	CLINICAL INVESTIGATION REPORT			
	Department	**Rep. Nr**	**Date**	**Version**
	Clinical Research	02	24-Apr-24	1.0

Study Title	**A Prospective Clinical Study Evaluating Clinical, Radiographic And Patient-Reported Outcomes Of THA With Cemented Acetabular Cups**
Short Title	**CEMENTED CUPS**
Protocol ID	**H-31**
Investigational Product	**Mueller Cemented Acetabular Cups**
ClinicalTrials.gov ID	**NCT04831918**
Study Phase	**Completed**
Last follow-up	**2 years FU**
Subject Population	**45 patients enrolled;** **40 patients completed 2 years FU**
Sponsor	**Limacorporate Spa** Via Nazionale 52, 33030, Villanova di San Daniele (UD), Italy
Sponsor representative	**Fabiana Pavan** Clinical Trial Lead, Limacorporate SpA
Principal Investigator	**Dr. Luca Marega** Istituto Figlie di San Camillo di Trento
Sub-Investigators	**Dr. Daniele Lamberti** **Dr. Carlo Marega** Istituto Figlie di San Camillo di Trento
Statistical Analysis	**Final statistical analysis:** Limacorporate Spa Luca Dozza, Clinical Data Manager

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List of Abbreviations

ADE	Adverse device effect
AE	Adverse event
AISI	American Iron and Steel Institute
AP	Antero-Posterior
eCRF	electronic Case Report Form
FU	Follow-Up
HHS	Harris Hip Score
HOOS	Hip Disability and Osteoarthritis Outcome Score
IC	Informed consent
ISO	International Organization for Standardization
NSAIDs	Non-steroidal anti-inflammatory drugs
ROM	Range of Moton
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
THA	Total hip arthroplasty
TUG	Timed Up and Go
UHMWPE	Ultra High Molecular Weight Polyethylene
USADE	Unexpected serious adverse device effect

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- Annex I: Instructions for Use
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1.0 SUMMARY

Name of sponsor/Company	Limacorporate S.p.A
Study ID	H-31
Study short title	CEMENTED CUPS
Study title	A Prospective Clinical Study Evaluating Clinical, Radiographic And Patient-Reported Outcomes Of THA With Cemented Acetabular Cups
Name of study product	Mueller Cemented Acetabular Cups
Investigator & study site	Dr. Luca Marega - Istituto Figlie di San Camillo di Trento
Study period:	Site initiation visit date: 15 January 2021 Date of first enrolment: 01 March 2021 Date of last enrolment: 25 October 2021 Last patient last visit: 19 September 2023 Study close-out date: 31 January 2024
Objectives:	1. Assessment of clinical and radiographic early outcomes of THA using cemented acetabular cup; 2. Short-term survivorship of the implant; 3. Incidence of early complications.
Number of patients:	Planned sample size: 45 Patients enrolled: 45 Patients who completed 2 years FU: 40 Drop-out patients: 5 - 1 intraoperative withdrawal (major protocol deviation) [pt. #84-25] - 2 deceased [pt. #84-03, #84-32] - 1 withdrawal (uncooperative) [pt. #84-27] - 1 lost-to-FU (progressive cognitive impairment) [pt. #84-45]
Inclusion and exclusion criteria:	Inclusion criteria: 1. The patient diagnosis is one or more of the following: - Advanced articular destruction generated by primary degenerative or post-traumatic arthrosis or rheumatoid arthritis; - Avascular necrosis of the femoral head or fracture of the femoral neck; - Congenital or acquired deformity;

