ZIMMER BIOMET

# A Multi-Centre Prospective Randomised Control Trial to compare two articulating bearing surfaces, ceramic-on-metal and metal-on-metal using 38 mm M2a acetabular cup, as used in cementless primary hip arthroplasty

**Protocol number: BMETEU.CR.EU11**

**NCT number: NCT00754520**

| | |
|---|---|
| **Complete Protocol Title** | A Multi-Centre Prospective Randomised Control Trial to compare two articulating bearing surfaces, ceramic-on-metal and metal-on-metal using 38 mm M2a acetabular cup, as used in cementless primary hip arthroplasty |
| **Protocol Number** | BMETEU.CR.EU11 |
| **Short Protocol Title** | COM vs MOM |
| **Sponsor** | Original: Biomet UK Ltd<br>Administratively transferred: Biomet GSCC<br>Administratively transferred: Zimmer GmbH, Zählerweg 4, 6300 Zug, Switzerland |
| **Manufacturer** | M2a-38 acetabular cup: Biomet Orthopaedics Inc, USA<br>M2a-38 38 mm cobalt chromium molybdenum (CoCrMo) modular heads: Biomet Orthopaedics Inc, USA<br>Biolox delta 38 mm ceramic femoral head: CeramTec AG now CeramTec GmbH, Germany<br>Bi-Metric femoral stem: Biomet UK Limited, Bridgend, UK |
| **Study Device(s)** | COM articulation: M2a38 acetabular cup with ceramic head articulation<br>Comparator: MOM articulation: M2a38 acetabular cup with metal head articualtion |
| **Technical Documentation Reference Number** | NA |
| **Study Objectives/Endpoints** | To evaluate the clinical outcome of the ceramic-on-metal (COM) articulation using M2a38 cup with metal-on-metal (MOM) articulation using the same cup.<br><br>The metal ion release and additional cellular markers will be evaluated at predetermined postoperative intervals during the first 36 months.<br><br>*Primary objective*<br>The aim of the study is to demonstrate the non-inferiority of the ceramic-on-metal articulation using M2a-38 cup compared to the metal-on-metal articulation using the same cup in regards to the CCS rate at 2 year postoperative (delta = 10 % minimum clinically significant difference in rates).<br>Each patient's CCS is defined as:<br><br>• Total Harris Hip Score $\geq$ 80 points, and |

| | |
|---|---|
| | • No acetabular or femoral revision or removal, and<br>• No pending acetabular or femoral revision or removal as defined in radiographic evaluation by:<br>▪ An acetabular radiographic assessment with all of the following:<br>• Migration < 4 mm, and<br>• Change in angle of inclination < 4°, and<br>• Absence of osteolysis, and<br>▪ A femoral radiographic assessment with all of the following:<br>• Subsidence < 5 mm, and<br>• Absence of osteolysis.<br><br>*Secondary objective*<br>• Any reduction in metal ion release when using the ceramic-on-metal articulation compared to using metal-on-metal articulation.<br>• Harris Hip Score at each post-operative visit.<br>• Oxford Hip Score at each post-operative visit.<br>• Womac Score at each post-operative visit.<br>• Radiographic analysis at each post-operative visit.<br>• Complications (including revisions/removals).<br>• Long-term survivorship. |
| **Indications/Target Population** | Patients suitable for primary Total Hip Replacement. |
| **Inclusion/Exclusion Criteria** | Inclusion Criteria<br>Patients suitable for primary Total Hip Replacement<br>Patients with degenerative joint disease (inflammatory or non-inflammatory) or any of the composite diagnoses of:<br>a. Osteoarthritis<br>b. Avascular necrosis<br>c. Legg Perthes<br>d. Rheumatoid Arthritis<br>e. Diastrophic variant<br>f. Fracture of the pelvis<br>g. Fused hip<br>h. Slipped capital epiphysis<br>i. Subcapital fractures<br>j. Traumatic arthritis |

