< A PROSPECTIVE SINGLE-CENTER STUDY ON E1 ACETABULAR LINER IN THA >

PROTOCOL NUMBER (Study ID): INT.CR.GH5.13

PROTOCOL VERSION: v 3.0

GENERAL INFORMATION

Investigator

Name	Contact (i.e. Postal address, Phone Number)	Role (Principal or co-investigator)
Shin-Yoon Kim	Kyungpook National University Hospital	Principal Investigator

Study Sponsor(s)

Biomet Korea

Study sponsors take responsibility for initiation, management, and/or financing of a clinical study at investigational sites

Project Leader(s)

Biomet Korea Anna Lee

Study monitors are responsible for carrying out the monitoring procedure as indicated in the protocol

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STUDY SUMMARY

TITLE	Prospective Single-Center Study on E1 Acetabular liner in THA
DESIGN	Prospective Observational Study
PURPOSE	Evaluate E1 wear, Clinical Performance of E1 liner in THA in Korean Patient Population
OUTCOME MEASURES	Clinical Outcomes (e.g. HHS, EQ5D, UCLA), Radiographic Assessment and Survivorship
POPULATION	100
ELIGIBILITY	Approved Indications for Uses for E1 liner in THA
DURATION	All cases will be followed up to 10 years. It is expected that the enrolment will be completed in 1 year; the total duration of the study is 11 years.

1. INTRODUCTION

1.1. BACKGROUND

Total hip arthroplasty (THA) is one of the most successful surgical procedures in general. Yet, a few problems remain unsolved, and aseptic loosening is probably the most important of them. One of the main reasons for aseptic loosening in THA is the foreign body reaction caused by the wear particles. Since the late 1990s, the orthopedic industry has been developing highly crosslinked polyethylene (HXLPE) materials to capitalize on the increased wear resistance. In 2007, E1® Antioxidant Infused Technology was developed to reduce wear rate, maintain mechanical properties and prevent oxidative degradation.

Also alumina ceramic was introduced as a bearing surface in the 1971 as an alternative to the metal on-polyethylene couplings. Since then, alumina ceramic has been used in THA successfully for more than 35 years. BIOLOX®Delta is designed with improved fracture toughness, further reduces the risk of fracture and also extends the design flexibility of the material.

However, there are a few clinical data collected on wear and performance of E1® Liners available for Caucasian population and no data for Koreans today. There is no clinical data of BIOLOX®Delta femoral head articulating against E1® Liner. Therefore, it is needed to collect clinical data to support marketing and validate design of E1® Liners in terms of its safety and efficacy.

1.2. DEVICE DESIGN AND DESCRIPTION

Vitamin E doping of highly cross-linked polyethylene is a proposed method for insuring long-term oxidative stability of highly cross-linked ultra-high molecular weight polyethylene for use in total joint arthroplasty. In vitro research and development studies have shown that this material has improved wear performance, retention of mechanical properties, and a high resistance to oxidation due to the anti-oxidative properties of Vitamin E.

All patients will receive the vitamin E treated polyethylene "E1® Liners". Short-term femoral head penetration and long-term steady state wear of the polyethylene will be measured using software.

- E1® Acetabular Liners: flat (MaxRom, MaxRom+).
- BIOLOX®Delta femoral heads: used for the investigational cohort. The BIOLOX® Delta ceramic femoral heads are manufactured from BIOLOX® delta, an alumina composite matrix
- Taperloc Complete Hip Stem.
- RingLoc® Universal Acetabular Shell System.

1.3. RATIONALE FOR CURRENT STUDY

It is important to conduct a detailed clinical follow-up study when materials or implant designs are introduced for clinical use. Validated patient administered questionnaires allow for functional assessment, patient satisfaction and cost effectiveness analysis. These well established assessment techniques are well suited for evaluating large patient populations.

1.4. PURPOSES

The purpose of the study is to evaluate clinical performance of E1 liner in THA in Korean patient population..
The clinical performance will be evaluated based on patient outcomes, radiographic assessment and survivorship.

