

**Corin U.S.A.  
Cormet 2000 Hip Resurfacing  
System PMA - P050016**

**Orthopedic and Rehabilitation Devices  
Advisory Panel Meeting**

**February 22, 2007**

FDA:

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# Outline

- Reasons for Panel Meeting
- Device Description
- Pre-Clinical Testing
- Study Design
- Clinical Results
- Statistical Overview
- Panel Questions

# Reasons for Panel Meeting

- Study Design Concerns
  - Historical Control Group
  - Revisions to primary safety and effectiveness endpoints
- Revision Rate

# Cormet 2000 Device Description

- Metal/Metal Resurfacing Hip Joint Prosthesis
- Cast Cobalt Chromium Molybdenum
- Femoral Head Resurfacing Component
  - Outer diameter 40-56mm, 4mm increments
  - Fixation - Cemented
- Acetabular Cup Component
  - Outer diameter 46-62mm, 2mm increments
  - Plasma sprayed titanium/HA Coating
  - Fixation – Uncemented, Press-Fit



# Pre-Clinical Testing

- Wear
- Frictional Torque
- Femoral Stem Fatigue Strength
- Surface Coating Characterization
- Range of Motion
- Luxation Wear
- Metal Ion

# 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:

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

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

# Contraindications

- Infection
- Inadequate bone stock to support the device
- Skeletal immaturity
- Any mental or neuromuscular disorder
- Obesity
- Women of child bearing age due to the unknown effects of metal ions on a fetus
- Severe or moderate renal insufficiency
- Known or suspected metal sensitivity

# Investigational Study Design



# Approved IDE Protocol

- Conditionally approved May 2001 and fully approved March 2003
- Prospective, multicenter, non-randomized, concurrently controlled clinical study
- Investigational device group
- Proposed two control groups
  - Metal-on-metal total hip replacement
  - Metal-on-polyethylene total hip replacement
- No control patients were enrolled

# Study Controls

	<b>Original IDE (G010047) March 2003</b>	<b>Original PMA (P050016) March 2005</b>	<b>P050016 Amendments 8 &amp; 13 February &amp; August 2006</b>
<b>Control</b>	Concurrent Metal-on-Metal System or Metal-on- Polyethylene System	Metal-on-Metal Historical Control	ABC Ceramic-on-Ceramic System (P000013) Data

# Approved IDE Patient Success Definition

At 24 months, a patient is defined as a Composite Clinical Success (CCS) if all four of the following are met:

1. Harris Hip Score (HHS)  $\geq$  20 point improvement
2. No revision
3. Radiographic Success:
  - Acetabular component
    - Migration  $<$  5mm
    - Migration  $<$  5°
    - No new or progressive radiolucencies  $>$ 1mm in any zones
  - Femoral component
    - Subsidence  $<$  5mm
    - Tilting  $<$  1°
    - No new or progressive radiolucencies  $>$ 2mm in any zones
- 4.No device related complications

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

# Revised Study Endpoints

	Original IDE (G010047) March 2003	Original PMA (P050016) March 2005	P050016 Amendments 8 & 13 February & August 2006
<b>HHS Endpoint</b>	≥ 20 point improvement	≥ 80	≥ 80
<b>Revision</b>	No revision surgery or planned revision surgery	No revision surgery or planned revision surgery	No revision surgery or planned revision surgery
<b>Adverse Events</b>	<b>Not specified</b>	<b>Inconsistencies</b>	<b>Redefined - Device related include component breakage; femoral neck fracture; collapse of the femoral head; femoral loosening; acetabular loosening; dislocation</b>

# Radiographic Measurement Techniques

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

# Radiographic Success Criteria

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

# Inclusion/Exclusion Criteria

Inclusion/Exclusion	Cornet 2000 Approved Protocol	Control Group Study
No extensive deformity of femoral head	X*	Not applicable
No Congenital Dysplasia of the Hip (CDH)	None Included	X
No known allergies to implants	X	None Included
Has preoperative HHS < 70 points	X	No limits
Age	No specified limits	21-75
Inflammatory Arthritis	X	None Included

X – Study Inclusion Criteria; \*Investigator Discretion

# Follow-up Intervals

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

# Patient Cohorts

## All Enrolled:

- Complete follow-up at 24+ Months: **50.7%** (348/686)
- Control follow-up at 24+ Months: **96.5%** (335/349)

