73%	64%	64%	.
(9) Harris Hip Total Score[10]	602	548	374	250	36	36	0
(10) Radiographic evaluation[11]		302	186	117	10	10	0
(11) CCS at Mos. 24, 24+ or HHS+radio. otherwise[12]		289	178	115	1	1	0
(12) Actual[B] % Follow-up for CCS or HHS+radio.CCS[13]		48%	35%	33%	2%	2%	
Within Window Accounting (Actual[A]) Among Expected Due[14]							
	I	I	I	I	I	I	I
(13) Harris Hip Total Score[15]	600	269	134	105	33	35	0
(14) Radiographic evaluation[15]		269	134	105	7	7	0
(15) CCS at Mos. 24, 24+ or HHS+radio otherwise[15]		269	134	105	1	1	0
(16) Actual[A] % Follow-up for CCS or HHS+radio.CCS[16]		45%	26%	30%	2%	2%	

[Source: Tables_Followup_Accounting_v2.sas]

Note: Row 8 - All Evaluated Visit Compliance (%) is calculated by dividing the Actual[B] patients with any data point available (not included in table above) by the expected due for clinic visit. Line 11 Actual[B] includes patients with **all** data available regardless of window.

Notes for Procedure Accounting and Follow-up Accounting Tables
[1] The theoretical follow-up is the number of implants that would have been examined if all patients returned on the exact anniversary of their respective initial surgery dates.
[2] Cumulative deaths up to and including the current interval. Although the cumulative numbers of deaths are recorded on this row, only deaths among implants that are theoretically due for that interval are subtracted from theoretical due to determine the number expected due.
[3] This row records the cumulative number of failures that have taken place according by the exact anniversary of scheduled follow-up visit. Although the cumulative numbers of failures are recorded on this row, only failures among implants that are theoretically due for that interval are subtracted from theoretical due to determine the number expected due. The cumulative revisions in Month 36 includes a revision in Month 39.
[4] Patients in this category are those who are theoretically due because their exact visit anniversary for that interval is on or before the date of database closure, they are within the evaluation time window, but have not been evaluated yet.
[5] Some of the deaths and revisions listed in rows 2 and 3 may not be included among theoretical due. This row provides the total number of cumulative deaths and revisions among those listed as theoretically due in row 1. This count is subtracted from theoretical due to obtain expected due for clinical evaluations (i.e.,. for HHS and radiography).
[6] Expected due for clinic visit is equal to Theoretical due (row 1) minus Not yet over due (row 4) minus not Deaths and revisions among theoretical due (row 5). This row serves as denominator for clinical evaluation % follow up.
[7] Expected due plus theoretical due revisions is computed by adding row 6 to the number of cumulative revisions among theoretical procedures. This row serves as the denominator for composite clinical success outcomes since revisions are known to be CCS failures.
[8] All Evaluated Accounting (Actual^{B}) is based on the evaluations on-file among those expected due without regard to whether assessment was within the assessment window.
[9] All Evaluated Visit Compliance (%) is computed as the number on-file among those expected due divided by the expected number due (row 6) expressed as a percentage. All evaluated compliance is based on the presence of any clinical data, even if incomplete, and demonstrates that the procedure is actively followed at least up to the specific interval.
[10] Harris Hip Total (Actual^{B}). This is the count of Harris Hip Total scores available for the that interval including those both within and out of window.
[11] Radiographic evaluation (Actual^{B}). The number of radiographic evaluations on-file including those both within and out of window. For Month 24 and Month 24+, this includes procedures evaluable and non-evaluable for the new composite radiographic endpoint.
[12] CCS at Mos. 24, 24+ or HHS+radiographic, otherwise (Actual^{B}). For Months 24 and 24+ this row indicates the numbers of procedures with all components on-file that are necessary to evaluate composite clinical success with revisions included as CCS failures. For other time points, this row only indicates that both Harris Hip Total scores and radiographic evaluations are on-file.
[13] Actual^{B} % Follow-up. The denominator for % follow-up for this row is row 7 for Months 24 and 24+ and is row 6 for other time intervals. This is because the status of revisions is known for CCS. For Months 24 and 24+ this row indicates (Actual^{B}) % follow-up for the primary efficacy endpoint (CCS) only counting radiographic assessments in which the new composite radiographic endpoint is determined. For other time intervals, this is row is equal to the % of procedures with HHS and radiographic assessments divided by row 6.
[14] Actual^{A} intervals: 6 weeks ± 2 weeks, 6 months ± 1 month, 12 months ± 2 months, 24 months ± 2 months, annually ± 2 months.
[15] Actual^{A} accounting excludes Harris Hip Total scores and radiographic evaluations that are outside of the intervals indicated in note 14.
[16] Actual^{A} % Follow-up is computed as row 16 divided by 7, expressed as a percentage.

One procedure (2%) in the "All Evaluated (Actual^{B}) Among Expected Due Procedures" group completed Month 24 postoperative follow-up. One procedure (2%) completed Month 24+ postoperative follow-up in the same group. Thirty-six procedures have Month 24 HHS data but radiographs have not been collected for this cohort yet. Twenty-three procedures did not return for their minimum Month 24 follow-up visit and no clinical data are available for these procedures. One patient (one procedure) died and one patient (one procedure) had one or more components removed before the Month 24 postoperative follow-up interval and were therefore excluded from the study.

5.3.3 Description of Deviations from Investigational Plan

As stated previously in Section 5.1.3, there were a total of six deviations in all enrolled procedures (pegged acetabular components) of which one occurred in the Continued Access Cohort. These procedures have been removed from the analysis. There were no other major protocol deviations reported for patients in the Continued Access Cohort.

5.3.4 Demographic Information

Of 609 Continued Access Cohort procedures, there was complete demographic information for all demographic fields with the exception of Charnley Class and preoperative Harris Hip Pain Score. Charnley class was received for one procedure after date of database closure and preoperative physical exam data including Harris Hip Pain Score was also received after date of database closure for another procedure. As a result, these two demographic fields represent data for 608 Continued Access procedures.

See Table 5.3 for a summary of baseline and demographic characteristics for procedures enrolled in the Continued Access Cohort.

Consistent with the pivotal unilateral and bilateral cohorts, there were more procedures performed in male patients (448; 73.6%) than female patients (161; 26.4%) enrolled in the Continued Access group. Similarly the mean age of patients in this group at surgery was 52.1 years (SD 9.4, 19-88). Over 91% of the procedures were performed in patients with a diagnosis of OA.

Table 5.3 Baseline and Demographic Characteristics - Investigational Continued Access Cohort

Table 5.3
Baseline and Demographic Characteristics
Investigational Continued Access Cohort

	Investigational			
	N	**%**		
Number of procedures	609			
Number of patients	562			
Males	448	73.6%		
Females	161	26.4%		
Primary diagnosis	**n**	**%**		
Osteoarthritis	559	91.8%		
Rheumatoid Arthritis	2	0.3%		
Avascular necrosis	48	7.9%		
Other Diagnosis Present	27	4.4%		
Charnely Class	**n**	**%**		
Unilateral joint, no other disability	308	50.7%		
Bilateral joint, no other disability	222	36.5%		
Uni or bilateral plus conditions affecting function	78	12.8%		
Contralateral hip	**n**	**%**		
Symptomatic	125	20.5%		
Replaced/Fused	68	11.2%		
Asymptomatic	416	68.3%		
Knee status	**n**	**%**		
Symptomatic (either knee)	146	24.0%		
Replaced/Fused (either knee)	4	0.7%		
Both asymptomatic	459	75.4%		
Surgery within 12 months	120	19.7%		
Harris Pain Category	**n**	**%**		
None/Ignores	1	0.2%		
Slight	1	0.2%		
Mild	5	0.8%		
Moderate	208	34.2%		
Marked	384	63.2%		
Totally disabled	9	1.5%		
	Mean	**SD**	**Min**	**Max**
Age at surgery (yrs)	52.1	9.4	19.0	88.0
Weight (lbs)	194.5	41.0	110.0	375.0
Duration of symptoms	48.0	50.0	2.0	480.0
Harris Hip Total Score	50.1	11.2	15.7	86.7

Source [Tables_BaselineDemo_v2.sas]

5.3.5 Surgical Details

Of 609 Continued Access Cohort procedures, there was complete surgical information for all surgical fields with the exception of femoral implant size, cup size and cup fixation method. These data points for

one procedure were received after date of database closure. As a result these three surgical fields represent data for 608 Continued Access procedures. See Table 6.3 for a summary of surgical details for procedures enrolled in the Continued Access Cohort.

A total of nine intraoperative AEs occurred in the Continued Access Cohort and include the following: femoral neck notching (two procedures), cardiovascular event (one procedure), leg length discrepancy (one procedure), muscle weakness (one procedure), nerve palsy (one procedure), low hemoglobin/hematocrit (one procedure), skin split (one procedure), and broken drill bit (one procedure).

Table 6.3 Surgical Details - Investigational Continued Access Cohort

Table 6.3
Surgical Details
Investigational Continued Access Cohort

	Investigational			
	N	**%**		
Number of procedures	609			
Number of patients	562			
Surgical Approach	**n**	**%**		
Lateral	42	6.9%		
Postero-lateral	500	82.1%		
Anterior	63	10.3%		
Trochanteric	1	0.2%		
Unspecified[a]	3	0.5%		
Femoral Implant Sizes[1]	**n**	**%**		
28mm	0	0%		
32mm	0	0%		
40mm	35	5.8%		
44mm	121	19.9%		
48mm	208	34.2%		
52mm	205	33.7%		
56mm	39	6.4%		
Cup Implant Sizes[1]	**n**	**%**		
46mm	23	3.8%		
48mm	11	1.8%		
50mm	97	16.0%		
52mm	23	3.8%		
54mm	178	29.3%		
56mm	32	5.3%		
58mm	199	32.7%		
60mm	6	1.0%		
62mm	39	6.4%		
64mm	0	0.0%		
Cup Fixation Method[1]	**n**	**%**		
Cemented	2	0.3%		
Press-Fit	606	99.7%		
Intraoperative Complications[2]	**n**	**%**		
Femoral neck notched	2	0.3%		
Femoral fracture	0	0.0%		
Cardiovascular/Arrhythmia	1	0.2%		
Ceramic Insert Chip	0	0.0%		
Other[b]	6	1.0%		

Notes:

[1] Information missing for one investigational continued access procedure.

[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 6 intraoperative complications designated as 'other' among 6 continued access procedures. These included single cases of leg length discrepancy, muscle weakness, nerve palsy, low hemoglobin/hematocrit, skin split, and broken drill bit.

[Source: Tables_Surgical_Details.sas]

5.3.6 Safety and Effectiveness Data

The Continued Access Cohort data is included in the all enrolled group safety results.

5.3.6.1 HHS

HHS analyses have not been provided separately for the Continued Access Cohort. The following information regarding scores <80 is provided as additional study information.

There were two patients with HHS of < 80 points at minimum Month 24 postoperative in the Continued Access group. One patient had spinal surgery for treatment of a herniated nucleus pulposis at L5-S1 with spinal stenosis and the other subject had experienced mild hip bursitis which could have contributed to the low score, but reported in Amendment 8 that the subject currently rides horses and seems to be doing fine.

5.3.6.2 Radiographic Success

Radiographic results have not been provided separately for the Continued Access Cohort.

5.3.6.3 Absence of Revision or Pending Revision

Thirteen revisions (2.1%) were reported for Continued Access Cohort at Month 24+ follow-up. Reasons for revision included: acetabular loosening (four procedures), and femoral neck fracture (nine procedures).

5.3.6.4 Absence of Device Related Events

Nineteen device related events (3.1%) among 18 procedures were reported for the Continued Access Cohort at Month 24+ follow-up. Reasons for device related events included: acetabular loosening (five procedures), dislocation (one procedure), femoral neck fracture (12 procedures), and femoral subsidence (one procedure).

There were no events of acetabular fracture, avulsed lesser trochanter, intraoperative femoral fracture, postoperative femoral fracture, femoral loosening or greater trochanter fracture in this cohort of procedures.

5.3.7 Safety

5.3.7.1 Adverse Events

Table 9.3(1) provides a summary of the number of procedures reporting AEs of the various types.

Table 9.3(1) Summary of Complications - Continued Access Cohort

Table 9.3(1)
Summary of Complications
Continued Access Cohort

	Investigational		
	n[8]	N[9]	%
Any complication	87	609	14.3%
Any hip-related complication	41	609	6.7%
Any device-related complication	18	609	3.0%
Any operative complication[1]	9	609	1.5%
Any post operative complication[2]	79	609	13.0%
Any post operative hip-related complication[3]	35	609	5.7%
Any post operative device-related complication[4]	18	609	3.0%
Any post operative serious complication[5]	25	609	4.1%
Any post operative serious hip-related complication[6]	2	609	0.3%
Any post operative serious device-related complication[7]	14	609	2.3%
Deaths	1	609	0.2%

Notes:
[1] Complications occuring during implant procedure as reported on Complication Form.
[2] Complications occuring after implant procedure as reported on Complication Form.
[3] Includes any post operative hip-related complication.
[4] Includes any post operative complication.
[5] Includes any post operative complication meeting the criteria for a serious complication as assessed by the investigator.
[6] Includes any post operative complication hip-related complication assessed by the investigator as serious.
[7] Includes any post operative complication.
[8] Number of procedures w ith at least one of the specific types of complications.
[9] Total number of procedures in this cohort of patients.

[Source: Tables_Safety_vs_ABCcontrols_CONTACC.sas]

Therefore, 87 procedures of the 609 procedures (14.3%) in the Continued Access Cohort reported a complication during the course of the study.

Hip related complications were defined as any AE related to the operative hip. Any AEs related to the contralateral hip were grouped with systemic AEs. There were 41 procedures reporting at least one hip related AE in the Continued Access group for a rate of 6.7%.

The rate of device related AEs in the Continued Access Cohort was 3.0% as 18 procedures reported at least one device related complication.

Operative complications in the Cormet 2000 Study were collected on the Operative Form. The timing of the events had to be used to classify events as “operative”. The Continued Access rate was 1.5% as 9 procedures reported at least one operative complication.

The rate of any postoperative complication in the Continued Access group was 13% and the rate of serious AEs was 4.1%.

The following sections provide a further analysis by AE type in the Continued Access Cohort, and an analysis of the time-course of adverse events experienced by the two populations.

5.3.7.2 Systemic Adverse Events

Systemic AEs were those reported events that did not relate directly to the operation or the operative site/device.

Table 9.3(2) represents a breakdown of systemic AEs for the Continued Access Cohort.

The first column (n) is the number of procedures with at least one of the specific types of complications. The second column (N) is the total number of procedures in the Continued Access Cohort, and the two are divided to provide the rate as a percentage in the third column.

Table 9.3(2) Specific Complications Continued Access Cohort

Table 9.3(2)
Specific Complications
Continued Access Cohort

	Investigational		
	n[1]	N[2]	%
Systemic			
Arrhythmia (operative)	0	609	0.0%
Bronchopulmonary	1	609	0.2%
Carcinoma	1	609	0.2%
Cardiovascular	2	609	0.3%
Death - unrelated to device	1	609	0.2%
DVT	3	609	0.5%
Gastrointestinal	0	609	0.0%
Genitourinary	2	609	0.3%
Infection remote location	3	609	0.5%
Lack of nutrition	0	609	0.0%
Low hemoglobin/hematocrit	2	609	0.3%
Neuropathy	0	609	0.0%
Neurosensory	0	609	0.0%
Nosebleed	0	609	0.0%
PE	1	609	0.2%
Rash	2	609	0.3%
Thrombophlebitis	0	609	0.0%
Trauma (non-hip related)	1	609	0.2%
Varicose veins	0	609	0.0%
Other	22	609	3.6%

Table 9.3(3) provides a time course of systemic events in the Continued Access group.

Table 9.3(3) Counts of Specific Complications by Time of Occurrence - Continued Access Cohort

Table 9.3(3)
Counts of Specific Complications by Time of Occurrence - Continued Access Cohort

	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		I		I		I		I		I		I	
Systemic														
Arrhythmia (operative)	0		0		0		0		0				0	
Bronchopulmonary	0		1		0		0		0				1	
Carcinoma	0		0		1		0		0				1	
Cardiovascular	1		1		0		0		0				2	
Death - unrelated to device	0		1		0		0		0				1	
DVT	0		2		1		0		0				3	
Gastrointestinal	0		0		0		0		0				0	
Genitourinary	0		1		1		0		0				2	
Infection remote location	0		2		0		1		0				3	
Lack of nutrition	0		0		0		0		0				0	
Low hemoglobin/hematocrit	1		1		0		0		0				2	
Neuropathy	0		0		0		0		0				0	
Neurosensory	0		0		0		0		0				0	
Nosebleed	0		0		0		0		0				0	
PE	0		1		0		0		0				1	
Rash	0		0		0		2		0				2	
Thrombophlebitis	0		0		0		0		0				0	
Trauma (non-hip related)	0		0		1		0		0				1	
Varicose veins	0		0		0		0		0				0	
Other	0		4		9		11		2				26	

There were 41 procedures with at least one systemic AE in the Continued Access group. The majority of systemic AEs took place at the Month 6 and Month 12 time frame. An analysis of the types of events reported and their time course shows expected rates of other body system complications for this type of population.

5.3.7.3 Hip Related Events

Hip related events were the most reported postoperative AEs concerning the hip or operative site. Table 9.3(4) gives a breakdown of the rates of hip related AEs for the Continued Access group. The first column (n) is the number of procedures with at least one of the specific types of complications. The second column (N) is the total number of procedures in the Continued Access Cohort, and the two are divided to provide the rate as a percentage in the third column.

Table 9.3(4) Specific Complications - Continued Access Cohort

Table 9.3(4) Specific Complications Continued Access Cohort			
	Investigational		
	n[1]	N[2]	%
Hip Related Events			
Acetabular Crack (operative)	0	609	0.0%
Acetabular malpositioned (operative)	1	609	0.2%
Broken drill bit (operative)	1	609	0.2%
Bursitis	8	609	1.3%
Deep infection	0	609	0.0%
Elevated metal ion level	0	609	0.0%
Femoral Crack (operative)	0	609	0.0%
Femoral neck notched (operative)	2	609	0.3%
Femoral radiolucency	1	609	0.2%
Greater Trochanter Notching (operative)	0	609	0.0%
Hematoma	4	609	0.7%
Heterotopic Bone Formation	1	609	0.2%
Hip Pain (operative side)	4	609	0.7%
Leg Length discrepancy	4	609	0.7%
Limp	1	609	0.2%
Loose Body	0	609	0.0%
Muscle Weakness	2	609	0.3%
Myositis ossificans	2	609	0.3%
Nerve palsy	2	609	0.3%
Skin split	1	609	0.2%
Soft Tissue Trauma	0	609	0.0%
Squeaking implant/clicking	1	609	0.2%
Subchondral cyst	0	609	0.0%
Subluxation	0	609	0.0%
Superficial infection	3	609	0.5%
Tendonitis	5	609	0.8%
Trochanteric Crack (operative)	0	609	0.0%
Wound Related (non-infected)	2	609	0.3%
Other	0	609	0.0%

There were a total of 45 hip related events reported among 41 procedures in the Continued Access group.

The majority of hip related complications had an occurrence rate of < 1%. Only bursitis was reported at a higher rate of occurrence (eight events; 1.3%).

Table 9.3(5) presents the hip related AEs over time for the Continued Access Cohort.

Table 9.3(5) Counts of Specific Complications by Time of Occurrence - Continued Access Cohort

Table 9.3(5) Counts of Specific Complications by Time of Occurrence - Continued Access Cohort	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		I		I		I		I		I		I	
Hip Related Events														
Acetabular Crack (operative)	0		0		0		0		0				0	
Acetabular malpositioned (operative)	0		0		1		0		0				1	
Broken drill bit (operative)	1		0		0		0		0				1	
Bursitis	0		0		4		3		1				8	
Deep infection	0		0		0		0		0				0	
Elevated metal ion level	0		0		0		0		0				0	
Femoral Crack (operative)	0		0		0		0		0				0	
Femoral neck notched (operative)	2		0		0		0		0				2	
Femoral radiolucency	0		0		0		1		0				1	
Greater Trochanter Notching (operative)	0		0		0		0		0				0	
Hematoma	0		2		0		1		1				4	
Heterotopic Bone Formation	0		0		1		0		0				1	
Hip Pain (operative side)	0		1		1		1		1				4	
Leg Length discrepancy	1		2		1		0		0				4	
Limp	0		0		1		0		0				1	
Loose Body	0		0		0		0		0				0	
Muscle Weakness	1		1		0		0		0				2	
Myositis ossificans	0		1		1		0		0				2	
Nerve palsy	1		1		0		0		0				2	
Skin split	1		0		0		0		0				1	
Soft Tissue Trauma	0		0		0		0		0				0	
Squeaking implant/clicking	0		0		1		0		0				1	
Subchondral cyst	0		0		0		0		0				0	
Subluxation	0		0		0		0		0				0	
Superficial infection	0		2		1		0		0				3	
Tendonitis	0		0		4		0		1				5	
Trochanteric Crack (operative)	0		0		0		0		0				0	
Wound Related (non-infected)	0		2		0		0		0				2	
Other	0		0		0		0		0				0	

5.3.7.4 Device Related Events

Table 9.3(6) provides a breakdown of the rate of device related AEs for the Continued Access group. The first column (n) is the number of procedures with at least one of the specific types of complications. The second column (N) is the total number of procedures in the Continued Access Cohort, and the two are divided to provide the rate as a percentage in the third column. There were a total of 19 device related events reported among 18 procedures in the Continued Access group.

Table 9.3(6) Specific Complications - Continued Access Cohort

Table 9.3(6)
Specific Complications
Continued Access Cohort

	Investigational		
	n[1]	N[2]	%
Device Related Events			
Acetabular Fracture	0	609	0.0%
Acetabular loosening	5	609	0.8%
Avulsed lesser trochanter	0	609	0.0%
Ceramic Insert Chip (operative)	0	609	0.0%
Dislocation	1	609	0.2%
Femoral Fracture (operative)	0	609	0.0%
Femoral Fracture (post-op)	0	609	0.0%
Femoral loosening	0	609	0.0%
Femoral neck fx	12	609	2.0%
Femoral subsidence	1	609	0.2%
Trochanter (greater) fx	0	609	0.0%

Notes:

[1] Number of procedures w ith at least one of the specific types of complications. The total number of procedures w ithat least one complications is smaller than the sum, since procedures can have more than one type of complication.

[2] Total number of procedures in this cohort of patients.

[Source: Tables_Safety_vs_ABCcontrols_CONTACC.sas]

Table 9.3(7) presents the device related AEs over time for the Continued Access Cohort.

Table 9.3(7) Counts of Specific Complication by Time of Occurrence

Table 9.3(7)
Counts of Specific Complications by Time of Occurrence - Continued Access Cohort

	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		I		I		I		I		I		I	
Device Related Events														
Acetabular Fracture	0		0		0		0		0				0	
Acetabular loosening	0		3		2		0		0				5	
Avulsed lesser trochanter	0		0		0		0		0				0	
Ceramic Insert Chip (operative)	0		0		0		0		0				0	
Dislocation	0		0		0		0		1				1	
Femoral Fracture (operative)	0		0		0		0		0				0	
Femoral Fracture (post-op)	0		0		0		0		0				0	
Femoral loosening	0		0		0		0		0				0	
Femoral neck fx	0		3		6		1		2				12	
Femoral subsidence	0		0		0		1		0				1	
Trochanter (greater) fx	0		0		0		0		0				0	

[Source: Tables_Safety_vs_ABCcontrols_CONTACC.sas]

Reviewing these events as they occurred over time, there were 5 (0.8%) events of acetabular loosening. There were also 12 (2.0%) events of postoperative femoral neck fracture in the Continued Access group.

5.3.7.5 Revisions / Removals Overview

Thirteen (2.1%) revisions were reported for the Continued Access Cohort at Month 24+ follow-up. Reasons for revision included: acetabular loosening (four patients) and femoral neck fracture (nine patients). There are two pending revisions in this group, one for radiographic evidence of malpositioned acetabular cup and one for radiographic evidence of non-healed femoral neck fracture.

5.3.7.6 Deaths

One death (0.2%) was reported in the Continued Access group.

5.3.8 Potential Lost to Follow-up

The following table demonstrates the potential lost to follow-up in the Continued Access Cohort.

Table 10.3 Potential Lost to Follow-Up – Cormet 2000 IDE Continued Access Cohort

Continued Access Cohort	Number of Procedures
Expected due for 24 month follow-up	61
Returned for 24 month follow-up	39
Missed 24 month follow-up	22
Returned for 24+ month follow-up	0
Potential Lost to Follow-up	22

5.3.9 Composite Clinical Success

The Continued Access Cohort was not used to determine CCS. A great majority of the patients in this cohort have not reached Month 24 follow-up and all CCS endpoints have not been evaluated. This cohort provides safety data for the Cormet 2000 Hip Resurfacing System.

5.4 All Enrolled
5.4.1 Safety

5.4.1.1 Adverse Events

Table 9.4(1) provides a summary of the number of procedures reporting AEs of the various types among All Enrolled investigational and control devices.

Table 9.4(1) Summary of Complication Comparisons Between All Enrolled Investigational and

Table 9.4(1)
Summary of Complication Comparisons between
All Enrolled Investigational and Control Devices - Summary

	Investigational			Control			Exact
	n[8]	N[9]	%	n[8]	N[9]	%	p-value
Any complication	427	1148	37.2%	229	349	65.6%	0.000
Any hip-related complication	219	1148	19.1%	97	349	27.8%	0.001
Any device-related complication	58	1148	5.1%	27	349	7.7%	0.064
Any operative complication[1]	31	1148	2.7%	52	349	14.9%	0.000
Any post operative complication[2]	412	1148	35.9%	212	349	60.7%	0.000
Any post operative hip-related complication[3]	208	1148	18.1%	79	349	22.6%	0.063
Any post operative device-related complication[4]	58	1148	5.1%	19	349	5.4%	0.782
Any post operative serious complication[5]	104	1148	9.1%				
Any post operative serious hip-related complication[6]	18	1148	1.6%				
Any post operative serious device-related complication[7]	49	1148	4.3%				
Deaths	6	1148	0.5%	5	349	1.4%	0.142

Notes:
[1] Complications occuring during implant procedure as reported on Complication Form.
[2] Complications occuring after implant procedure as reported on Complication Form.
[3] Includes any post operative hip-related complication.
[4] Includes any post operative complication.
[5] Includes any post operative complication meeting the criteria for a serious complication as assessed by the investigator.
[6] Includes any post operative complication hip-related complication assessed by the investigator as serious.
[7] Includes any post operative complication.
[8] Number of procedures w ith at least one of the specific types of complications.
[9] Total number of procedures in this cohort of patients.

[Source: Tables_Safety_vs_ABCcontrols_ENROLLED.sas]

Control Devices – Summary

The control group data is more mature as all patients have passed their two-year visit. In order to avoid extrapolation beyond the follow-up experience among investigational devices, control follow-up was censored to be no longer than the longest follow-up among investigational devices. This was 1490 days in Amendment 8 and 1803 days in Amendment 13 and final analyses. The control group has a higher rate of any reported complications (Fisher's exact test $p<0.0001$) and this suggests differences in reporting between the participating sites in the two studies.

There is no significant difference when comparing device related complications (Fisher's exact test p=0.064) between the two groups. Also there is no significant difference when comparing postoperative device related complications (p=0.782). This means that although the investigators may have had different philosophies about reporting systemic and hip related events, they tend to report more similarly for the device related events.

There was a significant difference (p<0.0001) in the rate of operative complications between the investigational and control groups with significantly more reported for the control group. Operative complications were collected on the Operative Form for the All Enrolled investigational group however; the control group did not employ a separate form so the timing of events had to be utilized in order to classify a complication as operative. The difference in rates between the two groups may be related to this difference in data collection.

Seriousness of the complications was not reported in the control group therefore a comparison between the groups could not be made. The investigational group All Enrolled cohort has a rate of serious AEs of 9.1% (104 procedures had at least one serious event among 1148 procedures). The percentage of procedures in which the patient died during the follow-up was larger among control devices (1.4%) compared to investigational devices (0.50%) but the difference in percentages was not statistically significant (p=0.142).

5.4.1.2 Systemic Adverse Events

Table 9.4(2) represents a breakdown of systemic AEs for the investigational and control All Enrolled groups. The first column (n) is the number of procedures in which a specific type of system AE was experienced. The second column (N) is the total number of at risk procedures. The first column is divided by the second column and multiple by 100% to provide the rate as a percentage in the third column.

Table 9.4(2) Complication Comparisons with Controls – Specific Complications - All Enrolled Investigational and Control Devices

Table 9.4(2) 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%	0.000
Carcinoma	4	1148	0.3%	18	349	5.2%	0.000
Cardiovascular	14	1148	1.2%	33	349	9.5%	0.000
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%	0.000
Genitourinary	8	1148	0.7%	20	349	5.7%	0.000
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%	0.000
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%	0.000
Varicose veins	1	1148	0.1%	0	349	0.0%	1.000
Other	218	1148	19.0%	102	349	29.2%	0.000

The rates of these systemic events over time for the All Enrolled groups are presented in Table 9.4(3). Note that in contrast to Table 9.4(2), these are events, and not procedures reporting events. Therefore, one procedure with repeated occurrences of an event will have each event reported separately in this table whereas they would only be counted as one procedure in the table above.

Table 9.4(3) Systemic Complications by Time of Occurrence – All Enrolled Procedures

Table 9.4(3)
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
Systemic														
Arrhythmia (operative)	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Bronchopulmonary	0	1	2	2	0	4	0	0	0	1	0	4	2	12
Carcinoma	0	0	0	0	2	2	1	2	1	2	0	13	4	19
Cardiovascular	4	7	3	8	0	1	1	3	4	3	2	12	14	34
Death - unrelated to device	0	0	1	0	0	0	0	1	2	1	3	3	6	5
DVT	0	0	5	0	3	0	1	0	0	0	0	0	9	0
Gastrointestinal	1	2	4	6	0	1	0	2	1	2	2	9	8	22
Genitourinary	0	5	5	8	2	3	0	0	1	1	0	3	8	20
Infection remote location	0	0	4	0	4	1	2	0	0	1	0	2	10	4
Lack of nutrition	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Low hemoglobin/hematocrit	1	0	1	0	0	0	0	0	0	0	1	0	3	0
Neuropathy	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Neurosensory	1	1	4	3	0	4	0	4	2	7	1	15	8	34
Nosebleed	0	0	1	0	0	0	0	0	0	0	0	0	1	0
PE	0	0	3	1	1	0	0	0	0	0	0	0	4	1
Rash	1	0	4	2	0	1	3	1	0	5	0	2	8	11
Thrombophlebitis	0	0	0	2	0	0	0	0	0	0	0	1	0	3
Trauma (non-hip related)	0	0	1	0	2	4	1	3	3	8	3	16	10	31
Varicose veins	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Other	8	3	66	12	59	10	50	13	51	25	39	59	273	122

5.4.1.3 Hip Related Events

Hip related events were the most reported postoperative AEs concerning the hip or operative site. Table 9.4(4) gives a breakdown of the rates for the All Enrolled groups.

Table 9.4(4) Hip Related Complication Comparisons with Controls

Table 9.4(4) 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]
Hip Related Events							
Acetabular Crack (operative)	0	1148	0.0%	1	349	0.3%	0.233
Acetabular malpositioned (operative)	4	1148	0.3%	0	349	0.0%	0.579
Broken drill bit (operative)	1	1148	0.1%	0	349	0.0%	1.000
Bursitis	32	1148	2.8%	16	349	4.6%	0.117
Deep infection	3	1148	0.3%	1	349	0.3%	1.000
Elevated metal ion level	1	1148	0.1%	0	349	0.0%	1.000
Femoral Crack (operative)	0	1148	0.0%	12	349	3.4%	0.000
Femoral neck notched (operative)	6	1148	0.5%	0	349	0.0%	0.346
Femoral radiolucency	12	1148	1.0%	0	349	0.0%	0.080
Greater Trochanter Notching (operative)	1	1148	0.1%	0	349	0.0%	1.000
Hematoma	8	1148	0.7%	3	349	0.9%	0.725
Heterotopic Bone Formation	12	1148	1.0%	13	349	3.7%	0.002
Hip Pain (operative side)	55	1148	4.8%	8	349	2.3%	0.047
Leg Length discrepancy	22	1148	1.9%	0	349	0.0%	0.004
Limp	13	1148	1.1%	0	349	0.0%	0.047
Loose Body	1	1148	0.1%	0	349	0.0%	1.000
Muscle Weakness	10	1148	0.9%	1	349	0.3%	0.474
Myositis ossificans	6	1148	0.5%	0	349	0.0%	0.346
Nerve palsy	4	1148	0.3%	5	349	1.4%	0.036
Skin split	1	1148	0.1%	0	349	0.0%	1.000
Soft Tissue Trauma	2	1148	0.2%	14	349	4.0%	0.000
Squeaking implant/clicking	20	1148	1.7%	2	349	0.6%	0.132
Subchondral cyst	1	1148	0.1%	0	349	0.0%	1.000
Subluxation	6	1148	0.5%	0	349	0.0%	0.346
Superficial infection	7	1148	0.6%	5	349	1.4%	0.165
Tendonitis	20	1148	1.7%	6	349	1.7%	1.000
Trochanteric Crack (operative)	0	1148	0.0%	7	349	2.0%	0.000
Wound Related (non-infected)	20	1148	1.7%	17	349	4.9%	0.002
Other	4	1148	0.3%	7	349	2.0%	0.005

For any hip related event, the All Enrolled control group had significantly more hip related AEs (p=0.001) with a rate of 27.8% compared to the investigational group's rate of 19.1%. This follows the higher rate of any complication in the control group as compared to the investigational group. The rate of any

postoperative hip related event was not significantly higher in the control group (p=0.063) with a rate of 22.6% compared to a rate of 18.1% in the investigational group.

Femoral neck notching is only associated with the investigational resurfacing group as the femoral neck is removed as an early step in total hip replacement. Notching of the femoral neck is known to be dependent on the surgical technique and would be expected to be higher in a multi-center trial such as this one. The rate of femoral neck notching was 0.5%. Neck notching is thought to be problematic as it may be a risk factor for future femoral neck fracture. None of the six cases with a reported femoral neck notching went on to have a femoral neck fracture.

Intraoperative femoral crack was only associated with the control group (12 events) as was intraoperative trochanteric fracture (seven events). Femoral and trochanteric cracks are more prevalent with total hip replacement as the resurfacing femoral stem does not invade the shaft of the femur or the trochanter.

Significantly (p=0.002) higher rates of heterotopic ossification (HO) in the control group may be related to the femoral canal intrusion in total hip replacement surgery causing more osteoblasts to be released into the surrounding tissues. The investigational group also reported six cases of myositis ossificans which is difficult to distinguish from HO on a radiograph. However, including these cases with the HO cases in the investigational group still resulted in a rate of HO that is almost half of that reported in the control group (1.5% vs. 3.7%).

Rates of bursitis (p=0.117) and tendonitis (p=1.0) were similar between the groups although reports of hip pain (p=0.047) were marginally higher in the investigational group. These three categories of AEs are all reported by the patient as pain in the operative hip. Combining the three categories, the rates are very similar between the groups (9.3% vs. 8.6%). In the previous submission of the data in January, many fewer reports of hip pain in the investigational group were in the database. The sponsor re-monitoring can be seen to be effective as many additional reports of hip pain were collected. The investigators often did not consider hip pain to be a complication, but rather an expected outcome from the surgery. Clarification of the threshold for reporting and diligence by the field monitoring staff has brought this reporting into line with what we could expect from this type of intervention.

Leg length discrepancy was significantly different in the two groups (p=0.004) with 22 events reported in the investigational group and none reported in the control group. It is important to note that resurfacing by design is less susceptible to iatrogenic leg length discrepancies than total hip arthroplasty thus the question remains as to why leg length discrepancy was reported more often in the resurfacing group. One explanation is surgeon expectation. In total hip arthroplasty, a certain amount of leg length change is expected and tolerated without concern. In resurfacing arthroplasty, the surgeons expect no leg length discrepancy after the surgery. This expectation is distorted by two factors: the patient's natural leg length discrepancy, and the effects of the underlying arthritis in leg shortening. Therefore, if a patient had a leg length discrepancy preoperatively, they would maintain that leg length discrepancy after resurfacing. Also, if a patient naturally had a 1cm leg length discrepancy at birth, and then developed arthritis on the longer side, that leg length could shorten to be more even with the contralateral side. When resurfacing occurred, the leg would then be lengthened to their native state of +1cm. In this study, an assessment of preoperative leg length discrepancy other than as reported in the preoperative HHS was not undertaken and so is not available for reference.

Table 9.4(5) presents the hip related AEs over time for both All Enrolled groups.

Table 9.4(5) Hip Related Complications by Time of Occurrence

Table 9.4(5)
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

It is important to caution that a direct comparison of the event counts between the groups is not appropriate. The much higher number of patients in the investigational group (1148) versus the control group (349) means that nearly four times as many events in the investigational group would give a similar rate of events between the groups. Reviewing these events as they occurred over time, the rates of hip pain events seem to be higher in the investigational group in the early postoperative timeframe with the difference diminishing over time. The rate of the implant clicking or squeaking was higher in the metal-on-metal investigational group than the ceramic-on-ceramic control. Also, the noise events occurred earlier in time post-operatively as the earliest noise events for the investigational group were reported in the Week 6 timeframe while the ceramic group did not experience any noise events until after Month 12. Also seen in this presentation of the data is the higher operative bone breakage (trochanteric crack, femoral crack) due to the difference in implantation surgeries between the two designs.

5.4.1.4 Device Related Events

Table 9.4(6) gives a breakdown of the rates of device related AEs for the All Enrolled investigational group and the corresponding control group. For both groups, the first column (n) is the number of patients experiencing this type of complication. The second column (N) is the total population number, and the two are divided to provide the rate as a percentage in the third column.

Table 9.4(6) Device Related Complication Comparisons with Controls

Table 9.4(6)
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]
Device Related Events							
Acetabular Fracture	0	1148	0.0%	1	349	0.3%	0.233
Acetabular loosening	11	1148	1.0%	0	349	0.0%	0.078
Avulsed lesser trochanter	1	1148	0.1%	1	349	0.3%	0.412
Ceramic Insert Chip (operative)	0	1148	0.0%	8	349	2.3%	0.000
Dislocation	2	1148	0.2%	10	349	2.9%	0.000
Femoral Fracture (operative)	0	1148	0.0%	1	349	0.3%	0.233
Femoral Fracture (post-op)	0	1148	0.0%	7	349	2.0%	0.000
Femoral loosening	14	1148	1.2%	0	349	0.0%	0.050
Femoral neck fx	26	1148	2.3%	0	349	0.0%	0.002
Femoral subsidence	4	1148	0.3%	2	349	0.6%	0.629
Trochanter (greater) fx	1	1148	0.1%	0	349	0.0%	1.000

Notes:

[1] Number of procedures with at least one of the specific types of complications. The total number of procedures with at least one complications is smaller than the sum, since procedures can have more than one type of complication.