	- Failures of previous operations, like osteosynthesis, articular reconstruction, arthrodesis, hemi-arthroplasty or total arthroplasty. 2. The patient has participated in the Informed Consent process and has signed the Informed Consent form previously approved by the Ethics Committee. 3. The patient is willing and able to complete scheduled follow-up evaluations as described in the Patient Information Sheet. Exclusion criteria: 1. Acute or chronic infections, local or systemic infections; 2. Serious muscular, neurological or vascular diseases affecting the concerned limb; 3. Any concomitant disease and dependence that might affect the implanted prosthesis; 4. Allergy to material; 5. Metal-on-metal systems: patients with renal impairment. 6. Age < 18 years; 7. Pregnancy, nursing, or planning a pregnancy.
Endpoints: **Efficacy** **Safety**	Primary endpoint: – Functional changes in Harris Hip Score (HHS) from preoperative (baseline) to 2 years after surgery; Secondary endpoints: – Radiographic implant evaluation and stability assessment at 6 weeks, 1 year and 2 years of follow-up; – Change in HOOS from preoperative up to 2 years after surgery (postoperative timeframe: 6 weeks, 1 year, and 2 years FU); – Change in HHS from preoperative up to 6 weeks FU and 1 year FU; – Change in TUG from preoperative up to 2 years after surgery (postoperative timeframe: 6 weeks, 1 year, and 2 years FU). – Implant survivorship (Kaplan-Meier estimate) at 2 years after surgery; – Incidence of device-related AE/SAE up to 2 years of follow-up.
Statistical methods:	Data were collected in an ad hoc e-CRF designed on the clinical study protocol and data collected have been analyzed using Microsoft® Excel 365 App for business and R language and environment for statistical computing (v 4.3) (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were provided for preoperative, intraoperative, and postoperative variables. Mean, standard deviation (SD) and median values were computed for continuous distributions variables, while absolute and relative frequencies were reported for categorical distributions.

	Overall implant survivorship was estimated following the Kaplan-Meier Method for survival analysis and the estimated survival probability was reported with the relative 95% confidence intervals. Primary and secondary endpoint results were compared over time by means of the paired t-test and presented using boxplot graphs. Histograms were also adopted to highlight trends in the score subdomains over time.
Summary results	
Efficacy results	Mean HHS increased from 43.9 (± 14.7) preoperatively to 74.5 (± 11.3), 93.4 (± 7.3) and 92.9 (± 8.9) at 6 weeks, 1 year and 2 years after surgery, respectively. 78% of patients (n = 31) reported an "excellent" result at 2 years follow-up. Mean TUG decreased from 24.1 s (± 24.8) preoperatively to 8.8 s (± 2.6) at 6 weeks follow-up, to 8.0 s (± 3.1) at 1 year follow-up, and 7.9 s (± 3.4) at 2 years FU. HOOS total score increased from preoperative (34.9 ± 14.1) to 6 weeks follow-up (76.0 ± 13.2) and further to 1 year FU (84.8 ± 13.9). HOOS total value remained almost unchanged at 2 years FU (84.1 ± 17.2). Radiographically, the implant showed good stability and integration up to 2 years after surgery. No radiographic complications were detected, e.g. osteolysis, relevant radiolucency, cement cracks, subsidence.
Safety results	No adverse events related to the medical device nor device deficiencies were reported.
Conclusion	Clinical, patient-reported and radiographic outcomes highlighted excellent performance and safety of Mueller cemented cups in total hip prosthesis up to 2 years after surgery.
Date of the report	24-Apr-2024

2.0 LAY SUMMARY

Study title	The study tested a hip prosthesis.
Who carried out the research?	Doctors are from one hospital in Trento, Italy. The study was sponsored by Limacorporate spa, a company that produces orthopedic implants, including the one used in this clinical study.
Public involvement	Patients who need a hip replacement were involved in the study.
Where and when the study took place	The study happened in Trento, Italy. It started in January 2021 and finished in January 2024.
Why was the study on the hip prosthesis needed	The company who made the hip prosthesis wanted to know if it was good for people with hip problems.
Main questions studied	The doctors wanted to see if the hip prosthesis helped people feel better and if it worked well over time.
Who took part in the study	45 people took part in the study. They had hip problems, and the doctors chose them based on certain rules, e.g. they couldn't have other health issues.
Treatments or other interventions/help	The participants got the hip prosthesis to see if it helped their hip problems.
What happened during the study?	The doctors checked how well the hip prosthesis worked for the people who took part. They used different tests to check if their hips felt better.
Results of the study	Two years after the study first started, the doctors found out that the hip prosthesis really helped. The majority of hips felt better, pain was reduced and the new hip stayed working well for 100% of the people.
How has the study helped patients?	The study shows that the hip prosthesis is good for people with hip problems.