All Enrolled  
1,030 I subjects  
1,148 I procedures  
349 C procedures

I – Investigational  
C – Control

Pivotal Study

Compassionate  
Use  
8 procedures

Continued Access  
562 subjects  
609 procedures

Bilateral  
53 I subjects  
102 I procedures  
83 C procedures

Unilateral  
337 I subjects  
266 C subjects

## Pivotal Study Unilateral Group:

- Complete follow-up at 24+ Months: **84.8%** (285/336)
- Control follow-up at 24+ Months: **96.2%** (254/264)

# Unilateral Cohort Patient Demographics

	Investigational		Control	
	N	%	N	%
Number of Procedures	337		266	
Number of Patients	337		266	
<b>Males</b>	<b>228</b>	<b>67.7%</b>	<b>165</b>	<b>62.0%</b>
Females	109	32.3%	101	38.0%
<b>Osteoarthritis</b>	<b>289</b>	<b>85.8%</b>	<b>206</b>	<b>83.7%</b>
RA	4	1.2%	0	0.0%
AVN	44	13.1%	40	16.3%
Other Diagnoses	7	2.1%	20	7.5%
<b>Age (yrs)</b>	<b>50.1 (mean)</b>	<b>9.6 (S.D.)</b>	<b>53.3 (mean)</b>	<b>11.1 (S.D.)</b>

# All Enrolled Patient Demographics

	Investigational		Control	
	N	%	N	%
Number of Procedures	1148		349	
Number of Patients	1030		318	
<b>Males</b>	<b>825</b>	<b>71.9%</b>	<b>227</b>	<b>65.0%</b>
Females	323	28.1%	122	35.0%
<b>Osteoarthritis</b>	<b>1023</b>	<b>89.1%</b>	<b>273</b>	<b>83.0%</b>
RA	9	0.8%	0	0.0%
AVN	116	10.1%	56	17.0%
Other Diagnoses	52	4.5%	20	5.7%
<b>Age (yrs)</b>	<b>51.2 (mean)</b>	<b>9.8 (S.D.)</b>	<b>53.1 (mean)</b>	<b>11.4 (S.D.)</b>

**Corin U.S.A.  
Cormet 2000 Hip Resurfacing  
System PMA - P050016  
Clinical Results**

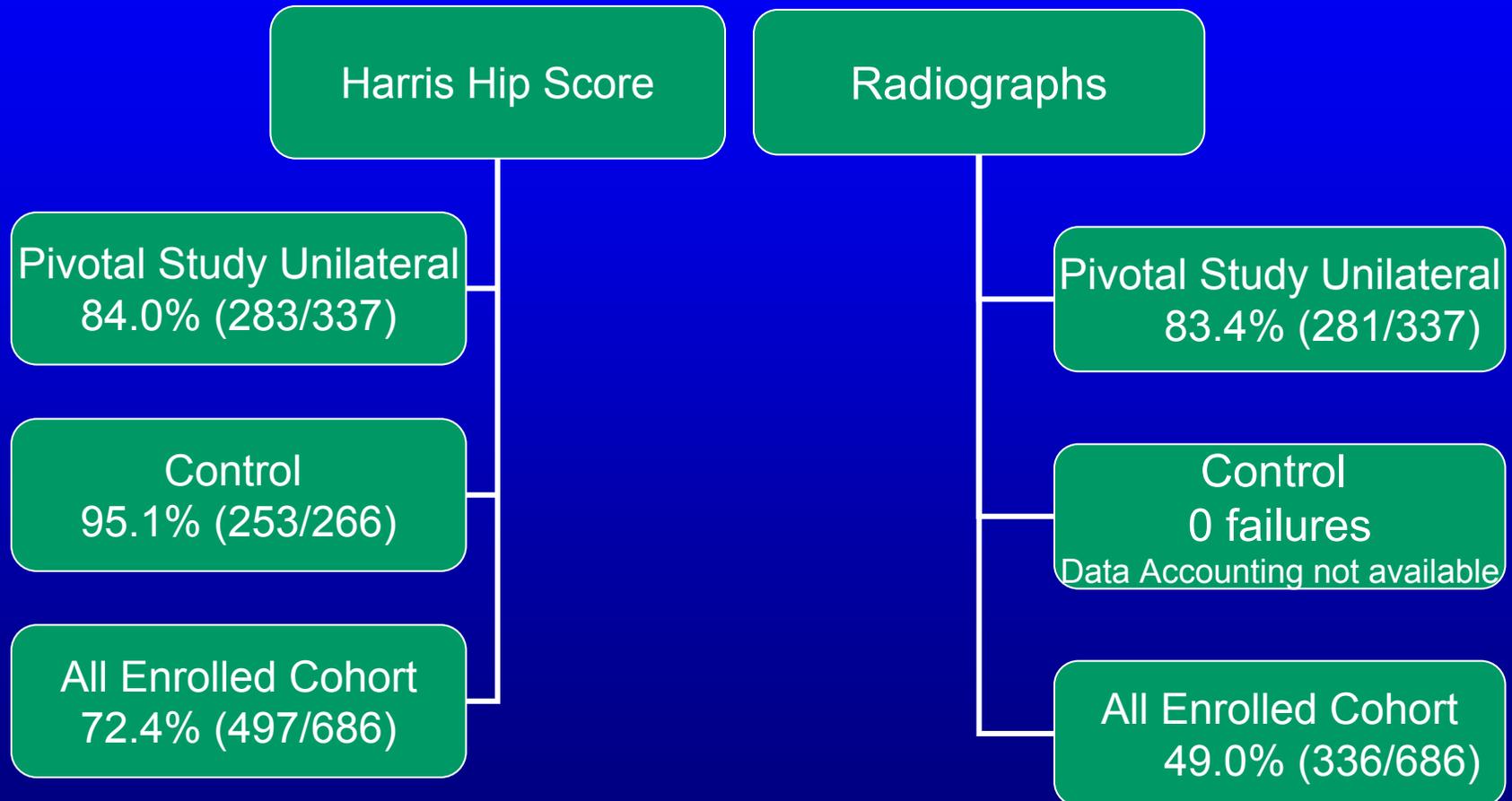
**FDA Presenter:  
Neven A. Popovic, D.V.M., M.D., Ph.D.**