[2] Total number of procedures in this cohort of patients.

[3] Two-sided Fisher's Exact tests. Comparisons were not performed for femoral neck notched (operative), greater Trochanter Notching (operative), ceramic insert chip (operative), and femoral neck fracture since both devices were not exposed to these types of events. Also, p-values are not reported when there were no events in either group.

[Source: Tables_Safety_vs_ABCcontrols_ENROLLED.sas]

The All Enrolled investigational group had a similar rate (5.1%) of any device related AE compared to the control group's rate of 7.7% (p=0.064). There was no significant difference in rates for any postoperative device related event between the two groups (p=0.78).

There were 11 events (1.0%) of acetabular loosening in the All Enrolled investigational group for which eight underwent revision surgery. There were no events of acetabular loosening in the control group.

There were eight events (2.3%) of chipping of the ceramic insert at surgical impaction in the control group, which is a known risk of devices using this bearing couple.

The rate of dislocation of the All Enrolled investigational group was significantly lower than that reported in the control group (p<0.0001). There were 10 events in the control group compared to two events in the investigational group. This difference highlights the benefits of a large diameter head, which is one of the common features of resurfacing devices such as the Cormet 2000.

Periprosthetic femoral fracture is more common in total hip arthroplasty than in resurfacing arthroplasty and that difference is shown by the significant difference in rate (p=0.00) between groups. There were seven events in the control group and none reported in the investigational group.

Femoral loosening is also more prevalent in resurfacing than in total hip arthroplasty. The All Enrolled investigational group reported 10 events for a rate of 0.9% of which nine cases underwent revision surgery. There were no events of femoral loosening reported in the total hip control group.

Femoral neck fracture is a known failure mechanism of hip resurfacing devices. In the All Enrolled investigational group, a 2.3% rate of postoperative femoral neck fracture was observed. Of the 26 events reported in the investigational group, 21 cases underwent revision surgery. This is not a reportable event among total hip arthroplasty as the surgical procedure sacrifices the femoral head and neck.

Table 9.4(7) presents the device related AEs over time for both All Enrolled groups.

Table 9.4(7) Device Related Complications by Time of Occurrence

Table 9.4(7)
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

[Source: Tables_Safety_vs_ABCcontrols_ENROLLED.sas]

5.4.1.5 Revisions / Removals Overview

Investigational Group

Forty-four (3.8%) revisions were reported for the All Enrolled investigational cohort at latest follow-up. Reasons for revision included: acetabular loosening (eight procedures), dislocation (one procedure), deep infection (two procedures), femoral loosening (eleven procedures), femoral neck fracture (21 procedures), and femoral subsidence (one procedure).

Control Group

Five patients (1.9%) were reported to have revision of one or more components of the ABC Ceramic-on-Ceramic System in the All Enrolled control group. The reasons for revision were femoral fracture, recurrent dislocation, deep joint infection, hip pain with suspected sepsis, and post traumatic femoral component subsidence and loosening.

Statistically, the All Enrolled investigational procedures identified the following factors as significant for revision when considering all enrolled procedures: female gender, small component size, preoperative leg length discrepancy of ≥ 1 cm, low preoperative HHS. Detailed analysis is provided in Section 6.0.

5.4.1.6 Deaths

Investigational

There were a total of six deaths (0.5%) in the All Enrolled investigational cohort.

Control

There were a total of five deaths (1.4%) during a comparable time frame in the control group.

6 Additional Revision Analysis

Patient selection is noted throughout the literature as critical to successful outcomes with hip resurfacing.

Amstutz, et al.[15] reported the results of the Wright Medical Conserve Plus U.S. IDE Study in which there were 12 revisions among 400 patients (3.0%) enrolled from November 1996 to November 2000 and identified the following as risk factors for femoral loosening:

- Large femoral head cysts (p=0.029)
- Patient height (p=0.032)
- Female gender (p=0.005)
- Smaller component size in males (p=0.005)

Schmalzried et al.[24] reported on a later series, those implanted from October 17, 2000 to December 20, 2004, in the same U.S. IDE study. Dr. Schmalzried is an associate of Dr. Amstutz at the Joint Replacement Institute at Orthopaedic Hospital, Los Angeles, CA. Dr. Schmalzried's initial series of hip resurfacing procedures used relatively strict patient selection eligibility criteria based on baseline characteristics of the proximal femur. In the publication, he reported no femoral neck fractures among the 147 procedures (121 patients) and only one component revision for femoral loosening thought to be due to AVN. In recent personal communications, Dr. Schmalzried reported that he now has more than 300 procedures with no femoral neck fractures.

The Australian Registry[22] provides considerable data related to the hip resurfacing procedure in general and to specific hip resurfacing designs. The 2005 results are summarized as follows:

- Resurfacing has higher rate of early revision than conventional THR (2.2% versus 1.9%)
- The main reason for early revision is femoral neck fracture (59% of the revisions)
- The rate of early revision is affected by diagnosis (AVN), gender (female) and age (>65 years).
- 70.5% of the hip resurfacing surgeries were performed in male patients but female patients have twice the risk of early revision compared to males.
- Appropriate patient selection is likely to reduce the revision rate: Recommended patient is a male, under the age of 65 years with a diagnosis of OA.

6.1 Overall device survival

Overall device survival among All Enrolled investigational device procedures is summarized in Table 12.4.1(a). Cumulative survival (SE) at 1 and 2 years are 0.9787 (0.005) and 0.9587 (0.0085), respectively. A comparison with All Enrolled Control procedures is displayed in Figure 12.4(1). Among controls, cumulative survival (SE) at 1 and 2 years are 0.9914 (0.005) and 0.9914 (0.005), respectively. Log rank statistics demonstrated a statistically significant difference in cumulative survival based on all follow-up (p<0.0001) and up to Month 24 (p=0.004). Table 12.1(a) provides a summary of device survival in the Pivotal Study Unilateral cohort. Cumulative survival (SE) at 1 and 2 years are 0.9789 (0.008) and 0.9498 (0.0125), respectively.

Table 12.4(a) Life Table Analysis

Table 12.4.1(a):
Life Table Analysis
Time to Revision/Replacement/Removal/Femoral Neck Fracture (censored at death)
All Enrolled Investigational Procedures

Interval	Pts. at start of interval t	# of failures	Censored at Month t	Failure rate at Month t	Survival rate at Month t	Cumulative survival rate[1]	SE[2]
At start	**1148**	**0**	**0**	0.0000	1.0000	1.0000	
Month 1	1148	**4**	**40**	0.0035	0.9965	0.9965	0.0017
Month 2	1104	**2**	**65**	0.0018	0.9982	0.9947	0.0022
Month 3	1037	**7**	**13**	0.0068	0.9932	0.9880	0.0034
Month 4	1017	**3**	**6**	0.0029	0.9971	0.9851	0.0038
Month 5	1008	**1**	**8**	0.0010	0.9990	0.9841	0.0039
Month 6	999	**1**	**36**	0.0010	0.9990	0.9831	0.0040
Month 7	962	**1**	**56**	0.0010	0.9990	0.9821	0.0042
Month 8	905	**1**	**31**	0.0011	0.9989	0.9810	0.0045
Month 9	873	**1**	**14**	0.0011	0.9989	0.9799	0.0047
Month 10	858	**0**	**10**	0.0000	1.0000	0.9799	0.0047
Month 11	848	**0**	**19**	0.0000	1.0000	0.9799	0.0048
Month 12	829	**1**	**67**	0.0012	0.9988	0.9787	0.0050
Months 13-14	761	**2**	**157**	0.0026	0.9974	0.9761	0.0055
Months 15-16	602	**3**	**38**	0.0050	0.9950	0.9713	0.0067
Months 17-18	561	**1**	**17**	0.0018	0.9982	0.9695	0.0072
Months 19-20	543	**2**	**10**	0.0037	0.9963	0.9660	0.0077
Months 21-22	531	**3**	**4**	0.0056	0.9944	0.9605	0.0083
Months 23-24	524	**1**	**89**	0.0019	0.9981	0.9587	0.0085
Months 25-26	434	**2**	**134**	0.0046	0.9954	0.9543	0.0098
Months 27-30	298	**1**	**76**	0.0034	0.9966	0.9511	0.0123
Months 31-33	221	**3**	**24**	0.0136	0.9864	0.9381	0.0159
Months 34-36	194	**2**	**48**	0.0103	0.9897	0.9285	0.0181
Months 37-60	144	**2**	**142**	0.0139	0.9861	0.9156	0.0227
Total		**44**	**1104**				

Notes:
1 SE errors computed using the Peto method
2 Cumulative survival (SE) at 1 and 2 years are 0.9787 (0.005) and 0.9587 (0.0085), respectively.

Source [Tables_Survival.sas]

Figure 12.4(1) Kaplan-Meir Survival Curves for All Enrolled Investigational and Control Devices

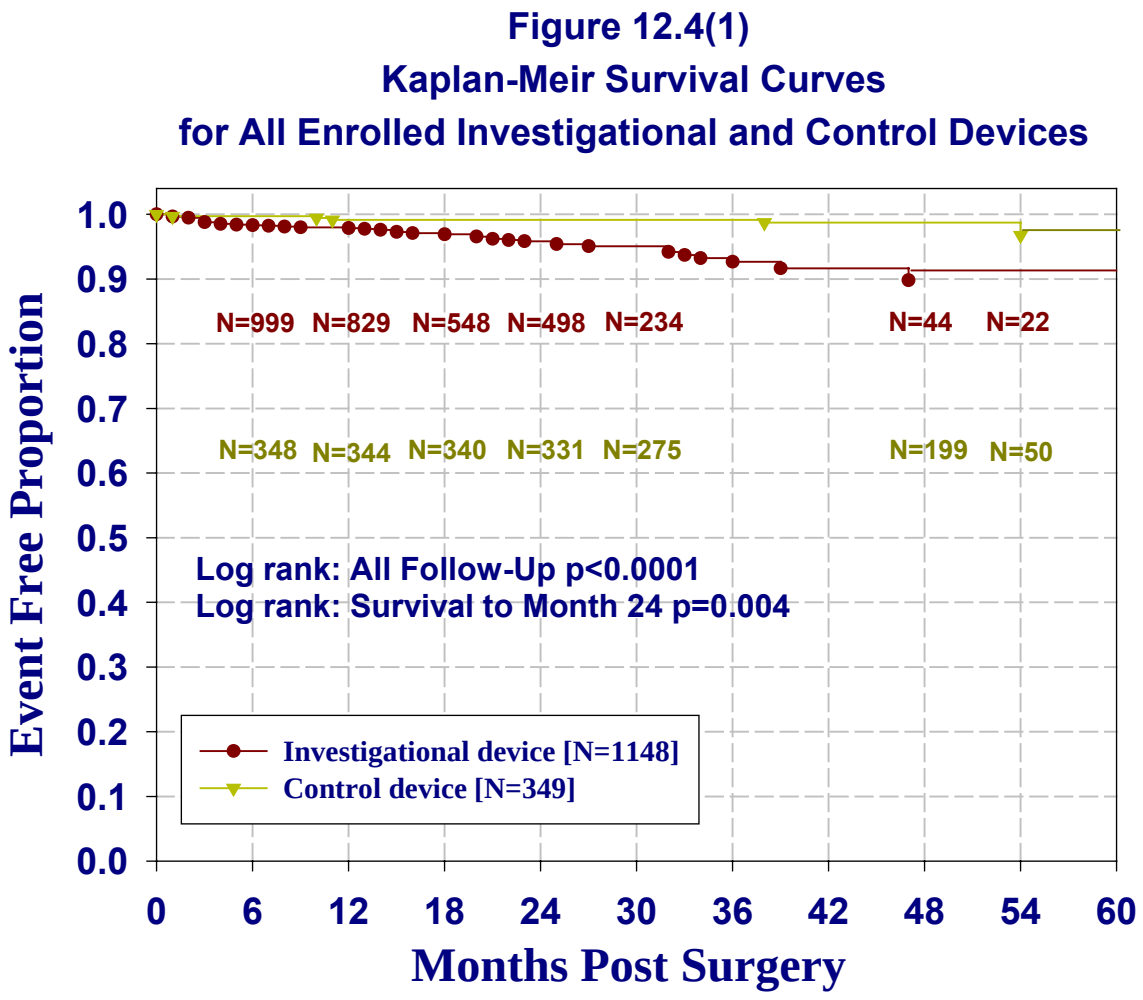

Table 12.1(a) Life Table Analysis

Table 12.1(a)
Life Table Analysis
Time to Revision/Replacement/Removal/Femoral Neck Fracture (censored at death)
Pivotal Study Unilateral Patients

Interval	Pts. at start of interval t	# of failures	Censored at Month t	Failure rate at Month t	Survival rate at Month t	Cumulative survival rate[1]	SE[2]
At start	**337**	**0**	**0**	0.0000	1.0000	1.0000	
Month 1	337	**1**	**0**	0.0030	0.9970	0.9970	0.0030
Month 2	336	**1**	**4**	0.0030	0.9970	0.9941	0.0042
Month 3	331	**1**	**0**	0.0030	0.9970	0.9911	0.0052
Month 4	330	**0**	**0**	0.0000	1.0000	0.9911	0.0052
Month 5	330	**1**	**0**	0.0030	0.9970	0.9881	0.0060
Month 6	329	**1**	**3**	0.0030	0.9970	0.9851	0.0066
Month 7	325	**1**	**4**	0.0031	0.9969	0.9820	0.0073
Month 8	320	**0**	**1**	0.0000	1.0000	0.9820	0.0074
Month 9	319	**1**	**1**	0.0031	0.9969	0.9789	0.0080
Month 10	317	**0**	**0**	0.0000	1.0000	0.9789	0.0080
Month 11	317	**0**	**2**	0.0000	1.0000	0.9789	0.0080
Month 12	315	**0**	**1**	0.0000	1.0000	0.9789	0.0080
Months 13-14	314	**2**	**11**	0.0064	0.9936	0.9727	0.0091
Months 15-16	301	**1**	**1**	0.0033	0.9967	0.9694	0.0098
Months 17-18	299	**0**	**2**	0.0000	1.0000	0.9694	0.0098
Months 19-20	297	**2**	**2**	0.0067	0.9933	0.9629	0.0108
Months 21-22	293	**3**	**0**	0.0102	0.9898	0.9530	0.0121
Months 23-24	290	**1**	**35**	0.0034	0.9966	0.9498	0.0125
Months 25-26	254	**2**	**54**	0.0079	0.9921	0.9423	0.0143
Months 27-30	198	**0**	**27**	0.0000	1.0000	0.9423	0.0163
Months 31-33	171	**2**	**18**	0.0117	0.9883	0.9313	0.0190
Months 34-36	151	**2**	**35**	0.0132	0.9868	0.9189	0.0217
Months 37-60	114	**2**	**112**	0.0175	0.9825	0.9028	0.0270
Total		**24**	**313**				

Notes:
1 SE errors computed using the Peto method
2 Cumulative survival (SE) at 1 and 2 years are 0.9789 (0.008) and 0.9498 (0.0125), respectively.

Source [Tables_Survival.sas]

6.2 Site Effect

Analysis examined variability across investigative sites and whether there was a significant site effect. Significance of site heterogeneity was assessed using a Cox regression that included only a site effect and that pooled the sites contributing ≤20 procedures. Among All Enrolled procedures, the site effect is statistically significant (χ^2=17.5, df=8, p=0.03). When procedures from Site 5 are excluded, the significance of the site effect disappears (χ^2=8.4, df=8, p=0.40), demonstrating homogeneity of survival among the remaining sites. The same result occurs among Pivotal Study procedures. Differences in survival are significant among sites when Site 5 is included (χ^2=14.5, df=6, p=0.02) but not when Site 5 is excluded (χ^2=1.5, df=5, p=0.91). Therefore, analysis of patient selection criteria was completed for all sites, all sites excluding Site 5, and for Site 5 only. See Table 2 for revision rate by site for both the pivotal unilateral group and for all enrolled patients.

Table 2 Revisions By Clinical Site

Table 2

Revisions By Clinical Sites

	All	Excl Site 5	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Site 10	Site 11	Site 12
Pivotal unilateral group														
Revisions	24	14	2	0	6	0	10	0	1	0	1	2	0	2
N	337	299	42	2	134	6	38	2	6	6	3	21	46	31
%	7.1	4.7	4.8	0.0	4.5	0.0	26.3	0.0	16.7	0.0	33.3	9.5	0.0	6.5
All enrolled group														
Revisions	44	29	2	0	11	3	15	0	2	0	1	3	2	5
N	1148	954	102	20	367	109	194	6	24	6	3	56	168	93
%	3.8	3.0	2.0	0.0	3.0	3.0	7.7	0.0	8.3	0.0	33.3	5.4	1.2	5.4

The revision rate for the Pivotal Unilateral group including all sites is 7.1% and without Site 5 it is notably lower at 4.7%. The high revision rate for Site 5 substantially impacts the overall revision rate. Interpretation of the following analysis will explain the results for all investigative sites combined. In instances where the inclusion of Site 5 has significant impact on results, differences will be explained.

6.3 Significant Patient Selection Criteria

Bivariate and multivariate analyses examined the relationship of specific patient selection criteria to revisions: demographics (sex, age, and weight), preoperative status (diagnosis, leg length discrepancy, baseline HHS, and duration of symptoms), and component size and are reported in the table below.

Table 3 provides a descriptive summary of the association between baseline risk factors and revisions for the pivotal study cohort and for all enrolled procedures. In order to provide meaningful comparisons of revision rates that accounted for varying follow-up times among cohorts, a summary is also provided for each of the cohorts that are restricted to the subgroup of patients who required revision no matter when the revision occurred plus all patients who had at least 24 months of follow-up in the survival analysis described above. Since this includes revisions among procedures not expected due for 24 month follow-up, revision rates in this subset are conservatively estimated. Risk factors evaluated include demographics, preoperative HHS, component size, and a learning curve indicator defined as the first 25 procedures within each specific site. Formal statistical analysis of these risk factors individually one-at-a time and in combination are presented below using survival analysis techniques in order to produce unbiased estimates of risk that account for variability in follow-up. The statistical significance for these

factors as well as the continuous factors of age, weight, and duration of symptoms based on survival analyses of one factor at a time are summarized in Table 4.

The results summarized in Table 3 suggest that except for the learning curve effect, these factors have potential to be powerful explanatory factors for revision risk.

Table 3 Risk of Revision in Pivotal Unilateral Cohort and All Enrolled Procedures: All Procedures and Procedures with At Least 24 Months Follow-up

Table 3
Risk of Revision in Pivotal Unilateral Cohort and All Enrolled Procedures: All Procedures and Procedures with At Least 24 Months Follow-up

		Pivotal Unilateral	Pivotal Unilateral 24+ month follow-up[1]	All Enrolled	All Enrolled 24+ month followup[1]
	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% (362)
Small component size	40/44 mm	16.7% (13/78)	17.3% (13/75)	7.4% (22/296)	15.2% (22/145)
	>40/44/mm	4.3% (11/259)	4.9% (11/227)	2.6% (22/843)	5.7% (22/387)
Non osteoarthritis Dx	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 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)

Note: [1] In order to provide meaningful comparisons of revision rates that accounted for varying followup times among subgroups, analyses were restricted to the subgroup of patients who required revision no matter when the revision occurred plus all patients who had at least 24 months of follow-up. Since this includes revisions among procedures not expected due for 24 month follow-up, revision rates in this subset are conservatively estimated.

Table 4 provides the prevalence of the key risk factors for the pivotal study cohort and all enrolled procedures overall, after excluding Site 5, and for Site 5 alone. This reveals that patient selection was very different for Site 5 compared to the other sites. For example, in the pivotal unilateral cohort, 86.8% of patients from Site 5 had a leg length discrepancy of at least 1 cm. This compares to only 19.7% among pivotal study patients from the remaining sites. Similarly, 55.3% of the pivotal unilateral cohort from Site 5 had baseline HHS in the lowest quartile compared to 21.4% from the remaining sites. In contrast, only 2.7% of patients from Site 5 in the pivotal study cohort had a diagnosis other than

osteoarthritis compared to 15.7% at the remaining sites. Although an over abundance of large leg length discrepancies remained among all enrolled procedures at Site 5, the percentage in the lowest quartile of function becomes more similar between Site 5 and the remaining sites. However, the difference in the percentage of patients with small component size became larger (35.6% at Site 5 versus 24.0% at remaining sites).

Together, Table 4 and 5 suggest the possibility that different principles of patient selection were utilized at Site 5 compared to the remaining sites.

Table 4 Prevalence of Risk Factors for Pivotal Unilateral and All Enrolled Procedures with and without Excluding Site 5

Table 4
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[1]	78	68	10	296	227	69
	N[2]	337	299	38	1139	945	194
Non osteoarthritis Dx	**%**	**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	**%**	**27.3%**	**19.7%**	**86.8%**	**25.9%**	**13.8%**	**85.1%**
greater than or equal	**n**	92	59	33	296	131	165
1 cm	**N**	337	299	38	1145	951	194
Baseline lowest	**%**	**25.2%**	**21.4%**	**55.3%**	**25.1%**	**24.8%**	**26.3%**
quartile of function (HHS)	**n**	85	64	21	283	233	50
	N	337	299	38	1129	939	190
Among 1st 25	**%**	**43.6%**	**41.8%**	**57.9%**	**20.4%**	**21.9%**	**12.9%**
procedures within a	**n**	147	125	22	234	209	25
specific site	**N**	337	299	38	1148	954	194

Notes: [1] n is the number with the characteristic present; [2] N is the total number of procedures evaluated.

Source: Tables_Survival.sas

Table 5 Statistical Significance of Relationship of Revisions to Baseline Risk Factors in Survival Analysis Assessing Each Risk Factor Alone

Table 5

Statistical Significance of Relationship of Revisions to Baseline Risk Factors in Survival Analyses Assessing Each Risk Factor Alone

	Pivotal unilateral group			All enrolled group		
	All sites	**Excl Site 5**	**Site 5**	**All sites**	**Excl Site 5**	**Site 5**
Gender	p = 0.03	NS	p = 0.04	p = 0.01	p = 0.02	NS
Age	NS	NS	NS	NS	NS	NS
Weight	NS	NS	NS	NS	NS	NS
Diagnosis	p = 0.06	p = 0.004	p <.0001	NS	p = 0.02	NS
Leg length discrepancy	p = 0.01	NS	NS	p = 0.02	NS	NS
Baseline HHS	p <.0001	p = 0.07	p = 0.007	p = 0.03	NS	p = 0.07
Duration of symptoms	NS	NS	p = 0.03	NS	NS	NS
Small component size	p = 0.001	p = 0.001	NS	p = 0.0008	p = 0.0006	NS
1st 25 procedures	NS	NS	NS	NS	NS	NS

Significant p-values are reported. NS identifies those that are not statistically significant. A report with complete listing of tables for bivariate relationships (pivotal and all enrolled groups, with and without Site 5) can be provided.

Site 5 exhibited a slightly different set of predictive factors than did the remainder of sites. Longer duration of symptoms (hazard ratio=1.3 for each 1 year increase, 95% CI 1.0 to 1.5) was a significant risk factor at this site while component size and leg length discrepancy were not. In the pivotal study group, Site 5 used nearly as many smaller sized femoral components (40% of all implants used) as larger components and relatively more when compared to the other investigative sites (13.2% of all implants used). Amendment 13 reported that baseline HHS scores for this site were lower on the average in the pivotal unilateral group than for the investigation in total.

It is important to note that the gender and component size are highly correlated. In the pivotal unilateral study group, 109 of the 337 were female and 85.9% of them received a smaller size femoral component (size 40mm or 44mm). There were 228 males in the pivotal unilateral study group with only 14.1% of males receiving the smaller size implant. The all enrolled group demonstrates a similar very large difference between sexes in the use of smaller size femoral components. As a result of the strong association between gender and component size, gender is not entered into the final multivariable models. In models in which smaller component size and gender are simultaneously included, component size remains statistically significant while gender does not (results not shown). However, gender is recognized as a significant risk factor in the literature.

6.4 Effect of Risk Factors

Analysis examines the hazard ratio associated with factors found to be significantly related with revisions, both as a direct effect but also in a multivariable model that partials out the effect of each factor while controlling for the effect of all others. Surgeons with experience with hip resurfacing and who understand patient selection criteria or risk factors will have better outcomes.

The hazard ratios for various risk factors are presented in Tables 6 and 7 for the pivotal study group and the all enrolled group, respectively. Each table includes analyses of all procedures in these cohorts, all procedures excluding Site 5, and for each investigative site. Blank table entries for site specific analyses indicate unstable or non-estimable parameter estimates due to lack of information (e.g., no revisions or too few revisions).

Table 6 Cox Regression Hazard Ratios and 95% Confidence Intervals for Each Potential Risk Factor Evaluated One-at-a-Time Pivotal Unilateral, Pivotal Unilatera Excluding Site 5, and by Site

Table 6
Cox Regression Hazard Ratios and 95% Confidence Intervals
for Each Potential Risk Factor Evaluated One-at-a-Time
Pivotal Unilateral, Pivotal Unilateral Excluding Site 5, and by Site

				Site Specific											
		All	Excl. Site 5	1	2	3	4	5	6	7	8	9	10	11	12
	Revisions	24	14	2	0	6	0	10	0	1	0	1	2	0	2
	N	337	299	42	2	134	6	38	2	6	6	3	21	46	31
	%	7.1	4.7	4.8	0.0	4.5	0.0	26.3	0.0	16.7	0.0	33.3	9.5	0.0	6.5
Small component size	Hazard	3.9	5.8			11.5		2.5							
	LB	1.7	1.9			2.1		0.7							
	UB	8.7	17.3			63.1		9.0							
Female gender	Hazard	2.4	2.6			9.6		3.9					1.4		
	LB	1.1	0.9			1.1		1.1					0.1		
	UB	5.5	7.6			81.9		13.8					21.6		
Non osteoarthritis Dx	Hazard	2.5	5.0			2.2							3.1		
	LB	1.0	1.8			0.4							0.2		
	UB	5.9	14.5			12.5							49.7		
Leg length discrepancy	Hazard	2.7	1.1			2.0		1.4					4.0		
greater than or equal	LB	1.2	0.3			0.4		0.2					0.2		
1 cm	UB	6.1	3.9			10.8		10.8					63.9		
Baseline lowest	Hazard	5.2	2.8	2.3		3.0		8.9					1.5		
quartile of function (HHS)	LB	2.3	1.0	0.1		0.5		1.1					0.1		
	UB	11.9	8.1	37.6		16.6		70.5					24.3		
Ten year increase in age	Hazard	0.9	0.8	2.5		0.9		0.9					1.0		0.1
	LB	0.6	0.5	0.3		0.4		0.5					0.3		0.0
	UB	1.3	1.3	18.5		2.1		1.8					3.4		3.2
Twenty pound increase	Hazard	1.0	0.9	0.4		0.9		1.0					1.0		1.0
in weight	LB	0.8	0.7	0.1		0.6		0.7					0.5		0.6
	UB	1.2	1.2	0.9		1.3		1.3					2.1		1.9
One year increase in	Hazard	1.1	1.0	0.6		0.6		1.3					1.1		0.5
duration of symptoms	LB	1.0	0.9	0.2		0.3		1.0					1.0		0.1
	UB	1.1	1.1	2.1		1.1		1.5					1.2		2.3
Among 1st 25	Hazard	1.0	0.5					2.0							
procedures within a	LB	0.5	0.2					0.5							
specific site	UB	2.3	1.7					7.7							

Table 7 Cox Regression Hazard Ratios and 95% Confidence Intervals for Each Potential Risk Factor Evaluated One-at-a-Time All Enrolled Procedures, All Enrolled Procedures Excluding Site 5, and by Site

Table 7
Cox Regression Hazard Ratios and 95% Confidence Intervals
for Each Potential Risk Factor Evaluated One-at-a-Time
All Enrolled Procedures, All Enrolled Procedures Excluding Site 5, and By Site

				Site Specific											
		All	Excl. Site 5	1	2	3	4	5	6	7	8	9	10	11	12
	Revisions	**44**	**29**	**2**	**0**	**11**	**3**	**15**	**0**	**2**	**0**	**1**	**3**	**2**	**5**
	N	**1148**	**954**	**102**	**20**	**367**	**109**	**194**	**6**	**24**	**6**	**3**	**56**	**168**	**93**
	%	**3.8**	**3.0**	**2.0**	**0.0**	**3.0**	**2.8**	**7.7**	**0.0**	**8.3**	**0.0**	**33.3**	**5.4**	**1.2**	**5.4**
Small component size	**Hazard**	**2.8**	**3.7**			**3.7**		**1.4**					**4.3**		**0.8**
	LB	1.6	1.8			1.1		0.5					0.4		0.1
	UB	5.1	7.6			12.3		4.1					47.8		5.2
Female gender	**Hazard**	**2.1**	**2.4**			**2.4**		**2.0**		**0.9**			**0.9**		**0.6**
	LB	1.2	1.2			0.7		0.7		0.1			0.1		0.1
	UB	3.9	5.0			7.8		5.8		14.6			10.3		3.9
Non osteoarthritis Dx	**Hazard**	**1.7**	**2.8**			**2.7**		**0.0**		**1.3**			**1.9**		**3.1**
	LB	0.8	1.3			0.8		0.0		0.1			0.2		0.5
	UB	3.7	6.2			9.5		.		21.0			21.4	.	19.3
Leg length discrepancy	**Hazard**	**2.1**	**1.2**			**1.1**	**1.8**	**1.4**					**3.0**	**15.9**	
greater than or equal	LB	1.2	0.4			0.2	0.2	0.3					0.3	1.0	
1 cm	UB	3.9	3.1			5.0	20.4	6.3					33.0	257.7	
Baseline lowest	**Hazard**	**2.0**	**1.2**	**2.4**		**1.7**	**0.6**	**2.7**		**1.1**			**1.2**		
quartile of function (HHS)	LB	1.1	0.5	0.2		0.5	0.1	0.9		0.1			0.1		
	UB	3.6	2.7	38.5		6.5	6.8	8.3		17.7			12.9		
Ten year increase in age	**Hazard**	**1.0**	**0.8**	**1.8**		**0.8**	**0.5**	**1.3**		**2.1**			**1.0**	**0.9**	**0.7**
	LB	0.7	0.6	0.4		0.4	0.2	0.8		0.4			0.3	0.2	0.2
	UB	1.3	1.1	7.6		1.4	1.3	2.0		12.1			4.1	4.9	2.1
Twenty pound increase	**Hazard**	**1.0**	**0.9**	**0.3**		**1.1**	**0.2**	**1.1**		**0.7**			**1.1**	**1.2**	**0.8**
in weight	LB	0.9	0.7	0.1		0.9	0.1	0.8		0.3			0.6	0.6	0.5
	UB	1.1	1.1	0.9		1.5	0.7	1.3		1.7			2.1	2.4	1.3
One year increase in	**Hazard**	**1.0**	**1.0**	**0.6**		**0.9**	**0.9**	**1.1**		**0.9**			**1.0**	**0.3**	**1.1**
duration of symptoms	LB	0.9	0.9	0.2		0.7	0.6	0.9		0.6			1.0	0.0	0.9
	UB	1.1	1.1	2.1		1.2	1.3	1.2		1.4			1.2	2.5	1.5
Among 1st 25	**Hazard**	**1.2**	**0.9**				**1.4**	**2.1**							**0.1**
procedures within a	LB	0.6	0.4				0.1	0.7							0.0
specific site	UB	2.3	2.1				16.1	6.3							1.6

Hazard ratios for all sites and for both the pivotal unilateral and the all enrolled groups show that small component size, female gender, those with a diagnosis of other than osteoarthritis, leg length discrepancy greater than or equal to 1 cm, and low baseline HHS have greater risk of revision than other patients.

Pivotal unilateral group

- low baseline HHS (<43) shows the greatest risk with a hazard ratio of 5.2 (95% CI 2.3 to 11.9 for all sites combined, noting that Site 5 had a hazard ratio of 8.9 (**Table 6**).
- when Site 5 is excluded from the analysis, the hazard ratios for small component size and diagnosis increase substantially from 3.9 and 2.5 to 5.8 and to 5.0, respectively, while low baseline HHS hazard ratio decreases significantly (from 5.2 to 2.8, **Table 6**).
- Site 5 had such differing results that its data confounds the overall results of the study and in the case of component size and diagnosis diminished the effect of these factors compared to the results for all sites.
- As noted above, survival (in terms of not requiring revision) among sites significantly differed when Site 5 was included (χ^2=14.5, df=6, p=0.02) but not when Site 5 is excluded (χ^2=1.5, df=5, p=0.91). Significance of site heterogeneity was assessed using a Cox regression that only included a site effect and that pooled the sites contributing ≤20 procedures.

All enrolled group

- The hazard ratios for all of the significant risk factors decreased from the pivotal study group to the all enrolled group – for example, small component size decreases from 3.9 for all sites and from 5.8 for all sites excluding Site 5 to 2.8 and 3.7, respectively.
- Experience with hip resurfacing and the development of an understanding of patient selection results in diminished risk factors for the all enrolled group.
- As noted above, survival among sites significantly differed when Site 5 was included (χ^2=17.5, df=8, p=0.03) but not when Site 5 is excluded (χ^2=8.4, df=8, p=0.40) Significance of site heterogeneity was assessed using a Cox regression that only included a site effect and that pooled the sites contributing ≤20 procedures.
- Table 7 demonstrates some variability across sites in terms of the relative importance of risk factors. However, the study design does not permit formal statistical analysis of site by risk factor interaction. Of note:
    - The learning curve effect as expressed as first 25 procedures within a site was only suggested at Site 5 (hazard ratio = 2.1, 95% CI = 0.7 to 6.3) and did not appear to be present when site 5 was excluded (hazard ratio = 0.9, 95% CI = 0.4 to 2.1).
    - In contrast, the effect of small femoral component size did not appear strong at Site 5 (hazard ratio = 1.4, 95% CI = 0.5 to 4.1) but was highly statistical significant (p=0.001, see Table 5) and large in magnitude when Site 5 was excluded (hazard ratio = 3.7, 95% CI = 1.8 to 7.6, Table 7).
    - Diagnosis other than osteoarthritis could not be evaluated at Site 5 since osteoarthritis was the diagnosis for most of the cases at that site. When Site 5 is excluded, diagnosis other than osteoarthritis becomes an important risk factor (hazard ratio = 2.8, 95% CI = 1.3 to 6.2, Table 7). For other sites in which this factor could be evaluated, the magnitude of the hazard ratio was at least moderately large.

6.5 Multivariable Model

Table 8 presents findings of final multivariable models that included eight baseline risk factors. Results were generally consistent with bivariate associations and independent risk factor analysis. In the pivotal study group, four risk factors were simultaneously significant including small component size (hazard ratio = 5.5, 95% CI = 2.3 to 13.5); diagnosis of other than osteoarthritis (hazard ratio = 5.0, 95% CI = 1.8 to 13.8); a leg length discrepancy greater than or equal to 1 cm (hazard ratio = 2.3, 95% CI = 1.0 to 5.1); and a baseline HHS in the lowest quartile (hazard ratio = 6.4, 95% CI = 2.6, 15.7). The final model also controlled for age, weight, duration of symptoms, and a learning curve effect defined as the first 25 procedures performed within each site. An index was created that reflected the number of risk factors

present among the four that emerged as statistically significant among pivotal study procedures. Analyses of the association between the number of risk factors and risk of revision are discussed below and summarized in Table 10. Among all enrolled procedures, the magnitudes of the hazard ratios generally diminished, but remained statistically significant except for baseline function. Results varied when Site 5 was excluded, where the hazard ratios increased in magnitude for small component size and diagnoses other than osteoarthritis but decreased in magnitude for leg length discrepancy and baseline function.

Table 8 Hazard Ratios and 95% Confidence Intervals from Final Multivariable Cox Regression Models for Pivotal Unilateral and All Enrolled Procedures with and without Excluding Site 5

Table 8 Hazard Ratios and 95% Confidence Intervals from Final Multivariable Cox Regression Models 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
	Revisions	**24**	**14**	**10**	**44**	**29**	**15**
	N	**337**	**299**	**38**	**1148**	**954**	**194**
	%	**7.1**	**4.7**	**26.3**	**3.8**	**3.0**	**7.7**
Small component size	**Hazard**	**5.5**	**11.1**	**5.4**	**3.2**	**4.4**	**1.5**
	LB	2.3	3.1	1.2	1.7	1.9	0.5
	UB	13.5	38.9	25.4	6.1	10.3	4.5
Non osteoarthritis Dx	**Hazard**	**5.0**	**9.4**		**2.2**	**3.0**	
	LB	1.8	2.7		1.0	1.3	
	UB	13.8	32.4		4.9	7.1	
Leg length discrepancy	**Hazard**	**2.3**	**0.8**	**1.7**	**2.0**	**1.1**	**1.4**
greater than or equal	LB	1.0	0.2	0.1	1.1	0.4	0.3
1 cm	UB	5.1	3.0	26.5	3.7	2.9	6.5
Baseline lowest	**Hazard**	**6.4**	**4.3**	**23.6**	**1.7**	**1.1**	**2.2**
quartile of function (HHS)	LB	2.6	1.3	1.8	0.9	0.5	0.6
	UB	15.7	14.4	304.4	3.1	2.5	7.3
Ten year increase in age	**Hazard**	**1.1**	**0.9**	**1.2**	**1.1**	**0.9**	**1.3**
	LB	0.7	0.5	0.5	0.8	0.6	0.7
	UB	1.7	1.6	3.0	1.4	1.3	2.4
Twenty pound increase	**Hazard**	**1.1**	**1.1**	**1.1**	**1.1**	**1.1**	**1.0**
in weight	LB	0.9	0.8	0.8	0.9	0.9	0.8
	UB	1.4	1.5	1.7	1.3	1.3	1.3
One year increase in	**Hazard**	**1.1**	**1.1**	**1.3**	**1.0**	**1.0**	**1.1**
duration of symptoms	LB	1.0	1.0	1.0	0.9	0.9	0.9
	UB	1.2	1.2	1.7	1.1	1.1	1.2
Among 1st 25	**Hazard**	**0.4**	**0.2**	**0.4**	**1.0**	**0.7**	**2.1**
procedures within a	LB	0.2	0.0	0.1	0.5	0.3	0.6
specific site	UB	1.0	0.6	2.5	1.9	1.6	7.1

6.6 Additive Effect of Risk Factors

Small component size, a diagnosis other than osteoarthritis, a preoperative leg length discrepancy of greater than or equal to 1 cm, and a low baseline Harris Hip Score (lower quartile defined as <43 points) emerged as significant risk factors for revisions among pivotal study procedures. However, only two risk factors, small component size and diagnosis other than osteoarthritis, are statistically significant in the multivariable models for both the pivotal study unilateral group and all enrolled group with or without Site 5 included in the analysis. Therefore, additional descriptive analyses were performed in order to characterize the association between risk of revision and the presence or absence of these two factors.