3.0 INTRODUCTION

Total hip arthroplasty (THA) is a frequently performed surgery for the treatment of patients with osteoarthritis, rheumatoid arthritis, avascular necrosis, developmental dysplasia, and many other forms of hip pathology. THA has become one of the most successful and cost-effective interventions in the history of medicine (Jenkins et al., 2013). Patient demands have increased significantly over time and THA is being offered to younger and fitter patients. Due to its widespread use, implant longevity after THA and satisfactory outcomes represent great challenges to achieve (Bhaskar et al., 2017).

Pain-free functionality of the endoprosthesis depends significantly on the implant fixation to the bone. This can be distinguished in primary, i.e. the immediate stability achieved by the surgeon during the surgical procedure, and secondary, which refers to long-term stability and it is the result of bone remodeling during the healing process leading to the integration of the implant on the bone.

A good primary stability improves the preconditions for osseointegration and, consequently, for sufficient secondary stability. Primary fixation of the acetabular cup can be achieved with two different main methods: through a cemented technique, which involves the penetration of bone cement in the front-end between bone and prosthesis, or through an uncemented technique, which requires the press-fit of the implant onto the bone, after an exact preparation of the bony implant bed (Willert & Buchhorn, 1999).

Both models provide excellent results both in the short and the long term, the choice of a certain type of fixation depends on the surgeon's personal preference and experience as well as on patient characteristics (Van Praet & Mulier, 2019). Despite the continuous improvement of the uncemented techniques performances the survival rate of the cemented implants remains superior (Morshed et al., 2007).

Mueller Cemented Cups are prosthesis used to replace completely the acetabular cavity using cement as the fixation agent. They can be used in association with or without the acetabular plates, which are supporting structures generally interposed in case of seriously compromised bone quality in the acetabular cavity. In both cases a layer of cement is used to efficiently fix the prosthesis system.

Mueller acetabular cups have been produced by Limacorporate since the 70s and are still widely distributed. In this study, Mueller acetabular cups are used according to their intended use. Indeed, this is a Post Marketing Clinical Follow Up trial that aims at collecting outcome data on this product, by analyzing clinical scoring systems, radiographs and adverse event records within two years after the surgery, and thus to assess the short-term performance and safety of this implant.

4.0 DEVICE

4.1 Device description

Mueller Cemented cups are hip prosthesis used to replace completely the acetabular cavity using cement as the fixation agent. Mueller cemented cups can be used in combination with the acetabular plates.

Mueller Cemented acetabular cups are entirely made of UHMWPE (according to ISO 5834-2) and are available with an outer diameter of 40, 42, 44, 46, 48, 50, 52, 54, 56, 58 mm.

An AISI 316L ring is inserted in the equatorial region to allow the evaluation of the device position through a radiography.

The acetabular cups are available in two different versions:

- standard
- protruded (or anti-dislocation)

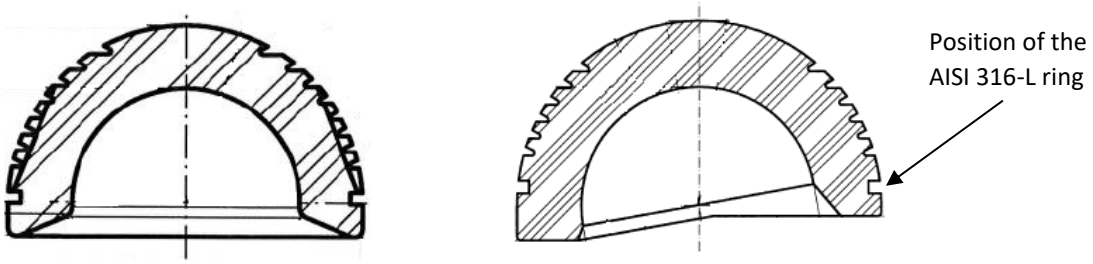

Figure 1 Sample of standard and protruded versions

The inner diameters of standard cups allow the coupling with 28 and 32 mm femoral heads, while the protruded cups are available also for 36 mm femoral heads.