# Clinical Results – Overview

- Harris Hip Score
- Radiographic Evaluations
- Composite Clinical Success
- Safety Evaluation

# Data Accounting with Month 24+ Follow-Up



# HHS for Unilateral Pivotal Study Patients

Category	Preoperative				Month 12			
	I		C		I		C	
	n	%	n	%	n	%	n	%
90-100	0	0.0	1	0.4	256	<b>89.8</b>	209	<b>85.0</b>
80-89	0	0.0	0	0.0	14	<b>4.9</b>	23	<b>9.3</b>
70-79	1	0.3	9	3.6	9	3.2	6	2.4
60-69	71	21	28	11.1	2	0.7	6	2.4
< 60	265	78.7	214	88.9	0	0	1	0.5

**I – Investigational**

**C- Control**

# Total HHS $\geq$ 20 Point Increase From the Baseline

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

# Total HHS $\geq$ 80 Points

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

# Radiographic Evaluation, All Enrolled Investigational, Initial vs. Modified Criteria

Radiographs Available for Review		Month 24+ N =336 (686*)	
		<u>n/N</u>	<u>%</u>
Radiolucency Acetabular Component			
▪ I		0/332	0.0%
▪ II		0/332	0.0%
▪ <b>III</b>		<b>4/332</b>	<b>1.2%</b>
▪ <b>All</b>		<b>0/332</b>	<b>0/0%</b>
Radiolucency Femoral Component			
▪ <b>Superior</b>		<b>2/232</b>	<b>0.6%</b>
▪ <b>Tip</b>		<b>4/332</b>	<b>1.2%</b>
▪ <b>Inferior</b>			<b>2/332</b> <b>0.6%</b>
▪ <b>All</b>		<b>2/332</b>	<b>0.6%</b>
Cup Migration and Tilt			
▪ Superior/Inferior migration $\geq$ 5 mm		2/328	0.6%
▪ Medial/Lateral migration $\geq$ 5 mm		1/328	0.3%
▪ Varus/Valgus Tilt $\geq$ 5 degrees		0/328	0.0%