Table 9 shows the combined risk of these two factors across study groups. In order to provide meaningful comparisons of revision rates that accounted for varying follow-up times among subgroups, analyses were restricted to the subgroup of patients who required revision no matter when the revision occurred plus all patients who had at least 24 months of follow-up in the survival analyses described above. Since this includes revisions among procedures not expected due for 24 month follow-up,

revision rates in this subset are conservatively estimated. Patients with a diagnosis other than osteoarthritis and receiving a small femoral component (most often females) have a much higher revision rate than those with only one of those factors or neither of those factors. For example, in the pivotal study cohort excluding Site 5, patients who have neither risk factor (that is, patients with a diagnosis of osteoarthritis who received a larger femoral component) were observed to have a revision rate of less than 1 % (0.6%), while those with both risk factors have a potential for revision of 30.0% (although the numbers of patients with both risk factors is small). This relationship was also observed among all enrolled procedures. Consistent with the diminished magnitude of the hazard ratios, the variability among percentages with revision was smaller (5.1% to 22.2%). Similar results were observed with or without excluding Site 5 with the exception that the revision rates among procedures with neither risk factor were substantially reduced when Site 5 was not included.

Table 9 Additive Effect of Risk Factors

Table 9
Additive Effect of Risk Factors

Diagnosis of AVN or RA	Small femoral components	All-enrolled 24+month follow-up[1]	All enrolled minus Site 5 with 24+ month follow-up[1]	Pivotal Unilaterals follow-up to 24 months[1]	Pivotal Unilaterals minus Site 5 follow-up to 24 months[1]
B=no	**B=no**	**17/335=5.1%**	**8/296=2.7%**	**7/195=3.6%**	**1/169=0.6%**
	A=yes	18/127=14.2%	12/104=11.5%	10/65=15.4%	6/55=10.9%
A=yes	B=no	5/52=9.6%	5/49=10.2%	4/32=12.5%	4/32=12.5%
	A=yes	**4/18=22.2%**	**4/18=22.2%**	**3/10=30.0%**	**3/10=30.0%**

Note: [1] In order to provide meaningful comparisons of revision rates that accounted for varying follow-up times among subgroups, analyses were restricted to the subgroup of patients who required revision no matter when the revision occurred plus all patients who had at least 24 months of follow-up. Since this includes revisions among procedures not expected due for 24 month follow-up, revision rates in this subset are conservatively estimated.

Schmalzried[24] discussed the optimal patient for hip resurfacing. He proposed a preoperative grading system that counted the number of accumulative preoperative risk factors as a basis for patient selection for hip resurfacing. His results demonstrated that patients with no preoperative risk factors were at the lowest risk of failure while those with multiple risk factors were at much greater risk of failure. While Dr. Schmalzried primarily focused on preoperative assessment of radiographs, our results support the premise that the additive effects of risk factors as an indication of potential risk for revision is important.

Table 10 summarizes the associations between number of risk factors and revision risk. In order to provide meaningful comparisons of revision rates that accounted for varying follow-up times among subgroups, analyses were restricted to the subgroup of patients who required revision no matter when the revision occurred plus all patients who had at least 24 months of follow-up. Since this includes revisions among procedures not expected due for 24 month follow-up, revision rates in this subset are conservatively estimated. For both the pivotal unilateral study group and the all enrolled study group all sites, the number of preoperative risk factors is significantly related to risk of revision (test for linear association among percentages $p < 0.0001$). In the pivotal group including all sites, one of 120 patients (0.8%) with no preoperative risk factors were revised, 5 of 106 patients (4.7%) with 1 preoperative risk factor were revised, 12 of 60 patients (20.0%) with 2 preoperative risk factors were revised, and 6 of 16 patients (37.5%) were revised. Results after excluding Site 5 and for Site 5 alone are also presented.

Among all enrolled procedures, when 0, 1, 2, or 3 of these risk factors were present, risk of revision was 6 of 456 (1.3%), 16 of 432 (3.7%), 15 of 213 (7.0%), and 7 of 46 (15.2%), respectively. There was one procedure that had four risk factors but has not been revised. To account for unequal follow-up, these analyses are repeated restricting attention to patients with at least 24 months followup (including all revisions). Revision risks for patients with 0, 1, 2, and 3 risk factors are 6 of 202 (3.0%), 16 of 206 (7.8%),

15 of 98 (15.3%), and 7 of 25 (28.0%), respectively, among procedures with at least 24 months of followup. There was one procedure with 4 risk factors. This patient has not been revised. The linear trend in percentages is statistically significant (p<0.0001).

Table 10 Additive Effect of Multiple Risk Factors on Revisions (sum of: small component size, diagnosis other than osteoarthritis, leg length discrepancy ≥1cm, low baseline HHS) Follow-up to Month 24

Table 10
Additive Effect of Multiple Risk Factors on Revisions
(sum of: small component size, diagnosis other than osteoarthritis, leg length discrepancy≥1 cm, low baseline HHS)
Follow-up to Month 24 *

	Pivotal Study Unilateral Cohort						All Enrolled Procedures Cohort					
	All sites *		Excl Site 5 *		Site 5 *		All sites *		Excl Site 5 *		Site 5 *	
	Revisions (N=302)		Revisions (N=266)		Revisions (N=36)		Revisions (N=532)		Revisions (N=467)		Revisions (N=65)	
	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N
0	**0.8%**	1/120	**0.9%**	1/118	**0.0%**	0/2	**3.0%**	6/202	**3.0%**	6/200	**0.0%**	0/2
1	**4.7%**	5/106	**5.3%**	5/95	**0.0%**	0/11	**7.8%**	16/206	**7.1%**	13/183	**13.0%**	3/23
2	**20.0%**	12/60	**10.0%**	4/40	**40.0%**	8/20	**15.3%**	15/98	**7.6%**	5/66	**31.3%**	10/32
3	**37.5%**	6/16	**30.8%**	4/13	**66.7%**	2/3	**28.0%**	7/25	**29.4%**	5/17	**25.0%**	2/8
4	**0.0%**	0/0	**0.0%**	0/0	**0.0%**	0/0	**0.0%**	0/1	**0.0%**	0/1	**0.0%**	0/0
Test for non-zero correlation	p<0.0001		p<0.0001		p 0.004		p<0.0001		p=0.002		p=0.15	

* Analyses were restricted to the subgroup of procedures that included all procedures that required revision no matter when the revision occurred plus all procedures that had at least 24 months of follow-up.

6.7 Summary for Revision Analysis

In summary, while preliminary analysis suggested learning curve as explanatory of the revision rate at one investigative site (Site 5), this detailed analysis found that patient selection criteria were predictive of patient outcomes and that different principles of patient selection were likely utilized at this site compared to the other clinical sites in the pivotal study.

Small component size, a diagnosis other than osteoarthritis, a preoperative leg length discrepancy of greater than or equal to 1 cm, and a low baseline Harris Hip Score (lower quartile) emerged as significant risk factors for revisions among pivotal unilateral study procedures. Gender, which is also a significant risk factor identified in the literature, is highly correlated with small component size, and thus was not entered into the final multivariate models. Two risk factors, small component size and diagnosis other than osteoarthritis, are statistically significant for both the pivotal study group and all enrolled group. The risk factors for revision identified in the Cormet study are consistent with those reported in the recent literature describing hip resurfacing studies.

More importantly, the additive effect of the number of these four risk factors present is significant such that the more risk factors a patient has, the greater the risk of procedure failure requiring a revision to the hip. In the pivotal study group including all sites, one of 120 patients (0.8%) with no preoperative risk factors were revised while 6 of 16 patients (37.5%) with 3 risk factors were revised. Informed patient selection based upon the identification and understanding of specific risk factors is important.

The results of this prospective multi-center IDE Study demonstrates that the observed revision rates across sites may be of reflective of surgeon experience with a new medical device, but reports results that are consistent with the literature. Surgeon training and careful patient selection to minimize the risks associated with the hip resurfacing procedure are important to optimization of individual patient results.

Furthermore, when the risk factors for revision in this Cormet IDE study are accounted for, the revision rates observed are also consistent with those reported in the hip resurfacing literature and other studies. Patients who had a diagnosis of osteoarthritis at baseline and who did not receive a small femoral component formed a sizeable subset of patients in the Cormet study and this important group of patients had a very low revision rate (<1%).

The Cormet 2000 Study is a prospective multi-center IDE Study with 1,148 surgeries performed at latest analysis. Variability across sites can be expected and the strength of a multi-center study in an IDE is that results will more accurately reflect the US surgeon experience with a new medical device.

The Cormet 2000 study revision rates, reasons for revision and populations at risk for revision are comparable to the literature for other total hip resurfacing systems (Table 11) and therefore, demonstrate risks associated with the hip resurfacing procedure itself, and not one specific hip resurfacing system. The importance of surgeon training and careful patient selection to minimize the risks associated with the hip resurfacing procedure and optimize individual patient results are also noted in the literature.

Corin's analysis of the Cormet 2000 Study revision rate reports findings that assess risk factors one-at-a-time as well as determine independent contribution to revision by partialing out the effect of other significant risk factors through the use of a multivariable proportional hazards Cox regression. Further analysis quantified the additive effect on revision risk for a patient having multiple significant risk factors. The more risk factors a patient has, the greater the risk of procedure failure requiring a revision to the hip. It is important that informed patient selection be based upon the identification and understanding of specific risk factors consistent with those reported in the literature.

The Cormet 2000 IDE Study was initiated in 2001, prior to publication of the majority of literature that has helped to define the optimal patient for total hip resurfacing, and was conducted by surgeons previously unfamiliar with the surgical procedure. As with the Australian Registry, begun in 2001, the risk factors associated with total hip resurfacing have been identified through data analysis. The results of the Cormet 2000 IDE Study corroborate the conclusions of other IDE studies and registry data. Cormet 2000 Study results are comparable to the study results presented in the literature for most current generation metal-on-metal total hip resurfacing systems. [9,12,15,16,17,21,23,24]

7 Risk/Benefit Analysis

As with any medical device, there are risks and benefits to potential patients that must be considered. When choosing a therapy for arthritis of the hip, these benefits and risks must be weighed. There are two types of risks and benefits described in this section – theoretical and study data supported. Theoretical risks and benefits derive from the device design and pre-clinical testing, which cannot or have not been elucidated by the pivotal study presented herein. In addition, this pivotal study data gives evidence to other risks and benefits that must be considered.

7.1 Risks

The following risks associated with the use of hip resurfacing devices were identified in IDE G010047 for the Cormet 2000 Hip Resurfacing System.

7.1.1 Femoral neck fracture

A small percentage of patients who underwent Cormet 2000 Hip Resurfacing procedures experienced femoral neck fracture (26/1148; 2.3%) in [redacted]. Twenty-one of these incidences resulted in revision of the investigational devices, comprising 48% of the reasons for revisions in the study. Femoral neck fracture is well identified as a risk associated with hip resurfacing arthroplasty. In Australia, hip resurfacing accounted for 8.9% of primary hip replacements undertaken for osteoarthritis in recent years.[22] The 2004 annual report of the AOA indicated that hip resurfacing has a higher early revision rate than conventional total hip arthroplasty due to fracture of the femoral neck, and that 59% of hip resurfacing revisions were due to femoral neck fracture. Female gender was indicated as a risk factor for early revision due to femoral neck fracture ($p < 0.01$). Other studies identified surgical technique, appropriate patient selection and careful placement of the devices as critical factors in avoiding femoral neck fracture.[1,15,17,24]

In order to reduce the risk of femoral neck fracture, instructions in the Cormet 2000 Resurfacing Hip System operative technique should be followed. These instructions include details on femoral component alignment calling for avoidance of varus placement of the device, templating procedures that assure that the integrity of the neck will not be compromised, and instrumentation instructions to avoid femoral neck notching.

Surgeon training in appropriate operative technique which includes avoiding varus stem placement and avoiding intraoperative neck notching, along with careful patient selection are important to reduce the incidence of this risk.

7.1.2 Femoral loosening

Eleven patients (1.2%) were revised for femoral component loosening. Avascular necrosis (AVN) has been identified in the literature as a failure mechanism of femoral loosening. The reason for loosening for five of these patients was either progression of existing stage III AVN or development of AVN of the femoral head identified during their revision procedure. Six patients with radiographic stem subsidence could not be ruled out for AVN, and it is unclear at this time if the subsidence is indicative of potential of femoral head collapse of these patients.

Including these six patients in the incidence of this hip resurfacing risk for the Cormet 2000 Hip Resurfacing System is within the frequency of reported events in the literature and other clinical studies of hip resurfacing devices.

In order to reduce the risk, the Cormet 2000 Hip Resurfacing System operative technique and package insert includes "patients with inadequate bone stock" as a contraindication as follows:

"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."

In addition, Corin has produced surgeon education videos and other materials that demonstrate surgical situations when it would be inappropriate to use the Cormet 2000 Hip Resurfacing device based on inadequate femoral head bone stock.

7.1.3 Increased circulating metal ions

While the concerns over the local and systemic effects of metal wear products including ions exists, there is no direct evidence linking metal-on-metal arthroplasty with long-term medical problems including cancer. Increased levels of metal ions in the blood and urine of metal-on-metal total hip and resurfacing patients have been identified.[25, 26] A study performed on patients with the Cormet 2000 Hip Resurfacing system indicated that metal ion levels for cobalt and chromium initially increase following a metal-on-metal hip resurfacing but then plateau and start to decrease between one and two years post implantation. The levels remained below their peak but did not return to the preoperative levels throughout seven years of follow-up. These ion levels are similar to those reported by other authors in the metal-on-metal resurfacing systems.[25,26] Importantly, no adverse health effects were reported as a result of increased blood metal ion levels in this study.

7.2 Benefits

The following benefits associated with the use of hip resurfacing devices were identified in [redacted] for the Cormet 2000 Hip Resurfacing System.

7.2.1 Reduced risk of dislocation

The potential benefit of reduction in dislocation rate with the use of large diameter heads was supported in the Cormet 2000 Hip Resurfacing System study. The dislocation rate in the Cormet 2000 Hip Resurfacing System pivotal study was reported as 0.2% in the All Enrolled Procedures group, which was a significant reduction from that reported in the control population of 2.9% (Fisher's exact, $p<0.01$). This difference highlights the benefits of a large diameter head, which is one of the common features of resurfacing devices such as the Cormet 2000 Hip Resurfacing System. Resurfacing the femoral head more closely approximates the natural geometry. The large diameter head in the Cormet 2000 Hip Resurfacing System, which ranges from 40-56mm, is less prone to dislocation than the 28-32mm heads used in the control group. It is well established that an increase in head size may decrease dislocation by increasing the range of motion available prior to impingement.[19] Two other publications reported dislocation in resurfacing at 0.75% which is similar to the results achieved in this study.[9,

7.2.2 Higher function at 6 and 12 months post-operative

The data in this pivotal study demonstrated that patients reported a higher mean Total Harris Hip Score at the Month 6 and Month 12 time-points. A further examination of the HHS categories reveals a gain in the HHS function category score with more Cormet patients in the Pivotal Study Unilateral group reporting normal function than the total hip control group. Specifically, the percentage of patients judged to have a normal (at least 40 out of maximum 47 points) function category was 91.9% and 93.3% for the Cormet 2000 Hip Resurfacing System at Month 6 and Month 12. In comparison, the total hip control revealed only 85.2% and 88.5% of patients with normal function at these same time-points (Wilcoxon rank sum $p=0.038$ and $p=0.019$ respectively). These results are replicated in a similar study that compared metal-

on-metal resurfacing with a total hip ceramic system.[27] In that study, the total HHS was reported as 97.9 in the resurfacing group and 92.1 in the ceramic THA group with 60.7% of resurfacing patients reporting strenuous activity and only 30.4% of THA patients reporting the same.

7.2.3 Advantages of hip resurfacing procedure in contrast to THA

In addition to clinical benefit, the hip resurfacing procedure offers several advantages compared to the total hip arthroplasty procedure.

Preservation of proximal bone stock

The surgery of resurfacing does not remove the femoral head and neck thereby preserving the patient's native bone stock. As patients begin to receive arthroplasty procedures at younger ages, preservation of the femoral bone becomes more important. Loss of proximal femur can occur after total hip arthroplasty due to stress shielding and osteolysis. Retaining this bone longer may be beneficial to patients who will require more than one arthroplasty device during their lifetime.

Surgery does not invade femoral canal

It has been published, "hip resurfacing is inherently a form of 'minimally invasive surgery', as the femoral head and neck are preserved, and the femoral canal is not violated."[12,] The theoretical benefits of this surgery over total hip replacement surgery would be a reduction in blood loss fat emboli, and perhaps a reduction in heterotopic ossification postoperatively. In this study, lower rates of cardiovascular and neurosensory events were reported for the Cormet 2000 Hip Resurfacing System All Enrolled population than the control in the intraoperative and postoperative periods. Also, a reduction in adverse events for heterotopic bone was reported for the investigational group (1.0% versus 3.7%, $p<0.01$). The preservation of the integrity of the femoral canal may be a contributing factor to these differences in observed adverse event rates.

Reduced proximal stress shielding

The pattern of loading the proximal femur after resurfacing produces compressive forces rather than hoop stresses which is more physiologic.[28] A dual-energy X-ray absorptiometry study[29] showed that the bone mineral density in the proximal femur improved by 12% in Gruen zone 7 two years after resurfacing, which is in stark comparison to the 7 to 52% decrease in bone mineral density in this area after total hip replacement.[30] Proximal bone density is essential for long-term implant stability. If patients may require more than one arthroplasty device, preserving the quality of this bone would be beneficial to the patient's long term outcome.

7.2.4 Benefits of the system design

The osteolytic reaction caused by polyethylene debris is well documented,[30,31] and the reduction in wear rates associated with the metal-on-metal articulation is well elucidated.[32,33] Reduced wear leads to a longer service life of the articulating surfaces before deformation leads to the need for revision. In addition, the release of polyethylene debris from the articulation is eliminated. In metal or ceramic-on-polyethylene bearing the linear wear in vivo has been reported of up to 0.55 mm per year.[33] Hard-on-hard bearings all have the advantage of allowing increased cycles of motion with lower wear from the articulating surface. The in-vivo wear of metal and ceramic is too small to be quantified, however, in-vitro tests of these systems have demonstrated a 4.2μm/year for metal-on-metal[34,35] and <1μm/year for ceramic-on-ceramic.

7.3 Overall risk benefit profile

The Cormet 2000 Hip Resurfacing System is a safe and effective treatment for reducing pain and restoring motion to patients affected with arthritis of the hip. The benefits of the system include reduced

dislocation rate and increased function scores over that reported in the total hip arthroplasty control. Other benefits include preservation of proximal femoral bone stock during a surgery that does not violate the femoral canal, and very low wear of the articulating surface. A lower rate of cardiovascular and neurological events in the peri-operative timeframe may be attributable to the surgical implantation avoiding violating the femoral canal. Also, a reduction in heterotopic ossification was observed which may also be attributed to this difference in surgical implantation technique.

Risks of the system include the failure modes previously reported for hip resurfacing systems in a small percentage of patients, such as femoral neck fracture (2.3%) and femoral loosening (1.2%), possibly caused by avascular necrosis of the femoral head. These risks may be minimized by surgeon education and careful patient selection. The 24 month implant survival is estimated at 95%. There are no known clinical consequences of metal ion release from the bearing surface, and blood levels of these ions is similar to that reported with other metal-on-metal bearing systems.

Overall, this system is a reasonable alternative to total hip arthroplasty for well-selected patients. Patients must have adequate femoral bone stock to support the implant. Motivated patients can achieve greater function at an earlier timeframe than can be expected with a total hip arthroplasty. Based on the results of this prospective multi-center IDE study, the Cormet 2000 Hip Resurfacing System is a safe and effective alternative to total hip arthroplasty.

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SUMMARY OF SAFETY AND EFFECTIVENESS DATA

PREMARKET APPROVAL APPLICATION P050016

CORIN CORMET 2000 HIP RESURFACING SYSTEM

Sponsor:	**Corin USA** **10500 University Center Drive, Suite 190** **Tampa, FL 33612**
Contact:	**Kathy Trier, PhD**
Last Updated:	**August 11, 2006 (Revised December 29, 2006)**

TABLE OF CONTENTS

1. GENERAL INFORMATION 5
2. INDICATIONS FOR USE 5
3. CONTRAINDICATIONS 6
4. WARNINGS AND PRECAUTIONS 6
5. DEVICE DESCRIPTION 7
5.1. GENERAL OVERVIEW 7
5.2. FEMORAL COMPONENT 7
5.3. ACETABULAR COMPONENT 7
5.4. COMPONENT MATCHING 8
6. ALTERNATE PRACTICES AND PROCEDURES 8
7. MARKETING HISTORY 8
8. POTENTIAL ADVERSE EFFECTS OF THE DEVICE 8
9. SUMMARY OF PRECLINICAL STUDIES 9
9.1. GENERAL OVERVIEW 9
9.2. STERILIZATION VALIDATION 9
9.3. WEAR 10
9.4. FATIGUE STRENGTH TESTING 11
9.5. FRICTIONAL TORQUE 12
9.6. CIRCULATING METAL IONS 12
9.7. SURFACE COATING VALIDATION 13
9.8. RANGE OF MOTION 14
9.9. LUXATION WEAR 14
10. SUMMARY OF CLINICAL STUDIES 15
10.1. OVERVIEW 15
10.2. PURPOSE OF THE INVESTIGATION 15
10.3. STUDY DESIGN 15
10.4. COMPOSITE CLINICAL SUCCESS ENDPOINTS 17
10.5. STUDY POPULATION 22
10.6. BASELINE CHARACTERISTICS OF INVESTIGATIONAL AND CONTROL GROUPS 22
10.7. OPERATIVE SITE ADVERSE EVENTS AMONG CASES 23
10.8. PATIENT DISCONTINUATION 31
10.9. PATIENT COMPLAINTS 32
10.10. DEVICE FAILURES AND REPLACEMENTS 32
10.11. RESULTS OF STATISTICAL ANALYSES OF THE CLINICAL INVESTIGATIONS 37
11. CONTRADICTIONS AND PRECAUTIONS FOR THE USE OF THE DEVICE 44
12. OTHER INFORMATION AS APPROPRIATE 45
13. CONCLUSIONS DRAWN FROM THE STUDY 46
14. RISK/BENEFIT ANALYSIS 50
15. PLAN FOR POST-APPROVAL STUDY 55

TABLE OF TABLES

TABLE 1: FEMORAL COMPONENT/ACETABULAR COMPONENT COMPATIBILITY 8
TABLE 2:WORLDWIDE MARKETING HISTORY 8
TABLE 3 – SUMMARY TABLE 'WORST-CASE' FRICTIONAL TORQUE STUDY (DECEMBER 2005) 12
TABLE 4: SUMMARY OF THE RANGE OF ANGULAR MOVEMENT OF EACH BEARING COUPLE IN THE CORMET 2000 HIP RESURFACING SYSTEM SIZE RANGE AND THE MINIMUM REQUIREMENTS AS SPECIFIED IN ISO 21535:2002 14
TABLE 5 – PROTOCOL COMPARISONS 16
TABLE 6: FOLLOW-UP INTERVALS COMPARISON 16
TABLE 7: INCLUSION/EXCLUSION COMPARISON 17
TABLE 8: SUMMARY OF THE COMPOSITE CLINICAL SUCCESS 18
TABLE 9: RADIOGRAPHIC MEASUREMENT TECHNIQUE 18
TABLE 10: RADIOGRAPHIC SUCCESS CRITERIA 19
TABLE 11 (11.1(1)): MONTH 24 AND MONTH 24+ COMPOSITE CLINICAL SUCCESS USING ORIGINAL HHS DEFINITION AND MODIFIED RADIOGRAPHIC ASSESSMENT 20
TABLE 12 (11.1(2)): MONTH 24 AND MONTH 24+COMPOSITE CLINICAL SUCCESS – USING 21
TABLE 13: STUDY COHORT DEFINITIONS 22
TABLE 14: COMPARISON OF PIVOTAL STUDY TO CONTROL 23
TABLE 15: REVISIONS 24
TABLE 16 (9.4(1)): SUMMARY OF COMPLICATIONS BETWEEN ALL ENROLLED INVESTIGATIONAL AND CONTROL DEVICES 27
TABLE 17 (9.4(2)): SYSTEMIC COMPLICATION COMPARISON WITH CONTROLS – SPECIFIC COMPLICATIONS ALL ENROLLED INVESTIGATIONAL AND CONTROL DEVICES 28
TABLE 18 (9.4(4)): HIP RELATED COMPLICATION COMPARISON WITH CONTROLS - SPECIFIC COMPLICATIONS ALL ENROLLED INVESTIGATIONAL AND CONTROL DEVICES 29
TABLE 19 (9.4(6)): DEVICE RELATED COMPLICATION COMPARISON WITH CONTROLS - SPECIFIC COMPLICATIONS ALL ENROLLED INVESTIGATIONAL AND CONTROL DEVICES 30
TABLE 20: RELATIVE COMPLICATIONS FOR THE CORMET 2000 HIP RESURFACING IDE PATIENTS COMPARED TO THE ABC CONTROL 35
TABLE 21 (11.1 (1)): COMPOSITE CLINICAL SUCCESS USING ORIGINAL HARRIS HIP SCORE DEFINITION AND MODIFIED RADIOGRAPHIC ASSESSMENT 40
TABLE 22 (11.1 (2)): COMPOSITE CLINICAL SUCCESS USING MODIFIED HARRIS HIP SCORE DEFINITION AND MODIFIED RADIOGRAPHIC ASSESSMEN 41

TABLE OF FIGURES

FIGURE 1 (12.4(1)): KAPLAN-MEIER SURVIVAL CURVE: ALL ENROLLED INVESTIGATIONAL DEVICES 42

1. General Information

Device Generic Name:	Metal-On-Metal Resurfacing System
Device Trade Name:	Cormet 2000 Hip Resurfacing System
Applicant Name	Corin USA
Applicant Address	10500 University Center Drive, Suite 190 Tampa, FL 33612
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Premarket Approval Number	P050016

Date of Panel Recommendation:

Date of Notice of Approval to Applicant:

2. 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.

3. 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 on 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).

4. Warnings and Precautions

WARNINGS

1. Patients on medications (such as high-dose or chronic aminoglycoside treatment) or with co-morbidities (such as diabetes) that increase the risk of future, significant renal impairment should be advised of the possibility of increase in systemic metal ion concentration. Preoperative and postoperative monitoring of renal function (such as cretinine, GFR, BUN) will be necessary.
2. Do not scratch the femoral or acetabular component articulating surfaces.
3. Do not use another manufacturer's device in place of components of the Cormet 2000 Hip Resurfacing System. Design differences between manufacturers can lead to device failure.
4. Do not use these components for patients undergoing revision total hip replacement surgery.
5. Single use only. Never reuse an implant even if it appears undamaged.
6. Avoid notching the femoral neck, as this may lead to femoral neck fracture.
7. Avoid placing the femoral component in varus. Varus placement of femoral component has been associated with femoral neck fracture.
8. Do not handle the hydroxylapatite (HA) treated regions as it may compromise the sterility or cause failure under load.
9. Do not contour or bend an implant as it may compromise its fatigue strength and cause failure under load.

PRECAUTIONS

1. Before clinical use, the surgeon should thoroughly understand all aspects of the surgical procedure and limitations of the device. Patients must be instructed in the limitations of the prosthesis, including, but not limited to, the impact of excessive loading through patient weight or activity, and be taught to govern their activities accordingly. If the patient is involved in an occupation or activity that includes substantial walking, running, lifting, or muscle strain, the resultant forces can cause failure of the fixation, the device, or both. The prosthesis will not restore function to the level expected with normal healthy bone, and the surgeon should advise the patient against having unrealistic functional expectations.
2. Surgeons should review the Cormet 2000 Hip Resurfacing System operative technique prior to implanting.
3. Clean articulating surfaces of debris prior to final reduction of the joint.
4. Avoid overly abducting the acetabular component, which can accelerate wear.
5. Ensure that the head outer diameter and acetabular inner diameter match prior to implanting.
6. Handle porous surfaces carefully so that particles are not dislodged from the component surface.
7. Routine postoperative follow-up is recommended to monitor implant position and patient well being over time.
8. Appropriate selection, placement and fixation of the resurfacing hip components are critical factors, which affect implant service life. As in the case of all prosthetic implants, the durability of these components is affected by numerous biologic, biomechanic and other extrinsic factors, which limit their service life. Accordingly, strict adherence to the indications, contraindications, precautions and warnings for this product is essential to potentially maximize service life.

5. Device Description

5.1. General Overview

The Cormet 2000 Hip Resurfacing System, a metal-on-metal hip resurfacing system, is comprised of two components – a resurfacing head and a monoblock acetabular component. When *in vivo*, the femoral head articulates in a multi-directional fashion within the acetabular component.

5.2. Femoral Component

The femoral component is manufactured from cast cobalt-chromium-molybdenum (Co-Cr-Mo) alloy per ASTM F75. The component is intended for use with bone cement and available in five sizes (diameters): 40, 44, 48, 52 and 56mm.

5.3. Acetabular Component

The acetabular component is manufactured from cast Co-Cr-Mo alloy per ASTM F75. The acetabular component is finished with a bi-coat comprised of HA on plasma sprayed unalloyed titanium, which provides the bone ongrowth surface on the back of the component. The component is intended for use without bone

cement and is available in nine sizes (diameters): 46, 48, 50, 52, 54, 56, 58, 60 and 62mm.

5.4. Component Matching

The matching of femoral and acetabular components is described in Table 1.

Table 1: Femoral Component/Acetabular Component Compatibility

Femoral Component Sizes	Mating Acetabular Component Sizes
40mm	46 or 48mm
44mm	50 or 52mm
48mm	54 or 56mm
52mm	58 or 60mm
56mm	62mm only

6. Alternate Practices and Procedures

1. Non-surgical treatment (e.g., medications, physical therapy) or no treatment at all;
2. Other commercially available total hip replacement devices;
3. Rotational osteotomy;
4. Hip fusion.

7. Marketing History

The Cormet 2000 Hip Resurfacing System was launched in Europe in 1995. It has been distributed in the countries listed in Table 2. To date, 13,110 hip resurfacing procedures have been completed.

Table 2:Worldwide Marketing History

Argentina	Ecuador	Italy	Spain
Australia	Egypt	Japan	Sri Lanka
Belgium	Finland	Lebanon	Sweden
Brazil	France	Malta	Switzerland
Canada	Germany	Mexico	Syria
Chile	Greece	Pakistan	Taiwan
China	Holland	Portugal	Turkey
Colombia	India	Qatar	U.A.E.
Croatia	Iran	Saudi Arabia	U.K.
Cyprus	Israel	South Africa	Venezuela

8. Potential Adverse Effects of the Device

1. While the expected life of hip resurfacing components is difficult to estimate, it is finite. These components are made of foreign materials, which are placed within the body for the potential restoration of mobility or reduction of pain. However, due to the many biological, mechanical and physiochemical factors that affect

these devices but cannot be evaluated *in vivo*, the components cannot be expected to indefinitely withstand the activity level and loads of normal healthy bone;

2. Dislocation of the hip resurfacing prosthesis can occur due to inappropriate patient activity, trauma or other biomechanical considerations;
3. Loosening of hip resurfacing components can occur. Early mechanical loosening may result from inadequate initial fixation, latent infection, premature loading of the prosthesis or trauma. Late loosening may result from trauma, infection, biological complications, including osteolysis, or mechanical problems, with the subsequent possibility of bone erosion and/or pain;
4. Metal sensitivity reactions or allergic reactions;
5. Fatigue fracture of the implants (as a result of excessive loading, malalignment, or trauma);
6. Metallosis and osteolysis;
7. Peripheral neuropathies, nerve damage, circulatory compromise and heterotopic bone formation may occur;
8. Serious complications may be associated with any total joint replacement surgery. These complications include, but are not limited to: genitourinary disorders; gastrointestinal disorders; vascular disorders, including thrombus; bronchopulmonary disorders, including emboli; myocardial infarction or death;
9. A sudden drop in blood pressure intraoperatively due to the use of bone cement;
10. Acetabular pain may occur due to loosening of the implant;
11. Adverse effects may necessitate reoperation, revision, arthrodesis of the involved joint, girdlestone and/or amputation of the limb. Surgeons should advise patients of these potential adverse effects;
12. Periarticular calcification or ossification;
13. Bone perforation or fracture (occurring either intraoperatively or occurring postoperatively as a result of trauma, excessive loading, osteolysis or osteoporosis);
14. Wear deformation of the articular surface (as a result of excessive loading).

9. Summary of Preclinical Studies

9.1. General Overview

The following preclinical studies were carried out on the Cormet 2000 Hip Resurfacing System: sterilization validation, wear, fatigue strength testing, frictional torque, circulating metal ions, surface coating validations, range of motion (ROM), and luxation wear. The preclinical tests that have been performed and given as part of this PMA Submission show that the Cormet 2000 Hip Resurfacing System should function as intended when used in accordance with the directions for use.

9.2. Sterilization Validation

Femoral head and acetabular components of the Cormet 2000 Hip Resurfacing System are sterilized by gamma irradiation delivered from a $cobalt_{60}$ source.

After manufacture, the implants are transferred to a clean room operating to the level of Class 8 as defined by BS EN ISO 14644-1:1999 *Clean rooms and associated controlled environments –Part 1—Classification of air cleanliness.* Here, the devices are subjected to a cleaning process following which they are packaged.

The sterilization process has been validated to achieve a routine sterility assurance level of 10^{-6} at a minimum dose of 25kGy in compliance with the requirements of BS EN 556:1995 *Sterilization of medical devices – Requirements for terminally sterilized devices to be labeled as "sterile."* The process is validated in accordance with the requirements of AAMI TIR 27, 2001, *Sterilization of Health Care Products - Radiation Sterilization - Substantiation Of 25 kGy As a Sterilization Dose - Method Vd Max.* The irradiation process is carried out by a subcontractor, Isotron PLC, Swindon, United Kingdom, in one of two dedicated facilities in Swindon, UK or Reading, UK.

9.3. Wear

Three studies are reported relating to wear testing. All the tests used the same component bearing material, that is Co-Cr-Mo alloy to ASTM F75.

The initial study was commissioned in 1998 on the Cormet 2000 Hip Resurfacing System. The aim was to determine the impact of improved manufacturing tolerances and metallurgy on wear and investigated sphericity, diametrical clearance and metallurgy. The test compared the 'heat-treated' (hot isostatically pressed and solution annealed) Cormet 2000 Hip Resurfacing System to an 'as-cast' type device also commercially available. Tests were carrie[redacted] Stanmore Mk111 simulator at AEA Technology, Harwell. Two [redacted] Cormet 200[redacted] Systems and one [redacted] device were run to [redacted] at [redacted] maximum load [redacted] io[redacted] diametral bearing clearances of [redacted] respectively. The report concluded that there was no difference between the 'heat-treated' Cormet 2000 Hip Resurfacing System and 'as-cast' devices but showed a major wear improvement over previously manufactured devices due to the improved sphericity control. It reported lower wear rates than other metal-on-metal devices measured by AEA and reported in the literature.

A second, more comprehensive study investigated different bearing sizes and was carried out by the Interdisciplinary Research Centre at Queen Mary, University of London as a contract test re[redacted]n 8-station MTS System hip joint simulator was used to investigate four [redacted] and four [redacted] 'double heat-treated' (hot isostatically pressed and solution annealed as per Cormet 2000 Hip Resurfacing System specification) metal-on-metal bearings to [redacted] under normal gait conditions. The results were then compared to [redacted] bearing data that was being researched for a different study.

The prostheses were manufactured to production ications with regard to radial clearance, sphericity and surface finish. A biaxial-rocking motion was used to represent the flexion/extension and a on/adduction movements of the femur during ambulation. The loading cycle was based on the 'Paul' cycle (see report) applying between and at New calf serum was used as the lubricant. Heads and cups were measured every million cycles.

The bearings indicated the highest steady-stat rate with the larg ear occurring in the . The group had unning-in and steady-state wear compared to the coupling. The bearings, however, produced the lowest steady-state wear of all the groups. Bearing diameter had no influence on observed wear patterns and wear mechanisms.

The final study investigated the effects of heat treatment on wear rates in metal-on-metal bearings and was carried out by the Interdisciplinary Research Centre at Queen Mary, University of London. System hip joint nvestigate four 'as-cast' and four (Cormet 2000 Hip Resurfacing Systems) metal-on-metal bearings under standard and 'severe' gait (fast-jogging) conditions up to cycles.

The prostheses were manufactured to production ications with regard to radial clearance, sphericity and surface finish. A biaxial-rocking motion was used to represent the flexion/extension and abduction/adduction movements of the femur during ambulation. All components were subject to th ion cycles of 'normal walking' (standard gait) with a maximum load of at Then 'fast-jogging' and additional 'normal walking' tests we rmed. Heads and cups were measured every million cycles.

The results concluded that the running-in, steady-state and total wear rates were similar for both material groups demonstrating that changes in alloy microstruc influence the wear behavior. The steady-state wear rates found during 'normal walking' were similar to those repor bearings reported in the literature. When 'normal walking' er the 'severe' wear then the steady state wear rates returned to the level found prior to the 'severe' test regime. There was no long-term detrimental effect from the 'severe test' regime.

To summarize, the long-term steady-state wear for the Cormet 2000 Hip Resurfacing System is similar to the results found in other metal-on-metal bearings. All the wear tests indicate a higher running-in wear rate compared to the minimal steady-state wear; evidence of fluid film type lubrication, as reported in the literature.

9.4. Fatigue Strength Testing

testing was performed on five static and five dynamic (fatigue) resurfacing heads that were identified as 'worst-case.'

The static test method was configured to simulate the fault condition of the resurfacing head similar to the ISO 7206-4 *Implants for surgery - Partial and total hip joint prostheses – Part 4 – Determination of endurance properties of stemmed femoral components* whereby the test sim es the loss of proxim bone fixation. A jig fixed the resurfacing at to the vertical and in of anteversion. The was selected using stem-to-neck angl ean stem-shaft angle reported by Beaule[1] et al.) and using a valgus angle of stem of the resurfacing head was held on the distal section at a distance of below the underside of the head. Five static tests were performed with the f point identified as the point on the load/extension graphs where the elastic region ended. The mean static failure load was in excess of All samples went on to survive higher loads without catastrophic failure albeit with permanent deformation of the femoral stem.