The **standard** version is completely hemispherical and therefore indicated for deep acetabulum.

The **protruded (anti-dislocation)** version has a lateral portion which guarantees a greater coverage of the femoral head and prevents any accidental dislocation.

4.2 Intended use of the device

Mueller Cemented cups are indicated for use in total arthroplasty for reduction or relief of pain and/or improved hip function in skeletally mature patients as per IFU (refer to Annex I).

4.3 Standard surgical technique

Mueller Cemented cups are suitable to be implanted with proper instrument set and procedure (as per standard surgical technique, Annex II).

4.4 Additional devices

Mueller Cemented cups are intended for use in total hip replacement, and might be implanted with additional medical devices, such as:

- Femoral stem
- Femoral head
- Acetabular plate
- Cement plug
- Centralizer
- Cerclage bands
- Bone screws

Implant data on additional devices listed above has been collected within this study.

5.0 STUDY DESIGN

5.1 Objectives

The objectives of this study are:

a) The assessment of the clinical and radiographic early outcomes of Total Hip Arthroplasty using cemented acetabular cup;

b) The assessment of the short-term survivorship of the implant;

c) The assessment of the incidence of early complications.

5.2 Study type

This study is a post-market clinical study since the device is registered, CE marked and used according to the intended use. It is an open-label, prospective and longitudinal cohort clinical trial.

This clinical trial is to be considered as interventional, since it involves the collection of two additional radiographies (antero-posterior view of the pelvis, lateral view of the proximal femur) that would not have been collected by the Principal Investigator as per his standard of care at 1-year and 2-year FU.

It is a monocentric study, conducted at "Istituto Figlie di San Camillo di Trento" (Trento, Italy) under the responsibility of the Principal Investigator Dr. Luca Marega.

5.3 Study endpoints

The primary endpoint of this study is the evaluation of the functional changes in the Harris Hip Score from preoperative (baseline) to 2 years after surgery.

The secondary endpoints are:

1. The radiographic evaluation of the implant and the stability assessment during the follow-up phase: at 6 weeks, 1 year and 2 years after surgery;
2. Change in HOOS from preoperative (baseline) up to 2 years after surgery (postoperative timeframe: 6 weeks, 1 year and 2 years FU);
3. Change in HHS from preoperative (baseline) up to 6 weeks FU and 1 year FU;
4. Change in TUG from preoperative (baseline) up to 2 years after surgery (postoperative timeframe: 6 weeks, 1 year and 2 years FU);
5. Implant survivorship (Kaplan-Meier estimate) at 2 years after surgery;
6. The incidence of device-related AE/SAE up to 2 years of follow-up.

5.4 Study schedule

The following timelines and temporal windows has been followed:

- Pre-operative visit: timing in accordance with current local practice
- Intraoperative visit: in accordance with current local practice
- Immediate postoperative visit: immediately after surgery
- Follow-Up 6 weeks: ± 2 weeks
- Follow-Up 1 year: ± 4 months
- Follow-Up 2 years: ± 4 months

5.5 Population

A total sample size of 45 subjects was included in this investigation.

Patients have been screened for participation in the study if requiring a total hip replacement according to the indications for use of the Mueller cemented acetabular cups. The decision to use the investigational device was taken by the Principal Investigator according to his standard clinical practice, independently and clearly separated from the decision to include the patient in the study.

Patients have been asked to sign a consent form, in order to provide their written consensus to the participation in the clinical study and to their personal data processing, before being considered for screening.

5.5.1 Eligibility criteria

Only after the Informed Consent process was performed and documented, patient could be screened for enrollment and the eligibility criteria checked, in order to evaluate the patient's potential to be included in the trial.