\*Theoretical total number of radiographs available for review at Month 24+

# Radiographic Evaluation, All Enrolled Investigational, Initial vs. Modified Criteria (Continued)

		Month 24+	
Radiographs Available for Review		N =336 (686*)	
Stem Migration and Tilt		<u>n/N</u>	<u>%</u>
▪	Subsidence of the Femoral Component $\geq$ 5 mm	12/325	3.7%
▪	<b>Stem Tilting <math>\geq</math> 1 degree</b>	<b>242/32</b>	<b>73.8%</b>
▪	<b>Subsidence of the Femoral Component <math>\geq</math> 5 mm and Stem Tilting <math>\geq</math> 1 degree</b>	<b>12/328</b>	<b>3.7%</b>
Other Assessments			
▪	Anteroversion of the Head $\geq$ 5 mm	68/320	21.3%
▪	Retroversion of the Head $\geq$ 5 mm	08/320	33.8%
▪	Hypertrophy in any Zone	0/332	0.0%
▪	Resorption in any Zone	0/332	0.0%
▪	<b>Lysis in any Zone</b>	<b>15/332</b>	<b>4.5%</b>
<b>Composite Radiographic Failure</b>		<b>13/332</b>	<b>3.9%</b>

\*Theoretical total number of radiographs available for review at Month 24+

# Composite Clinical Success, Unilateral Pivotal Cohort, Initial vs. Modified Criteria

The composite clinical success (CCS) criterion is defined as no device revision and no device-related adverse event(s) prior to the Month 24 follow-up.

- The initial CCS criterion required a **Harris Hip Total score  $\geq 20$  points.**
- The modified CCS criterion required a **Harris Hip Total score  $\geq 80$  points.**

No appreciable differences were noted between both groups using the HHS **if the radiographic success changes are not taken in account.**

# Complications by Time of Occurrence, All Enrolled

	Intra-operative		Post Surgery to Month 24+	
	I	C	I	C
Bursitis	0	0	<b>33</b>	16
Femoral Fx	0	<b>12</b>	0	<b>12</b>
Femoral Neck Notched	6	0	6	0
Femoral Radiolucency	0	<b>12</b>	0	
Heterotopic Bone	0	0	13	13
Hip Pain, Operated Side	0	1	<b>61</b>	9
Leg Length Discrepancy	1	0	<b>22</b>	0
Limp	0	0	<b>13</b>	0
Muscle weakness	2	0	<b>10</b>	1
Soft tissue Trauma	0	0	2	<b>14</b>
Deep Infection	0	0	3	1
Superficial Infection	0	0	7	5
Squeaking implant/clicking	0	0	<b>20</b>	2

# Device Related Adverse Events

	Total	
	I	C
Acetabular Fracture	0	1
Acetabular Loosening	11	0
Ceramic Insert Chipping	-	8
Dislocation	2	10
Femoral Fracture (post-op)	0	7
Femoral Loosening	14	0
Femoral Neck Fracture	26	0
Femoral Subsidence	4	2

# Revisions

- 44 revisions (total) in All-Enrolled Cohort
- 24 revisions (total) in Pivotal Unilateral Study
  - 16 prior to 24 months
- 5 revisions in Control Group

Kaplan-Meier Estimates of Revision Rates		
	Revision rate (24 months)	Revision rate (24+ months)
All-Enrolled Cohort (n=1148)	4.2%	<b>7.2%</b>
Control (N=349)	0.9%	not available
Pivotal Unilateral Cohort (N=337)	5.0%	<b>8.1%</b>

# Summary of Revisions

Month 24+

Adverse Event Type	All-Enrolled Investigational N=44 Revisions		Control N=5 Revisions	
	n/N	%	n/N	%
Femoral Neck Fracture	21/44	47.7%	0/5	0.0%
Femoral Loosening	12/44	27.2%	1/5	20.0%
Acetabular Loosening	8/44	18.2%	0/5	0.0%
Deep Infection	2/44	4.5%	1/5	20.0%
Dislocation	1/44	2.3%	1/5	20.0%
Peri-Prosthetic Fracture	0/44	0.0%	1/5	20.0%
Excessive Hip Pain	0/44	0.0%	1/5	20.0%

# Revisions in Pivotal Unilateral Cohort

		Pivotal Unilateral 24+ Month Follow-up
	<b>Revisions</b>	<b>24</b>
	<b>N</b>	<b>302</b>
	<b>%</b>	<b>7.9%</b>
<b>Gender</b>	Female	<b>12.8% (13/102)</b>
	Male	<b>5.5% (11/200)</b>
<b>Small Component Size</b>	40/44mm	<b>17.3% (13/75)</b>
	>40/44mm	<b>4.9% (11/227)</b>
<b>Non Osteoarthritis Diagnosis</b>	AVN/RA	<b>16.7% (7/42)</b>
	Osteoarthritis	<b>6.5% (17/260)</b>