9.5. Frictional Torque

Three independent frictional torque tests have bee the Cormet 2000 Hip Resurfacing System. In the latest study samples (head diameter) with the minimum specified radial clear as 'worst-case' since torque is proportional to head diameter) were uniquely paired with five The frictional torque of each bearing pair was recorded independently in flexion/extension and internal/external rotation under a joint load of and The experimental protocol was the same as that previously reported in the February 2005 study. The maximum torque was found to occur during flexion/extension mo maximum absolute (modulus) as r d at an average of and under a test load of and respectively.

To conclude, the studies indicate torq ificantly less than the torques to failure reported by Andersson et al.[2] being suggested by Andersson et al.[2] as being the torque required to remove a 'well'-cemented acetabular cup from a cadaveric socket). Such torques reported are thought unlikely to, therefore, be of relevance *in vivo*. Table 3 summarizes the results of the 'worst-case' frictional torque study at

Table 3 – Summary Table 'Worst-Case' Frictional Torque Study (December 2005)

	Load, N	Bearing Diameter, mm	Maximum Torque, Nm	Radial Clearance, µm
Test 3 (Dec 2005) Flexion-extension				
			Mean =	*Mean =*

9.6. Circulating Metal Ions

A series of patients who underwent a unilateral metal-on-metal hip resurfacing were prospectively followed over a period. All patients underwent the procedure by the same surgeon, who did not participate in the IDE study, but who has extensive experience with resurfacing. of the patients underwent a metal-on-metal hip resurfacing procedure o second hip during the course of the study. These patients along with other patients who had a previous hip resurfacing o ther hip had their m on levels assessed over time to determine the effect of bilateral hip resurfacing on metal ion levels.

Blood samples were taken from each patient following a strict technique so as to minimize the risk of sample contamination. A plastic intravenous cannula was inserted, the metal needle removed and of blo ere withdrawn and discarded. Samples were then taken and placed in 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.

Measurements were taken from patients with of those having bilateral resurfacings. Preoperative metal ion levels wer ailable for of the patients. Metal ion levels were available on all bilateral patients. For patients with one resurfacing device, results of the study indicate that metal ion levels for cobalt and chromium initially increase following a metal-on-metal hip resurfacing, but plateau and start to decrease between one and two years post-implantation. The levels remained below their peak but did not return to preoperative levels throughout the follow-up reported in this study. Implantation of a metal-on-metal resurfacing 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 years. Chromium levels following bilateral surgery did not return to normal but were only slightly higher when compared to levels of a unilateral resurfacing.

9.7. Surface Coating Validation

The acetabular component coating, consisting of plasma sprayed unalloyed titanium and HA, was validated. The coating was tested for static and dynamic shear, static tension and abrasion. Surface roughness was also calculated.

A total of five samples were tested according to ASTM F1044, resulting in an average strength of ± Shear fatigue strength testing was performed per ASTM F1160 *Standard test method for shear and bending fatigue of calcium phosphate and metallic medical and composite calcium phospha lic coatings*. Six samples were tested to ten million cycles at a stress of with no failures. Three samples were tested in sta n accordan ASTM F1147, resulting in an average strength of with a standard deviation of For abrasion, six samples were tested for an average ± of weight loss. Surface roughness measured from six sections of

prepared material resulted in an average Ra of ± The HA was validated across a wide range of variables, including density, particle size, porosity, solubility, dissolution, and bonding strength.

These validations showed appropriate levels of control over the coatings process in accordance with applicable guidelines.

9.8. Range of Motion

A study was conducted using a 3D CAD nvestigation of the Cormet 2000 Hip Resurfacing System size range. The resurfacing head and cup cup combination has been sho represent the 'worst-c stem in the size range as it provides the lowest range of angular motion in internal/external rotation, flexion/extension and abduction/adduction. Using a 'worst-case' femoral neck model, the results show that the Cormet 2000 Hip Resurfacing System, for all sizes, complies with ISO 21535:2002 *Evaluation of Relative Angular Motion of Components*. The results are presented below in Table 4.

Table 4: Summary of the Range of Angular Movement of each Bearing Couple in the Cormet 2000 Hip Resurfacing System Size Range and the Minimum Requirements as specified in ISO 21535:2002

Head-cup combination, mm	**Internal/external rotation, deg**	**Flexion/extension, deg**	**Abduction/adduction, deg**
ISO 21535	*90 (min)*	*80 (min)*	*60 (min)*

9.9. Luxation Wear

Luxation testing has been performed on five and five Cormet 2000 Hip Resurfacing System bearings. The procedure described *rmination of Resistance to Luxations and Repositions of Total Hip Joint Prostheses* by Kaddick et al.[3], in *Bioceramics in Orthopedics*, edited by Wofart Phuhl, 1998 was used. These bearing couples represent the lower and upper ends of the Cormet 2000 Hip Resurfacing System size range. Bearing clearances were controlled to the maximum specified in the manufacturing tolerances to represent 'worst-case'. The forces required to cause luxation of the bearings during the first cycle were recorded and the displacement note e cups were examined and then repeated luxations were p ed (a further cycles per bearing couple). A displacement of was pre- e thi reater than the displacement required to cause luxation in the and diameter bearings found during the first luxation.

After the first luxation cycle a small decrease in luxation force occurred for all bearing couples thought 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 bo e head and cup bearing surfaces. Forces to cause luxation were in excess of for both the and bearings. Visual surface analysis of the bearings showed scra at the end of the tests and is documented.

Literature is presented discussing the increased resistance to dislocation of large diameter metal-on-metal bearings and the effects of subluxation are presented.

10. Summary of Clinical Studies

10.1. Overview

A prospective, multi-center, investigational device exemption (IDE) study was conducted utilizing the Cormet 2000 Hip Resurfacing System in the United States under

The following is a brief recounting of the major event timelines for this investigation.

1. May 17, 2001 Cormet 2000 Hip Resurfacing System enrolled first patient;
2. August 5, 2003 Pivotal IDE study completed enrollment;
3. August 21, 2003 Continued Access study began;
4. March 26, 2005 PMA P050016 submitted to FDA;
5. January 31, 2006 submission of PMA Amendment (Amendment 8);
6. August 11, 2006 submission of updated PMA Amendment (Amendment 13).

The information in this PMA Amendment is sufficient to support the safety and effectiveness of the Cormet 2000 Hip Resurfacing System.

10.2. Purpose of the Investigation

The purpose of was to test the hypothesis that the Cormet 2000 Hip Resurfacing System is as effective as conventional hip arthroplasty. The Cormet 2000 Hip Resurfacing System was the investigational treatment and a conventional total hip arthroplasty system served as the control group. Safety was determined by collection of the incidence of perioperative and postoperative complications.

10.3. Study Design

A prospective, multi-center, IDE study was conducted utilizing components of the Cormet 2000 Hip Resurfacing System in the United States under

Control Group

The control group was comprised of total hip arthroplasty Osteonics ABC (Alumina Bearing Couple) enrolled under [redacted]. These ceramic bearings were approved via PMA P000013 on February 3, 2003. Table 5 compares the investigational and study parameters.

Table 5 – Protocol Comparisons

Protocol Element	Cormet 2000 IDE Study	ABC IDE Study (Control)
Type of Study	IDE – Hip Resurfacing	IDE – Total Hip Arthroplasty
Bearing Type	Metal-on-Metal	Ceramic-on-Ceramic
Study Design	Prospective, non-randomized, historical control	Prospective, randomized
Number of centers	14	16
Dates of enrollment	5/17/2001- 8/5/2003 (pivotal) Continued access through July 2006 (ongoing)	10/29/1996 – 10/20/1998
Number of procedures	1148	349
Intervals	Preoperative, 6 weeks, 6, 12, 24 and 24+ months	Preoperative, 6 weeks, 6, 12, 24 and 24+ months
Measures	Harris Hip Score Adverse Events Radiographs Questionnaire	Harris Hip Score Adverse Events Radiographs Questionnaire

The core data collected from these studies was the same. In addition, the follow-up time-points and the intervals around these time-points were very similar as illustrated in Table 6.

Table 6: Follow-up Intervals 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	±2months/+expanded	±2 months
2 years	±2 months	±2 months/+ expanded	±2 months
2+ years		Any evaluation 22+ months=24+ months	

The patient population recruited into both studies was similar. A side-by-side comparison of the inclusion/exclusion criteria between the studies is presented in Table 7.

Table 7: Inclusion/Exclusion Comparison

	Inclusion/Exclusion	Cormet 2000 Approved Protocol	Control Group Study
Well matched	Is skeletally mature	X	X
	Is mentally capable of follow-up	X	X
	Will be available for 2-year 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 Effect	No extensive deformity of femoral head	X*	Not relevant
	No known allergy 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
Differences	Has preoperative HHS <70 points	X	No limits
	No Congenital Dysplasia of the Hip (CDH)	X	Included in study
	Age	No limits	21-75 years
	Inflammatory arthritis	Included in study	X

*PI discretion

The majority of the eligibility criteria (10 of 18) were consistent for both studies. There were four criteria that were of no consequence to the study population comparison. The remaining four criteria were slightly different between the studies, yet comparisons of the populations enrolled found these parameters (age, diagnosis and preoperative HHS) to be similar between the populations.

The ABC control group meets the purpose of the study, which is to provide a recent series of total hip arthroplasty patients where there is adequate data available for comparison purposes. As the control group is ceramic-on-ceramic, both groups have a hard-on-hard bearing surface without the risk of issues associated with polyethylene debris. In addition, excellent results have been reported for the control device both in the PMA[4] and in the literature[5,6], making the control a formidable total hip arthroplasty challenge for the Cormet 2000 Hip Resurfacing System. The new resurfacing device and its new surgical technique will naturally be compared to proven hard bearing total hip arthroplasty results such as this control group provides.

10.4. Composite Clinical Success Endpoints

Table 8 provides a summary of the Composite Clinical Success (CCS) based on the approved protocol HHS success criteria and on the modified HHS success criteria. CCS data is being reported from the Month 24+ timeframe.

Table 8: Summary of the Composite Clinical Success

Composite Clinical Success Criteria	Original IDE Protocol	Criteria for PMA Amendment 8 and Amendment 13
1)Harris Hip Score	At least 20 point improvement at Month 24+ over preoperative	➔SAME ➔Also ≥80 at Month 24+ ("modified CCS")
2) No revisions/ pending revisions	no revisions/ pending revisions	➔SAME
3) Radiographic Success	Original definitions	Modified definitions
4) Device Related Adverse Events	Not Defined	Defined

1) Harris Hip Score (HHS) – The study protocol called for an improvement of ≥ 20 points at Month 24 and Month 24+ postoperative over preoperative status. The Sponsor also analyzed the data using a HHS ≥80 at Month 24 and Month 24+ postoperative to define clinical success. HHS data are presented both ways.

2) Radiographic Success – The review of the radiographs in accordance with the approved protocol revealed that some measurements could not be made because of bony landmarks and inconsistencies in patient positioning resulting in rotation of the femur in serial radiographs. Therefore, the data as requested by FDA is presented according to the schema summarized below in Table 9 and Table 10.

Table 9: Radiographic Measurement Technique

Radiographic Measurement Technique	Original IDE Study Protocol	Technique in PMA Amendment 8 and in Amendment 13
Acetabular Migration vertical/horizontal	Reference inferior teardrops	➔SAME
Acetabular Migration varus/valgus	Mid tear drop and center of head	➔SAME
Acetabular Radiolucencies	Serial	➔SAME
Femoral Subsidence axis femoral canal	Line to lateral femoral cortex	Line from head center to top of greater trochanter[7,8]
Femoral Tilt varus/valgus	Lines through femur midpoint and stem	➔SAME
Femoral Radiolucencies	Serial	➔SAME

Table 10: Radiographic Success Criteria

Radiographic Success Criteria	Original IDE Study Protocol	Criteria in this PMA Amendment 8 and in Amendment 13
Acetabular Migration vertical/horizontal	<5mm	➔SAME
Acetabular Migration varus/valgus	<5º	➔SAME
Acetabular Radiolucencies	None in any zone	Not in all zones
Femoral Subsidence axis femoral canal	<5mm	➔SAME Combined (must have both for failure)
Femoral Tilt varus/valgus	<1º	➔SAME
Femoral Radiolucencies	None in any zone	Not in all zones

3) Absence of revision or pending revision of any components of the Cormet 2000 Hip Resurfacing System – All revisions and pending revisions of the Cormet 2000 Hip Resurfacing System were reported and were included in the safety cohort for 1148 resurfacing procedures performed. All revisions and pending revisions in the Pivotal Study Unilateral Patients group were included in the CCS.

4) Absence of device related Adverse Events (AEs) – The following were identified as AEs that are considered "device related":

- Bone breakage around the implanted components;
- Aseptic loosening of the components, including complete radiolucency around the stem or evidence of 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.

The Composite Clinical Success (CCS) is presented in two ways:

- According to the original HHS criterion, absence of revision or pending revision, no device related AEs as clarified in this amendment, and modified radiographic assessment.
- According to the modified HHS criterion, absence of revision or pending revision, no device related AEs as clarified in this amendment, and modified radiographic assessment.

The CCS results are presented in Table 11 (11.1(1)).

Table 11 (11.1(1)): Month 24 and Month 24+ Composite Clinical Success using Original HHS Definition and Modified Radiographic Assessment

Table 11.1(1)
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 was 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.

Source [Tables_Clinical_Followup_vs_controls_PRIMEFFxz.sas]

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 control. To achieve this goal, it was necessary to determine clinical success status in as large a percentage of procedures as possible. This was necessary to insure that bias arising from losses to follow-up was small enough to permit valid inference. For procedures in the Pivotal Study Unilateral Cohort for which Month 24 Harris Hip Total score was missing, a later Harris Hip Total score was used. Our analysis demonstrated that these later scores were an accurate predictor of Month 24 score, and as such minimized bias by imputing missing Month 24 values with these later values.

It is conventionally believed 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. The data available from the current study is consistent with this *a priori* expectation.

In order to provide a complete summary description for Month 24 CCS, Month 24+ CCS Actual[B] Pivotal Study Unilateral Patients was defined to be the primary

comparison. Analyses were performed in order to demonstrate that the rollback imputation as well as the out of window procedures had no effect on the overall results. As was demonstrated in the table above, the study goal was achieved as the CCS for the investigational group was determined to be not inferior to the control group with the lower bound of the one-sided 95% confidence interval exceeding –0.08 (the study delta).

A modified CCS was also presented. The Sponsor believes that a dichotomization of the HHS at the 80-point cut-off line is more widely used as an indicator of patient success[9,10]. Scores of ≥80 are considered good to excellent results. In contrast, severely debilitated patients may increase their preoperative HHS by ≥20 points postoperatively and still have a score <80. Design of the HHS was proposed with the predictor of future prosthesis success or failure as a goal. In the original article that introduced HHS parameters and numeric values, Harris applied the categories of excellent (90-100 points), good (80-90 points), fair (70-80 points) and poor (less than 70 points). Clinical results of patients examined using the newly defined instrument showed that there was no significant deterioration of the good to excellent arthroplasty results with time. HHS of fair are more likely to deteriorate to poor over time.

Table 12 presents the clinical non-inferiority analyses based upon this modified CCS using a HHS ≥80 at Month 24+.

Table 12 (11.1(2)): Month 24 and Month 24+Composite Clinical Success – Using HHS≥80

Table 11.1(2)
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 Total 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 was 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.

[Source: Tables_Clinical_Followup_vs_controls_PRIMEFFz.sas]

Presentation of the data based upon the approved protocol HHS success criteria and the modified success criteria demonstrate non-inferiority of the Cormet 2000 Hip Resurfacing System 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, the Sponsor believes that the modified definitions of CCS provide an accurate and complete presentation of patient results for this study and as such provides FDA with the information necessary to make an evaluation of the safety and effectiveness of the Cormet 2000 Hip Resurfacing System.

10.5. Study Population

Corin collected US IDE clinical trial data for 1154 cases implanted with the Cormet 2000 Hip Resurfacing System. Six procedures involved use of a pegged acetabular component, not part of the IDE. These cases were analyzed separately. Study data were therefore presented on 1148 study cases. There were no major protocol deviations reported during a comparable timeframe in the control group, however, there was one approved deviation for inflammatory arthritis. These data are not included in this submission. Eight investigational procedures involved enrolment under the compassionate use provisions. The study populations are identified in Table 13.

Table 13: Study Cohort Definitions

Cohort Name	Definition	Procedures/patients
All Enrolled	All patients enrolled in either the pivotal study or continued access	1148/1030
Pivotal Study Unilateral	Unilateral patients enrolled in the pivotal study. Includes patients who had second side replaced after two years of follow-up (730 days)	337/337
Pivotal Study Bilateral	Patients with first implant in the pivotal study who had their second hip replaced within 730 days of the index procedure. Four incidences where second hip was not included in this study group because of use of pegged cups	102/53
Continued Access	Patients implanted after the pivotal study close (Aug 6, 2003) under continued access provision. Note: seven of these patients are also included in the pivotal study bilateral patient population above.	698/640
Compassionate Use	Implanted with investigational device under compassionate use between end of pivotal IDE study and beginning of continued access approval.	8/7

10.6. Baseline Characteristics of Investigational and Control Groups

To further support the use of the control group for this investigation, a comparison of baseline demographic and clinical characteristics between Cormet 2000 Hip

Resurfacing System patients and ABC Ceramic-on-Ceramic control patients in the unilateral patient cohorts were compared; refer to Table 14.

Table 14: Comparison of Pivotal Study to Control

Population	IDE Pivotal Study Unilateral Patients	ABC control Pivotal Study Unilateral patients	Wilcoxon (continuous) or Chi-squared (discrete) P values
Number of procedures	337	266	
Number of patients	337	266	
Mean Age	50.1	53.3	<0.01
Gender M/F	67.7%/32.3%	62%/38%	0.150
Mean weight (lbs)	190.4	188.7	0.692
Diagnosis	85.8% OA, 1.2% RA, 13.1% AVN	83.7%OA, 16.3% AVN	For Diagnosis=OA p=0.135
Preoperative HHS mean total score	50.1, SD=11.6	49.7, SD=11.3	0.233

There was no statistically significant difference in patient gender. Approximately two-thirds of both cohorts were male. There were no statistically significant differences in the distributions of diagnoses with approximately 85% of both cohorts presenting with a primary diagnosis of osteoarthritis. Mean weights were similar between these two groups. Height was not obtained during the Cormet 2000 study precluding comparisons involving body mass index (BMI).

Baseline overall function as reflected in mean Harris Hip Total scores also was very similar between the investigational and control Pivotal Study Unilateral device groups. The one difference, which presented from the analysis, was that the mean ages were statistically significant between groups. Although the group difference was statistically significant, a difference in mean age of just three years may not have clinical significance. Propensity score analyses were performed to assess the magnitude of and to adjust for potential selection bias. The propensity model included age, weight, baseline HHS, gender, and pre surgery presence of marked pain. The mean propensity scores were very similar in the Cormet 2000 and ABC control groups, [0.589 (0.088 SD) and 0.550 (0.103 SD), respectively]. The values were very similar in magnitude suggesting that, taken as a set, these variables had relatively little impact on characterizing what kind of patients received the Cormet 2000 implant relative to what kind of patients received the ABC control device. This implies that any impact of selection bias from these variables on the results is minimal.

10.7. Operative Site Adverse Events Among Cases

Revisions:
Investigational Group (N=1148)

Forty-four patients (3.8%) were reported to have revision of one or more components of the Cormet 2000 Hip Resurfacing System. Table 15 identifies the study cohort and reason for revision and or removal of study components.

Table 15: Revisions

	Pivotal Study Unilateral	Pivotal Study Bilateral	Continued Access	Compassionate Use	Total
Number	337	105	698	8	1148
Femoral Neck Fracture	8	2	11	0	21
Acetabular Component Loosening	4	0	4	0	8
Femoral Component Loosening	11	0	0	0	11
Deep Joint Infection	0	1	1	0	2
Dislocation	1	0	0	0	1
Femoral Subsidence	0	1	0	0	1
Total	24	4	16	0	44

Statistical review of the revision cohort identified the following factors as significant for revision when considering all enrolled procedures: female gender, small component size, preoperative leg length discrepancy of ≥ 1 cm, and low preoperative HHS. Twenty-one revisions occurred among the 323 procedures for female patients (6.5%) compared to 23 revisions for the 825 procedures for male patients (2.8%; p=0.015). Crude (single predictor variable) survival analyses were performed in order to account for unequal follow-up. Analyses revealed a hazard ratio for risk of revision equal to 2.1 (95% CI 1.2 to 3.9; p=0.01) comparing females to males. There were 22 revisions of patients with size 40mm or 44mm femoral components (296 procedures; 7.4%) compared to 22 revisions for patients implanted with sizes 48mm, 52mm or 56mm (843 procedures; 2.6%) [Note: implant size was unavailable for nine patients]. The hazard ratio for risk of revision was equal to 2.8 (95% CI 1.6 to 5.1; p=0.0006) comparing size 40mm or 44mm to larger sizes. When the effects of gender and size of component are simultaneous estimated, component size (p=0.02) but not gender (p=0.81) retains statistical significance. Reduced baseline function was associated with increased revision risk. The hazard ratio comparing patients in the lowest quartile of HHS scores (<43) to those with higher scores was 2.0 (95% CI 1.1 to 3.6; p=0.03). Having a preoperative leg length discrepancy ≥ 1cm was also associated with increased risk of revision. The crude hazard ratio was 2.2 (95% CI 1.2 to 3.9; p=0.01).

Two investigative sites (site 5 and site 10) had higher revision rates. These sites accounted for 17 of the 44 (38.6%) revisions in the study but only 250 of 1148 total procedures (21.8%). There were 27 revisions among the remaining 930 procedures (2.9% revision rate). When site 5 and site 10 were excluded, the small component size and female gender hazard ratios were 3.3 (95% CI 1.6 to 7.0, p=0.002) and 2.5 (95% CI = 1.2 to 5.4; p=0.02), respectively. Therefore, removing these two sites from the analysis did not affect the clinical or statistical significance of these two risk factors.

Patient age, diagnosis and preoperative weight were associated with increased risk for revision when all sites were included in the analysis. However, when site 5 (15 of the 44 revisions) was removed from the analysis, diagnosis other than

osteoarthritis, emerged as a statistically significant risk factor in both the pivotal study unilateral patients and all enrolled procedures. The hazard ratio was 2.8 (95% CI 1.3 to 6.2) comparing procedures with diagnoses other than osteoarthritis (i.e., AVN and rheumatoid arthritis) to those with osteoarthritis after excluding site 5. A diagnosis other than osteoarthritis was a significant risk factor in the Pivotal Study Unilateral cohort (hazard ratio=2.5, 95% CI = 1.0 to 5.9). All of the other risk factors noted above were also statistically significant in the Pivotal Study Unilateral cohort.

A multivariable Cox regression model (hazard ratio; 95% CI) was estimated based on data from the Pivotal Unilateral cohort. The following factors were simultaneously associated with increased revision risk: 40mm or 44mm component size (HR=5.5; 2.3 to 13.5), a non osteoarthritis diagnosis (HR=5.0; 1.8 to 13.8), a leg length discrepancy ≥ 1 cm (HR=2.3; 1.0 to 5.0), and HHS<43 (HR=6.4; 2.6 to 15.7). When 0, 1, 2, or 3 of these risk factors were present, risk of revision was 1 of 136 (0.7%), 5 of 117 (4.3%), 12 of 66 (18.2%), and 3 of 18 (33.3%), respectively. Restricting attention to patients with at least 24 months follow-up (including all revisions), revision risk for patients with 0, 1, 2, and 3 risk factors was 1 of 120 (0.8%), 5 of 106 (4.7%), 12 of 60 (20.0%), and 6 of 16 (37.5%). The linear trend was statistically significant (p<0.0001).

Control Group (N=349)

Five patients (1.4%) were reported to have revision of one or more components of the ABC Ceramic-on-Ceramic System. These patients were among the 266 unilateral patients. No patient in the bilateral group was revised; the reasons for revision are as follows:

- For one patient, the femoral component and alumina head were revised. The patient fell approximately one month post surgery and sustained a periprosthetic fracture, which was treated with Open Reduction Internal Fixation (ORIF) and a cast. The patient went on to non-union and the femoral component and head were revised nine months post original surgery.
- For one patient, the acetabular component, insert and femoral head were revised due to recurrent anterior dislocation five days post original surgery.
- One patient had all components revised due to deep joint infection approximately 10 months post implantation. The patient was reported to have a girdlestone procedure performed after the components were removed.
- One patient had all components removed due to hip pain approximately three years postoperatively. Sepsis was suspected, but not confirmed.
- One patient had femoral stem and head revised 4.5 years postoperative due to stem loosening post a traumatic event that took place 15 months after the index procedure.

Intraoperative Events:

Thirty-one cases (2.7%) reported intraoperative adverse events in the Cormet 2000 IDE study compared to 52 cases (14.9%) reported for the control population.

Postoperative Events:

Two hundred eight cases (18.1%) with postoperative hip related events were reported for the Cormet 2000 IDE population compared to 79 (22.6%) for the control population.

Fifty-eight cases (5.1%) with postoperative device related events were reported for the Cormet 2000 IDE population compared to 19 (5.4%) for the control population (p=0.782).

Systemic Events Among Patients

Systemic AEs were those reported events that did not relate directly to the operation or the operative site/device. An analysis of the types of events reported and their time course showed expected rates of other body system complications for this type of population.

The control group's higher rates of systemic AEs were distributed over time. These trends may be attributable to the greater maturity of the control database. In the control database, all patients had greater than 24 months of experience reported whereas only a fraction of the investigational group has experience past Month 24.

Deaths:

Six Cormet 2000 Hip Resurfacing System patients died during the course of the investigation. One patient died five days postoperatively, possibly due to a pulmonary embolism. Two patients died due to cardiac disease, both greater than 24 months postoperatively. Two patients died of lung cancer, one 16 months postoperatively and one 25 months postoperatively. One patient died 22 months postoperatively of unknown causes.

Two ABC control patients died prior to the two-year anniversary during the course of the investigation. One patient died of a massive myocardial infarction approximately 10 months post surgery. Another patient died approximately 18 months post surgery due to carcinoma.

Tables 16 and 17 provide a summary of systemic and operative site complications for the 1148 Cormet 2000 Hip Resurfacing System procedures and the ABC control.

Table 16 (9.4(1)): Summary of Complications between All Enrolled Investigational and Control Devices

Table 9.4(1)
Summary of Complication Comparisons between
All Enrolled Investigational and Control Devices - Summary

	Investigational			Control			Exact
	n[8]	N[9]	%	n[8]	N[9]	%	p-value
Any complication	427	1148	37.2%	229	349	65.6%	0.000
Any hip-related complication	219	1148	19.1%	97	349	27.8%	0.001
Any device-related complication	58	1148	5.1%	27	349	7.7%	0.064
Any operative complication[1]	31	1148	2.7%	52	349	14.9%	0.000
Any post operative complication[2]	412	1148	35.9%	212	349	60.7%	0.000
Any post operative hip-related complication[3]	208	1148	18.1%	79	349	22.6%	0.063
Any post operative device-related complication[4]	58	1148	5.1%	19	349	5.4%	0.782
Any post operative serious complication[5]	104	1148	9.1%				
Any post operative serious hip-related complication[6]	18	1148	1.6%				
Any post operative serious device-related complication[7]	49	1148	4.3%				
Deaths	6	1148	0.5%	5	349	1.4%	0.142

Notes:
[1] Complications occuring during implant procedure as reported on Complication Form.
[2] Complications occuring after implant procedure as reported on Complication Form.
[3] Includes any post operative hip-related complication.
[4] Includes any post operative complication.
[5] Includes any post operative complication meeting the criteria for a serious complication as assessed by the investigator.
[6] Includes any post operative complication hip-related complication assessed by the investigator as serious.
[7] Includes any post operative complication.
[8] Number of procedures w ith at least one of the specific types of complications.
[9] Total number of procedures in this cohort of patients.

[Source: Tables_Safety_vs_ABCcontrols_ENROLLED.sas]

Table 17 (9.4(2)): Systemic Complication Comparison with Controls – Specific Complications All Enrolled Investigational and Control Devices

Table 9.4(2)
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%	0.000
Carcinoma	4	1148	0.3%	18	349	5.2%	0.000
Cardiovascular	14	1148	1.2%	33	349	9.5%	0.000
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%	0.000
Genitourinary	8	1148	0.7%	20	349	5.7%	0.000
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%	0.000
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%	0.000
Varicose veins	1	1148	0.1%	0	349	0.0%	1.000
Other	218	1148	19.0%	102	349	29.2%	0.000

Table 18 (9.4(4)): Hip Related Complication Comparison with Controls - Specific Complications All Enrolled Investigational and Control Devices

Table 9.4(4)
Complication Comparisons with Controls - Specific Complications
All Enrolled Investigational and Control Devices

	Investigational			Control			0.017
	n[1]	N[2]	%	n[1]	N[2]	%	p-value[3]
Hip Related Events							
Acetabular Crack (operative)	0	1148	0.0%	1	349	0.3%	0.233
Acetabular malpositioned (operative)	4	1148	0.3%	0	349	0.0%	0.579
Broken drill bit (operative)	1	1148	0.1%	0	349	0.0%	1.000
Bursitis	32	1148	2.8%	16	349	4.6%	0.117
Deep infection	3	1148	0.3%	1	349	0.3%	1.000
Elevated metal ion level	1	1148	0.1%	0	349	0.0%	1.000
Femoral Crack (operative)	0	1148	0.0%	12	349	3.4%	0.000
Femoral neck notched (operative)	6	1148	0.5%	0	349	0.0%	0.346
Femoral radiolucency	12	1148	1.0%	0	349	0.0%	0.080
Greater Trochanter Notching (operative)	1	1148	0.1%	0	349	0.0%	1.000
Hematoma	8	1148	0.7%	3	349	0.9%	0.725
Heterotopic Bone Formation	12	1148	1.0%	13	349	3.7%	0.002
Hip Pain (operative side)	55	1148	4.8%	8	349	2.3%	0.047
Leg Length discrepancy	22	1148	1.9%	0	349	0.0%	0.004
Limp	13	1148	1.1%	0	349	0.0%	0.047
Loose Body	1	1148	0.1%	0	349	0.0%	1.000
Muscle Weakness	10	1148	0.9%	1	349	0.3%	0.474
Myositis ossificans	6	1148	0.5%	0	349	0.0%	0.346
Nerve palsy	4	1148	0.3%	5	349	1.4%	0.036
Skin split	1	1148	0.1%	0	349	0.0%	1.000
Soft Tissue Trauma	2	1148	0.2%	14	349	4.0%	0.000
Squeaking implant/clicking	20	1148	1.7%	2	349	0.6%	0.132
Subchondral cyst	1	1148	0.1%	0	349	0.0%	1.000
Subluxation	6	1148	0.5%	0	349	0.0%	0.346
Superficial infection	7	1148	0.6%	5	349	1.4%	0.165
Tendonitis	20	1148	1.7%	6	349	1.7%	1.000
Trochanteric Crack (operative)	0	1148	0.0%	7	349	2.0%	0.000
Wound Related (non-infected)	20	1148	1.7%	17	349	4.9%	0.002
Other	4	1148	0.3%	7	349	2.0%	0.005

Table 19 (9.4(6)): Device Related Complication Comparison with Controls - Specific Complications All Enrolled Investigational and Control Devices

Table 9.4(6)
Complication Comparisons with Controls - Specific Complications
All Enrolled Investigational and Control Devices

	Investigational			Control			0.017
	n[1]	N[2]	%	n[1]	N[2]	%	p-value[3]
Device Related Events							
Acetabular Fracture	0	1148	0.0%	1	349	0.3%	0.233
Acetabular loosening	11	1148	1.0%	0	349	0.0%	0.078
Avulsed lesser trochanter	1	1148	0.1%	1	349	0.3%	0.412
Ceramic Insert Chip (operative)	0	1148	0.0%	8	349	2.3%	0.000
Dislocation	2	1148	0.2%	10	349	2.9%	0.000
Femoral Fracture (operative)	0	1148	0.0%	1	349	0.3%	0.233
Femoral Fracture (post-op)	0	1148	0.0%	7	349	2.0%	0.000
Femoral loosening	14	1148	1.2%	0	349	0.0%	0.050
Femoral neck fx	26	1148	2.3%	0	349	0.0%	0.002
Femoral subsidence	4	1148	0.3%	2	349	0.6%	0.629
Trochanter (greater) fx	1	1148	0.1%	0	349	0.0%	1.000

Notes:

[1] Number of procedures with at least one of the specific types of complications. The total number of procedures with at least one complications is smaller than the sum, since procedures can have more than one type of complication.

[2] Total number of procedures in this cohort of patients.

[3] Two-sided Fisher's Exact tests. Comparisons were not performed for femoral neck notched (operative), greater Trochanter Notching (operative), ceramic insert chip (operative), and femoral neck fracture since both devices were not exposed to these types of events. Also, p-values are not reported when there were no events in either group.

[Source: Tables_Safety_vs_ABCcontrols_ENROLLED.sas]

Summary of Adverse Events

There were more operative site and systemic AE incidences reported for the control ABC Ceramic-on-Ceramic group than were reported for the Cormet 2000 Hip Resurfacing System. However, the difference between the groups has grown less profound as the investigational group data has matured. The control group data is still more mature as all patients have passed their 2-year visit. In order to avoid extrapolating beyond the follow-up experience in the investigational group, the control follow-up was truncated at the maximum number of days encountered in the investigational group (1803 days). The control group has a higher rate of reported complications and differences in reporting between the participating sites in the two studies should be assumed.

Among comparable AE types there were more incidences of dislocation ($p < 0.01$) among control patients. There was no difference in the incidence of device related AEs ($p=0.064$) between the investigational (58 procedures; 5.1%) and the

control (27 procedures; 7.7%). There were more revisions (44 of 1148; 3.8%) in the investigational group than the control group (5 of 349; 1.9%).

10.8. Patient Discontinuation

Pivotal Study Unilateral Patients

Investigational Group (N=337)

All 337 patients in the Pivotal Study Unilateral group were theoretically due for Month 24+ follow-up evaluation. Of these 320 patients were expected due for the Month 24+ follow-up evaluation. One patient died prior to the Month 24+ follow-up and 16 patients had one or more of the components of the Cormet 2000 Hip Resurfacing System revised or removed prior to the Month 24+ visit. A total of 292 of the 336 patients (86.9%) who did not die prior to Month 24 were included in the CCS analysis. Of the 44 patients not included, two died after Month 24, nine had complete HHS (all success) only, and five had complete radiographs (all success) only. Twenty-eight patients did not return for Month 24+ follow-up.

Control Group (N=266)

Of the 266 patients in the control group, 261 patients were due for Month 24+ follow-up. One patient had one or more components of the ABC Ceramic-on-Ceramic System revised, two patients died prior to the Month 24 follow-up visit. A total of 256 of a possible 264 patients (97.0%) were included in the CCS analysis. Of the nine patients not included, five had incomplete HHS scores and four patients were considered lost to follow-up.

Pivotal Study Bilateral Procedures

Investigational Group (N=105)

Of the 105 procedures (55 patients) in the bilateral group, 99 procedures were theoretically due for the Month 24+ follow-up evaluation including 1 procedure not yet overdue. Three patients (three hips) had one or more of the components of the Cormet 2000 Hip Resurfacing System revised or removed prior to the Month 24 visit and one patient is not yet overdue for the Month 24+ visit. Of the 95 procedures expected to be seen, 76 procedures (80%) had at least some clinical follow-up at Month 24 follow-up. Patients representing 19 procedures did not complete Month 24 follow-up.

Control Group (N=83)

For the 52 patients (83 procedures) in the bilateral ABC control group, 82 hips were evaluated at Month 24+. No patients died or were revised. One patient was lost to follow-up. This patient was last seen at the Month 6 evaluation at which time a HHS of 97 points was reported.

Continued Access (N=698)

The 698 patients representing 640 hips continue to be followed in the Continued Access study. Two hundred thirty-six procedures are expected due for Month 24+ evaluation and 32 procedures are not yet overdue for the Month 24+ evaluation. The Sponsor continues to enroll and follow patients according to the study protocol. To date, 18 patients have discontinued in the study; two patients died and 16 patients had revision to one or more components of the Cormet 2000 Hip Resurfacing System.

10.9. Patient complaints

Investigational Group

There were no specific complaints related to the use of the Cormet 2000 Hip Resurfacing System from patients involved in the IDE. The Short Musculoskeletal Functional Assessment (SMFA) is a 46-item assessment of patient function and a subset of 12 questions, the "bother index," is an assessment of how patients are bothered by functional problems. Study patients completed the SMFA during the course of the investigation. Overall there were large improvements in scores over time, which may be an indicator of general satisfaction.

Eight Product Experience Reports were received by the Sponsor for product marketed outside the US from December 2003 through November 10, 2005. There were no complaints by patients reported in this series.

Control Group

Study results indicate that no patients were reported to specifically complain about their total hip replacement. However, this study asked the question: "Are you satisfied with the results of your surgery?" at each follow-up interval. Six patients (2.2%) answered "no" to this question at the Month 24 follow-up interval. Reasons included two incidences of patients involved in traumatic events, one post revision of femoral stem, one patient with multiple medical problems and two patients with pain at or near the operative site.

10.10. Device failures and replacements

As stated previously, any one of the following events was considered a device failure in the Cormet 2000 Hip Resurfacing study conducted under

1. The surgical revision or removal of any components or pending revision/removal;
2. The presence of a device related AE;
3. The determination of a HHS of <80 points at Month 24 postoperatively;
4. Radiographic instability as measured by any one of the following: Radiolucent lines around the entire acetabular component of >1mm;

Radiolucent lines around the entire femoral component of >2mm;
Migration of the acetabular component by ≥5mm;
Subsidence of the femoral component of ≥5mm and femoral component tilt of ≥1º.

The determination of safety and efficacy of the Cormet 2000 Hip Resurfacing System was based on the evaluation of these parameters.

The safety and effectiveness data (CCS) for the Pivotal Study Unilateral group is being reported for the Month 24+ timeframe.

The Surgical Revision or Removal of Any Components/Pending Revision/Removal

Investigational Group

A total of 1148 Cormet 2000 Hip Resurfacing System procedures were performed during the course of the IDE and Continued Access. Forty-four procedures (3.8%) resulted in the revision or removal of one or more components. There were two pending revisions at the time of database lock for this report.

Twenty-four revisions were performed for patients in the Pivotal Study Unilateral group. Reasons for revision included: acetabular loosening (four patients), dislocation (one patient), femoral loosening (eleven patients), and femoral neck fracture (eight patients).