2. STUDY DESIGN

2.1. OVERALL DESIGN

This study will be a single-center observational study on patients received E1 liner in THA. Patient demographic, preoperative clinical outcomes and operative information will be collected prospectively per defined follow-up intervals.

2.2. NUMBER OF SITES AND SUBJECTS/PROCEDURES

There is one site in Korea to participate in this study.

2.3. EFFICACY AND/OR SAFETY HYPOTHESES

Not applicable as this is a Post Market Study.

2.4. PRIMARY AND SECONDARY ENDPOINTS

Primary endpoint is HHS score at 1 year follow-up.

Secondary endpoints include

- HHS at other follow-up visits
- EQ5D, UCLA at 6month, 1 year, 2 year, 5 year postop
- Radiographic Assessment at Immediate post-op, 6 months, 1 year, 2 year, 5 year postop
- Survivorship up to 10 years

2.5. ASSESSMENT PROCEDURE

2.5.1. ASESSMENT PARAMETERS AND METHODS

Medical History and Demographic Data

Demographic information will be collected which will include but is not limited to gender, age at surgery, height, weight, primary diagnosis & medical history

Clinical Assessments

Clinical assessments will include functional scores, radiographic analysis.

An operative record will be completed upon the surgery. The operative record will include but are not restricted to date of surgery, surgical approach, implant components (part number).

Radiographic Assessments

Radiographic assessments including polyethylene wear analysis and cup inclination angle will be completed at each follow-up period.

The X-rays must be taken which requires an A/P pelvis view centered over the pubis.
For the polyethylene wear analysis, all Radiographic images will be determined and the penetration rate will be measured by an independent analyst. (PolyWare pro 3D distal version 7.02 software)

2.5.2. ASEESMENT TIMELINES/SCHEDULE

Clinical and Radiographic Exams									
Data Collection item	**Pre-operative**	**Intra-operative**	**Immediate Post-operative**	**6 Months**	**1 Year**	**2years**	**5 years**	**7 years**	**10 years**
Demographic and Medical History	**X**								
Operative Record		**X**							
Clinical Evaluation – HHS, EQ5D, UCLA	**X**			**X**	**X**	**X**	**X**		
Radiographic assessment			**X**	**X**	**X**	**X**	**X**		**X**
Wear Analysis				**X**	**X**	**X**	**X**		**X**
Phone Interview								**X**	
Adverse events including revisions	*As required*								

2.5.3. ALLOWED WINDOW OF EACH SCHEDULE

Allowed Window of Each Prospective Visit Schedule:

- 6 months (+/- 1 month)
- 12 months (+/- 3 months)
- 2 years (+/- 3 months)
- 5 years (+/- 3 months)
- 7 years (+/- 3 months)
- 10 years (+/- 3 months)

Each follow-up visit time point will be determined based on the date of surgery.

2.6. DURATION OF THE STUDY

All cases will be followed up to 10 years. It is expected that the enrollment will be completed in 1 year, the total duration of the study is 11 years.

3. SELECTION AND WITHDRAWAL OF SUBJECTS

All subjects, regardless of sex, race, or geographic location, must fit into the scope of the Inclusion/Exclusion criteria to be eligible for the study. If required per applicable regulations, all participants must sign an Informed Consent to be enrolled into the study.

3.1 INCLUSION CRITERIA

Patients will be included in this study if they received Ringloc acetabular system with E1 liner per the approved indications for use by KFDA in Korea. Specifically,

a. Osteoarthritis
b. Avascular necrosis
c. Legg Perthes
d. Rheumatoid Arthritis
e. Diastrophic variant
f. Fracture of the pelvis
g. Fused hip
h. Slipped capital epiphysis
i. Subcapital fractures
j. Traumatic arthritis

Patients aged over 20
Patients with limited co-morbidity – ASA I – III

3.2 EXCLUSION CRITERIA

Exclusion Criteria for this study should comply with the stated contraindications on package inserts of Ringloc acetabular system with E1 liner. These indications are stated below:

Absolute contraindications include: infection, sepsis, and osteomyelitis

Relative contraindications include:

1) uncooperative patient or patient with neurologic disorders who are incapable of following directions,
2) osteoporosis,
3) metabolic disorders which may impair bone formation,
4) osteomalacia,
5) distant foci of infections which may spread to the implant site,
6) rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram, and
7) vascular insufficiency, muscular atrophy, or neuromuscular disease.
8) pregnancy
.