# Revisions in Pivotal Unilateral Cohort

		Pivotal Unilateral 24+ Month Follow-up
	Revisions	24
	N	302
	%	7.9%
Leg length discrepancy greater than or equal to 1 cm	≥ 1 cm	14.5% (12/83)
	<1 cm	5.5% (12/219)
Baseline lowest quartile of function (HHS)	<42.58	20.3% (15/74)
	≥ 42.58	4.0% (9/228)
Among 1st 25 procedures within a specific site	First 25	8.9% (12/135)
	After 1st 25	7.2% (12/167)

**P050016**  
**Statistical Overview**

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**February 22, 2007**



# Outline

- Study Design and Analysis
- Testing of the Non-inferiority Hypothesis
  - Primary Endpoint
- Comparability of Cormet and Control Patients
  - Propensity Score Analysis
- Estimation of Revision Rate
  - Kaplan-Meier Analysis
- Factors Associated with Revision
  - Cox Regression
- Missing Data
  - Sensitivity Analysis
- Summary of Statistical Issues

# Study Design and Analysis

Significant changes were made to the control group and patient success criteria after IDE approval

- Control group selected after the Cormet results were known
- Radiographic results first removed from CCS then put back in as modified success criteria
- Non-inferiority delta changed from 5% to 8%
  - Delta is defined as the maximum difference that is clinically unimportant
- Multiple analysis cohorts
  - 24 months, 24+ months
  - In and out of follow-up window
  - Original and modified HHS criteria

# Study Design and Analysis (cont.)

Net result of changes and multiple analyses is that the Probability of Type 1 error will be inflated

- Type 1 error is defined as the probability of seeing a significant result by chance alone
  - In our case, inferring non-inferiority when there is not
- Amount of inflation is not known

**A well designed clinical trial does not deviate from the original specifications**

# Testing of the Non-Inferiority Hypothesis

- The primary endpoint is the difference in Composite Clinical Success rates between the Cormet Hip and ABC Control patients
- We are testing to see if the CSS for the Cormet patients is less than 8% lower than the CSS for the control
- Hypotheses are set up so that statistical significance implies non-inferiority
- Results are based not on the observed difference, but on the lower limit of a one-sided 95% confidence interval
- Non-inferiority was not met using original radiographic success criteria

# Month 24 Composite Clinical Success

## (Original Radiographic, Original HHS Criteria)

### (Per Protocol)

	Investigational			Controls			Non-inferiority Test	
	n	N	Prop.	n	N	Prop.	Diff	95% CI LB
Month 24+ CCS (In & out of window)	71	296	0.240	213	243	0.877	-0.637	-0.690
Month 24+ CCS (In window)	70	284	0.246	212	241	0.880	-0.633	-0.688
Month 24 CCS (In & out of window)	55	246	0.224	207	237	0.873	-0.650	-0.706
Month 24 CCS (In window)	49	202	0.243	174	196	0.888	-0.645	-0.707

# Month 24 Composite Clinical Success

(Revised Radiographic, Original HHS Criteria)

(Per Protocol)

	Investigational			Controls			Non-inferiority Test	
	n	N	Prop.	n	N	Prop.	Diff	95% CI LB
Month 24+ CCS (In & out of window)	256	291	0.880	213	243	0.877	0.003	-0.044
Month 24+ CCS (In window)	251	284	0.884	212	241	0.880	0.004	-0.042
Month 24 CCS In & out of window)	210	242	0.868	207	237	0.873	-0.006	-0.056
Month 24 CCS (In window)	173	202	0.856	174	196	0.888	-0.031	-0.086

# Month 24 Composite Clinical Success

## (Revised Radiographic, Modified HHS Criteria)

### (Per Protocol)

	Investigational			Controls			Non-inferiority Test	
	n	N	Prop.	n	N	Prop.	Diff	95% CI LB
Month 24+ CCS (In & out of window)	251	292	0.860	224	256	0.875	-0.015	-0.063
Month 24+ CCS (In window)	246	285	0.863	223	254	0.878	-0.015	-0.062
Month 24 CCS (In & out of window)	207	243	0.852	219	250	0.876	-0.024	-0.075
Month 24 CCS (In window)	171	202	0.847	187	209	0.895	-0.048	-0.103