Four revisions were performed for patients in the IDE Pivotal Study Bilateral group: one deep infection, two femoral neck fractures, and one incidence of femoral component subsidence.

Sixteen revisions were performed for patients in the Continued Access portion of the study: eleven femoral neck fractures, four acetabular loosening, and one deep joint infection. A complication report for aseptic loosening of the acetabular component was submitted for one patient in the Continued Access portion of the study. This patient was considered pending revision. Another patient with femoral neck fracture that has not healed is being monitored for potential revision surgery.

Control Group

There were five device failures (1.4%) during a comparable time frame in the control group. Reasons for revision included post-traumatic femoral component non-union, one dislocation in the perioperative time frame, one deep joint infection less than one year postoperative, one hip pain with suspected sepsis three years postoperative and one patient with post-traumatic subsidence of the femoral component. These patients were all in the Pivotal Study Unilateral group.

Statistical review of the revision population identified the following factors as significant for revision: female gender, small component size, preoperative leg length discrepancy of ≥1 cm and preoperative HHS.

Kaplan Meier survivorship analysis results demonstrated a cumulative survival rate of 95.9% at a maximum of Month 24 postoperatively for the entire Cormet 2000 Hip Resurfacing System patient population. This was compared to 99.1% survivorship for the ABC Ceramic-on-Ceramic control at the same time frame.

The Presence of a Device Related Adverse Event

As identified previously, the following complications are considered to be device related adverse events for any hip resurfacing surgery:

- Component breakage;
- Femoral neck fracture;
- Collapse or AVN of the femoral head;
- Femoral loosening;
- Acetabular loosening;
- Dislocation.

Additional complications specific to total hip arthroplasty are included to compare the control ABC Ceramic-on-Ceramic device:

- Intraoperative chipping of the ceramic insert;
- Periprosthetic bone fractures.

Table 20 identifies the complications for the 1148 Cormet 2000 Hip Resurfacing System IDE patients compared to the ABC Ceramic-on-Ceramic control. Both of these US IDE studies were monitored during the course of the investigation to assure accurate and complete reporting of any and all events associated with the use of the devices.

Table 20: Relative Complications for the Cormet 2000 Hip Resurfacing IDE Patients Compared to the ABC control

	Pivotal Study Unilateral (N=337)	**Total IDE study (N=1148)**	**ABC Pivotal Study Unilateral Control (N=266)**
Study Design	Multi-center IDE, Prospective, non-randomized	Multi-center IDE, Prospective, non-randomized	Multi-center IDE, Prospective, randomized
Femoral neck fracture	11	26	NA
Femoral loosening	13	14	0
Femoral subsidence	1	4	2
Acetabular loosening	5	11	0
Dislocation	1	2	7
Implant fracture	0	0	0
Intraoperative chipping	NA	NA	6
Periprosthetic fracture	2	2	9
AVN head/neck	0	0	NA
Femoral head collapse	0	0	NA
Total	33 events in 32 patients (9.5%)	59 events in 58 patients (5.1%)	24 events in 21 patients (7.9%)

There was no statistically significant difference in the rates of device related AEs between the investigational and control groups in either All Enrolled Procedures (p=0.064) or in the Pivotal Study Unilateral group (p=0.563).

The Determination of a Composite Harris Hip Score of less than 80 points at Month 24+ Postoperative Interval

Investigational Group

Eleven patients (3.9%) of 283 evaluable Pivotal Study Unilateral patients had a HHS <80 points at the Month 24+ follow-up interval. Two of these patients were subsequently revised, one patient for acetabular component loosening and the other for femoral component loosening. Another subsequently reported with acetabular loosening. One patient was reported to have knee pain that contributed to the low HHS. Investigators did not report specific concerns for the other five patients that would contribute to the low scores. Two patients, not evaluated at Month 24, had a HHS <80 points at the Month 36 interval. One patient was status post a motor vehicle accident and the other patient stated that the limitations were due to the contralateral hip. There were no patients in the Pivotal Study Bilateral group with a HHS <80 points at Month 24 or Month 24+.

Control Group

Twelve patients in the Unilateral Control group (4.8%) had a HHS <80 points at the Month 24+ follow-up interval. Two patients had hip pain associated with the device, six patients had pain associated with other joint or medical issues, and two patients had mild or occasional pain limiting the HHS. One patient in the bilateral group had a HHS <80 points at Month 24 postoperatively due to back pain. One patient did not have a complete score at Month 24 but had a score <80 at Month 36 due to contralateral hip disease and compensatory strain on the ipsilateral side.

There was no statistical difference in mean HHS or number of patients with HHS ≥80 points in the Month 24 and Month 24+ between investigational Cormet 2000 Hip Resurfacing System and control ABC Ceramic-on-Ceramic groups. The mean HHS at Month 24+ was 96.7 and 96.2 (p=0.52) and percentage of patients with ≥80 points was 96.1% and 95.3% (p=0.67) for the Pivotal Study Unilateral and Unilateral Control groups, respectively.

Evidence of Radiographic Component Instability at Month 24+ Postoperative Interval

Investigational Group

There were ten patients with radiographic evidence of femoral component instability at ≥Month 24 in the Pivotal Study Unilateral group. Instability was evidenced by femoral subsidence of >5mm and tilt of >1º. One patient also exhibited three-zone radiolucency around the femoral component. One of these patients had a HHS of 63 points at Month 24, considered a study failure. Another patient with femoral subsidence of >5mm had device related AEs of femoral neck fracture and subsequent femoral subsidence at Month 3 postoperatively. At Month 6, the fracture healed and the component did not move further. The patient remains asymptomatic at Month 36 postoperatively. Two patients had revision of the femoral components due to femoral component loosening. The remaining patients do not have clinical symptoms associated with the femoral component instability as evidenced by HHS in the excellent range at minimum Month 24 postoperatively.

Three patients in the Pivotal Study Bilateral group were radiographic failures. One patient demonstrated femoral component subsidence at Month 24 postoperatively without clinical complications and one patient demonstrated acetabular and femoral instability. A third patient demonstrated acetabular and femoral instability at Month 36 also without clinical symptoms.

Control Group

One patient in the unilateral control group was determined to be radiographically unstable at Month 24 postoperatively. The patient, status post a traumatic fall, exhibited radiolucency around the femoral device, 10mm of femoral subsidence and component tilt at the Month 24 postoperative interval. The patient was

subsequently revised for femoral component loosening. No patient in the bilateral control group was determined to be radiographically unstable.

10.11. Results of statistical analyses of the clinical investigations

Control Group

oup is comprised of ABC Ceramic-on-Ceramic patients enrolled in The ABC Ceramic-on-Ceramic was approved via PMA P000013 on February 3, 2003. The Sponsor has received permission from the ABC study Sponsor to use datasets from the ABC Ceramic-on-Ceramic study as a control for the Cormet 2000 Hip Resurfacing System investigational devices.

Baseline demographic and clinical characteristics between Cormet 2000 Hip Resurfacing System patients in Pivotal Study Unilateral group and ABC Ceramic-on-Ceramic Unilateral Control group patients were compared. There was no statistically significant difference in patient gender. Approximately two-thirds of both cohorts were male (67.7% versus 62.0%). There were no statistically significant differences in the distributions of diagnoses with approximately 85% of both cohorts presenting with a primary diagnosis of osteoarthritis, (85.8% versus 83.7%). Mean weights were similar between these two groups (190.4, SD=40.7 lbs versus 188.7 lbs; SD=39.7). Height was not obtained during the Cormet 2000 Hip Resurfacing System study precluding comparisons involving BMI.

Baseline overall function as reflected in mean Harris Hip Total scores also was very similar between the Pivotal Study Unilateral investigational and control groups. In contrast, the difference in mean ages was statistically significant between groups (50.1, SD=9.6 versus 53.3, SD=11.1, Wilcoxon rank sum $p<0.01$). Although statistically significant, a difference in mean age of just three years is unlikely to be of clinical significance.

A propensity score analysis was performed using data from the Cormet 2000 Pivotal Study Unilateral group and ABC Ceramic-on-Ceramic unilateral controls. The analysis compares patients receiving the Cormet 2000 Hip Resurfacing System to those receiving the ABC Ceramic-on-Ceramic control in terms of their likelihood (or propensity) of receiving the Cormet 2000 Hip Resurfacing System based on the variables in the propensity model. The propensity model included age (in decades), weight (in 40lb increments), male gender, baseline Harris Hip Total score in 10-unit increments, and having a baseline Harris Hip Pain category of 'marked pain' or 'totally disabled.' The mean (SD) propensity scores were 0.589 (0.088) and 0.550 (0.103) in the Cormet 2000 Hip Resurfacing System and ABC Ceramic-on-Ceramic control groups, respectively. The mean values are very similar in magnitude suggesting that, taken as a set, these variables have relatively little impact on characterizing what kind of patients received the Cormet 2000 Hip Resurfacing System relative to what kind of patients received the ABC Ceramic-on-Ceramic control device. This implies that any impact of selection bias from these variables on the results is minimal.

Composite Clinical Success

The CCS of patients receiving the Cormet 2000 Hip Resurfacing System was demonstrated using two sets of endpoints. The main difference in interpretation of clinical success was the definition of clinical success derived from the HHS component. The original protocol defined Harris success as an improvement of ≥20 points in HHS at Month 24 over baseline preoperative score. The Sponsor modified this definition of success to include patients with an HHS of ≥80 points at Month 24, regardless of baseline score. Therefore, the first presentation of CCS is based on the original HHS criterion, absence of revision or pending revision, no device related AEs, and modified radiographic assessment.

The second presentation of CCS is according to the modified Harris Hip Score criterion, absence of revision or pending revision, no device related AEs, and modified radiographic assessment. At FDA's request the data were analyzed using both endpoints.

The following non-inferiority hypothesis was used in the primary efficacy analysis of CCS comparing the investigational group to the historical control group (HCG).

The null and alternative non-inferiority hypotheses were formulated to be consistent with the Blackwelder approach[11] and are as follows:

H_o: $P_{Cormet2000} - P_{HCG} \leq 0.08$ (clinically inferior to control)
H_a: $P_{Cormet2000} - P_{HCG} > 0.08$ (not clinically inferior to control)

The study was designed to reject the null hypothesis that the investigational device is clinically inferior to the control. The non-inferiority delta was specified to be equal to 0.08. Thus, the study was designed to reject the null hypothesis that proportion of patients achieving composite clinical success with the investigational device is at least 0.08 less than the proportion of patients achieving composite clinical success with the control device.

A one-sided 95% non-inferiority confidence interval for the difference in proportions was determined. If the lower bound of this confidence interval exceeds -0.08 then the null hypothesis is rejected and we many conclude that in terms of composite clinical success, the investigational device is not clinically inferior to the control device.

The criteria for CCS are as follows:

- Device survival at Month 24+ with at least good clinical results as defined by a Harris Hip Total Score of at least 20 points higher at Month 24+ as compared to preoperative baseline score, absence of revision of any of the components of the investigational device, absence of device related AEs, and absence of radiographic failure;

- Device survival at Month 24+ with at least good clinical results as defined by a Harris Hip Total score of at least 80 points at Month 24+ absence of revision of any of the components of the investigational device, absence of device related AEs, and absence of radiographic failure.

The first row of the following table summarizes the results of the primary non-inferiority test using original definition of CCS. A procedure is defined as a composite clinical success if there was at least a 20 point improvement in HHS at Month 24+ HHS relative to the baseline preoperative score, absence of revision of any of the components of the investigational device, absence of device related AEs, and absence of radiographic failure.

Table 21 (11.1 (1)): Composite Clinical Success Using Original Harris Hip Score Definition and Modified Radiographic Assessment

Table 11.1(1)
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 low er 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 follow s: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] Low er bounds of 1-sided 95% confidence intervals for differences betw een proportions w ith 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 low er bound of the confidence interval is larger than -0.08.

Source [Tables_Clinical_Followup_vs_controls_PRIMEFFxz.sas]

Among Pivotal Study Unilateral patients, 256 of 291 (proportion=0.880) patients achieved Month 24+ composite clinical success. Similarly, 213 of 243 (proportion=0.877) Unilateral Control patients achieved composite clinical success. The difference in proportions is equal to +0.003. The lower bound of the one-sided 95% non-inferiority confidence interval is -0.044. Since -0.044 exceeds -0.08, the null hypothesis of inferiority is rejected with $p<0.05$ and it is concluded that the investigational device is not clinically inferior to the control device on the basis of this CCS. Sensitivity analyses in the remaining three rows of this table provide non-inferiority results varying the procedures included in analyses. The primary analysis is the most inclusive.

Similarly, the first row of the following table summarizes the results of the primary non-inferiority test using modified definition of CCS. A procedure is defined as a composite clinical success if the Harris Hip Total score is at least 80 points at Month 24+, absence of revision of any of the components of the investigational device, absence of device related AEs, and absence of radiographic failure.

Table 22 (11.1 (2)): Composite Clinical Success Using Modified Harris Hip Score Definition and Modified Radiographic Assessment

Table 11.1(2)
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 Total 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 was 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.

[Source: Tables_Clinical_Followup_vs_controls_PRIMEFFz.sas]

Among Pivotal Study Unilateral patients, 251 of 292 (proportion=0.860) patients achieved Month 24+ composite clinical success. Similarly, 224 of 256 (proportion=0.875) Unilateral Control patients achieved composite clinical success. The difference in proportions is only -0.015. The lower bound of the one-sided 95% non-inferiority confidence interval is -0.063. Since -0.063 exceeds -0.08, the null hypothesis of inferiority is rejected with $p<0.05$ and it is concluded that the investigational device is not clinically inferior to the control device on the basis of this CCS. Sensitivity analyses in the remaining three rows of this table provide non-inferiority results varying the procedures included in analyses. The primary analysis is the most inclusive.

The Sponsor proposes the Month 24+ Actual[B] analysis as the most relevant presentation of the data. Clinically, patients post hip replacement have a stable course in the Month 24 to Month 36 postoperative timeframe. Therefore, including data after Month 24 (730 days) is not expected to improve the clinical results and the rollback imputation is valid. Additionally, only 11 Actual[B] patients (seven investigational; four control) had their Month 24 visit before the start of the visit window (i.e., before 670 days), and only three of these patients (one investigational patient at three days out of window; two control patients at

four and 45 days out of window, respectively) had data available for CCS, all of which were considered to be successes. Therefore, the control device is favored by including all Month 24 visits out of window

Presentation of the CCS based on the approved protocol HHS success criteria and on the modified HHS success criteria demonstrates non-inferiority of the Cormet 2000 Hip Resurfacing System to the ABC Ceramic-on-Ceramic control for the Month 24 evaluation or Month 24+ with expanded windows for patient follow-up.

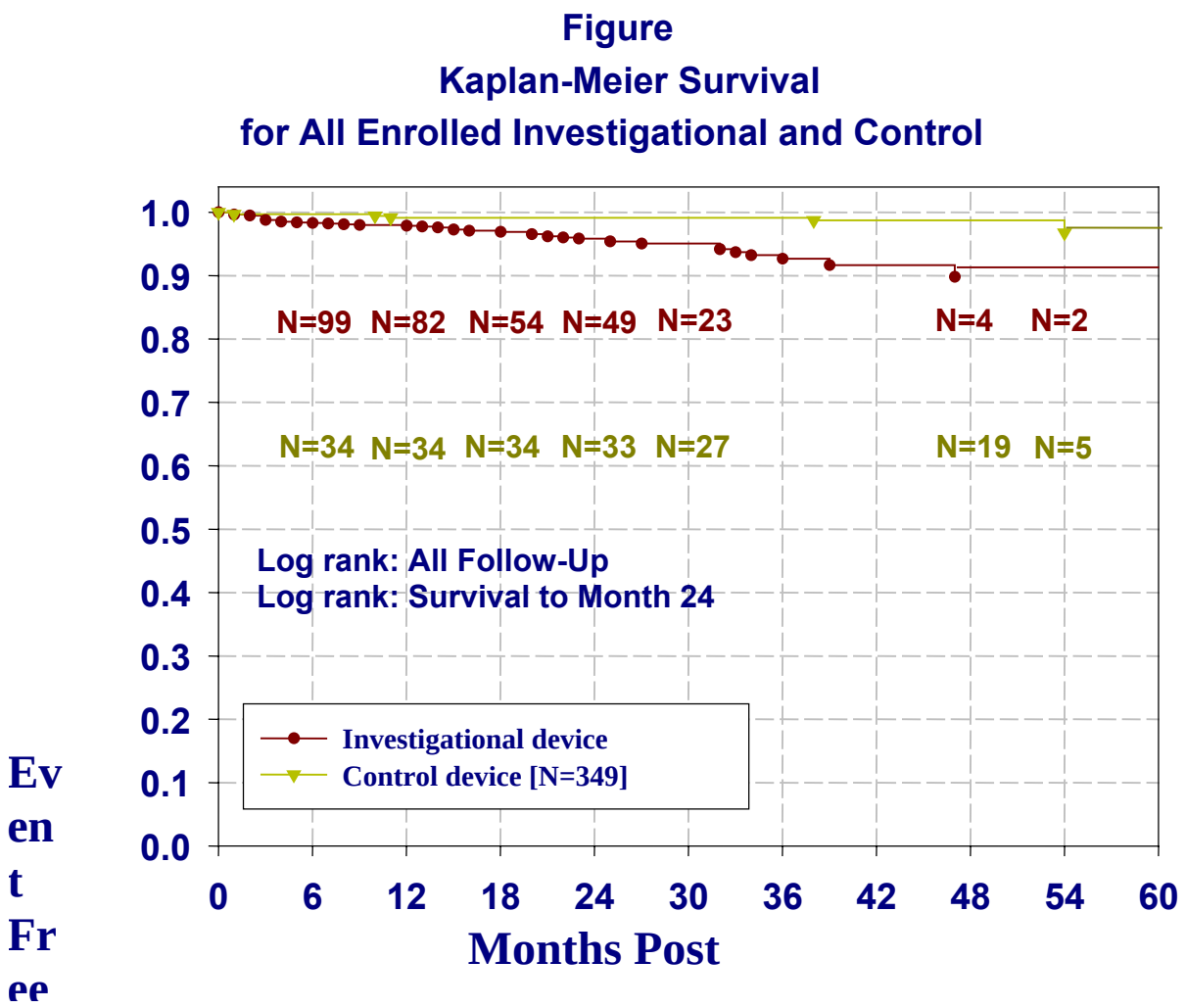
Survival Analysis

The primary study cohort for safety is considered the All Enrolled Procedures group. The distribution of study device failure over time was summarized by constructing a life-table that indicated the number of failures and the number of at-risk procedures over time. The distribution of failures over time was further assessed using Kaplan-Meier survival curves[12] in order to provide graphical representations of survivorship over time.

The primary survival analysis defined device failure as any revision, no matter the model of failure, censoring only at death. The groups exhibit a Month 24 device survivorship of 99% and 96% for the control and investigational groups respectively.

As detailed above, survival among Pivotal Unilateral Study devices depended upon the number of risk factors present. The same was true in the All Enrolled Procedures cohort. Among all enrolled procedures, when 0, 1, 2, or 3 of these risk factors were present, risk of revision was 6 of 456 (1.3%), 16 of 432 (3.7%), 15 of 213 (7.0%), and 7 of 46 (15.2%), respectively. There was one procedure that had four risk factors but has not been revised. To account for unequal follow-up, these analyses are repeated restricting attention to patients with at least 24 months follow-up (including all revisions). Revision risks for patients with 0, 1, 2, and 3 risk factors are 6 of 202 (3.0%), 16 of 206 (7.8%), 15 of 98 (15.3%), and 7 of 25 (28.0%), respectively, among procedures with at least 24 months of follow-up. There was one procedure with 4 risk factors. This patient has not been revised. The linear trend in percentages is statistically significant ($p<0.0001$).

FIGURE 1 (12.4(1)): KAPLAN-MEIER SURVIVAL CURVE: ALL ENROLLED INVESTIGATIONAL DEVICES



11. Contradictions and precautions for the use of the device

Contradictions and precautions for the use of the Cormet 2000 Hip Resurfacing System as described in the package labeling are as follows:

Contraindications

1. Active or suspected infection in or about 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 who are pregnant or are planning on becoming pregnant due to unknown effects on 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).

Warnings and Precautions

WARNINGS

1. Patients on medications (such as high-dose or chronic aminoglycoside treatment) or with co-morbidities (such as diabetes) that increase the risk of future, significant renal impairment should be advised of the possibility of increase in systemic metal ion concentration. Preoperative and postoperative monitoring of renal function (such cretinine, GFR, BUN) will be necessary.
2. Do not scratch the femoral or acetabular components' articulating surfaces.
3. Do not use another manufacturer's device in place of components of the Cormet 2000 Resurfacing Hip System. Design differences between manufacturers can lead to device failure.
4. Do not use these components for patients undergoing revision total hip replacement surgery.
5. Single use only. Never reuse an implant even if it appears undamaged.
6. Avoid notching the femoral neck, as this may lead to femoral neck fracture.
7. Avoid placing the femoral component in varus. Varus placement of femoral component has been associated with femoral neck fracture.
8. Do not handle the HA treated regions as it may compromise the sterility or cause failure under load.

9. Do not contour or bend an implant as it may compromise its fatigue strength and cause failure under load.

PRECAUTIONS

1. Before clinical use, the surgeon should thoroughly understand all aspects of the surgical procedure and limitations of the device. Patients must be instructed in the limitations of the prosthesis, including, but not limited to, the impact of excessive loading through patient weight or activity, and be taught to govern their activities accordingly. If the patient is involved in an occupation or activity that includes substantial walking, running, lifting, or muscle strain, the resultant forces can cause failure of the fixation, the device, or both. The prosthesis will not restore function to the level expected with normal healthy bone, and the surgeon should advise the patient against having unrealistic functional expectations.
2. Surgeons should review the Cormet 2000 Hip Resurfacing System operative technique prior to implanting.
3. Clean articulating surfaces of debris prior to final reduction of the joint.
4. Avoid overly abducting the acetabular component, which can accelerate wear.
5. Ensure that the head outer diameter and acetabular inner diameter match prior to implanting.
6. Handle porous surfaces carefully so that particles are not dislodged from the component surface.
7. Routine postoperative follow-up is recommended to monitor implant position and patient well-being over time.
8. Appropriate selection, placement and fixation of the resurfacing hip components are critical factors, which affect implant service life. As in the case of all prosthetic implants, the durability of these components is affected by numerous biologic, biomechanic and other extrinsic factors, which limit their service life. Accordingly, strict adherence to the indications, contraindications, precautions and warnings for this product is essential to potentially maximize service life.

12. Other information as appropriate

OMD Study Design

The OMD clinical study is an ongoing, prospective, single-center study with the purpose of evaluating the clinical performance and safety of the Cormet 2000 Hip Resurfacing System in the United Kingdom. Two hundred eighteen patients have been enrolled from 1997 to present.

The OMD study has been removed from the main body of the clinical section of this PMA. The patients were consented under a protocol for web-based data collection. The data provided in the PMA P050016 included all procedures implanted by a single surgeon since 1997. During review of the data to expand the information for the PMA Amendment, the Sponsor realized that the devices implanted in many of the patients were for a predecessor acetabular component

without plasma spray titanium beneath the HA coating. The surgeon implanted the predecessor cups from September 1997 to July 2001 then switched to The Cormet 2000 bi-coated cups (with plasma spray titanium beneath the HA coating) from August 2001 to the present day. Two hundred thirty-eight hip resurfacing devices were implanted in 218 patients during this time interval. However, all acetabular shells that were implanted were of the pegged design that was not included as a study device in this PMA Submission. Therefore, data for consented patients collected under the web-based data collection protocol, is provided as additional information in this PMA Amendment. These data are not intended to be used to support the safety and effectiveness of the devices under investigation. However, the study provides additional information concerning the use of the Cormet 2000 Hip Resurfacing System used in a single surgeon's practice of medicine. There were six revisions among the 238 procedures (2.5%) at a mean three to four years postoperatively. There was one revision among 135 males implanted with the hip resurfacing device (0.7%) and five revisions among the 78 females implanted (6.4%). Three revisions (50%) were for femoral neck fracture. The higher incidence of revisions in female patients and femoral neck fracture as reason for revision is consistent with the US IDE study and registry data associated with the use of hip resurfacing devices.

Conclusions drawn from the study

Discussion of Valid Scientific Evidence

Title 21 Code of Federal Regulation § 860.7 defines valid scientific evidence as "evidence from well-controlled investigations, partially controlled studies and objective trials without matched-controls, well documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is a reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions and the extent of experience with its use." The data collected under [redacted] satisfy these requirements.

Discussion of the Safety and Effectiveness

The predefined study success criterion of demonstrating clinical non-inferiority of the investigational device relative to total hip arthroplasty population (ABC Ceramic-on-Ceramic control) based on an 8% non-inferiority delta was met. The CCS rate for the investigational group was 86.0% versus 87.5% for the control. The lower bound (LB) of 95%CI non-inferiority confidence interval was –6.3% which exceeds the -8.0% target. There were 292 patients receiving the investigational device included in the Month 24+ Actual [B] population. This represents 86.9% follow-up compliance which provides confidence that the results are generalizable. The non-inferiority confidence interval lower bounds exceeds the delta = -8.0% for three of the four presentations of the data. Actual[A] Month 24 CCS is slightly below the target (LB = -10.3%) which is partially

explained by the loss of statistical precision observed from excluding patients not seen in the visit windows. The CCS rate for the investigational group was 84.7% versus 89.5% for the control for this comparison. However, results using Actual[A] (within interval accounting) but allowing for missing Month 24 clinical evaluations to be imputed using results obtained after the Month 24 interval produces a lower bound for the non-inferiority confidence interval equal to -6.2% which does exceed -8.0%. In this case the CCS rate for the investigational group was 86.3% versus 87.8% among control patients.

To reiterate, the following four components of the CCS criteria were required to be simultaneously achieved in order for a procedure to be defined as a composite clinical success:

- HHS ≥80;
- Radiographic Success;
- Absence of Revision/Removal or pending Revision/Removal;
- Absence of Device Related Adverse Events.

The effectiveness of the Cormet 2000 Hip Resurfacing System was demonstrated through the compilation of data demonstrating the relief of pain and return to normal function that was collected during the course of the prospective IDE study. The primary effectiveness tool used to demonstrate relief of pain and return to function was the Harris Hip Score (HHS). The mean Harris Hip Total score for the 283 evaluable patients in the Pivotal Unilateral Study cohort was 96.7 with 96.1% (272/283) of the patients demonstrating excellent/good results at Month 24+ postoperatively. Eleven patients, nine at Month 24 postoperatively and two at Month 36 postoperatively, had scores <80 points indicating failure of the effectiveness criteria. This establishes comparable effectiveness to the ABC Ceramic-on-Ceramic control group which had a mean Harris Hip Total Score of 96.2 for the 252 evaluable patients (p=0.44) with 95.3% of the patients (241/253) reporting excellent/good results at Month 24+ postoperatively (p=0.67). Eleven control patients had scores <80 points at Month 24 and one at Month 36 postoperatively indicating failure of the effectiveness criteria.

The primary radiographic effectiveness parameters of acetabular cup and femoral head stability and absence of radiolucencies around the components are additional evidence of the stability of the Cormet 2000 Hip Resurfacing System. Seven patients did not have clinical symptoms associated with femoral component instability as evidenced by Harris Hip Scores in the excellent range at minimum Month 24. Only a small number of patients (10/279=3.9%) had radiographic evidence of femoral component instability at Month 24 or greater in the Pivotal Study Unilateral group. Instability was evidenced by femoral subsidence of ≥5mm and tilt of ≥1º. One stem failure also had three-zone radiolucency in addition to component subsidence and tilt. One patient had a HHS of 63 points at Month 24, considered a study failure. Another patient with femoral subsidence of >5mm had device related AEs of femoral neck fracture and subsequent femoral subsidence at Month 3 postoperatively. At Month 6, the fracture healed and the component did not move further. The patient remains asymptomatic at Month 36 postoperatively. In the ABC Ceramic-on-Ceramic control group, one patient

demonstrated femoral instability of component secondary to femoral subsidence after a fall.

There were 58 device related AEs reported among the 1148 Cormet 2000 Hip Resurfacing System surgeries (5.1%) performed under [redacted] Of these 58 patients with device related AEs in the Cormet 2000 Hip Resurfacing study, 32 of these were for Pivotal Study Unilateral patients (32/337=9.5%). This is comparable to the number of device related AEs reported for the pivotal study ABC Ceramic-on-Ceramic control population (21/266=7.9%) (p=0.56).

There were 44 revisions reported among the 1148 Cormet 2000 Hip Resurfacing System procedures performed (3.8%). One additional revision for femoral component loosening occurred in one of the six pegged cup protocol violations that were analyzed separately. There were no revisions for the eight compassionate use procedures performed. Of the 44 revisions in the 1148 procedures in study population, 48% (21/44) were for femoral neck fracture. Other reasons for revision included: eleven incidences of femoral component loosening, eight incidences of acetabular component loosening, two incidences of deep joint infection, one incidence of dislocation and one incidence of femoral subsidence.

Femoral neck fracture is identified in the literature as a risk of hip resurfacing **arthroplasty[13,14,15].** Steffen et al.'s review of literature of resurfacing arthroplasty of the femoral head identified an incidence of femoral neck fracture ranging from 0 to 12%[16]. One factor that is thought to affect femoral neck fracture is the learning curve for surgeons unfamiliar with the procedure[17,18]. Michael Mont M. D., a US orthopaedic surgeon involved in a hip resurfacing IDE study, suggests that US surgeons unfamiliar with the procedure visit surgeons that have performed greater than 50 procedures before contemplating the surgery. He further states that the orthopaedic surgeon performs hip resurfacing arthroplasty on less challenging hips. Then, careful patient selection related to preoperative characteristics of the proximal femur, avoidance of an elderly patient population with osteoporotic bone, and avoidance of varus placement of the femoral component and femoral neck notching, may contribute to a reduced incidence of this AE associated with the procedure[13].

Statistical review of the revision cohort identified the following factors as significant for revision when considering all enrolled procedures: female gender, small component size, preoperative leg length discrepancy of ≥ 1 cm, low preoperative HHS. Twenty-one revisions occurred among the 323 procedures for female patients (6.5%) compared to 23 revisions for the 825 procedures for male patients (2.8%). Crude (single predictor variable) survival analyses accounting for unequal follow-up revealed a hazard ratio for risk of revision equal to 2.1 (95% CI 1.2 to 3.9; p=0.01) comparing females to males. There were 22 revisions of patients with size 40mm or 44mm femoral components (296 procedures; 7.4%) compared to 22 revisions for patients implanted with sizes 48mm, 52mm or 56mm (843 procedures; 2.6%) [Note: implant size was unavailable for nine patients]. The hazard ratio for risk of revision was equal to 2.8 (95% CI 1.6 to 5.1;

p=0.0006) comparing size 40mm or 44mm to larger sizes. When the effects of gender and size of component are simultaneous estimated, component size (p=0.02) but not gender (p=0.81) retains statistical significance. Reduced baseline function was associated with increased revision risk. The hazard ratio comparing patients in the lowest quartile of HHS scores (<43) to those with higher scores was 2.0 (95% CI 1.1 to 3.6; p=0.03). Having a preoperative leg length discrepancy ≥ 1cm was also associated with increased revision. The crude hazard ratio was 2.2 (95% CI 1.2 to 3.9; p=0.01).

Further statistical analyses revealed individual site influence and the effect of cumulative risk factors for revision. Variability across investigative sites was assessed. When all investigative sites were simultaneously assessed there was a significant site effect (p=0.03) that disappeared (p=0.40) when Site 5 (representing 15 of the 44 revisions) was removed from the analysis, indicating homogeneity of the results among the remaining sites. Statistical analyses performed with and without Site 5 provided further understanding of the risk factors for revision and the cumulative effect of those risk factors. For example, when Site 5 was removed from the analysis, the magnitude for leg length discrepancy and preoperative function decreased. However, two factors, small component size and diagnosis other than osteoarthritis emerged as consistently statistically significant for both pivotal study unilateral patients and all enrolled procedures. The following table emphasizes the combined effect of these factors when analyzing revisions among patients with minimum 24+ month follow-up. Risk is smallest when neither risk factor is present, intermediate if either risk factor is present and maximum when both risk factors are present.

Additive Effect of Risk Factors

DIAGNOSIS OF AVN OR RA	SMALL FEMORAL COMPONENTS	**All-enrolled 24+month follow-up[1]**	**All enrolled minus Site 5 with 24+ month follow-up[1]**	**Pivotal Unilaterals follow-up to 24 months[1]**	**Pivotal Unilaterals minus Site 5 follow-up to 24 months[1]**
B=no	**B=no**	**17/335=5.1%**	**8/296=2.7%**	**7/195=3.6%**	**1/169=0.6%**
	A=yes	18/127=14.2%	12/104=11.5%	10/65=15.4%	6/55=10.9%
A=yes	B=no	5/52=9.6%	5/49=10.2%	4/32=12.5%	4/32=12.5%
	A=yes	**4/18=22.2%**	**4/18=22.2%**	**3/10=30%**	**3/10=30%**

Note: [1] In order to provide meaningful comparisons of revision rates that accounted for varying follow-up times among subgroups, analyses were restricted to the subgroup of patients who required revision no matter when the revision occurred plus all patients who had at least 24 months of follow-up. Since this includes revisions among procedures not expected due for 24 month follow-up, revision rates in this subset are conservatively estimated.

Schmalzried[19] discussed the optimal patient for hip resurfacing. He proposed a preoperative grading system that counted the number of accumulative preoperative risk factors as a basis for patient selection for hip resurfacing. His results demonstrated that patients with no preoperative risk factors were at the lowest risk of failure while those with multiple risk factors were at much greater risk of failure. While Dr. Schmalzried primarily focused on preoperative

assessment of radiographs, our results support the notion that the additive effects of risk factors as an indication of potential risk for revision is important.

The Cormet 2000 IDE Study was initiated in 2001, prior to publication of the majority of literature that has helped to define the optimal patient for total hip resurfacing, and was conducted by surgeons previously unfamiliar with the surgical procedure. As with the Australian Registry, begun in 2001, the risk factors associated with total hip resurfacing have been identified through data analysis. The results of the Cormet 2000 IDE Study corroborate the conclusions of other IDE studies and registry data. Cormet 2000 Study results are comparable to the study results presented in the literature for most current generation metal-on-metal total hip resurfacing systems.[17,18,19,20,21,22,23,24,25] The Cormet 2000 IDE Study results appear to be comparable to other US IDE studies based on publication of individual surgeon results.[17,18,19,20] The overriding theme presented in the literature as a result of individual surgeon expertise[17,18,19,20,23,25] registry data and multicenter premarket study results is that the success of total hip resurfacing is dependent on the proper patient selection.

The results of this study, therefore, represent those associated with the hip resurfacing procedure and not a specific hip resurfacing device. The results underscore the importance of surgeon training and careful patient selection to minimize the risk of femoral neck fracture, and optimize the results of the procedure.

Kaplan Meier survivorship analysis results demonstrated a cumulative survival rate of 95.9% at Month 24 postoperatively for the entire Cormet 2000 Hip Resurfacing System patient population. This was compared to 99.1% survivorship for the ABC Ceramic-on Ceramic control at the same time frame. However, risk of revision significantly varied according to the number of risk factors present. To account for unequal follow-up, these analyses restrict attention to patients with at least 24 months follow-up (including all revisions). Revision risks for patients with 0, 1, 2, and 3 risk factors are 6 of 202 (3.0%), 16 of 206 (7.8%), 15 of 98 (15.3%), and 7 of 25 (28.0%), respectively. There was one procedure with 4 risk factors. This patient has not been revised. The increase in percentages is statistically significant ($p<0.0001$).

Risk/benefit analysis

As with any medical device, there are risks and benefits to potential patients that must be considered. When choosing a therapy for arthritis of the hip, these benefits and risks must be weighed. There are two types of risks and benefits described in this section – theoretical and study data supported. Theoretical risks and benefits derive from the device design and pre-clinical testing, which cannot or have not been elucidated by the pivotal study presented herein. In addition, this pivotal study data gives evidence to other risks and benefits that must be considered.

Risks:

The followi[redacted]ciated with the use of hip resurfacing devices were identified in[redacted] for the Cormet 2000 Hip Resurfacing System.

Femoral neck fracture*:*

A small percentage of patients who underwent Cormet 2000 Hip Resurfacing procedures experienced femoral neck fracture (26/1148; 2.3%) in[redacted] Twenty-one of these incidences resulted in revision of the investigational devices, comprising 48% of the reasons for revisions in the study. Femoral neck fracture is well identified as a risk associated with hip resurfacing arthroplasty. In Australia, hip resurfacing accounted for 8.9% of primary hip replacements undertaken for osteoarthritis in recent years.[13] The 2005 annual report of the AOA indicated that hip resurfacing has a higher early revision rate than conventional total hip arthroplasty due to fracture of the femoral neck, and that 59% of hip resurfacing revisions were due to femoral neck fracture. Female gender was indicated as a risk factor for early revision due to femoral neck fracture ($p < 0.01$). Other studies identified surgical technique and careful placement of the devices as critical factors in avoiding femoral neck fracture.[14,15,16,19]

In order to reduce the risk of femoral neck fracture, instructions in the Cormet 2000 Resurfacing Hip System operative technique should be followed. These instructions include details on femoral component alignment calling for avoidance of varus placement of the device, templating procedures that assure that the integrity of the neck will not be compromised, and instrumentation instructions to avoid femoral neck notching.

Surgeon training in appropriate operative technique which includes avoiding varus stem placement and avoiding intraoperative neck notching, along with careful patient selection are important to reduce the incidence of this risk.

Femoral loosening:

Eleven patients (1.2%) were revised for femoral component loosening. Avascular necrosis (AVN) has been identified in the literature as a failure mechanism of femoral loosening. The reason for loosening for five of these patients was either progression of existing stage III AVN or development of AVN of the femoral head identified during their revision procedure. Six patients with radiographic stem subsidence could not be ruled out for AVN, and it is unclear at this time if the subsidence is indicative of potential of femoral head collapse of these patients.

Including these six patients in the incidence of this hip resurfacing risk for the Cormet 2000 Hip Resurfacing System is within the frequency of reported events in the literature[13,14,26] and other clinical studies of hip resurfacing devices.

In order to reduce the risk, the Cormet 2000 Hip Resurfacing System operative technique and package insert includes "patients with inadequate bone stock" as a contraindication as follows:

> *"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."*

In addition, Corin has produced surgeon education videos and other materials that demonstrate surgical situations when it would be inappropriate to use the Cormet 2000 Hip Resurfacing device based on inadequate femoral head bone stock.