3.3. SUBJECT WITHDRAWAL

It is recognized that the subject's participation in this trial is entirely voluntary, and that she/he may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the investigator, at his/her discretion, may withdraw a subject from this study based upon his/her professional judgment. In event of subject withdrawal, applicable local procedures should be followed

4. PROTOCOL DEVIATION MANAGEMENT AND REPORTING

Protocol deviations are unplanned and unintentional events. Any changes in the research protocol during the period, for which IRB approval has already been given, may not be initiated without submission of an amendment for IRB review and approval.
In any protocol deviations occur during the trial will be reported to any necessary institutions to manage. And that information also be reported to IRB and sponsor.

5. ADVERSE EVENT MANAGEMENT AND REPORTING

A record of <u>all</u> adverse events, including details of the nature, onset, duration, severity, relationship to the device, relationship to the operative procedure and outcome, will be made and provide to the study sponsor. The subject will be questioned about any adverse event(s) at each subsequent follow-up assessment visit.

6. STATISTICAL ANALYSIS PLAN

6.1 SAMPLE SIZE CALCULATION

The primary objective of this study is to show that there is a significant increase in Harris Hip Scores from baseline to 1 year post-surgery. The hypothesis can be stated as follows:

$$H_0: \mu_d = 0 \qquad \text{vs.} \qquad H_A: \mu_d \neq 0,$$

Where μ_d = the mean of the paired differences ($HHS_{1Year} - HHS_{preop}$).

This hypothesis will be tested using a paired t-test of mean difference equal to zero.

Harris Hip Score difference of **4 points** was shown to be the best cutoff point for optimal sensitivity and specificity to detect clinical improvement (Hoeskma et al. Ann Rheum Dis 2003; 62: 935–938).

If we choose to detect a least clinical acceptable difference in Harris Hip Score of **5 points** with the following assumptions:

$\alpha = 0.05$ Probability of Type I Error
$\beta = 0.10$ Probability of Type II Error
$s_d = 15.16$ Estimated standard deviation of the differences (based on Biomet previous Arcom and ArcomXL study)

Sample size required is N= 99 rounds to 100 subjects.

6.2 HANDLING OF MISSING AND INCOMPLETE DATA

Attempt will be made to ensure that patients come back for scheduled follow-up evaluations. In case of missing data, for clinical outcome scores, Last Observation Carried Forward will be used to impute the missing data. For survivorship analysis, the data including implant in situ collected in the next follow-up will be used to calculate survivorship

6.3 DATA ANALYSES

The following analyses will be performed:

1. Primary Endpoint – mean HHS score at 1 year
2. Second Endpoints – mean HHS score at other postop time points
3. Other Clinical Outcomes scores including EQ5D and UCLA
4. Comparison in clinical outcomes scores between preoperative and various postoperative time points
5. Survivorship with endpoint being revisions.

7. DATA COLLECTION, HANDLING AND RETENTION

7.1 SOURCE DOCUMENTATION REQUIREMENTS

Source documentation for this study will be maintained to document the treatment and study course of a subject and to substantiate the integrity of the data. Source documentation will include, but not be limited to, worksheets, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, pharmacy records, device accountability records, and medical consultations (as applicable).

7.2. CASE REPORT FORMS

Data for this clinical trial will be collected and documented on the subject Case Report Forms (CRFs) provided, which may be in paper form or in an electronic form. Authorized study site personnel will complete CRFs only. CRFs must be reviewed and signed by the Investigator or his/her designees.