Inclusion criteria:

1. The patient has participated in the Informed Consent process and has signed the Informed Consent form previously approved by the Ethics Committee;
2. The patient diagnosis is one or more of the following:
    - Patient with advanced articular destruction generated by primary degenerative or post-traumatic arthrosis or rheumatoid arthritis;
    - Patient with avascular necrosis of the femoral head or fracture of the femoral neck;
    - Patient with congenital or acquired deformity;

- Patient with failures of previous operations, like osteosynthesis, articular reconstruction, arthrodesis, hemi-arthroplasty or total arthroplasty.

3. The patient is willing and able to complete scheduled follow-up evaluations as described in the Patient Information Sheet;

Exclusion criteria:

1. Acute or chronic infections, local or systemic infections;
2. Serious muscular, neurological or vascular diseases affecting the concerned limb;
3. Any concomitant disease and dependence that might affect the implanted prosthesis;
4. Allergy to material;
5. Metal-on-metal systems: patients with renal impairment.
6. With age < 18 years;
7. Female patients who are pregnant, nursing, or planning a pregnancy.

A patient could be enrolled in the study if he/she signed the IC, was considered eligible for the study (satisfying all enrolment criteria) and received the investigational device. Once enrolled, patients were identified with a unique ID code (i.e. 84-xx, where 84 is the ID for the investigational site) in order to ensure the pseudonymization of their identity.

Any patient's discontinuation/withdrawal (preoperative, intraoperative or postoperative) occurring during the study has been reported.

5.6 Efficacy and safety evaluations

5.6.1 Clinical assessment

Clinical evaluation was performed at the preoperative visit (baseline), 6 weeks, 1 year and 2 years after surgery. The evaluation was made based on changes in the Harris Hip Score (HHS), Time Up-and-Go test (TUG) as well as the HOOS score. HHS is a disease-specific scoring system that is divided in four domains for the evaluation of function (which is further split into gait and activities of daily living), pain, motion and deformity (Harris, 1969). Absolute HHS has a maximum score of 100 points, wherein pain contributes 44 points, function 47, ROM 5 and absence of deformity 4 points. Results are considered "excellent" for scores between 90-100, "good" between 80-89, "fair" between 70-79, "poor" between 60-69, while below 60 it is considered as a failed result. HHS outcome is considered satisfactory for scores higher than 80 (Soderman & Malchau, 2001).

Range of movements (ROM) includes active flexion/extension, abduction/adduction, internal and external rotation measured in degrees.

TUG is used to evaluate mobility in elderly patients by measuring the time it takes for a patient to rise from an unarmed chair, walk 3 m, turn, and return to sit in the same chair. For this test, subjects are told to walk as quickly as they are comfortable and safe with. It is allowed to use the arms of the chair to stand up and sit down (Podsiadlo D & Richardson S, 1991).

The HOOS is a patient-reported outcomes widely used after THA. It contains 40 items and assesses five separate patient-related dimensions: pain (10 items), symptoms (5 items, including stiffness and range of motion), activity limitations-daily living (17 items), sport and recreation function (4 items) and hip related quality of life (4 items). Each item is score from 0 to 4 and each subscale is calculated as a sum of the items included. To improve interpretations, HOOS is transformed into a 0-100 scale (0 worst result, 100 best result). Subscores can be graphically presented as a HOOS profile. Missing data are handled as follows: one or two missing values are substituted with the average value of the dimension, whereas when more items are omitted the response for the corresponding dimension should be considered invalid (Nilsdotter et al., 2003).

5.6.2 Radiographic assessment

Radiographic evaluation includes antero-posterior and lateral x-ray views performed according to the following table.

Time-point	Type of X-rays performed
Pre-operative	Antero-posterior view of the pelvis; Antero-posterior and lateral views of the proximal femur
Immediate post-operative	Antero-posterior and lateral views of proximal femur
6 weeks FU	Antero-posterior view of the pelvis; Antero-posterior and lateral views of the proximal femur
1 year FU	Antero-posterior view of the pelvis; Lateral view of the proximal femur
2 years FU	Antero-posterior view of the pelvis; Lateral view of the proximal femur

Table 1 List of x-ray views performed at each timepoint.