# Comparability of Cormet and ABC Control Patients

- In a non-randomized study, comparability of patients groups must be assessed
- Fisher's Exact and Wilcoxon Rank Sum Tests were used to assess baseline comparability between Cormet and ABC control
  - No significant differences in gender, mean weight, diagnosis, or baseline HHS
  - Significant difference in age (50.1 Cormet vs 53.3 control), unadjusted for multiple comparisons
    - o Difference not considered clinically meaningful

# Comparability of Cormet and ABC Control Patients (cont.)

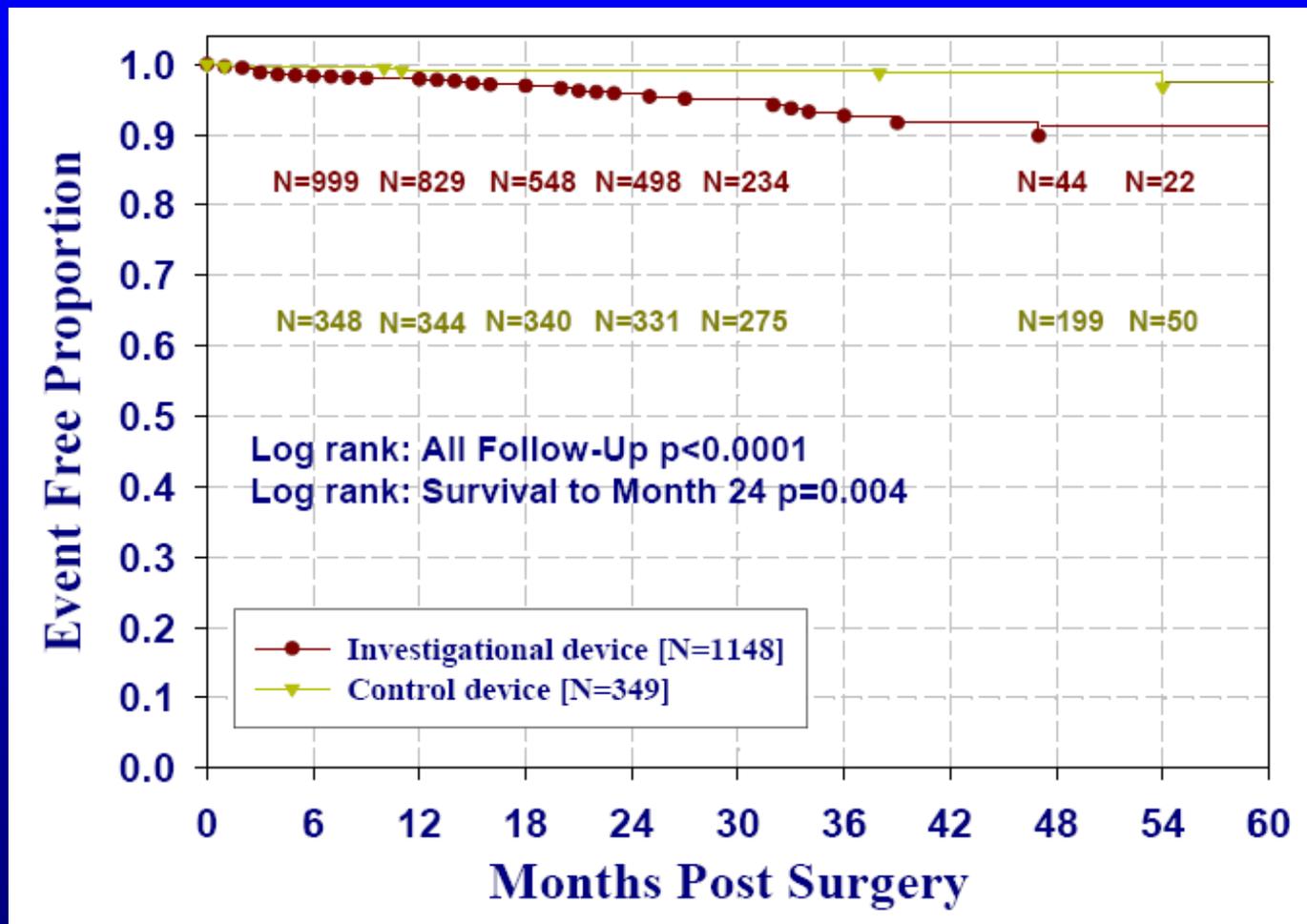
- **Propensity Score Analysis**

- Used to determine if the two treatment groups are comparable enough that they would have had approximately equal chances of receiving either treatment, had this been a randomized study.
- Covariates available that could potentially impact patient outcome were included:
  - Gender, age, weight, marked pain at baseline, HHS at baseline
- Analysis showed treatment groups were comparable on above covariates
  - Age difference disappeared with propensity score adjustment
- Using only 5 covariates is not very comprehensive for a propensity score analysis
  - Unlike randomization, Propensity Scores will not balance for covariates not in the model

# Estimation of Revision Rate

- **Kaplan-Meier Survival Analysis**
  - Used to estimate revision rates
  - independent of non-inferiority test of Composite Clinical Success (CCS)
  - Generally plotted as “Event-Free” timeline
  - Patients remain in the analysis risk set until they either “fail”, (i.e. revised) or become “censored”
    - Censored for death or lost-to-follow-up – exit pool at risk

# Kaplan-Meier Survival Curves For All-Enrolled Investigational and Control Devices



# Estimation of Revision Rate (Cont.)

- At 24 months, revision-free rates were 95.8% ( $\pm 1.6\%$ ) for Cormet, 99.1% ( $\pm 1\%$ ) for control
  - $p < 0.01$ , (control superior)
  - Based on the All-Enrolled Safety Cohort, N=1148  
Cormet, 349 control to start
  - ~50% of All-Enrolled Cohort were not yet due for 24 mo. visit
- A Kaplan-Meier rate based on the Pivotal Study Unilateral Cohort (N=337) gave a revision-free rate of 95% ( $\pm 2.3\%$ ) at 24 months
- Based on All-Enrolled and Pivotal Cohort K-M Analyses, a reasonable estimate of revision rate at 24 months would be 5%