Since there is a potential for errors, inaccuracies, and misinterpretation in transcribing data onto the CRFs, the following documents must be available at all times for inspection and comparison to the CRFs by the study monitor where appropriate:

- data query forms
- originals and photocopies/certified copies of all relevant records and reports
- copies of test results

7.3. ELECTRONIC DATA ENTRY

When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).
- Maintain SOPs for using these systems.
- Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).
- Maintain a security system that prevents unauthorized access to the data.
- Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
- Maintain adequate backup of the data.
- Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

7.4. STUDY DOCUMENT RETENTION

Study documents should be retained for a season after the study is complete as required by local, state, national, or international health authorities.

8. DATA REPORTING

8.1 INTERIM REPORT

An interim report will be provided after each follow-up period.

8.2 FINAL REPORT

Final report will be provided after 10 yr follow-up period.

9. MONITORING PLAN

Biomet, as the sponsor of this study, may monitor the data collection to ensure that the investigation is being conducted consistent with the protocol. The following describes the monitoring activities, which may take place during the course of the study.

9.1. FREQUENCY

Pre-Investigational Visit/Conference:
Prior to initiation of the study, the study manager will provide the Investigator with all the necessary information to enable him to carry out his responsibilities. This prepares the site with an in-depth training on the protocol, case report forms, and data collection process for the length of the study. The study manager will also train the site on using the Biomet Joint Assist database.

Monitoring of the Data

Monitoring of the data will occur at least annually, and as often as monthly. Times when this may be appropriate include:

- Monthly Invoicing
- Quarterly Review
- Annual Reports
- While performing data analysis for marketing material or publication.

9.2. SAMPLING PLAN

All data will be monitored for completeness and accuracy on at least an annual basis.

9.3. MONITORING TASKS

Biomet will continually monitor the progress of the clinical trial. These activities include:

- Tracking of patient enrollment
- Review of all electronic patient data forms received by Biomet for completeness
- Tracking of patients to ensure follow-ups are being completed at appropriate intervals
- Review of all adverse reactions
- Maintaining open communication with all investigational sites in order to ensure the quality of the clinical trial.
- In-House Audits as needed

Upon completion of any type of monitoring, the site is responsible for resolving all discrepancies found in a timely manner. These will be sent to the site with an audit report by the study manager. All discrepancies found within the Joint Assist database will be queried and sent directly to the site. Delays in resolving queries are to be avoided at all costs; this provides the study with the most accurate data, prevents delay in reporting procedures & publication, and safeguards in the event of an audit by the relative regulatory authority in the region.

9.4. STUDY CLOSE-OUT

When a site has completed their data collection, a visit may be necessary by a Biomet monitor to ensure all data has been obtained. Data will be reviewed for completeness, and monitored to ensure that all discrepancies have been resolved.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1. CODE OF CONDUCT

The Investigator will ensure that the clinical study is conducted in accordance with

1. Protocol
2. Regulatory and IRB/EC requirements
3. ISO 14155, GCP

10.2. INSTITUTIONAL REVIEW/ETHICS COMMITTEE

If required, the Investigator must obtain appropriate Independent Ethics Committee (IEC) approval before the study can be initiated. A copy of the written approval from the IEC and a copy of the approved informed consent form should be sent to the Sponsor.
Any changes to the protocol must be discussed and approved by the Sponsor in writing unless the change is made to assure the safety of the subject. In the non-emergent setting, after agreement on the changes has been reached, an amendment to the protocol will be provided by the Sponsor for submission to the IEC for review and approval prior to initiation of the change. Any change made emergently must be documented in the subject's medical record and reported to the Sponsor within the time period required by local SOPs and applicable regulations.

The Investigator must immediately forward to the IEC any written safety reports or updates from the Sponsor.

The Investigator must keep the IEC informed of the progress of the study as required by the IEC but at least annually.