The following parameters were collected from the preoperative radiographic assessment:

- Leg-Length Discrepancy, defined from the AP Pelvic view as the difference between the distances from the teardrop line to the lesser trochanters of each femur;
- Varus/valgus deformity;
- Presence of osteophytes (and the site where they eventually are located);

- Presence of cysts (and the site where they eventually are located);
- Osteoarthritis severity (if the pathology that has led to the arthroplasty is osteoarthritis).

In the postoperative radiographic assessment, the parameters collected at each follow up (immediate postoperative, 6 weeks, 1 year, 2 years after surgery) are described in the following Table 2.

Cup	Presence of radiolucent lines around the cup according to DeLee Charnley classification [10]
	Acetabular cup abduction angle
	Presence of heterotopic ossification according to Brooker classification [11] [12]
Stem	Stem sizing (normal, undersized, oversized)
	Stem position (neutral, varus, valgus)
	Angle (measured indegrees) between diaphyseal axis and stem axis
	Radiolucent lines, reported for each of the Gruen zones [13]
	Osteolysis around the stem
Overall implant stability	Any sign of loosening of both acetabular and femoral component
	Any sign of subsidence of both acetabular and femoral component
	Any sign of cement cracks around both acetabular and femoral component
	Other features

Table 2 Radiographic assessment performed at each post-operative time point.

5.6.3 Safety

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE): adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE) adverse event that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in:

1) A life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

Serious Adverse Device Effect (SADE): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Device Deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors and inadequate labelling.

Unanticipated Serious Adverse Device Effects (USADE): any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

The Investigator is responsible for identifying clinical implant-related AE/SAE which occur to each subject throughout the study and for recording them.

The Investigator should report all the relevant Adverse Events, which are related to the patient's condition, that can affect the study procedures and evaluations.

Each adverse event must be registered reporting:

- Onset date/end date;
- Description (symptoms);
- Diagnosis (results of any diagnostic performed tests);
- Severity (mild, moderate, severe);
- Assessment of causality (unknown, definitely not, unlikely, possible, probable, highly probable);
- Therapy (description of any treatment implemented);
- Outcome (recovered, recovered with residual effects, ongoing, death, unknown).

The Investigator should report adverse events in the appropriate section of the eCRF in a timely manner. The Investigator must report every SAE within 24 hours from their awareness of the event. All implant-related AEs/SAEs are monitored through the data collected in the eCRF.

The unexpected SADEs should be reported by the Investigator to the Ethics Committee and competent health authorities.

The Investigator and/or other professional personnel in attendance are responsible to undertake the appropriate therapy. The Investigator shall continue to clinically monitor the adverse events until they are resolved, stabilized or return to the baseline.

In case of revision of the investigational device, the details on the explant and implant surgeries should be reported in the proper section of the eCRF.

5.7 Statistical analysis

Data were collected in an ad hoc e-CRF designed on the clinical study protocol and data collected have been analyzed using Microsoft® Excel 365 App for business and R language and environment for statistical computing (v 4.3) (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics were provided for preoperative, intraoperative, and postoperative variables. Mean, standard deviation (SD) and median values were computed for continuous distributions variables, while absolute and relative frequencies were reported for categorical distributions.

Overall implant survivorship was estimated following the Kaplan-Meier Method for survival analysis and the estimated survival probability was reported with the relative 95% confidence intervals.

Primary and secondary endpoint results were compared over time by means of the paired t-test and presented using boxplot graphs. Histograms were also adopted to highlight trends in the score subdomains over time.