Increased circulating metal ions:

While the concerns over the local and systemic effects of metal wear products including ions exists, there is no direct evidence linking metal-on-metal arthroplasty with long-term medical problems including cancer. Increased levels of metal ions in the blood and urine of metal-on-metal total hip and resurfacing patients have been identified.[26,27] A study performed on patients with the Cormet 2000 Hip Resurfacing system indicated that metal ion levels for cobalt and chromium initially increase following a metal-on-metal hip resurfacing but then plateau and start to decrease between one and two years post implantation. The levels remained below their peak but did not return to the preoperative levels throughout seven years of follow-up. These ion levels are similar to those reported by other authors in the metal-on-metal resurfacing systems.[28] Importantly, no adverse health effects were reported as a result of increased blood metal ion levels in this study.

Benefits:

The followi ociated with the use of hip resurfacing devices were identified in for the Cormet 2000 Hip Resurfacing System.

Reduced risk of dislocation:

The potential benefit of reduction in dislocation rate with the use of large diameter heads was supported in the Cormet 2000 Hip Resurfacing System study. The dislocation rate in the Cormet 2000 Hip Resurfacing System pivotal study was reported as 0.2% in the All Enrolled Procedures group, which was a significant reduction from that reported in the control population of 2.9% (Fisher's exact, $p<0.01$). This difference highlights the benefits of a large diameter head, which is one of the common features of resurfacing devices such as the Cormet 2000 Hip Resurfacing System. Resurfacing the femoral head more closely approximates the natural geometry. The large diameter head in the Cormet 2000 Hip Resurfacing System, which ranges from 40-56mm, is less prone to dislocation than the 28-32mm heads used in the control group. It is well established that an increase in head size may decrease dislocation by increasing the range of motion available prior to impingement.[29,30,31] Two other

publications reported dislocation in resurfacing at 0.75% which is similar to the results achieved in this study.[20,32]

Higher function at 6 and 12 months post-operative:

The data in this pivotal study demonstrated that patients reported a higher mean Total Harris Hip Score at the Month 6 and Month 12 time-points. A further examination of the HHS categories reveals a gain in the HHS function category score with more Cormet patients in the Pivotal Study Unilateral group reporting normal function than the total hip control group. Specifically, the percentage of patients judged to have a normal (at least 40 out of maximum 47 points) function category was 91.9% and 93.3% for the Cormet 2000 Hip Resurfacing System at Month 6 and Month 12. In comparison, the total hip control revealed only 85.2% and 88.5% of patients with normal function at these same time-points (Wilcoxon rank sum p=0.038 and p=0.019 respectively). These results are replicated in a similar study that compared metal-on-metal resurfacing with a total hip ceramic system.[33] In that study, the total HHS was reported as 97.9 in the resurfacing group and 92.1 in the ceramic THA group with 60.7% of resurfacing patients reporting strenuous activity and only 30.4% of THA patients reporting the same.

Advantages of hip resurfacing procedure in contrast to THA

In addition to clinical benefit, the hip resurfacing procedure offers several advantages compared to the total hip arthroplasty procedure.

- **Preservation of proximal bone stock**
  The surgery of resurfacing does not remove the femoral head and neck thereby preserving the patient's native bone stock. As patients begin to receive arthroplasty procedures at younger ages, preservation of the femoral bone becomes more important. Loss of proximal femur can occur after total hip arthroplasty due to stress shielding and osteolysis. Retaining this bone longer may be beneficial to patients who will require more than one arthroplasty device during their lifetime.
- **Surgery does not invade femoral canal**
  It has been published, "hip resurfacing is inherently a form of 'minimally invasive surgery', as the femoral head and neck are preserved, and the femoral canal is not violated."[34] The theoretical benefits of this surgery over total hip replacement surgery would be a reduction in blood loss fat emboli, and perhaps a reduction in heterotopic ossification postoperatively. In this study, lower rates of cardiovascular and neurosensory events were reported for the Cormet 2000 Hip Resurfacing System All Enrolled population than the control in the intraoperative and postoperative periods. Also, a reduction in adverse events for heterotopic bone was reported for the investigational group (1.0% versus 3.7%, p<0.01). The preservation of the integrity of the femoral canal may be a contributing factor to these differences in observed adverse event rates.
- **Reduced proximal stress shielding**

The pattern of loading the proximal femur after resurfacing produces compressive forces rather than hoop stresses which is more physiologic.[35] A dual-energy X-ray absorptiometry study[36] showed that the bone mineral density in the proximal femur improved by 12% in Gruen zone 7 two years after resurfacing, which is in stark comparison to the 7 to 52% decrease in bone mineral density in this area after total hip replacement.[34] Proximal bone density is essential for long-term implant stability. If patients may require more than one arthroplasty device, preserving the quality of this bone would be beneficial to the patient's long term outcome.

Benefits of the system design

The osteolytic reaction caused by polyethylene debris is well documented,[37] and the reduction in wear rates associated with the metal-on-metal articulation is well elucidated.[26,27] Reduced wear leads to a longer service life of the articulating surfaces before deformation leads to the need for revision. In addition, the release of polyethylene debris from the articulation is eliminated. In metal or ceramic-on-polyethylene bearing the linear wear in vivo has been reported of up to 0.55 mm per year.[38] Hard-on-hard bearings all have the advantage of allowing increased cycles of motion with lower wear from the articulating surface. The in-vivo wear of metal and ceramic is too small to be quantified, however, in-vitro tests of these systems have demonstrated a 4.2µm/year for metal-on-metal[19] and <1µm/year for ceramic-on-ceramic.[39]

Overall risk benefit profile

The Cormet 2000 Hip Resurfacing System is a safe and effective treatment for reducing pain and restoring motion to patients affected with arthritis of the hip. The benefits of the system include reduced dislocation rate and increased function scores over that reported in the total hip arthroplasty control. Other benefits include preservation of proximal femoral bone stock during a surgery that does not violate the femoral canal, and very low wear of the articulating surface. A lower rate of cardiovascular and neurological events in the peri-operative timeframe may be attributable to the surgical implantation avoiding violating the femoral canal. Also, a reduction in heterotopic ossification was observed which may also be attributed to this difference in surgical implantation technique.

Risks of the system include the failure modes previously reported for hip resurfacing systems in a small percentage of patients, such as femoral neck fracture (2.3%) and femoral loosening (1.2%), possibly caused by avascular necrosis of the femoral head. These risks may be minimized by surgeon education and careful patient selection. The 24 month implant survival is estimated at 95%. There are no known clinical consequences of metal ion release from the bearing surface, and blood levels of these ions is similar to that reported with other metal-on-metal bearing systems.[40]

Overall, this system is a reasonable alternative to total hip arthroplasty for well-selected patients. Patients must have adequate femoral bone stock to support the implant. Motivated patients can achieve greater function at an earlier timeframe than can be expected with a total hip arthroplasty. Based on the results of this prospective multi-center IDE study, the Cormet 2000 Hip Resurfacing System is a safe and effective alternative to total hip arthroplasty.

Plan for post-approval study

The safety and effectiveness of t_____Hip Resurfacing System has been demonstrated and the IDE [redacted] objectives were met, reported in PMA P050016. The primary objective of the "Post-Approval Study" will be to continue evaluating and annually reporting on the ongoing safety and effectiveness of the devices for five postoperative years, and the ongoing status of the hip from six to ten years postoperatively. Specifically, the objectives for the Post-Approval Study are:

- To continue demonstrating the safety of the Cormet 2000 Hip Resurfacing System. The incidence of revisions and complications will be reported annually to 10 years postoperative;
- To continue demonstrating the efficacy of the Cormet 2000 Hip Resurfacing System by overall functional performance, pain relief, ROM, and radiographic evaluation. These measures will be taken annually to five years. Additionally, a brief hip follow-up questionnaire will be done annually from six to 10 years postoperatively to assess the ongoing status of the hip.

The Cormet 2000 IDE study included 441 cases implanted with the Cormet 2000 Hip Resurfacing System at twelve institutions. Five surgeons performed 86% (377 hips; 334 patients) of the Ceramic-on-Ceramic Post-Approval Study that is being conducted by Stryker® Orthopaedics. Data from that study will be available to serve as control to the Cormet 2000 Hip Resurfacing System Post-Approval Study.

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Patient Labeling Cormet 2000 Hip Resurfacing System

Patient Product Information

Table of Contents

Glossary of Terms 1
1. What is the Cormet 2000 Hip Resurfacing System? 2
2. What are the reasons for hip resurfacing? (Indications for Use) 4
3. What are the reasons to avoid hip resurfacing? (Contraindications) 4
4. What are some of the limitations of the Cormet 2000 Hip Resurfacing procedure? .. 4
5. What are some of the potential benefits of the Cormet 2000 Hip Resurfacing System? 5
6. What are the adverse events, complications, and risks expected from hip resurfacing? 6
7. Why choose the Cormet 2000 Hip Resurfacing System? 7
   Safety and Effectiveness 7
8. What other ways can a damaged hip joint be treated? 11
9. How is hip resurfacing performed? 11
10. What may happen after a Cormet 2000 Hip Resurfacing? 11
11. Is there anything else to know about hip resurfacing? 12
12. How to obtain user assistance information? 13

Glossary of Terms

Acetabulum – Hip socket
Adverse - Harmful or unfavorable
Anesthetic - Drug used to eliminate the feeling of pain
Arthroplasty – Creation of an artificial or man-made joint
Artificial – Man-made
Avascular necrosis – Death of bone
Brittle - Easily broken, cracked or shattered.
Calcification – Hardening of tissue
Debris -An accumulation of foreign material
Deterioration - To weaken or grow worse
Degenerative – Gradual loss of function
Femoral - Related to the thighbone
Fixation - The stabilization of an implant to surrounding bone or cement
Friction - The act of rubbing
Fusion - Uniting or bringing together
Intra-operative – During surgery
Invasive - Involving entry into the body through incision of the skin or insertion of an instrument
Latent - Potential for development, though currently inactive
Lubrication - To make smooth or slippery
Metal ions – Particles from the hip implant that are released into the body in trace amounts as the parts rub against each other

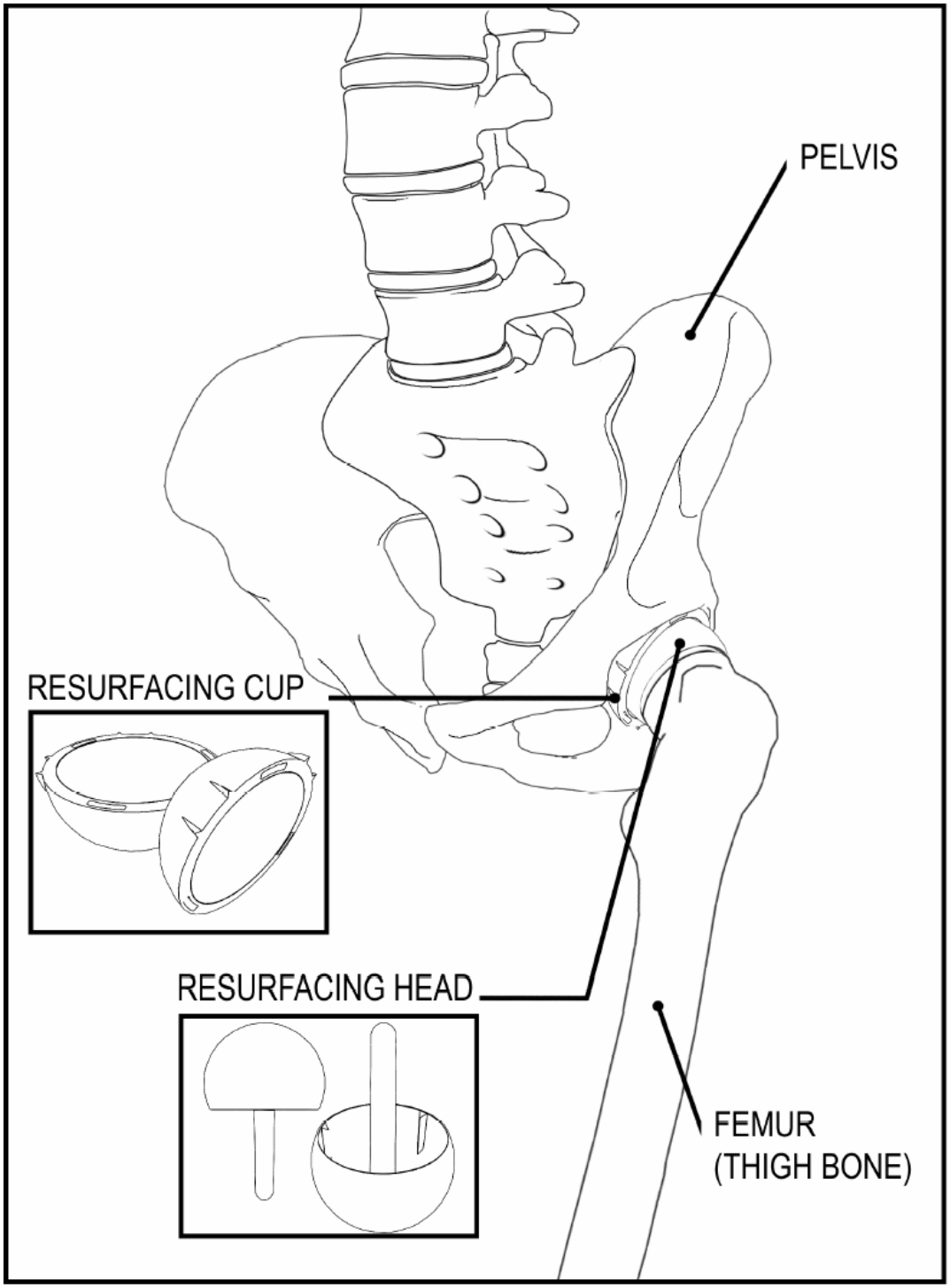
Modifications (limits) - Small alterations or adjustments
Mortality - The number of deaths in a given time or place
Osteoarthritis – Non-inflammatory degenerative disease of the joint characterized by degeneration of cartilage
Osteotomy - The removal of a wedge of bone to improve alignment
Postoperative – Following surgery
Predecessor - One that comes before another
Preoperative – Before surgery
Rehabilitating (recovering) - To restore to good health or useful life, as through therapy and education
Revision - Replacement of a failed implant with a new implant
Rheumatoid arthritis – Condition occurring from the body's own immune system attacking the lining of the joints as it would with foreign bacteria
Skeletal immaturity - Bones lacking complete growth or development
Subsidence - To sink or settle down
Traumatic arthritis - Condition resulting when the joint or the ligaments surrounding it are damaged by fracture, dislocation, or accident related injury
Wear Resistance - Able to withstand deterioration

1. What is the Cormet 2000 Hip Resurfacing System?

The Cormet 2000 Hip Resurfacing System consists of two parts: an acetabular component (or cup), and a femoral resurfacing component (or head).

- Acetabular component: The cup is used to replace the damaged surface of your hip socket without the use of bone cement for fixation.
- Femoral resurfacing component: The head is used to cover the ball of your hip (the ball shaped part of your hip at the top of the thighbone). The head component features a small stem that is inserted into the top of your thighbone. Bone cement is used for fixation of the head to the bone.

The Cormet 2000 head swivels within the cup. The surfaces that rub against each other are both made from highly polished metal. This type of hip device, therefore, is called a *metal-on-metal* hip surface replacement device.


PELVIS
RESURFACING CUP
RESURFACING HEAD
FEMUR
(THIGH BONE)

2. What are the reasons for hip resurfacing? (Indications for Use)

Hip resurfacing is most appropriate for physically active patients with good bone quality near the ball and socket of the hip joint with the following conditions:

- Non-inflammatory degenerative joint disease such as osteoarthritis and avascular necrosis;
- Inflammatory joint disease such as rheumatoid arthritis.

Hip resurfacing arthroplasty is intended as a first line joint replacement for patients who are at risk of requiring more than one hip joint replacement over their lifetimes. 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 surgery.

3. What are the reasons to avoid hip resurfacing? (Contraindications)

Hip resurfacing is not recommended for patients with the following conditions:

- Active or suspected infection in or about the hip joint;
- Any nerve or muscle disease that your doctor feels would compromise the success of the procedure;
- Poor bone quality which your doctor feels could not support the implant;
- Patients who are expected to grow taller after the surgery;
- Any known allergy to metal (e.g., jewelry);
- Extreme overweight (overload on device that would lead to failure);
- Pregnancy;
- Plans for pregnancy;
- Kidney failure;
- Inability to follow post surgery life style directions;
- Inability to appear for repeated doctor's visits, and
- Inability to face repeated surgeries.

4. What are some of the limitations of the Cormet 2000 Hip Resurfacing procedure?

- Hip resurfacing implants have limitations. For example, extreme forces placed on the implants through excessive patient weight or activities such as running and jumping can affect the artificial joint. Patients should govern their activities accordingly.
- The artificial hip joint may not restore function to the same level as normal, healthy bone so the patient should not have unrealistic expectations.

- The life span of the artificial hip joint components is difficult to estimate, however, it cannot be expected to equal that of normal healthy bone.
- The components of the artificial hip joint are affected by many biological and mechanical factors, which cannot be determined ahead of time.
- Metal sensitivity reactions have been reported following joint replacement.
- Adverse effects may result in a need for additional surgeries including the removal of the implants and replacing them with total hip replacement implants.

5. <u>What are some of the potential benefits of the Cormet 2000 Hip Resurfacing System?</u>

Your surgeon has decided that you will benefit from hip replacement surgery. When thinking about the benefits of the Cormet 2000 Hip Resurfacing System, you should compare the possible risks and benefits of the Cormet 2000 Hip Resurfacing System to the risks and benefits of other types of artificial hip replacement devices:

- Hip resurfacing versus a total hip replacement:
  With a hip resurfacing device, the surgeon covers your hip socket with a metal cup and covers your femoral head with a metal cap. The Cormet 2000 System is a hip-resurfacing device. With a total hip replacement device, the surgeon covers your hip socket with a cup and replaces your femoral head with a metal ball attached to a long metal stem. The metal stem is inserted into your thighbone.

- Metal-on-metal versus metal-on-plastic or ceramic-on-ceramic:
  With metal-on-metal systems, the cap (ball) and the socket components are made from highly polished metal. The Cormet 2000 System is a metal-on-metal system. Other hip systems can have a metal ball with a plastic lined socket (metal-on-plastic), or a ceramic ball with a ceramic-lined socket (ceramic-on-ceramic).

Each of the device types discussed above can significantly improve hip pain and function. However, specific potential benefits of the Cormet 2000 System include:

- The Cormet 2000 System's metal cup will not chip or crack as ceramic components can.
- The Cormet 2000 System does not cause thighbone (femoral shaft) fractures as total hip replacement systems can.
- The Cormet 2000 System may make future revision surgery easier because hip-resurfacing surgery leaves your femoral head in place and

there is no large metal stem placed in the thighbone. Revision surgery of a total hip replacement where your femoral head has already been removed and a large stem is already in place can be a more difficult operation.

- Dislocation of the ball head from the socket is less common with the Cormet 2000 device than with total hip replacement devices. In the clinical study, 0.2% of the all enrolled population of the Cormet 2000 hips experienced dislocation. Two other publications (Amstutz, et al. and Shimmin AJ, et al.) reported dislocation in resurfacing at 0.75% which is similar to the results achieved in this study.

6. What are the adverse events, complications, and risks expected from hip resurfacing?

Possible complications of any metal on metal hip resurfacing system are:

- Ball and socket may separate (hip dislocation);
- Device loosening from the surrounding bone;
- Allergic reaction to the implant's materials. As the parts rub against each other, metal ions are released into the body, which may cause an allergy. There are no known medical consequences of these ions at this time, however, studies are ongoing.
- Audible sounds during motion;
- Femoral neck fracture-your bone below the ball of the hip may break;
- Femoral head collapse- the bone in the ball of the hip could break;
- Premature wear or breakage of the implants;
- Bone loss around the implant;
- Change in the length of the treated leg;
- Hip pain and stiffness;
- Loss of flexibility of the hip joint;
- Nerve damage;
- Calcification.

The surgery to implant the device may also be complicated by:

- Nerve damage;
- Allergic reaction to medical treatments during surgery and/or blood transfusion;
- Excessive bleeding;
- Infection;
- Blood clots in the legs and/or lungs due to the surgery;
- Other medical problems such as heart attack or pneumonia while awaiting or recovering from surgery.

7. Why choose the Cormet 2000 Hip Resurfacing System?

Laboratory testing and the long use of metals have shown them to be hard, and have excellent lubrication, friction, and wear properties.

There are total hip systems that also feature metal-on-metal sockets. When compared with these devices, the potential benefit of the metal-on-metal Cormet 2000 Resurfacing device is that the resurfacing device leaves your femoral head in place. This means that if you eventually wear out this resurfacing device, your surgeon may have an easier time replacing your hip in the future as more of your original, natural bone is left intact.

If you were to get a *total* hip replacement, however, your surgeon must remove the top of your femur (thighbone) neck shaft. This means that if you eventually wear out your first total hip replacement, your surgeon may have a more difficult surgery and may need to take even more of your natural bone.

Safety and Effectiveness

A clinical study was performed to evaluate the safety and effectiveness of the Cormet 2000 device. Complication (safety) information was collected from the entire group of 1148 study procedures. Effectiveness information was collected from the 337 Pivotal Study Unilateral Patients. There is at least two year follow-up for 283 of these 337 patients.

Harris Hip Score

The Harris Hip Score (HHS), the most widely used scoring system for evaluating the effectiveness of total hip arthroplasty, has been demonstrated to be both valid and reliable.[i] Published literature tends to present HHS patient success based on a total point value at a specific postoperative interval rather than on a point differential. This includes literature associated with the use of modern hip resurfacing systems.[ii] FDA approved the effectiveness of the control ABC Ceramic-on-Ceramic System[iii] based on a composite HHS of 70 points or more as indicating patient success. A total HHS of 80 or greater is considered good to excellent[ivv]. Hip arthroplasty procedures are known to be highly successful with high patient satisfaction. Separating the population into those with HHS greater than or equal to 80 and those below 80 gives an evaluation of patient success based on at least adequate (good) relief of pain and return to function that has come to be expected as a result of the surgery.

There was no statistically significant difference with the control population for the Composite Clinical Success with over 95% of the patients in each group having a composite HHS of > 80 points at Month 24 (p=0.650). Refer to **Tables 1.0 and 2.0 [7.1(4) and 7.1(5)].**

Table 1.0 [7.1(4)]: Pivotal Study Unilateral Patients and Unilateral Controls – Harris Hip Total Score Category All Evaluated (Actual[B])

Table 7.1(4)
Pivotal Study Unilateral Patients and Unilateral Controls
Harris Hip Total Score Category
All Evaluated (Actual[B])

	Preoperative				Week 6				Month 6				Month 12			
	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%	56	17.0%	38	15.4%	261	90.6%	189	79.1%	256	89.8%	209	85.0%
80-89	0	0.0%	0	0.0%	72	21.9%	95	38.6%	11	3.8%	31	13.0%	14	4.9%	23	9.3%
70-79	1	0.3%	9	3.6%	126	38.3%	70	28.5%	10	3.5%	9	3.8%	9	3.2%	6	2.4%
<70	336	99.7%	242	96.0%	75	22.8%	43	17.5%	6	2.1%	10	4.2%	6	2.1%	8	3.3%

	Month 24				Month 24+				Month 36			
	I		C		I		C		I		C	
Category	n	%	n	%	n	%	n	%	n	%	n	%
90 -100	240	91.3%	225	91.1%	258	91.2%	230	90.9%	70	87.5%	166	88.8%
80-89	14	5.3%	11	4.5%	14	4.9%	11	4.3%	4	5.0%	12	6.4%
70-79	2	0.8%	5	2.0%	4	1.4%	6	2.4%	5	6.3%	4	2.1%
<70	7	2.7%	6	2.4%	7	2.5%	6	2.4%	1	1.3%	5	2.7%

[Source: Tables_Clinical_Followup_PRIMEFF_v2.sas]

Wilcoxon Rank Sum p-values	
Interval	p-value
Preoperative	0.001
Week 6	0.012
Month 6	0.000
Month 12	0.102
Month 24	0.933
Month 24+	0.904
Month 36	0.750

Table 2.0 [7.1(5)]: Pivotal Study Unilateral Patients and Unilateral Controls –
Harris Hip Total Score Greater Than or Equal to 80
All Evaluated (Actual[B])

Table 7.1(5)
Pivotal Study Unilateral Patients
and Unilateral Controls
Harris Hip Total Score Greater Than or Equal to 80
All Evaluated (Actual[B])

	Number and Percentage Meeting Criteria						
	Investigational			Controls			
	N	n	%	N	n	%	p-value[1]
Pre-op	337	0	0.0%	252	1	0.4%	0.428
Week 6	329	128	38.9%	246	133	54.1%	0.000
Month 6	288	272	94.4%	239	220	92.1%	0.295
Month 12	285	270	94.7%	246	232	94.3%	0.850
Month 24	263	254	96.6%	247	236	95.5%	0.650
Month 24+	283	272	96.1%	253	241	95.3%	0.673
Month 36	80	74	92.5%	187	178	95.2%	0.393

Notes: [1] Fisher's Exact test.

[Source: Tables_Clinical_Followup_PRIMEFF_v2.sas]

Device Related Events

The protocol definition of device related adverse event (AE) was “an AE that occurs due to the design and/or material composition of the implant and/or implant instrumentation”. From this definition, the category was refined to include:

- Bone breakage around the implanted components;
- Loosening of the components for reasons other than infection;
- Breakage of the device components (stem fracture, acetabular liner fracture, etc.);
- Movement of the components in the bone;
- Dislocation of the hip.

Table 3.0 [9.4(6)] gives a breakdown of the rates of device related AEs for the investigational group and the corresponding control group.

Table 3.0 [9.4(6)]: Complication Comparisons with Controls – Specific Complications
All Enrolled Investigational and Control Devices

Table 9.4(6)
Complication Comparisons with Controls - Specific Complications
All Enrolled Investigational and Control Devices

	Investigational			Control			0.017
	n[1]	N[2]	%	n[1]	N[2]	%	p-value[3]
Device Related Events							
Acetabular Fracture	0	1148	0.0%	1	349	0.3%	0.233
Acetabular loosening	11	1148	1.0%	0	349	0.0%	0.078
Avulsed lesser trochanter	1	1148	0.1%	1	349	0.3%	0.412
Ceramic Insert Chip (operative)	0	1148	0.0%	8	349	2.3%	0.000
Dislocation	2	1148	0.2%	10	349	2.9%	0.000
Femoral Fracture (operative)	0	1148	0.0%	1	349	0.3%	0.233
Femoral Fracture (post-op)	0	1148	0.0%	7	349	2.0%	0.000
Femoral loosening	14	1148	1.2%	0	349	0.0%	0.050
Femoral neck fx	26	1148	2.3%	0	349	0.0%	0.002
Femoral subsidence	4	1148	0.3%	2	349	0.6%	0.629
Trochanter (greater) fx	1	1148	0.1%	0	349	0.0%	1.000

Notes:

[1] Number of procedures with at least one of the specific types of complications. The total number of procedures with at least one complications is smaller than the sum, since procedures can have more than one type of complication.

[2] Total number of procedures in this cohort of patients.

[3] Two-sided Fisher's Exact tests. Comparisons were not performed for femoral neck notched (operative), greater Trochanter Notching (operative), ceramic insert chip (operative), and femoral neck fracture since both devices were not exposed to these types of events. Also, p-values are not reported when there were no events in either group.

[Source: Tables_Safety_vs_ABCcontrols_ENROLLED.sas]

These complications very rarely could lead to leg amputation or death. Speak to your doctor about your risks.

- The risk of acetabular component loosening - There were 11 events **(**1.0%**)** of acetabular loosening in the All Enrolled investigational group of the clinical study.
- The rate of dislocation was two events (0.2%) in the investigational group in the clinical study.
- The risk of femoral component loosening - The All Enrolled investigational group reported 14 events of femoral loosening for a rate of 1.2%.
- The risk of femoral neck fracture - In the All Enrolled investigational group, a 2.3% rate (26 events) of postoperative femoral neck fracture was observed.

8. What other ways can a damaged hip joint be treated?

Your doctor should discuss with you other procedures that could be used for your condition. These include:

- Conservative, non-surgical treatment, such as activity modification, weight reduction, pain medication, physical therapy, cortisone injections, and walking aids
- Hip osteotomy – cutting a hole in the bone to relieve pressure and promote healing
- Hip fusion – making the thigh bone and hip socket a stable, yet unbending joint.
- A total hip replacement, which can be made of a combination of metal, plastic and/or ceramic parts.

After discussing the above options with your doctor, you may decide to have no treatment at all at the present time.

9. How is hip resurfacing performed?

Resurfacing a hip is similar to a total hip replacement from a surgical perspective. Instead of cutting off the arthritic femoral head (top of the thigh bone), the head is reshaped and resurfaced with a metal mushroom-like cap. This is secured in place with a type of cement. The hip socket is prepared in a similar fashion to a total hip replacement. Once the diseased cartilage is removed, a cup is press-fitted into place. Hip resurfacing leaves more of your natural bone in place and does not remove the femur (thigh bone) neck shaft. The hip resurfacing surgery usually takes two to four hours to perform. The procedure may be performed under epidural, spinal or general anesthesia. The choice is made in consultation with your surgeon and anesthesia provider.

All components of the hip resurfacing implants are made of standard materials that have a long history of use in the human body.

10. What may happen after a Cormet 2000 Hip Resurfacing?

Recovery from any operation varies from patient to patient and post-operative rehabilitation programs vary from hospital to hospital and surgeon to surgeon.

After surgery you will need to rest your hip to allow proper healing. Your activity will be restricted during this healing period. During the first weeks after surgery, you may be advised to put a pillow between your legs when turning over in bed, wear elastic stockings, use raised toilet seat, take showers rather than baths, restrict activities such as sudden twisting or turning, crossing legs, exposing the scar to sunlight, and driving. Follow carefully your doctor's

instructions regarding progression to normal weight bearing and resumption of normal physical activity. Individual results will vary and all patients will experience different activity levels post-surgery.

Your surgeon will give you detailed post-operative instructions before you leave the hospital.

Even after the healing period, excessive loads placed on the implants through sudden trauma or high impact activities, such as running and jumping, can damage the artificial joint.

The majority of your therapy and rehabilitation will occur once you are discharged from the hospital. Your Physical Therapist (PT) will design an exercise program to increase the motion and strength of your hip and will make sure that you know proper form before you begin the program. The rate and effectiveness of your rehabilitation is critically dependent on your commitment to the physical therapy program.

Your doctor may want you to meet with a PT even before the surgery. The PT may give you some tips on preparing your house for rehabilitation and on how you should sleep, get out of bed, sit, stand from a sitting position, and walk following surgery.

Special precautions
Call your doctor if you experience any of the following symptoms:

- Redness, burning, swelling, or drainage from your operated area;
- Fever of 100 degrees or higher;
- Pain that does not lessen with rest;
- Acute, severe pain in the hip associated with twisting, turning, or injury.

Please ask your surgeon to discuss with you any of the above complications that are not familiar to you.

11. Is there anything else to know about hip resurfacing?

Consult your doctor regarding preoperative considerations, post-operative rehabilitation, and expectations for surgery. It is important to begin planning for your return home from the hospital before your surgical procedure. Your physical therapist (PT) or occupational therapist (OT) may suggest tips to prepare your home for after surgery. For example, get an apron or belt with pockets to carry things while you are on crutches, buy or borrow a cordless phone, remove scatter rugs and other obstacles for safe walking using crutches, have a high seated chair and commode accessories available. Above all, during this time, treat yourself well, eat balanced meals, get plenty of rest, and, if requested by your surgeon, donate your own blood so it can be transfused during and after surgery.

Because you will need to rest your hip properly, your post-surgical activities are limited. During the first weeks after surgery, you may be advised to put a pillow between your legs when turning over in bed, wear elastic stockings, use raised toilet seats, take showers rather than baths, restrict activities such as sudden twisting or turning, crossing legs, exposing the scar to sunlight since sunlight has a tendency to "activate" scars, which increases the redness and sensitivity, and driving.

12. How to obtain user assistance information?

Please discuss any questions regarding your hip surgery with your surgeon. For further information regarding the Cormet 2000 Hip Resurfacing System components, you may also contact the device manufacturer:

Corin USA
10500 University center Drive
Suite 190
Tampa, FL 33612

Tel. 1-888-302-6746
www.coringroup.com

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[ii] Amstutz HC, Beaule PE, Dorey FJ, Le Duff MJ, Campbell PA, Gruen TA. Metal-on-metal hybrid surface arthroplasty: two to six-year follow-up study. J Bone Joint Surg Am, 86(1): 28-39, 2004.
[iii] Food and Drug Administration (FDA) Center for Device and Radiological Health (CDRH) Osteonics® ABC System; Trident™ System - P000013. Issued February 3, 2003. [web site] http://www.fda.gov/cdrh/pdf/p000013.html. (reference available upon request)
[iv] Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fracture: Treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am, 51:737-755, 1969.
[v] Guidance for Industry and FDA Staff Clinical Data Presentations for Orthopedic Device Applications Document issued on: December 2, 2004 by FDA Center for Devices and Radiological Health, Orthopedic Devices Branch, Office of Device Evaluation.

GENERAL INFORMATION

IMPORTANT Please read carefully before using this product.

The surgeon must be fully conversant with the applicable operative technique and/or instructions for use where available. If additional information concerning the operative technique is required the information should be requested from the applicable Corin Group Sales Department or distributor. The surgeon or the surgical team must inspect the implants, surgical instruments and single use disposable devices prior to surgery to ensure they are undamaged and appropriate for use in the surgical procedure.

The Cormet 2000 Resurfacing Hip System is a metal-on-metal hip resurfacing system, and does not require removal of the natural femoral head. The system consists of a stemmed resurfacing femoral head component designed for cemented fixation and an acetabular component designed for cementless fixation. The acetabular component has a bi-coating™ of plasma sprayed titanium and hydroxylapatite (HA).

Materials

Component	Material	Standard
Femoral Resurfacing Head	Cobalt Chromium Alloy	ASTM F75
Acetabular Component	Cobalt Chromium Alloy Unalloyed Pure Titanium Hydroxyapatite powder	ASTM F75 ISO 5832 Part 2 ASTM F1185

Sizing and System Compatibility

Each femoral head component is compatible with two acetabular components with the exception of the 56mm diameter head, which is only compatible with the 62mm Nominal Outside Diameter (OD) acetabular cup.

Femoral Head (Nominal Outside Diameter)	**Acetabular Component** (Nominal Inside Diameter of cup x Nominal Outside Diameter of cup)
40mm	40 x 46mm, 40 x 48mm
44mm	44 x 50mm, 44 x 52mm
48mm	48 x 54mm, 48 x 56mm
52mm	52 x 58mm, 52 x 60mm
56mm	56 x 62mm

Indications for Use

The Cormet metal- on- metal hip resurfacing device 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;
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 surgery.

Contraindications

1. Active or suspected infection in or about 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 post-operative 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 on 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).

Warnings

1. Patients on medications (such as high-dose or chronic aminoglycoside treatment) or with co-morbidities (such as diabetes) that increase the risk of future, significant renal impairment should be advised of the possibility of increase in systemic metal ion concentration. Preoperative and postoperative monitoring of renal function (such cretinine, GFR, BUN) will be necessary.
2. Do not scratch the femoral or acetabular components' articulating surfaces.
3. Do not use another manufacturer's device in place of components of the Cormet 2000 Resurfacing Hip System. Design differences between manufacturers can lead to device failure.
4. Do not use these components for patients undergoing revision total hip replacement surgery.
5. Single use only. Never reuse an implant even if it appears undamaged.
6. Avoid notching the femoral neck, as this may lead to femoral neck fracture.
7. Avoid placing the femoral component in varus. Varus placement of femoral component has been associated with femoral neck fracture.
8. Do not handle the hydroxyapatite treated regions as it may compromise the sterility or cause failure under load.
9. Do not contour or bend an implant as it may compromise its fatigue strength and cause failure under load.

Precautions

1. Before clinical use, the surgeon should thoroughly understand all aspects of the surgical procedure and limitations of the device. Patients must be instructed in the limitations of the prosthesis, including, but not limited to, the impact of excessive loading through patient weight or activity, and be taught to govern their activities accordingly. If the patient is involved in an occupation or activity which includes substantial walking, running, lifting, or muscle strain, the resultant forces can cause failure of the fixation, the device, or both. The prosthesis will not restore function to the level expected with normal healthy bone, and the surgeon should advise the patient against having unrealistic functional expectations.
2. Surgeons should review the Cormet 2000 Hip Resurfacing System operative technique prior to implanting.
3. Clean articulating surfaces of debris prior to final reduction of the joint.
4. Avoid overly abducting the acetabular component, which can accelerate wear.

5. Ensure that the head outer diameter and acetabular inner diameter match prior to implanting.
6. Handle porous surfaces carefully so that particles are not dislodged from the component surface.
7. Routine postoperative follow-up is recommended to monitor implant position and patient well-being over time.
8. Appropriate selection, placement and fixation of the resurfacing hip components are critical factors which affect implant service life. As in the case of all prosthetic implants, the durability of these components is affected by numerous biologic, biomechanic and other extrinsic factors, which limit their service life. Accordingly, strict adherence to the indications, contraindications, precautions and warnings for this product is essential to potentially maximize service life.

Clinical Study

The safety and effectiveness of the Corin Cormet 2000 Hip Resurfacing System were demonstrated through a prospective, multi-center clinical study. The clinical performance of the Corin Cormet 2000 Hip Resurfacing System was compared with the clinical performance of a PMA approved ceramic-on-ceramic total hip system (control) in patients undergoing primary total hip replacement for non-inflammatory degenerative joint disease. Adverse events, revision rates, Harris Hip Scores, and radiographic evaluations were compared at Month 24+ post-operatively. The follow-up at the Month 24+ interval was 87% for the Cormet 2000® group and 97% for the control group. The results are summarized below.

Patient Demographics

Category	Cormet 2000®	Control
No. Cases	337	266
Male/female	228/109	165/101
Mean Age (yrs.)	50.1	53.3
Mean Weight (lbs.)	190.4	188.7
Primary diagnosis= Osteoarthritis (%)	85.8%	83.7%

Safety Data (Adverse Events)

Refer to Table 1.0 [9.1(7)] for Time course distribution of operative site adverse events and revisions for Cormet and control hip systems out to 24 months post-operatively.