# Estimation of Revision Rate (Cont.)

- At 36 months, Kaplan-Meier estimate of the revision-free rates are:
  - 92.8% ( $\pm 3.3$ ) for All-Enrolled Cohort
  - 91.9% ( $\pm 3.9\%$ ) for Pivotal Unilateral Cohort
- Reasonable estimate of revision rate for 24+ month data would be 7%-8%

# Factors Associated with Revision

- **Cox Regression**

- A time-to-event analysis that can measure the effects of covariates
- Significant covariates associated with revision were gender, component size, pre-op HHS, non-OA
  - Gender and component size correlated; size more important
  - Pre-op HHS strongest predictor of revision (hazard ratio=6.4)
- Site 5 (N=38) differed in patient risk factors
  - More patients with revision “risk factors”
  - Site 5 had 10 of the 24 revisions in the Unilateral Cohort
  - Patient mix cannot be separated from surgeon skill due to single physician performing procedure at each site

# Missing Data

- Sponsor used “rollback” imputation for those missing 24 month data but had a later visit.
- Sensitivity Analysis for Non-Inferiority Test of CCS
  - Performed on revised radiographic and modified HHS cohort
  - Used to evaluate sensitivity of results to missing data
    - CCS missing for 44 Cormet (pivotal unilateral) and 10 control
  - 4 other methods of imputation used for missing data
    - Including all missing as failures
    - Including all missing as successes
    - Stepwise imputation
    - Multiple imputation
      - o Can adjust for covariates
  - Most imputation methods supported non-inferiority hypothesis for Pivotal Unilateral Study (N=337)

# Summary of Statistical Issues

- Multiple analysis cohorts have inflated probability of Type 1 error
- Protocol changes weaken confirmatory nature of study
  - HHS success criteria changes
  - Radiographic success criteria changes
  - Selection of control group knowing investigational results
- Kaplan-Meier Analysis shows fewer revisions in the control than the Cormet group at 24 months ( $p < 0.01$ )
- Propensity Score Analysis not comprehensive enough to ensure comparability of treatment groups
- The impact of the statistical issues identified should be taken into consideration as part of your panel deliberations for questions concerning safety and effectiveness

# Thank you