6.0 RESULTS

6.1 Study Flow

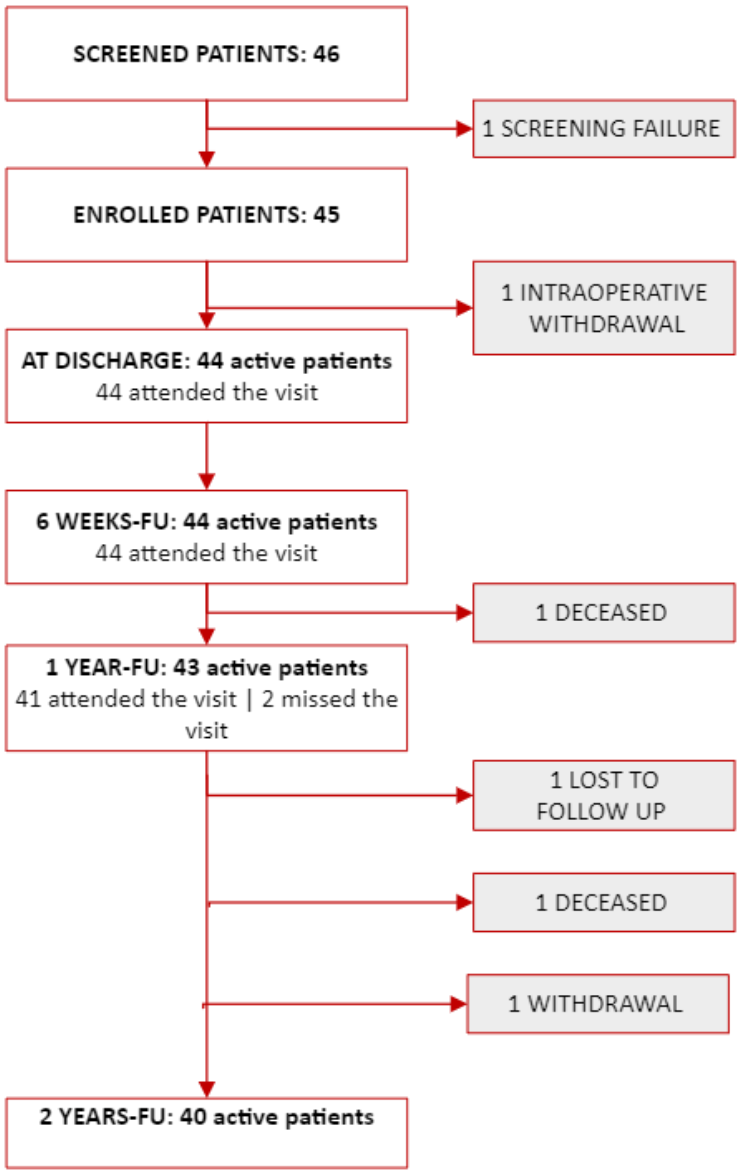

Figure 2 Patients flowchart.

In this study, a total of 46 patients were screened after providing their written informed consent to the trial participation and data processing. One screening failure (pt #84-39) was recorded, thus the recruitment process resulted in a sample size of 45 subjects, as per protocol requirements.

One intraoperative withdrawal was registered (pt #84-25) since Mueller acetabular cup was not implanted as per standard surgical technique (see par. *6.6 Protocol Deviation*).

The first patient was enrolled on 1st March 2021 and the last patient on 25th October 2021.

All 44 active patients attended the 6 weeks of follow-up visit.

One patient (pt #84-32) died after this timepoint, due to the worsening of health conditions related to an endometrial cancer diagnosed prior to participation to H-31 clinical study. The cause of death was considered definitely not related both to the investigational device and to the procedure (refer to paragraph *6.5.1 Adverse events*).

Out of the 43 active patients, 41 attended the visit 1 year after surgery. 2 patients missed the visit because of health conditions resulting in adverse events, in particular pt #84-02 received a partial implant revision after a traumatic event and #84-09 had a heart failure.

After the 1-year FU, 3 patients' discontinuations were recorded. More in detail, one subject (pt #84-03) deceased due to causes unknown to the Investigators, as it was not possible to retrieve additional information due to privacy reason. The cause of patient's death was declared definitely not related to the investigational device nor to the surgical procedure, because the patient's conditions were very positive at 1-year follow up, both from a radiographical, clinical and subjective perspective.