Table 1.0 [9.1(7)]: Specific Complications by Time of Occurrence – Pivotal Study Unilateral Patients and Unilateral Controls

Table 9.1(7)
Specific Complications by Time of Occurrence - Pivotal Study Unilateral Patients and Unilateral Controls

	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	0	0	1	0	0	0	2	0	2	0	5	0
Avulsed lesser trochanter	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Ceramic Insert Chip (operative)	0	6	0	0	0	0	0	0	0	0	0	0	0	6
Dislocation	0	0	1	7	0	0	0	0	0	0	0	0	1	7
Femoral Fracture (operative)	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Femoral Fracture (post-op)	0	0	0	3	0	2	0	0	0	0	0	1	0	6
Femoral loosening	0	0	0	0	0	0	1	0	7	0	5	0	13	0
Femoral neck fx	0	0	0	0	3	0	5	0	3	0	0	0	11	0
Femoral subsidence	0	0	0	0	1	0	0	1	0	1	0	0	1	2
Trochanter (greater) fx	0	0	0	0	0	0	0	0	0	0	1	0	1	0

[Source: Tables_Safety_vs_ABCcontrols_PRIMEFF.sas]

Other Potential Adverse Events

The following potential adverse events were either reported in the study or in the literature for hip resurfacing procedures:

Hip Related Events

- Acetabular component malpositioned
- Bursitis
- Deep Infection
- Elevated metal ion levels
- Femoral neck notched during surgery
- Greater trochanter notching
- Hematoma
- Heterotopic bone formation
- Hip Pain
- Leg Length Discrepancy
- Limp
- Muscle weakness
- Myositis ossificans
- Nerve palsy
- Soft tissue trauma
- Squeaking/ clicking implant
- Subchondral cyst
- Subluxation
- Tendonitis
- Wound related (not infected)

Systemic Events

- Arrhythmia
- Bronchopulmonary
- Carcinoma
- Cardiovascular
- Death (unrelated to device)
- Deep vein thrombosis
- Gastrointestinal
- Genitourinary
- Infection – remote location
- Lack of Nutrition
- Low hemoglobin/ hematocrit
- Neuropathy
- Neurosensory
- Nosebleed
- Pulmonary embolism
- Rash
- Thrombophlebitis
- Trauma (non hip related)
- Varicose Veins
- Other

Effectiveness Data

Harris Hip Scores and Radiographic Assessments

Efficacy Assessment	Cormet®	Control
Preoperative mean HHS	50.1	49.7
2-year postop mean HHS	96.7	96.2
Femoral radiolucency (all zones)	0.4%	0%
Femoral subsidence	3.6%	0.4%
Acetabular radiolucency (all zones)	0%	0%

24+ Month patient success was defined as HHS≥80, no radiographic failure at 24+ months, no device related AEs, and no revision at any time.

Patient Failure Criteria	Cormet (# of patients)	Control (# of patients)
Revision	24	5
Total HHS <80	11	12
Device related AE	32	21
Radiographic failures	10	1
Patient Failure Rate	14.0 %	12.5 %
Patient Success Rate*	86.0 %	87.5 %

*Note: Patient success/failure rate cannot be derived from adding the rates of the individual criteria as one patient may have failed more than one category

Adverse Effects

1. While the expected life of hip resurfacing components is difficult to estimate, it is finite. These components are made of foreign materials which are placed within the body for the potential restoration of mobility or reduction of pain. However, due to the many biological, mechanical and physiochemical factors which affect these devices but cannot be evaluated in vivo, the components cannot be expected to indefinitely withstand the activity level and loads of normal healthy bone.
2. Dislocation of the hip resurfacing prosthesis can occur due to inappropriate patient activity, trauma or other biomechanical considerations.
3. Loosening of hip resurfacing components can occur. Early mechanical loosening may result from inadequate initial fixation, latent infection, premature loading of the prosthesis or trauma. Late loosening may result from trauma, infection, biological complications, including osteolysis, or mechanical problems, with the subsequent possibility of bone erosion and/or pain.
4. Fatigue fracture of the implants (as a result of excessive loading, malalignment, or trauma).
5. Metallosis and osteolysis.
6. Peripheral neuropathies, nerve damage, circulatory compromise and heterotopic bone formation may occur.
7. Serious complications may be associated with any total joint replacement surgery. These complications include, but are not limited to: genitourinary disorders; gastrointestinal

disorders; vascular disorders, including thrombus; bronchopulmonary disorders, including emboli; myocardial infarction or death.
8. A sudden drop in blood pressure intra-operatively due to the use of bone cement.
9. Acetabular pain may occur due to loosening of the implant.
10. Metal sensitivity reactions have been reported following joint replacement.
11. Adverse effects may necessitate reoperation, revision, arthrodesis of the involved joint, Girdlestone and/or amputation of the limb. Surgeons should advise patients of these potential adverse effects.
12. Periarticular calcification or ossification.
13. Bone perforation or fracture (occurring either intraoperatively or occurring postoperatively as a result of trauma, excessive loading, osteolysis or osteoporosis).
14. Wear deformation of the articular surface (as a result of excessive loading)

Utilization and Implantation

- Radiographic templates are available to assist in the preoperative prediction of component size and style.
- Use the recommended trial components for size determination, trial reduction and range of motion evaluation, thus preserving the integrity of the actual implants and their sterile packaging.
- Care should be taken to remove bone chips, bone cement fragments and metallic debris from the implant site to reduce the risk of debris induced accelerated wear of the articular surfaces of the implant.
- The Corin operative techniques provide additional procedural information.

Sterility

The Cormet implants are supplied sterile. The integrity of the packaging of each component should be checked carefully to ensure that product sterility has not been compromised.

1 These components have been sterilized by gamma radiation.
2 Do NOT re-sterilize.
3 Inspect the packaging of ALL sterile products for flaws before opening. Assume the product is not sterile in the presence of any flaws.
4 Take care to prevent contamination of ANY components.
5 Discard ALL nonsterile or contaminated product.

Re-sterilization

Corin Group implants must not be re-sterilized and/or re-used by the customer. Any implants which, for whatever reason, are required to be re-sterilized must be returned to Corin for assessment of the feasibility for re-sterilization in accordance with the approved validated method.

The manufacturer and distributor take no responsibility for sterilization or re-sterilization of implants undertaken by the hospital.

Pre-operative Planning

Corin Group provides written operative techniques to ensure that the surgeon and the surgical team are fully versed with the operative procedure.

The trials prostheses should not be implanted. If, during pre-operative planning, an appropriately sized component is not available the procedure should not take place. An appropriate size range of implants should be available prior to performing the surgical procedure.

Cautions

Federal Law restricts this device for sale by or on the order of a physician in the USA.

Post-operative Care and Follow-up

The surgeon must provide the patient with appropriate instructions, preferably in writing, regarding exercises and limitations on activities, prior to discharge from hospital, in order to protect the implant from unreasonable stresses. High stress and contact activities should be avoided. The patient should present for post-operative review by the surgeon at defined intervals. The patient should be encouraged to report any post-operative complications to the surgeon.

USA version

Corin

cormet precision instrumentation

restoring quality of life

pre-operative planning

Using the scaled Cormet templates provided, the X-ray is templated to assess the component sizes for the Cormet acetabular cup and femoral head using the separate head and cup templates provided.

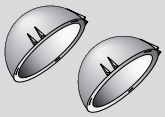
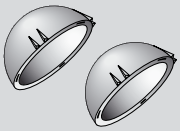
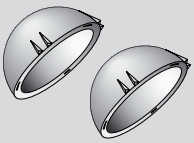
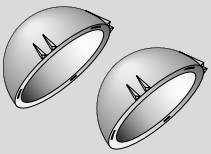
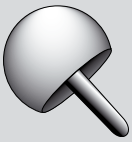
Femoral component alignment is also determined pre-operatively and is an important part of the templating procedure. The femoral component should be positioned in neutral or slight valgus alignment; varus positioning should be avoided[1].

Access to the acetabulum is generally made easier by preparing the femur first, as this will debulk the femoral head.

Initial preparation of the femur may be carried out to one size larger than that templated, in order to ensure that there is sufficient clearance around the femoral neck for the definitive implant. Further preparation (to the templated size) may then be carried out if it is evident that there is sufficient clearance around the neck, and that the integrity of the neck will not be compromised.

Sufficient clearance may occasionally still remain to allow a smaller size to be used than was suggested by templating. In this case, further preparation to the smaller size should be carried out, ensuring the use of the most appropriate size of femoral component and minimising the amount of bone removed from the acetabulum.

implant sizing and instrument colour coding

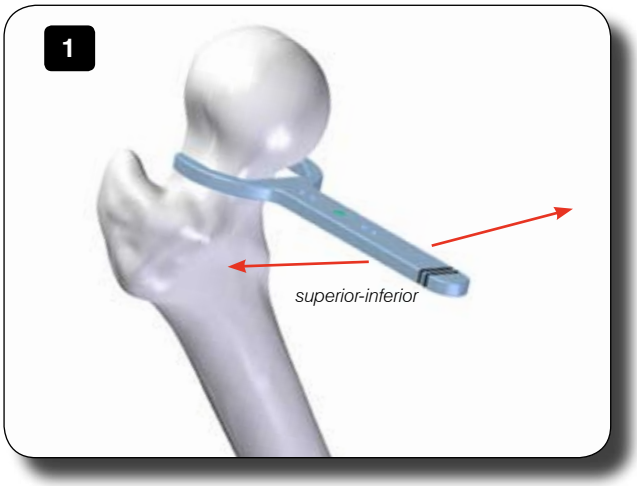
Heads		Cups	
size 2 **40mm**		size 2 **46mm**	 size 2 **48mm**
size 4 **44mm**		size 4 **50mm**	 size 4 **52mm**
size 6 **48mm**		size 6 **54mm**	 size 6 **56mm**
size 8 **52mm**		size 8 **58mm**	 size 8 **60mm**
size 10 **56mm**		size 10 **62mm**	

Note: coloured rings denote corresponding markings on instruments

femoral neck sizing

The femoral neck is sized using the head template. The template represents the internal dimensions of the femoral head. It is important to remove large osteophytes and soft tissue in order to gain an accurate measurement. The femoral neck is usually oval in shape and should be sized in its largest dimension, typically superior-inferior.

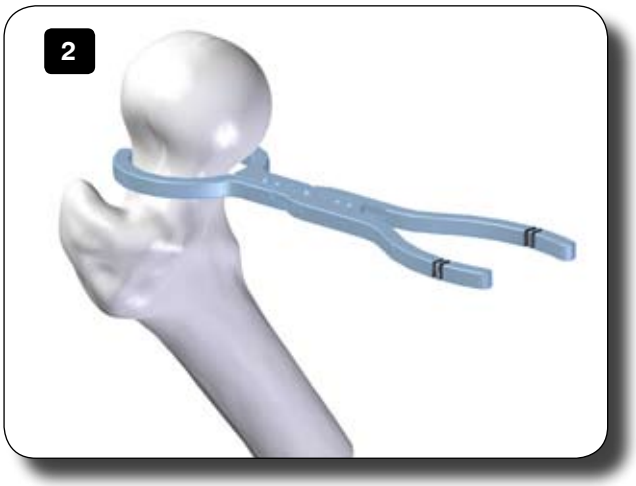
Important: The template which fits the most closely around the neck without catching corresponds to the smallest head size that may be used without notching the neck. Notching the neck increases the probability of a fractured neck of femur.



positioning the locking ring

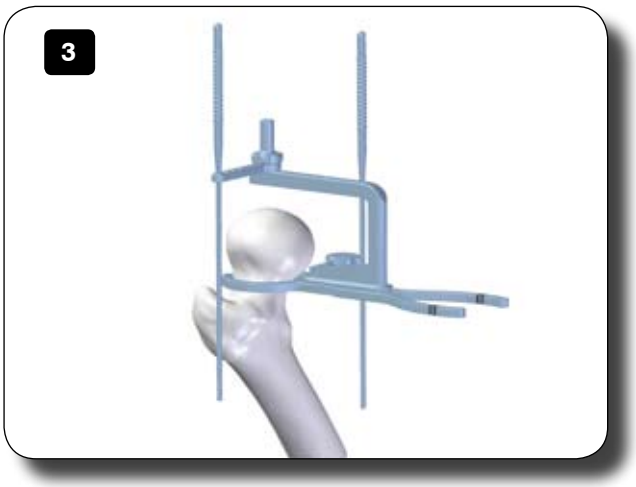
The appropriate sized locking ring (size 6 shown) is assembled around the femoral neck. It is essential that the ring closes fully using the handles since the internal diameter of the ring matches the internal diameter of the barrel cutter.

Important: The ring used represents the smallest head size that may be used without notching the neck.



assembling the drill guide

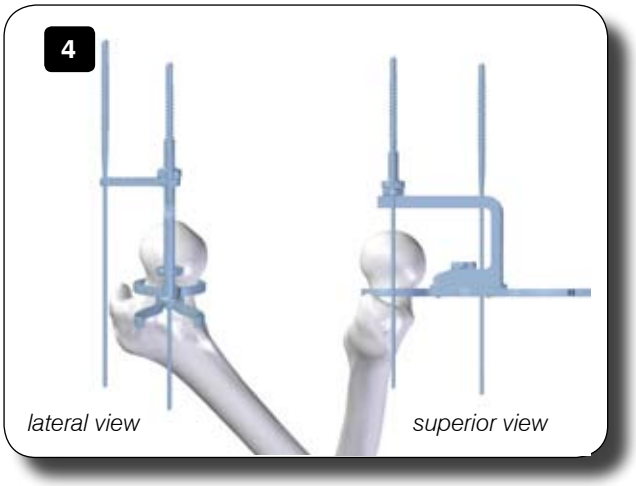
The drill guide is assembled on to the locking ring and held in place with the captive screw. The drill guide tube is centred over the centre of the locking ring, providing accurate placement of the fluted guide wire.



positioning the orientation guide wires

There are two holes for a guide wire in the side of the drill guide. The short arm can be used to position a second guide wire at 90 degrees (either side of the head). These guide wires are intended to show the varus/valgus (lateral view) and anteversion/ retroversion (superior view) of the drill guide tube and hence the position of the definitive fluted guide wire.

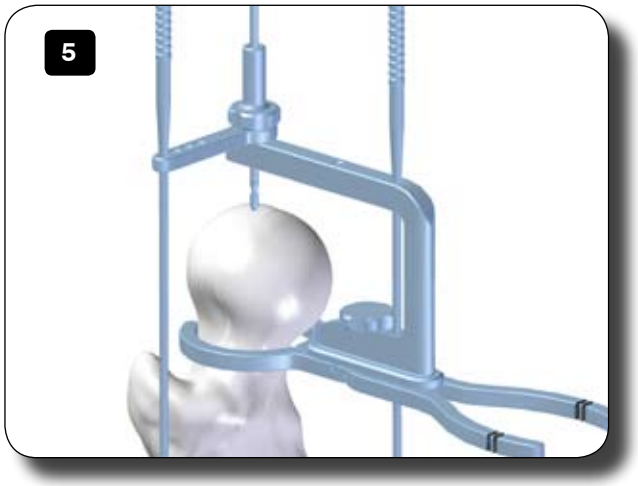
Important: The guide wire should be placed in neutral or slightly valgus position. A varus position should not be chosen as this may lead to a fractured neck of femur.



drilling the guide wire

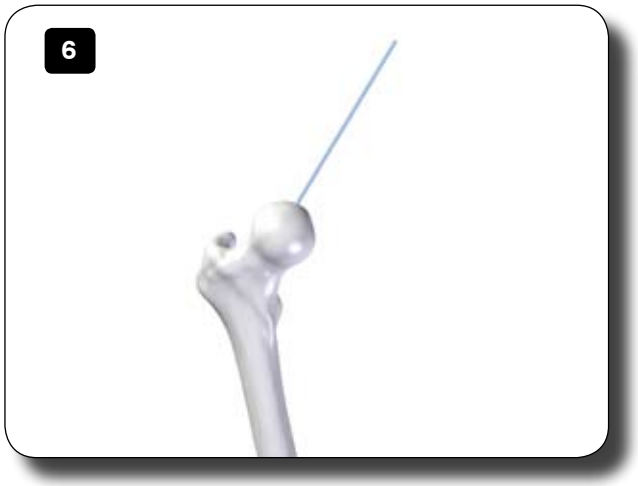
With the jig orientated correctly, the definitive fluted guide wire can now be drilled into the femoral head. Do not apply power until the tip of the guide wire touches the apex of the femoral head.

Important – care should be taken not to bend the wire during introduction.



removing the centering jig

Remove the head centering jig by removing the orientation wires, loosening the captive screw and dis-assembling the jig.

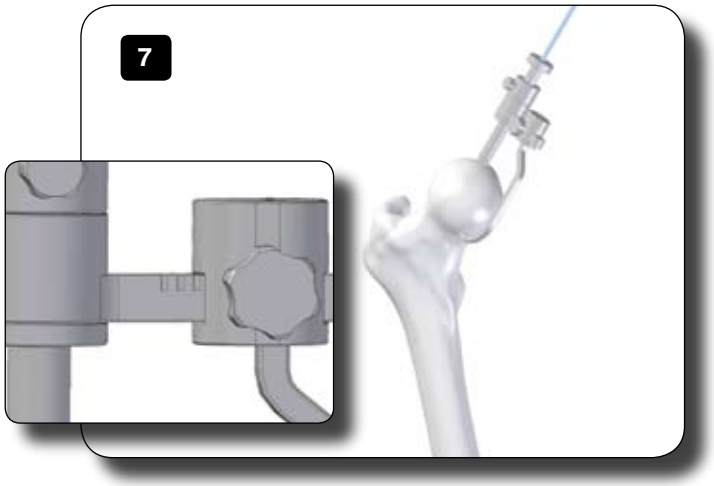


checking the position of the guide wire

The stylus can be used to check the position of the guide wire, by placing it over the guidewire and running the stylus around the neck at a pre-set size.

The diagram shows the stylus set to size 6 (for a 48mm head). The inner most line represents the size 2 and the outer most size 10.

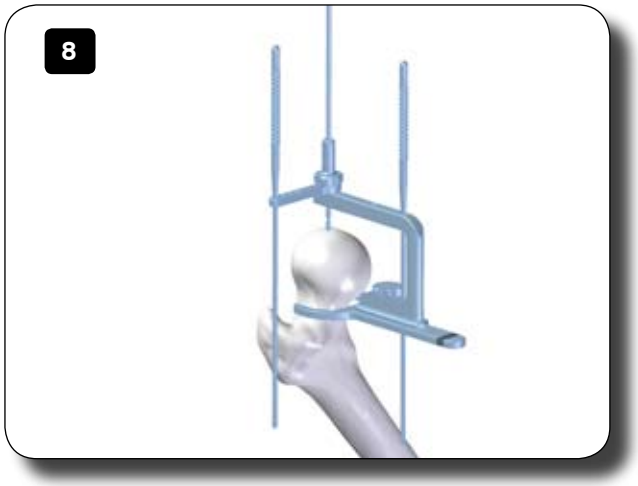
To avoid notching the neck, the stylus should run freely around the neck without catching.



alternative head centering using head templates

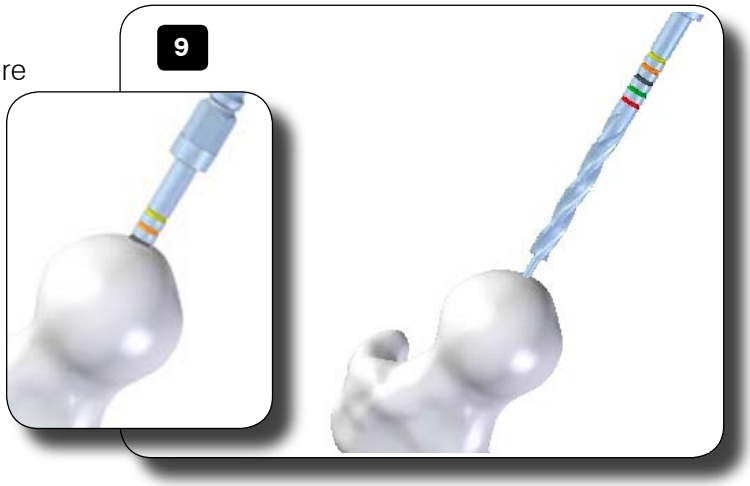
It is also possible to assemble the drill guide and guide wires onto the head templates. This may be helpful in cases where the femoral head is very distorted and the locking ring cannot be used.

Using the head templates for the alignment involves a greater amount of ‘eyeballing’ to find the centre of the femoral neck. Care should be taken not to position the guide wire too posteriorly due to the oval nature of the femoral neck to avoid notching. The anteversion/retroversion guide wire may be helpful in judging the correct position of the guide wire.



cannulated drill

The cannulated drill is advanced over the guide wire as far as the corresponding coloured line for the head size (see page 2).



placing the guide rod

Both the drill and the pin are removed and the guide rod is inserted.

making the initial head cut

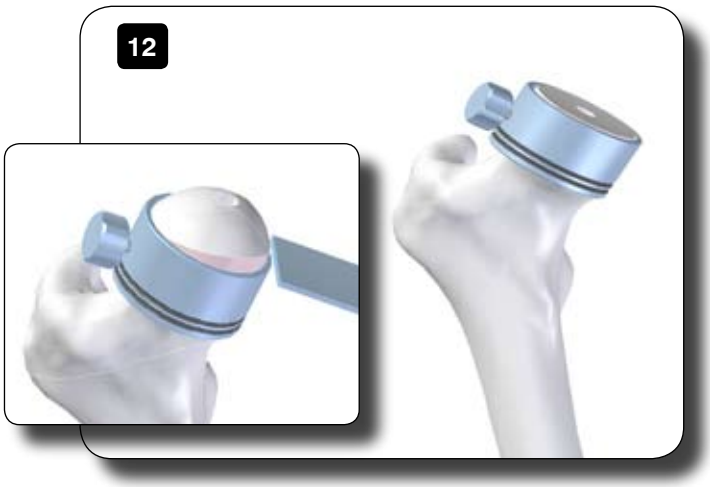
The appropriate size of barrel cutter is advanced over the guide rod, as far as the head-neck junction. This ensures the neck is not notched. **A head template can be placed over the greater trochanter and neck to protect them from being notched.** Swabs can be used to prevent bone debris entering the soft tissue.

Important – One size larger head cutter can be used for the initial preparation. This will debulk the head before preparation of the final size. At this point the acetabulum can be prepared before final preparation of the head giving the choice of four sizes of acetabular cups.

top femoral head resection

Remove the guide rod. The top head guide should be positioned so that the inferior edge is in line with the head-neck junction.

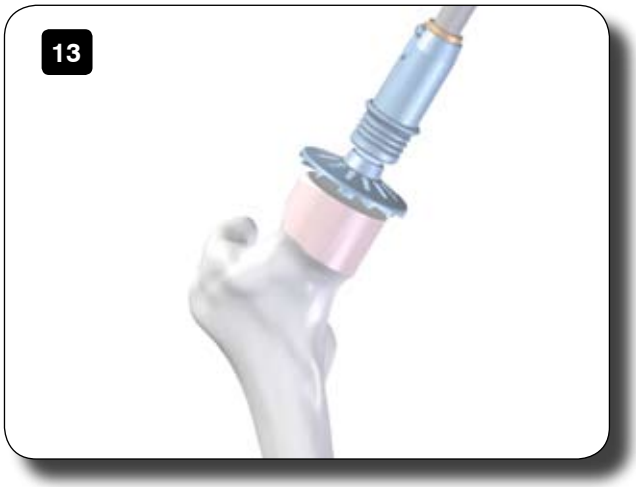
The head is then resected with an oscilllating saw.



finishing the top head cut

The guide rod is re-inserted and the top head cutter is advanced to create a surface perpendicular to the neck axis.

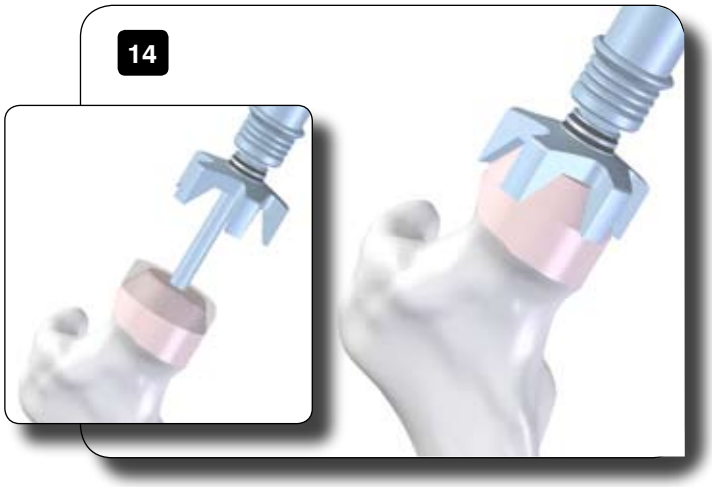
Important – care must be taken as this instrument should only remove a small amount of bone which will not change the depth of the definitive implant.



making the chamfer cut

The appropriate head chamfer cutter is then used to create the bevel.

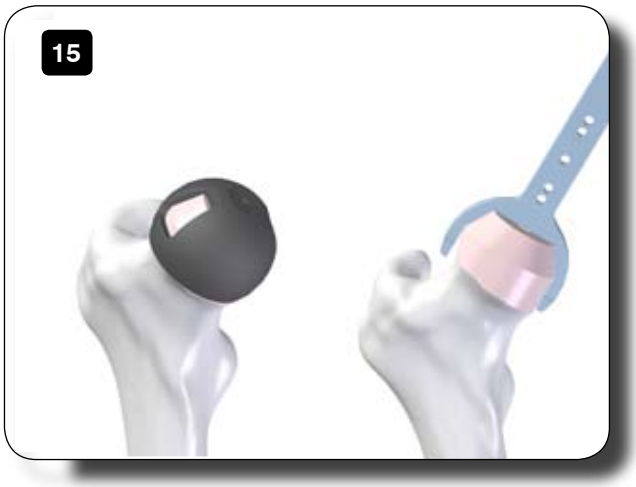
Important – care should be taken with this instrument; the cutter should be advanced slowly to avoid "snatching". "High speed" rather than "ream" should be used on the power tool.



checking the femoral cuts

The corresponding size of head template or trial head can be used to check the prepared shape. The head template can be used to make a mark on the head-neck junction to indicate how far the femoral component should be advanced when fully seated.

Cement keyholes can be drilled into the femoral head at this stage if required.

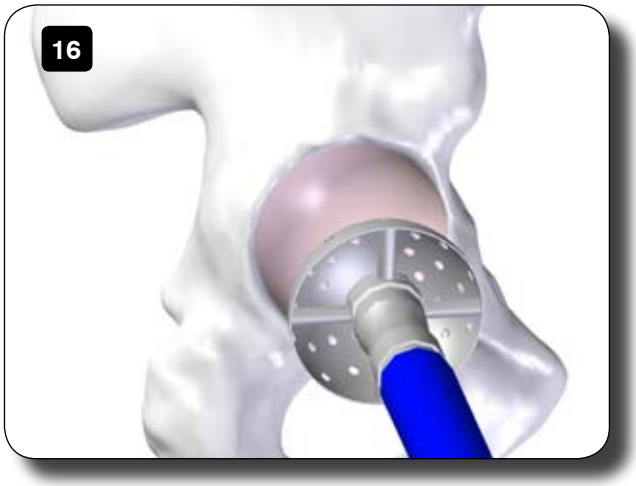


reaming the acetabulum

The acetabulum is exposed such that the entire acetabular margin may be seen. The acetabulum is then reamed sequentially until the true floor is exposed and the required size is reached.

Important - since the Cormet cup is equatorially expanded, the acetabulum is reamed to the nominal cup size i.e. the cup size stated. For example, for a size 54mm cup, the acetabulum is reamed to 54mm.

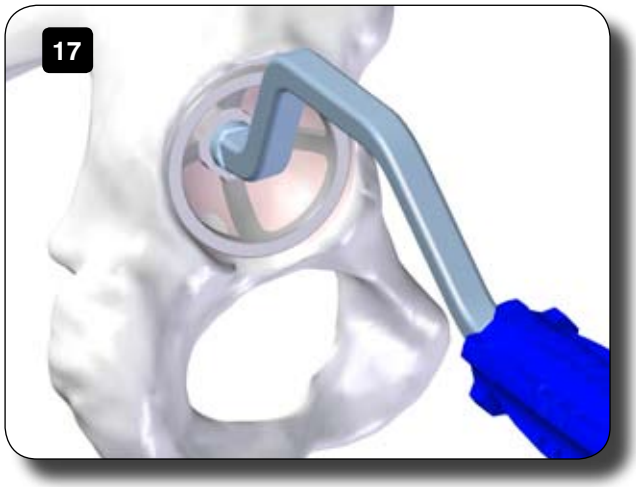
To allow unhindered cup insertion, all osteophytes should be removed and soft tissue cleared from the acetabular margin.



trialing the acetabular cup

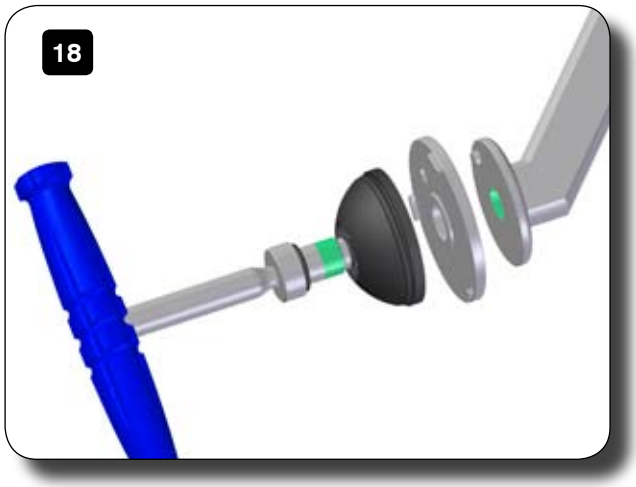
The appropriate acetabular trial is assembled on to the trial handle and placed 45° to the horizontal, with 10-15° of anteversion. It should fit snugly into the reamed acetabulum.

Important – the trial is NOT equatorially expanded.



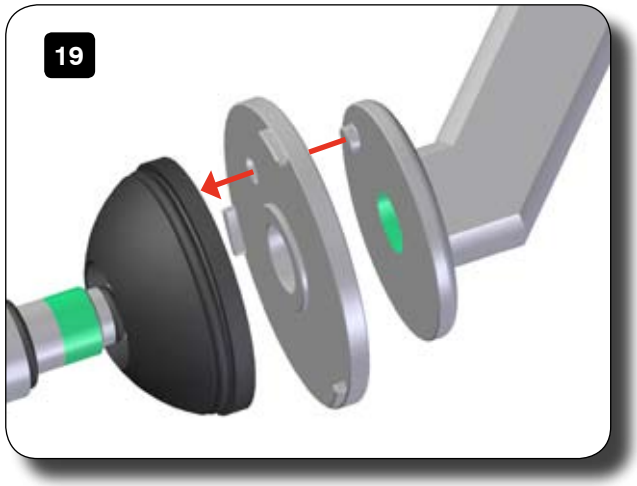
assembling the vacuum cup introducer

The introducer is assembled as shown ensuring that the baseplate and plastic insert are paired correctly according to size.



alignment of vacuum cup introducer components

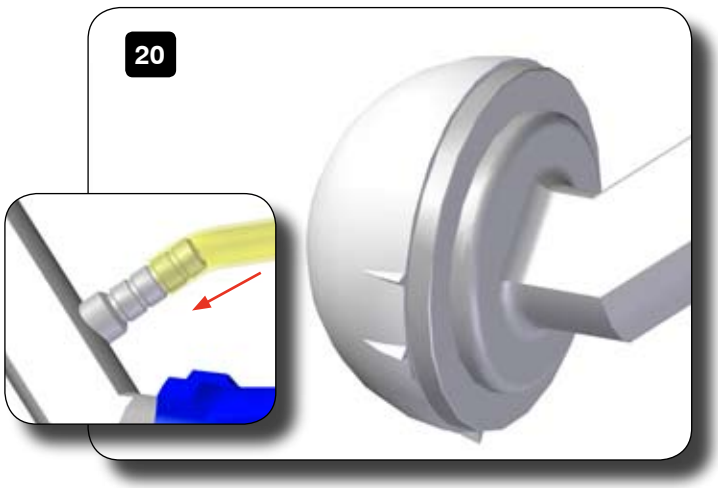
The hole in the baseplate must be lined up with the alignment peg on the base of the handle, as shown, prior to the locking nut being fully tightened.



mounting the cup onto the vacuum introducer

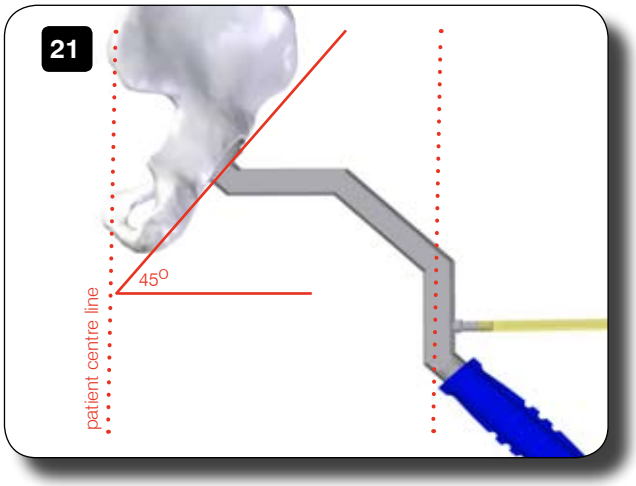
The cup is now mounted as shown onto the introducer and then the suction tubing applied.

The cup can be mounted in three different positions but the ideal position would allow the splines to be at 5 and 7 o'clock and the introducer handle at 12 o'clock if the cup is viewed face on.



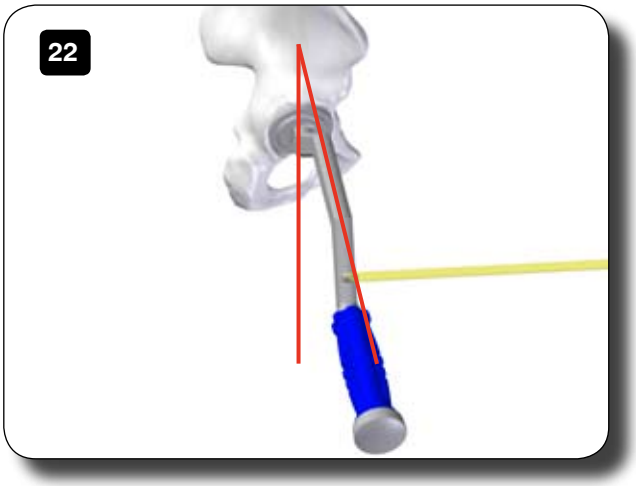
alignment of the cup

As shown the handle can be used to align the cup at 45° to the horizontal.



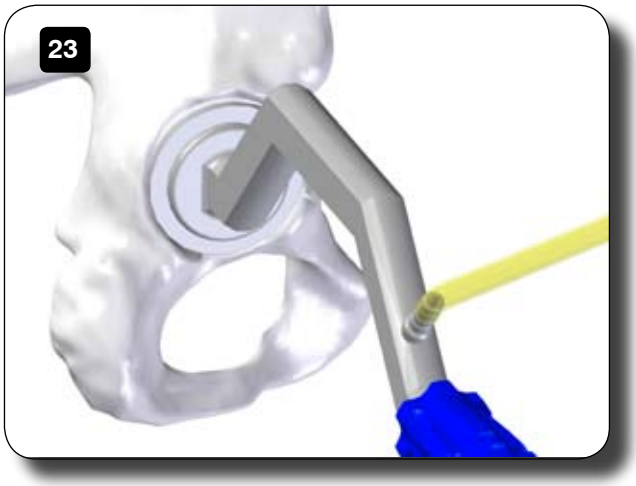
anteversion of the cup

The introducer can then be placed with 10-15° of anteversion.



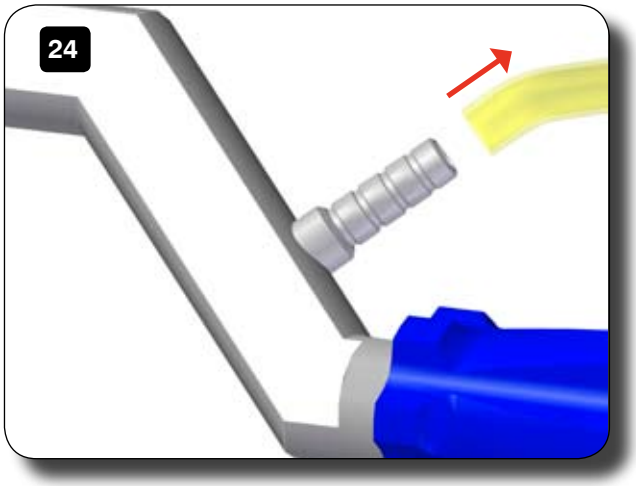
introducing the cup

The cup is introduced into the acetabulum such that the two sets of anti-rotation fins engage with the ischium and pubis.



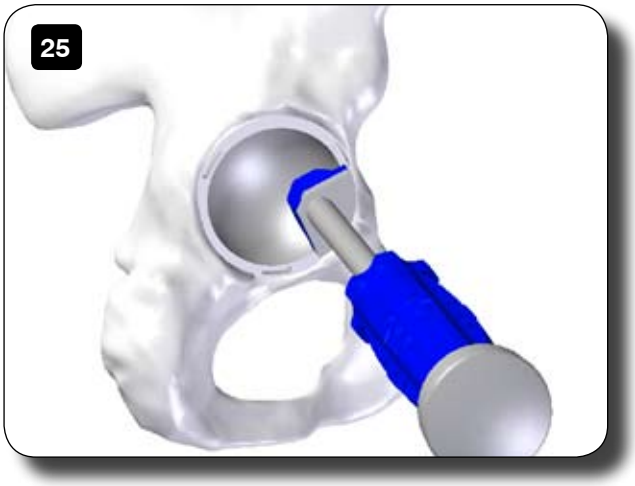
removing the vacuum cup introducer

Once the cup is firmly impacted the suction can be released and the introducer removed.



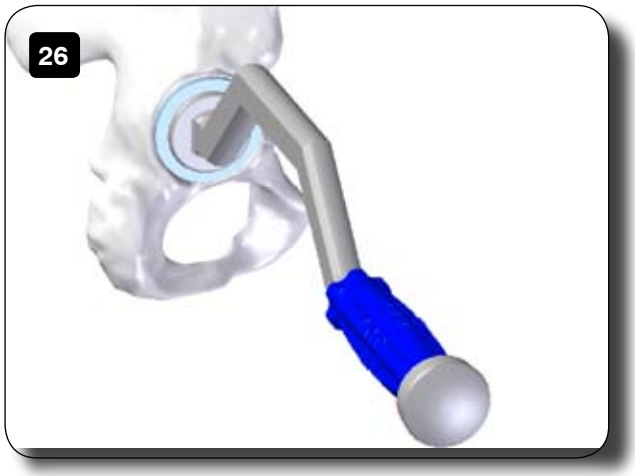
repositioning the cup

If the position of the cup is not satisfactory, the rim impactor can be placed on one segment of the rim of the acetabular component, and gently impacted to reposition the cup.