10.3. INFORMED CONSENT

Subjects (or the subject's legally authorized representative) will be provided with an informed consent and patient information sheet in order to give ample opportunity to review the consent and ask questions. The signed informed consent will be obtained before any study procedures begin. If the subject agrees to participate in the study, the subject/representative must sign the informed consent form. The witness and the Investigator must also sign the informed consent form. A copy of the informed consent form should be given to the subject/representative. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any of the exclusion criteria will be excluded from the trial.

The informed consent form must be approved by the institution’s IEC. Subjects will be informed of new information learned during the study, which may affect the subject’s decision to continue participation in the study.

An Informed Consent Log will be completed to document the existence of the signed informed consent form. The log will contain: Subject ID, date informed consent form signed, and the version signed. The monitor will initial and date the log once the executed informed consent form has been reviewed. Signed informed consent forms (or copies) are to be maintained in the study file and must be available for verification by monitors or inspectors.

10.4. SUBJECT CONFIDENTIALITY

To ensure study patients’ privacy, all patients will be identified by unique identification numbers. All case report forms will only include patient IDs. It is the responsibility of the investigator to maintain a list of patient identification and Joint Assist.

Further the Joint Assist database is restricted, allowing a doctor to only view and enter data from his own patients. User authentication is required to view research data. The data is transmitted to a centralized database through a secured (SSL) channel on the Internet. Data in transit is in 128-bit encryption. The access to the centralized database is limited to those who are responsible for maintaining the database.

The Sponsor will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in their study records. The Sponsor will also instruct the study investigators in the importance of maintaining the confidentiality of study records. The records will be made available as required for review by governing regulatory agency such as FDA and a reviewing IEC/IRB, however to the extent possible, the subject's identity will not be disclosed.

11 RISK ANALYSIS

The following warnings, precautions, and possible adverse effects associated with Total Hip Arthroplasty are as stated in the package insert for this device (attached).

WARNINGS

Improper selection, placement, positioning, alignment and/or fixation of the implant components may result in unusual stress conditions which may lead to subsequent reduction in the service life of the prosthetic components. Malalignment of the components or inaccurate implantation can lead to excessive wear and/or failure of the implant or procedure. Inadequate preclosure cleaning (removal of surgical debris) can lead to excessive wear. Improper preoperative or intraoperative implant handling or damage (scratches, dents, etc.) can lead to crevice corrosion, fretting, fatigue fracture, and/or excessive wear. Do not modify implants. The surgeon is to be thoroughly familiar with the implants and instruments prior to performing surgery.

1. Acetabular screws are to be fully seated to assure stable fixation and to avoid interference with the acetabular liner component.
2. Prior to seating the liner into the shell component, all surgical debris (tissue fragments, etc.) must be removed from the interior of the shell component, as debris may inhibit the locking mechanism from engaging and securing the liner into the shell component.
3. Care is to be taken to assure complete support of all parts of the device embedded in bone cement to prevent stress concentrations, which may lead to failure of the procedure. Complete preclosure cleaning and removal of bone cement debris, metallic debris, and other surgical debris at the implant site is critical to minimize wear of the implant articular surfaces. Implant fracture due to cement failure has been reported.
4. In an instance where a liner engages the RingLoc™ locking ring and the liner is subsequently removed or replaced, the RingLoc™ locking ring should be replaced with a new ring.
5. Patient smoking may result in delayed healing, non-healing and/or compromised stability in or around the placement site.
6. The use of an elevated lip or offset polyethylene liner to correct for cup/liner malposition (cup abduction and/or anteversion) can lead to adverse loading of the unsupported portion of the polyethylene liner and increase the risk of liner fracture.

Biomet® joint replacement prostheses provide the surgeon with a means of reducing pain and restoring function for many patients. While these devices are generally successful in attaining these goals, they cannot be expected to withstand the activity levels and loads of normal, healthy bone, and joint tissue.