| | |
|---|---|
| | Patients preoperative Harris Hip Score < 70 points<br>Patients aged over 18<br>Patients with limited co-morbidity – ASA I – III<br>Patients with normal urea and electrolyte levels and creatinine levels<br>Patients must be able to understand instructions and be willing to return for follow-up<br>Patients willing to provide blood and urine samples for metal ion analysis at follow-up<br><br>Exclusion Criteria<br>Patients preoperative Harris Hip Score > 70 points<br>Pre-existing metal implants<br>Patients with significant co-morbidity - ASA IV - V<br>Dementia and inability to understand and follow instructions<br>Neurological conditions affecting movement<br>Pregnancy<br>Presence of symptomatic arthritis in other lower limb joints |
| **Study Design** | Prospective Randomised Controlled Trial<br>Group 1:<br>Ø 38 mm metal femoral head articulating against Metal M2a-38 mm acetabular cup<br>Group 2:<br>Ø 38 mm ceramic femoral head articulating against Metal M2a-38 mm acetabular cup |
| **Clinical Phase** | Pre-market; COM articulation is not CE-marked |
| **Sample Size** | 300 planned, 150 per arm.<br>211 patients enrolled and included in study |
| **Length of Study** | 12 years (2 year enrollment, with a follow-up of 10 years) |
| **Materials and Methods** | Case report forms will be completed either in-office or hospital at Pre-op, Surgery, Discharge, and the 6 week, 1-year, 2-year, and 5-year intervals. Case report forms will be completed at the 3-year, 7-year, and 10-year intervals either in-office, by phone or by mail. |
| **Data Collection** | Paper / electronic<br>(Database: UK data in Access database; Finnish data in Joint Assist, study #339) |

| | |
|---|---|
| **Statistical Reporting** | Data collected will be summarized and reported to each participating investigator. Statistical analysis will be conducted by Zimmer Biomet or its designee. Survivorship will be evaluated using Kaplan-Meier. |
| **Scores/Performance Assessments** | Harris Hip Score, Oxford Hip Score and WOMAC score |
| **Standards** | The PMCF is compliant with the below:<br>• ISO 14155: 2020 - Clinical investigation of medical devices for human subjects - Good clinical practice.*<br>• The Declaration of Helsinki (DoH) - Ethical principles for medical research involving human subjects.<br>(*) The study protocol was drafted according to another version of the ISO 14155. Adverse Event definitions and reporting are according to ISO 14155:2020. |
| **Study Funding** | Funding for this clinical study is made available by Zimmer Biomet to support clinical data collection, IRB/EC review fees and other expenses associated with the conduct and execution of this study protocol as outlined in the fully executed Clinical Trial Agreement. |

# 1 STATISTICAL ANALYSIS PLAN

## 1.1 Sample Size

The sample size is determined by the primary end-point of composite clinical success (CCS) at two years post-operative. Since the aim is to demonstrate the non-inferiority of the COM compared to the MOM group in terms of CCS, the sample size calculation is based on the Blackwelder method[15].

NULL hypothesis: $p_2 - p_1 > \delta$

ALTERNATIVE hypothesis: $p_2 - p_1 \leq \delta$

$\delta = 0.10$ Difference in CCS rate between the MOM and COM groups that can be considered clinically significant

Type I error ($\alpha$): The error of rejecting Null hypothesis when it is actually true (false positive)

Type II error ($\beta$): The error of failing to reject Null hypothesis when the alternative hypothesis is true (false negative)

**1.2**

$Z_\alpha$ = 1.645 When $\alpha$ = 0.05

$Z_\beta$ = 1.28 When $\beta$ = 0.10, commonly used value in non-inferiority test

$p_1$ = 0.92 Estimate CCS rate of COM group

$p_2$ = 0.92 Estimate CCS rate of MOM group

Sample size required, *N*:

$$N = \frac{(Z_\alpha + Z_\beta)^2 [p_1(1-p_1) + p_2(1-p_2)]}{\delta^2}$$

$$N = \frac{(1.645 + 1.28)^2 [0.92(1-0.92) + 0.92(1-0.92)]}{0.10^2} = 126$$

Consider 7.5 % lost to follow-up per year, there will be 15 % cases lost to follow-up at 2 years post-operative.

Final sample size: $\frac{126}{(1-0.15)} = 150$

## 1.3 Statistical Analysis

Statistical Analysis of the results will be conducted using a suitable method by a qualified statistician.