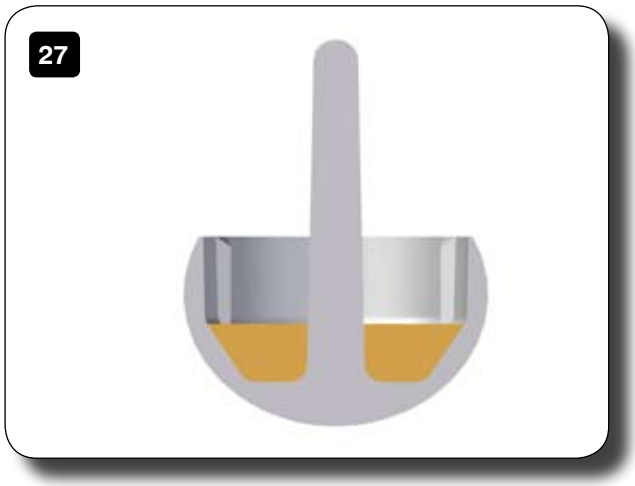
final cup impaction

If the rim impactor is used or the cup is not fully seated then the cup impactor should be used.



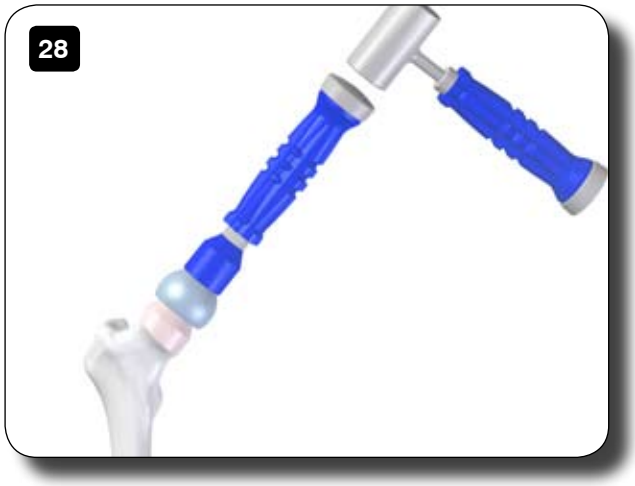
preparing the femoral component

Low viscosity cement is poured into the femoral component up to the line shown.



impacting the femoral component

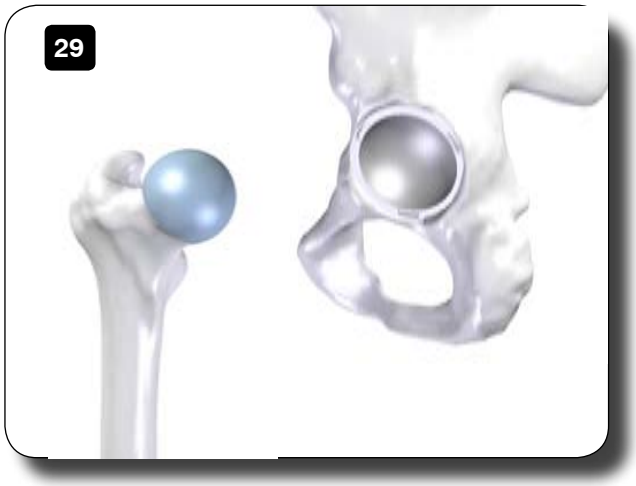
The definitive component is placed onto the femoral head and impacted in to position with the head impactor. Excess bone cement is removed.



reduction and final checks

The hip is then reduced, avoiding scratching of the femoral component against the cup.

A full check is then made to ensure there is no impingement and that the range of motion and stability are satisfactory.



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Cormet Heads	
40mm	179.040
44mm	179.044
48mm	179.048
52mm	179.052
56mm	179.056

Cormet Cups	
46mm OD	179.246B
48mm OD	179.248B
50mm OD	179.250B
52mm OD	179.252B
54mm OD	179.254B
56mm OD	179.256B
58mm OD	179.258B
60mm OD	179.260B
62mm OD	179.262B

Reference:

1. Beaule P, Lee J, Le Duff M, Amstutz H, Ebramzadeh E. Orientation of the femoral component in surface arthroplasty of the hip. JBJS, Vol 86-A, Number 9, September 2004, 2015-2021.

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Corin Cormet Training Protocol
Hip Resurfacing

OVERVIEW

This document describes a first in class, multi-tiered curriculum paradigm for Hip Resurfacing that will set the standard for product training in Orthopaedics. This paradigm includes a multi-tiered training program that provides information on the surgical technique, observation of live surgery, hands on experience with saw bones and cadavers, as well as continued mentoring of first surgeries.

Tier 1 Surgical Technique
- Web-based E-Simulation Overview

Tier 2 Observation
- Live Surgery Observation with Surgeon Trainer

Tier 3 Hands on Experience
- National and Regional Center Training
    - Interactive Live Surgery (Tier 3A)
    - Interactive E-Simulation (Tier 3B)
    - Sawbone Workshop (Tier 3C)
    - Tissue Surgery Practice (Tier 3D)

Tier 4 Continued Mentoring
- Post Program Reinforcement
    - First Surgery Mentoring (Tier 4A)
    - Access to Web-based Interactive E-Simulation (Tier 4B)

Full description is provided below TRAINING PROGRAM DESCRIPTION

TRAINING PROGRAM DESCRIPTION

Tier 1 – Web-based E-Simulation Review

A surgeon interested in the Corin Cormet Resurfacing Hip program will be granted access to a web-based E-Simulation Review that will provide an overview of the instruments, surgical technique and implants.

Tier 2 – Live Surgery Observation

Upon completion of Tier 1, the surgeon will then be invited to observe an experienced surgeon perform a live Corin Cormet surgery at the experienced surgeon's hospital. The surgeon will be encouraged to scrub in on the case in hospitals where this is permitted.

Tier 3 – National and Regional Center Training

Upon completion of Tier 1 and 2, surgeons will be invited to come to either the Stryker national or regional training center location with their respective Sales Representative.

Tier 3A – Interactive Live Surgery
The program would begin with a live Corin Cormet surgery demonstrating the instrumentation, surgical technique and implants. Surgeons participating at the training center will be able to ask questions of the expert surgeon performing the technique.

Tier 3B – Interactive E-Simulation
Following the live surgery session, participants via laptops will perform the Corin Cormet procedure in a simulated fashion. This interactive, user-centered experience, in which the user perceives and interacts with simulated objects in a realistic synthetic environment, will provide initial experience with proper instrumentation as well as the surgical technique and will offer performance history that can monitor technique success.

Tier 3C – Sawbone Workshop
Following the interactive E-simulation session, participants will perform the procedure on sawbones. This will give the participants hands-on practice with the instrumentation and feel of the procedure.

Tier 3D – Tissue Surgery Practice
Participants will work with cadaver tissue in the Bioskills lab to further master the instrumentation, surgical technique and implants.

Tier 4 – Post Program Reinforcement
To reinforce the techniques the surgeon learned two programs would be provided at the participant's request after the surgeon has received training at the national or regional training center.

Tier 4A – First Surgery Mentoring
The newly trained surgeon may request that an expert surgeon observe the first Corin Cormet case he performs. The expert surgeon will scrub in with the newly trained surgeon where this is permitted by the hospital.

Tier 4B – Access to Web-based Interactive E-Simulation
The newly trained surgeon will continue to have unlimited 24/7 access to the web-based interactive E-simulation training to reinforce the techniques and instrumentation training learned at the training center.

Approved
IDE Study Protocol

A non-randomized, safety and efficacy study of the Cormet 2000 metal on metal resurfacing hip system – An FDA investigational device study

Introduction and background

A review by Schmalzried and Callaghan[1] showed that the incidence of total hip component loosening will occur in younger and/or active patients due to amount of use *in vivo* and not necessarily due only to time *in vivo*. That is, with all other demographics being equal (gender, age, co-morbidities), the patient who puts his/her conventional prosthesis through a greater number of cycles will face revision sooner.

It follows, therefore, that as life expectancy increases, revisions of conventional metal on polyethylene hip replacement devices will comprise a larger proportion of hip replacement surgery. Revision hip replacement surgery increases the patient morbidity and cost associated with surgical treatment of arthritic hip disease. Revision surgery is highly complex and costly and requires considerable scientific and technical expertise, an array of expensive technological options, a supportive health care environment, and a skilled health care team.[2] A hip prosthesis that could outlive the patient, thereby avoiding the need for revision surgery, and could do so under high use conditions, would be a major advance in the surgical treatment of arthritic hip disease.

Modern metal on metal bearing surfaces may prove to provide a long-term solution to the need for revision surgery caused by atraumatic failure (osteolysis). However, the only metal on metal hip replacement devices currently cleared by FDA utilize conventional stemmed femoral components. The femoral component of Cormet 2000 represents a more conservative, bone-sparing approach to replacement of the arthritic femur by replacing only the surface of the femoral head. Cormet 2000, therefore, offers the benefit of proximal femoral bone retention, including the entire neck and all but 4 to 8mm of the head surface, with the benefit of a metal on metal articulation, which may provide long-term durability in the active patient with no need for revision. A similar device, currently under an investigational device exemption study, is the Conserve Plus (Wright Medical, Arlington, TN). Both Cormet 2000 and Conserve Plus aim at addressing the failures of previous full surface replacement by incorporating metal on metal technology into a more conservative, bone-sparing procedure.

The purpose of the proposed study under this Investigational Device Exemption is to test the hypothesis that the Cormet 2000 Resurfacing Total Hip System is as effective as conventional total hip arthroplasty. The Cormet 2000 Resurfacing Hip System will be the experimental treatment and the conventional total hip arthroplasty will serve as the control group. Safety will be determined by close monitoring and tracking of perioperative and postoperative complication incidence.

Study design

We propose a multi-center, non-inferiority, non-randomized, prospective design. This design will provide comparison of the investigational device (Group I) to two control groups – a metal on metal total hip replacement device control (Group II) and a metal on polyethylene total hip replacement control (Group III). Groups II and III data will come from patients, gathered from each enrolled center, who have either already had total hip replacement or who will have total hip replacement. Control group patients who have had implantations have all been followed prospectively with the protocol presented herein, with the exception of the Musculoskeletal Function Assessment questionnaire (MFA). Similarly, control group patients who will have implantations will be followed prospectively with the protocol presented herein. Group I patients include all patients who receive the investigational device at one the participating centers. Each center will generate data for Groups I and II or Groups I and III.

Each center will recruit patients in one of the following orders. "Control group" indicates either Group II or Group III patients.

Control group → Group I

OR

Group I → Control group

The order in which a particular center recruits patients will be determined by whether or not they have already implanted control group devices using the current protocol. Centers that have implanted control group devices and followed each subject with the proposed protocol will follow the first order listed above. Centers that have not yet implanted control group devices using the proposed protocol will implant the investigational device consecutively (Group I) and then proceed to recruit control group patients (Groups II and III).

All data generated will be collected prospectively, from baseline (preoperative) to 2 years postoperative. Success/failure outcome criteria, as defined below, will be used to determine *safety* and *efficacy* of the investigational device versus controls.

Rationale and justification for the elements of this study design are provided below.

Definition of success/failure

Successful outcome is defined as a patient who meets the following four (4) criteria, as they are each defined, at 2 years postoperatively:

1. Harris Hip Score ≥20 points greater than baseline
2. Has not had and is not pending revision

   a. Revision - a re-operation (see definition of re-operation below) that is performed on the replaced hip to remove and replace any component(s) that were implanted at the index operation

   b. Re-operation – any surgical procedure that is performed on the replaced hip or the surrounding bone and/or soft tissues

3. Radiographic success

   a. Acetabular component
      - migration <5mm in vertical or horizontal direction
      - migration <5º in varus/valgus direction
      - new or progressive complete radiolucencies ≤1mm in any or all zones

   b. Femoral component
      - subsidence (lateral movement of the resurfacing head) <5mm
      - tilting <1º in varus/valgus direction
      - new or progressive complete radiolucencies ≤2mm in any or all zones

4. No device related complications

   a. Device-related complication – an adverse event that occurs due to the design and/or material composition of the implant and/or implant instrumentation; device-related versus non device-related complications will be discriminated by the investigator

Patients who do not meet all of these criteria during any postoperative interval will be deemed "failures".

The combination of criteria 2 and 4 will provide for the tracking of complications that result in re-operations, as well as complications that are not treated operatively. Consequently, a broader range of complications, if occurring, will be identified. Along with being included in the definition of success/failure, complication rates between the groups will be compared.

Hypothesis

In order to establish *safety* and *efficacy*, we will attempt to detect a difference of 5% between Group I and II and between Group I and III, in terms of the success/failure proportion.

Rejection of the null hypothesis, indicating treatment equivalence, will occur if:

$P_{II \text{ or } III}$(control group) < $P_{I} + 0.05$, since

$H_{0:}$ $P_{II} \geq P_{I} + 0.05$, and
$H_{0:}$ $P_{III} \geq P_{I} + 0.05$, where

P_{I}, P_{II}, P_{III} are the success rates in the experimental, metal/metal THA control and metal/polyethylene THA control groups, respectively.

Number of subjects needed

Number of subjects needed was calculated for the Groups I/II comparison and the Groups I/III comparison using a formula for hypotheses of specified differences (Blackwelder, 1982). The formula and result is as follows:

$$N_{\text{each group}} = \frac{(z_{1-\alpha} + z_{1-\beta})^2 \, [P_{II \text{ or } III}\,(1 - P_{II \text{ or } III}) + P_{I}(1 - P_{I})}{(P_{II \text{ or } III} - P_{I} - \delta)^2}$$

where, P_{I} and $P_{II \text{ or } III}$ is the expected success/failure proportion in Groups I and II/III, $z_{1-\alpha}$ and $z_{1-\beta}$ are upper percentage points of the standard normal distribution, δ is the specified difference that is clinically meaningful, α=0.05 and β=0.10.

If P_{II} and P_{III} are both estimated to be 0.95 success/failure at the 2-year follow-up interval, $z_{1-\alpha}$ and $z_{1-\beta}$ are 1.645 and 1.28 respectively, and δ=0.05, then:

$$N_{\text{each group}} \approx 325$$

Since the Harris Hip Score cannot differentiate between sides in bilaterally replaced patients, only unilateral patients are included in the 325 per group estimate. In addition to these 325 patients, an additional 32 bilateral patients will be recruited. A patient initially having unilateral replacement and subsequent contralateral replacement will be counted as bilateral and placed in the bilateral group.

Assuming a 10% loss to follow-up rate, we will recruit a total of 392 patients in each group.

Summary of numbers needed per group:

Statistically	325
Bilaterals (add 10%)	32
Subtotal	357
Loss rate (add 10%)	35
Total per group	**392**

Inclusion/exclusion criteria

INCLUSION: **Patient:**

- is skeletally mature
- is mentally capable of completing follow-up forms
- will be available for follow-up out to 2 years
- has a preoperative Harris Hip Score <70 points
- has been deemed a candidate for hip replacement by diagnosis of the investigator

EXCLUSION: **Patient:**

- has active infection (PI discretion)
- has had previous Girdlestone procedure
- has had previous hip arthrodesis (fusion)
- has had above knee amputation of either extremity
- has neoplastic disease (PI discretion)
- has been diagnosed with congenital dislocation of the hip
- has a need for a structural bone graft in the operative side (PI discretion)
- has an ipsilateral hemi-resurfacing, total resurfacing, total bipolar, total unipolar or total hip replacement device
- has a nonunion or malunion of any part of the femur on operative side
- has extensive deformity of femoral head on operative side (PI discretion)
- has severe osteoporosis of the pelvis and/or femur (PI discretion)
- is a prisoner
- is pregnant
- is known to be allergic to implant materials
- is morbidly obese (PI discretion)

Outcome measures

All patients will be evaluated annually, as defined below, until the last patient entered into the study has reaches the two-year time point. Allowable time windows for each timepoint interval will be as follows: 6 weeks (±2 weeks), 6 months (±1 month), 1 year (±2 months), and 2 years (±2 months).

The following outcome measures will be taken at each prescribed interval:

- Harris Hip Examination
- Radiographs
- Musculoskeletal Function Assessment (Experiment group only)
- Complications

HARRIS HIP EXAMINATION: The Harris Hip Examination will be performed by the Investigator during the patient's clinic visit. This examination consists of two parts: 1) the Investigator questioning the patient as to their pain level and location, ability to perform activities of daily living; 2) the Investigator performing a standard, routine physical examination which determines range of motion and extent of any existing deformities.

RADIOGRAPHS: Anterior/posterior and lateral radiographs will be taken at each interval and interpreted by the Investigator. The radiographs will be measured using standardized techniques for determining acetabular and femoral component position. Each Investigator will also give a subjective impression of radiolucencies and bone quality.

Both component migration and radiolucencies will be evaluated in serial fashion (compared to the previous radiograph), rather than at single points in time only, to provide a meaningful indication of implant position.

1. Acetabular component position/migration

The measurement technique outlined by Massin et al[3], will be used for determining acetabular component migration as follows:

> On each radiograph, the vertical distance between the center of the cup and a horizontal line through the inferior part of the teardrops is measured. This distance measures superior/inferior migration. The distance between a vertical line through the mid-teardrop and one through the center of the head (made at right angles to the horizontal line through the teardrops) is measured. This distance measures medial/lateral migration.

Radiolucencies will be measured in the acetabular component using the zones delineated by DeLee and Charnley[4] (Figure 1). This delineation divides the anterior/posterior view of the component into 3 sections.

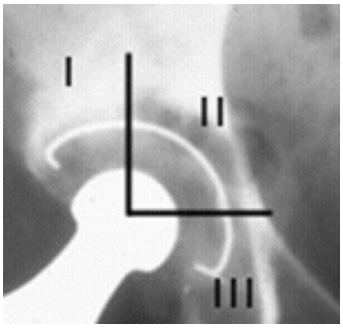


Fig 1. DeLee-Charnley zones

2. Femoral component position/migration

Subsidence measurement technique- A longitudinal line will be drawn, from the most proximal point of the stem, through the middle of the stem, to the lateral femoral cortex. The length of the line will be measured and recorded

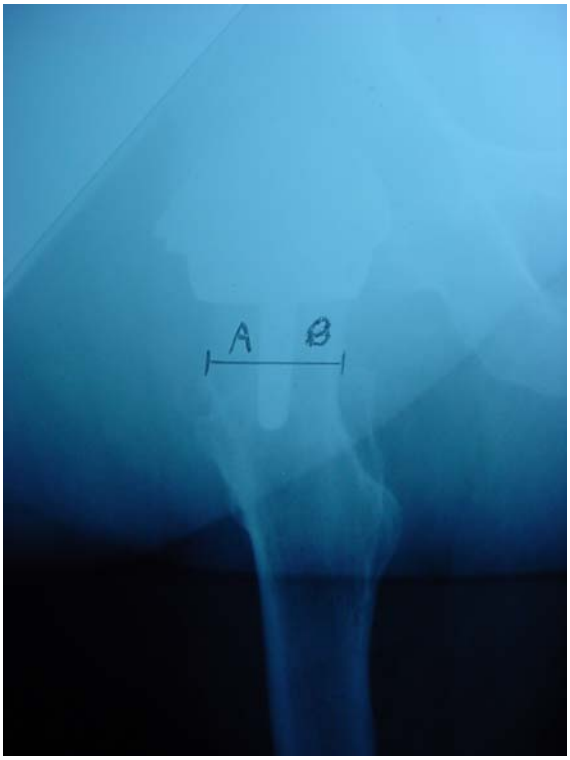
Tilting measurement technique – A longitudinal line will be drawn through the femur, ensuring that the line passes through the midpoint of the femur at each point. The angle that is formed between the newly drawn line (line B) and the previously drawn subsidence line (line A) will be measured and recorded.

Femoral component position in the axial plane (perhaps best described as an anteversion/retroversion plane) will be measured on the lateral film using the following technique:

The mid-point between the most proximal and distal points of the stem will be located. A line will be drawn across the femoral neck, from cortex to cortex, through the located mid-point. The distance between the point on the line touching the posterior part of the stem and the posterior cortex will be measurement “A”. The distance between the point on the line touching the anterior part of the stem and the anterior cortex will be measurement “B”.

An increase in “A” and decrease in “B” will indicate retroversion and an increase in “B” and “decrease in “A” will indicate anteversion.

This technique can be illustrated as follows:



Radiolucencies will be assessed by dividing the stem of the component into 3 zones on the A/P radiograph: superior, inferior, and tip. New or progressive radiolucent lines measuring >2mm will be recorded on the Case Report Form.

3. Femoral component bone changes

Proximal femoral bone will be assessed using zones (see Fig. 2) around the femoral neck to describe any atrophic or hypertrophic changes that would suggest stress shielding.

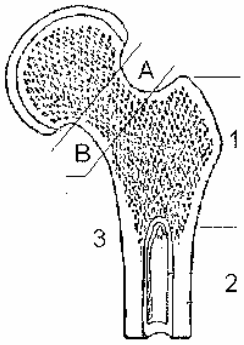


Fig 2. Femoral zones

MUSCULOSKELETAL FUNCTION ASSESSMENT (MFA): The MFA is a validated, patient questionnaire that measures patient satisfaction over time. The questionnaire

will be completed at each interval and scored using the MFA algorithm. A copy of the MFA is attached at the end of this protocol.

COMPLICATIONS: Post-operative complications will be recorded during each clinic visit. The Investigator will examine the patient for complications during the physical examination. The complications will be recorded and tracked thoroughly, so that causes and means of resolution can be used to determine the level of safety in each group of devices.

Statistical methods

Analyses will be performed for each follow-up interval and for overall outcomes where appropriate. For instance, HHS analysis will be performed for each follow-up interval (time-series). Confidence limits will be reported with all *p* values.

Descriptive statistics will be generated for: subject demographics, percent follow up at each interval and primary/secondary measures. Further analysis will be carried out as follows:

Between center and between group (Groups I/II, GroupsI/III) comparisons will be performed using Chi-square analysis.

Analysis of variance (ANOVA) will be used to compare results from the MFA questionnaire. The MFA algorithm will be used to generate the raw scores from which to run this analysis.

Complication rates will be reported for perioperative and postoperative time periods. Any adverse events and complications, device-related or not, will be documented. Frequency tables will be generated that include all complications that were observed and those that were reported in previous studies.

Radiographic variables (migration, radiolucencies, atrophy/hypertrophy) will also be reported in frequency tables. Emphasis on progression of these variables will be made with correlation to clinical scores (HHS and MFA).

Significance and impact of research

The investigational device provides potential benefits to the study population immediately, as well as to the general population if the product is cleared for use. These benefits, when compared to conventional total hip replacement, include, retention of more host bone on the femur, elimination of stress shielding potential in the metaphysis of the proximal femur, and reduced rate of dislocation. Previous work has suggested that the young and/or active total hip replacement patient is at higher risk for failure. The potential benefits of the investigational device, if elucidated in the proposed study, may provide surgeons with the ability to treat the young and/or active patient without the concern of long-term failure associated with conventional total-hip replacement.

References

1. Schmalzried T and Callaghan J. Current concepts review: wear in total joint hip and knee replacements. *Journal of Bone and Joint Surgery* 81-A: 115-136, Jan 1999.

2. Total Hip Joint Replacement. NIH Consensus Statement Online, 1994 Sep 12 – 14; 12(5): 1-31.

3. Massin P et al. Evaluation of cementless acetabular component migration. An experimental study. *Journal of Arthroplasty* 4: 245-251, 1989.

4. DeLee JG and Charnley J. Radiological demarcation of cemented sockets in total hip replacement. *Clinical Orthopaedics and Related Research* (121): 20-32, 1976.

Implemented
IDE Study Protocol

A non-randomized, safety and efficacy study of the Cormet 2000 metal on metal resurfacing hip system – An FDA investigational device study

Introduction and background

A review by Schmalzried and Callaghan[1] showed that the incidence of total hip component loosening will occur in younger and/or active patients due to amount of use *in vivo* and not necessarily due only to time *in vivo*. That is, with all other demographics being equal (gender, age, co-morbidities), the patient who puts his/her conventional prosthesis through a greater number of cycles will face revision sooner.

It follows, therefore, that as life expectancy increases, revisions of conventional metal on polyethylene hip replacement devices will comprise a larger proportion of hip replacement surgery. Revision hip replacement surgery increases the patient morbidity and cost associated with surgical treatment of arthritic hip disease. Revision surgery is highly complex and costly and requires considerable scientific and technical expertise, an array of expensive technological options, a supportive health care environment, and a skilled health care team.[2] A hip prosthesis that could outlive the patient, thereby avoiding the need for revision surgery, and could do so under high use conditions, would be a major advance in the surgical treatment of arthritic hip disease.

Modern metal on metal bearing surfaces may prove to provide a long-term solution to the need for revision surgery caused by atraumatic failure (osteolysis). However, the only metal on metal hip replacement devices currently cleared by FDA utilize conventional stemmed femoral components. The femoral component of Cormet 2000 represents a more conservative, bone-sparing approach to replacement of the arthritic femur by replacing only the surface of the femoral head. Cormet 2000, therefore, offers the benefit of proximal femoral bone retention, including the entire neck and all but 4 to 8mm of the head surface, with the benefit of a metal on metal articulation, which may provide long-term durability in the active patient with no need for revision. A similar device, currently under an investigational device exemption study, is the Conserve Plus (Wright Medical, Arlington, TN). Both Cormet 2000 and Conserve Plus aim at addressing the failures of previous full surface replacement by incorporating metal on metal technology into a more conservative, bone-sparing procedure.

The purpose of the proposed study under this Investigational Device Exemption was to test the hypothesis that the Cormet 2000 Resurfacing Total Hip System was as effective as conventional total hip arthroplasty. However, the purpose of the study was modified to a non-inferiority study that compares the Cormet 2000 experimental treatment to a total hip arthroplasty population with the use of an historical control of a ceramic-on-ceramic total hip system manufactured by Stryker (Howmedica Osteonics Corp).

Study design

This study is a prospective, multi-center, non-randomized, historically controlled study of the Cormet 2000 Hip Resurfacing System. The control group is a ceramic-on-ceramic THA system (Howmedica Osteonics Corp ABC systems). These Ceramic Bearings were the subject of an IDE clinical trial (G960148) and approved via PMA P000013 on February 3, 2003. The sponsor has received permission from the ABC study sponsor to use datasets from this study as a control for the Cormet 2000 Hip Resurfacing Investigational devices.

The use of this historical control in the following design provides a scientifically valid assessment of both relative and absolute clinical efficacy and safety.

Effectiveness of the Cormet 2000 Hip Resurfacing System will be evaluated with respect to function, pain, complications, and radiographic indicators, as well as survival. Thus, this controlled clinical trial aims to demonstrate that the use of Cormet 2000 Hip Resurfacing implants represent a safe and effective alternative to this PMA approved (P000013) ceramic-on-ceramic total hip replacement procedure over 24 months of follow-up.

All data generated will be collected prospectively, from baseline (preoperative) until the last patient enrolled reaches the two-year evaluation. Success/Failure outcome criteria, as defined below, will be used to determine *safety* and *efficacy* of the investigational device to the control.

Definition of success/failure

Successful outcome is defined as a patient who meets the following four (4) criteria, as they are each defined, at 2 years postoperatively:

1. Harris Hip Score ≥20 points greater than baseline
2. Has not had and is not pending revision

    a. Revision - a re-operation (see definition of re-operation below) that is performed on the replaced hip to remove and replace any component(s) that were implanted at the index operation

    b. Re-operation – any surgical procedure that is performed on the replaced hip or the surrounding bone and/or soft tissues

3. Radiographic success

    a. Acetabular component
    - migration <5mm in vertical or horizontal direction
    - migration <5º in varus/valgus direction
    - new or progressive complete radiolucencies ≤1mm in any or all zones

b. Femoral component

- subsidence (lateral movement of the resurfacing head) <5mm
- tilting <1º in varus/valgus direction
- new or progressive complete radiolucencies ≤2mm in any or all zones

4. No device related complications

a. Device-related complication – an adverse event that occurs due to the design and/or material composition of the implant and/or implant instrumentation; device-related versus non device-related complications will be discriminated by the investigator

Patients who do not meet all of these criteria during any postoperative interval will be deemed "failures".

The combination of criteria 2 and 4 will provide for the tracking of complications that result in re-operations, as well as complications that are not treated operatively. Consequently, a broader range of complications, if occurring, will be identified. Along with being included in the definition of success/failure, complication rates between the groups will be compared.

Hypothesis

In order to establish *safety* and *efficacy*, we will attempt to detect a difference of 5% between the investigational group Cormet 2000 and the control group ceramic-on-ceramic, in terms of the success/failure proportion.

The primary efficacy objective of this study is to demonstrate clinical non-inferiority with regard to the likelihood of clinical success at Month 24 relative to control.

The following non-inferiority hypothesis was used to demonstrate clinical success of the investigational group as compared to the control group.

The null and alternative non-inferiority hypotheses were formulated to be consistent with the Blackwelder (1982) approach and are as follow:

$H_{0:}$ $P_{Cormet2000} - P_{ceramic} \leq 0.05$
(clinically inferior to control)

$H_{a:}$ $P_{Cormet2000} - P_{ceramic} \geq 0.05$
(not clinically inferior to control)

The study is designed to reject the null hypothesis when that difference in proportions of procedures meeting the criteria for success is less than or equal to 0.05.

Number of subjects needed

Number of subjects needed was calculated for the comparison of experimental to control using a formula for hypotheses of specified differences (Blackwelder, 1982). The formula and result is as follows:

$$N_{each\ group} = \frac{(z_{1-\alpha} + z_{1-\beta})^2 \left[P_{ceramic}(1 - P_{ceramic}) + P_{Cormet2000}(1 - P_{Cormet2000})\right]}{(P_{ceramic} - P_I - \delta)^2}$$

where, $P_{Cormet2000}$ and $P_{ceramic}$ is the expected success/failure proportion in the investigational group and control group, $z_{1-\alpha}$ and $z_{1-\beta}$ are upper percentage points of the standard normal distribution, δ is the specified difference that is clinically meaningful, α=0.05 and β=0.10.

If $P_{ceramic}$ is estimated to be 0.95 success/failure at the 2-year follow-up interval, $z_{1-\alpha}$ and $z_{1-\beta}$ are 1.645 and 1.28 respectively, and δ=0.05, then:

$$N_{each\ group} \approx 325$$

Since the Harris Hip Score cannot differentiate between sides in bilaterally replaced patients, only unilateral patients are included in the 325 per group estimate. In addition to these 325 patients, an additional 32 bilateral patients will be recruited. A patient initially having unilateral replacement and subsequent contralateral replacement will be counted as bilateral and placed in the bilateral group.

Assuming a 10% loss to follow-up rate, we will recruit a total of 392 patients in each group.

Summary of numbers needed per group:

Statistically	325
Bilaterals (add 10%)	32
Subtotal	357
Loss rate (add 10%)	35
Total per group	**392**

Inclusion/exclusion criteria

INCLUSION: **Patient:**

- is skeletally mature
- is mentally capable of completing follow-up forms
- will be available for follow-up out to 2 years and annually thereafter until the last patient reaches the two-year evaluation

- has a preoperative Harris Hip Score <70 points
- has been deemed a candidate for hip replacement by diagnosis of the investigator

EXCLUSION: **Patient:**

- has active infection (PI discretion)
- has had previous Girdlestone procedure
- has had previous hip arthrodesis (fusion)
- has had above knee amputation of either extremity
- has neoplastic disease (PI discretion)
- has been diagnosed with congenital dislocation of the hip
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- has a nonunion or malunion of any part of the femur on operative side
- has extensive deformity of femoral head on operative side (PI discretion)
- has severe osteoporosis of the pelvis and/or femur (PI discretion)
- is a prisoner
- is pregnant
- is known to be allergic to implant materials
- is morbidly obese (PI discretion)

Outcome measures

All patients will be evaluated annually, as defined below, until the last patient reaches the two-year evaluation. Allowable time windows for each time point interval will be as follows: 6 weeks (±2 weeks), 6 months (±1 month), 1 year (±2 months), 2 years (±2 months), and annually (±2 months) thereafter until the last patient reaches the two-year evaluation.

The following outcome measures will be taken at each prescribed interval:

- Harris Hip Examination
- Radiographs
- Musculoskeletal Function Assessment (Experiment group only)
- Complications

HARRIS HIP EXAMINATION: The Harris Hip Examination will be performed by the Investigator during the patient's clinic visit. This examination consists of two parts: 1) the Investigator, or trained authorized designee, questioning the patient as to their pain level and location, ability to perform activities of daily living; 2) the Investigator, or trained authorized designee, performing a standard, routine physical

examination which determines range of motion and extent of any existing deformities.

RADIOGRAPHS: Anterior/posterior and lateral radiographs will be taken at each interval. All radiographs will be qualitatively reanalyzed by an independent medical reviewer in terms of radiolucency, hypertrophy, resorption, and lysis. Quantitative measurements, in terms of cup and head migration, will also be conducted by another independent radiographic reviewer.

Both component migration and radiolucencies will be evaluated in serial fashion (compared to the previous radiograph), rather than at single points in time only, to provide a meaningful indication of implant position.

1. Acetabular component position/migration

The measurement technique outlined by Massin et al[3], will be used for determining acetabular component migration as follows:

> On each radiograph, the vertical distance between the center of the cup and a horizontal line through the inferior part of the teardrops is measured. This distance measures superior/inferior migration. The distance between a vertical line through the mid-teardrop and one through the center of the head (made at right angles to the horizontal line through the teardrops) is measured. This distance measures medial/lateral migration.

Radiolucencies will be measured in the acetabular component using the zones delineated by DeLee and Charnley[4] (Figure 1). This delineation divides the anterior/posterior view of the component into 3 sections.

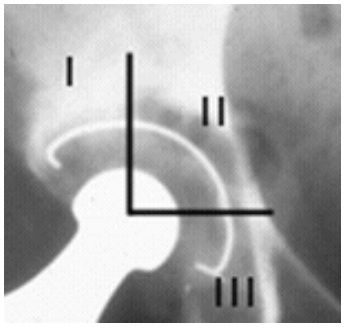

Fig 1. DeLee-Charnley zones

2. Femoral component position/migration

Subsidence measurement technique- A longitudinal line will be drawn, from the most proximal point of the stem, through the middle of the stem, to the lateral femoral cortex. The length of the line will be measured and recorded

Tilting measurement technique – A longitudinal line will be drawn through the femur, ensuring that the line passes through the midpoint of the femur at each point. The angle that is formed between the newly drawn line (line B) and the previously drawn subsidence line (line A) will be measured and recorded.

Femoral component position in the axial plane (perhaps best described as an anteversion/retroversion plane) will be measured on the lateral film using the following technique:

The mid-point between the most proximal and distal points of the stem will be located. A line will be drawn across the femoral neck, from cortex to cortex, through the located mid-point. The distance between the point on the line touching the posterior part of the stem and the posterior cortex will be measurement "A". The distance between the point on the line touching the anterior part of the stem and the anterior cortex will be measurement "B".

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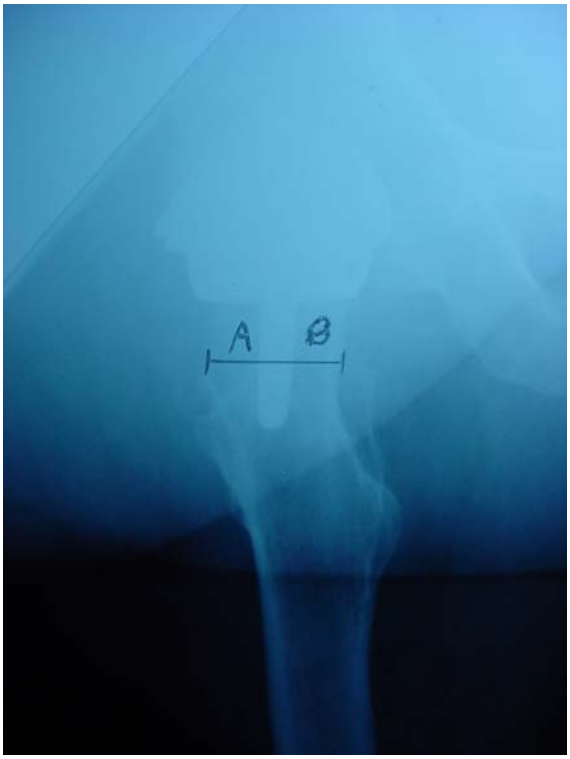

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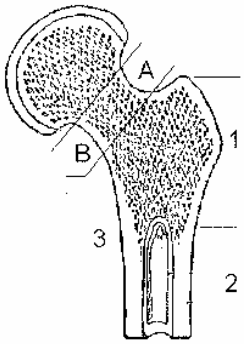

Fig 2. Femoral zones

MUSCULOSKELETAL FUNCTION ASSESSMENT (MFA): The MFA is a validated, patient questionnaire that measures patient satisfaction over time. The questionnaire will be completed at each interval and scored using the MFA algorithm. A copy of the MFA is attached at the end of this protocol.

COMPLICATIONS: Post-operative complications will be recorded during each clinic visit. The Investigator will examine the patient for complications during the physical examination. The complications will be recorded and tracked thoroughly, so that causes and means of resolution can be used to determine the level of safety in each group of devices.

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Analyses will be performed for each follow-up interval and for overall outcomes where appropriate. For instance, HHS analysis will be performed for each follow-up interval (time-series). Confidence limits will be reported with all *p* values.

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Between center and between group comparisons will be performed using Chi-square analysis.

Analysis of variance (ANOVA) will be used to compare results from the MFA questionnaire. The MFA algorithm will be used to generate the raw scores from which to run this analysis.

Complication rates will be reported for perioperative and postoperative time periods. Any adverse events and complications, device-related or not, will be documented. Frequency tables will be generated that include all complications that were observed and those that were reported in previous studies.

Radiographic variables (migration, radiolucencies, atrophy/hypertrophy) will also be reported in frequency tables. Emphasis on progression of these variables will be made with correlation to clinical scores (HHS and MFA).

Significance and impact of research

The investigational device provides potential benefits to the study population immediately, as well as to the general population if the product is cleared for use. These benefits, when compared to conventional total hip replacement, include, retention of more host bone on the femur, elimination of stress shielding potential in the metaphysis of the proximal femur, and reduced rate of dislocation. Previous work has suggested that the young and/or active total hip replacement patient is at higher risk for failure. The potential benefits of the investigational device, if elucidated in the proposed study, may provide surgeons with the ability to treat the young and/or active patient without the concern of long-term failure associated with conventional total-hip replacement.

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