Accepted practices in postoperative care are important. Failure of the patient to follow postoperative care instructions involving rehabilitation can compromise the success of the procedure. The patient is to be advised of the limitation of the reconstruction and the need for protection of the implants from full load bearing until adequate fixation and healing have occurred. Excessive, unusual and/or awkward movement and/or activity, trauma, excessive weight gain, and obesity have been implicated with premature failure of certain implants by loosening, fracture, dislocation, subluxation and/or wear. Loosening of the implants can result in increased production of wear particles, as well as

accelerate damage to bone making successful revision surgery more difficult. The patient is to be made aware and warned of general surgical risks, possible adverse effects as listed, and to follow the instructions of the treating physician including follow-up visits.
Patient selection factors to be considered include: 1) need to obtain pain relief and improve function, 2) ability and willingness of the patient to follow instructions, including control of weight and activity level, 3) a good nutritional state of the patient, and 4) the patient must have reached full skeletal maturity.

PRECAUTIONS

Specialized instruments are designed for Biomet® joint replacement systems to aid in the accurate implantation of the prosthetic components. The use of instruments or implant components from other systems can result in inaccurate fit, sizing, excessive wear, and device failure. Intraoperative fracture or breaking of instruments has been reported. Surgical instruments are subject to wear with normal usage. Instruments that have experienced extensive use or excessive force are susceptible to fracture. Surgical instruments should only be used for their intended purpose. Biomet recommends that all instruments be regularly inspected for wear and disfigurement.
Devices are single-use only. Do not reuse implants. While an implant may appear undamaged, previous stress may have created imperfections that would reduce the service life of the implant. Do not treat patients with implants that have been placed, even momentarily, in a different patient.

POSSIBLE ADVERSE EFFECTS

1. Material sensitivity reactions. Implantation of foreign material in tissues can result in histological reactions involving various sizes of macrophages and fibroblasts. The clinical significance of this effect is uncertain, as similar changes may occur as a precursor to or during the healing process. Particulate wear debris and discoloration from metallic and polyethylene components of joint implants may be present in adjacent tissue or fluid. It has been reported that wear debris may initiate a cellular response resulting in osteolysis or osteolysis may be a result of loosening of the implant. Further, there has been a report regarding an association between articulating surfaces of: 1) CoCrMo alloy on CoCrMo alloy, 2) CoCrMo alloy on polyethylene, and 3) Titanium alloy on polyethylene in hip replacements and increased genotoxicity. This report, however, did not assess either the clinical relevance of the data or make any definite conclusions as to which metal ions or interactions between metal ions or particulate metals might be responsible for the observed data. The report further cautioned that an association does not necessarily mean a causal relationship, and that any potentially increased risk associated with metal ions needs to be balanced against the benefits resulting from hip replacement.
2. Early or late postoperative infection and allergic reaction.
3. Intraoperative bone perforation or fracture may occur, particularly in the presence of poor bone stock caused by osteoporosis, bone defects from previous surgery, bone resorption, or while inserting the device
4.Loosening, migration, or fracture of the implants can occur due to loss of fixation, trauma, malalignment, malposition, non-union, bone resorption, and/or excessive, unusual and/or awkward movement and/or activity.
5. Periarticular calcification or ossification with or without impediment of joint mobility.
6. Inadequate range of motion due to improper selection or positioning of components.
7. Undesirable shortening of limb.
8. Dislocation and subluxation due to inadequate fixation, malalignment, malposition, excessive, unusual and/or awkward movement and/or activity, trauma, weight gain, or obesity. Muscle and fibrous tissue laxity can also contribute to these conditions.

9. Fatigue fracture of component can occur as a result of loss of fixation, strenuous activity, malalignment, trauma, non-union, and/or excessive weight.
10. Fretting and crevice corrosion can occur at interfaces between components.
11. Wear and/or deformation of articulating surfaces.
12. Trochanteric avulsion or non-union as a result of excess muscular tension, early weight bearing, or inadequate reattachment.
13. Problems of the knee or ankle of the affected limb or contralateral limb aggravated by leg length discrepancy, too much femoral medialization or muscle deficiencies.
14. Postoperative bone fracture and pain.

E1™ Implants – MRI Information

The effects of the MR environment have not been determined for this device. This device has not been tested for heating or migration in the MR environment.