Another patient (pt #84-27) withdrew his consent and refused to participate to the last FU visit (despite the study staff attempts to schedule it). Nonetheless, this patient reported via telephone no complications to the treated hip. One patient (pt #84-45) recorded a progressive cognitive impairment that prevented him from leaving home. This patient did not attend the last follow-up visit and was thus considered lost to follow-up. More details are provided in paragraph *6.5.1 Adverse events.*

Overall, out of the 45 enrolled, 40 patients attended the 2 years FU visit.

6.2 Patients

Among the 45 patients enrolled, 67% were female (n = 30) and 33% were male (n = 15) (**Table 3**).

Demographics	Mean ± SD	Min	Max	Median
Weight (kg)	70 ± 12	38	100	70
Height (cm)	165 ± 8	148	185	165
BMI (kg/m^2)	26 ± 4	17	38	25
Age (years)	79 ± 6	69	90	79

Table 3 Demographics of study population.

The enrolled population was composed of elderly subjects with an average age of 79 years, whose lifestyle was predominantly sedentary (62%) (**Table 4**).

Activity	n	%
Intense	5	11
Normal	12	27
Sedentary	28	62

Table 4 Lifestyle of study population.

Subjects enrolled in the study were mostly affected by primary arthrosis (91.1%, n = 41), whilst the remaining population suffered from rheumatoid arthritis (2.2%, n = 1), post-traumatic arthrosis (2.2%, n = 1), fracture of the femoral neck (2.2%, n = 1) and avascular necrosis of the femoral head (2.2%, n = 1). The affected limb was equally distributed between right and left side, 44.5% (n = 20) and 55.6% (n = 25), respectively. Furthermore, 80% of the subjects (n = 36) were positive to the Trendelenburg sign (**Table 5**).

Diagnosis	**n**	**%**
Primary arthrosis	41	91.2
Rheumatoid arthritis	1	2.2
Post-traumatic arthrosis	1	2.2
Fracture of the femoral neck	1	2.2
Avascular necrosis of the femoral head	1	2.2
Affected side	**n**	**%**
Right	20	44.4
Left	25	55.6
Trendelenburg	**n**	**%**
Positive	36	80
Negative	9	20

Table 5 Medical history of study population in terms of diagnosis, affected hip side and Trendelenburg sign.

Regarding patients' level of pain before surgery, 42.2% reported pain with every movement (n = 19), 31.1% (n = 14) described start-up pain, 11.1% (n = 5) were unable to describe, weight-bearing pain was suffered by 8.9% (n = 4) or occasionally by 4.4% (n = 2), whilst 2.2% (n = 1) of the patients reported rest pain.

In terms of pain therapy before surgery, NSAIDs were used regularly by 53.3% (n = 24) of the patients and occasionally by 33.3% (n = 15). 2.2% (n = 1) of the patients used to take steroids regularly while 11.1% (n = 5) did not take any medication for pain management (**Table 6**).

Description of pain	**n**	**%**
At rest	1	2.2
Start-up pain, always	14	31.2
Unable to describe	5	11.1
Weight-bearing, always	4	8.8
Weight-bearing, occasional	2	4.4
With every movement	19	42.3
Pain therapy	**n**	**%**
None	5	11.1
NSAIDs, occasionally	24	53.4
NSAIDs, regularly	15	33.3
Steroids, regularly	1	2.2

Table 6 Medical history of study population in terms of pain level and pain management.

6.3 Intraoperative data

All surgeries were performed through posterolateral approach, as per hospital standard of care. All but one patient underwent subarachnoid anesthesia and the mean skin to skin surgery time was 48 (± 11) min, while the mean blood loss was 227 (± 120) cc. No intraoperative complications occurred, and all subjects underwent antibiotic, antithrombotic as well as antihemorrhagic prophylaxis. All implants were fixed with DePuy CMW 2 cement (**Table 7** and **Table 8**).

Surgical approach	**n**	**%**
Posterolateral	45	100
Anesthesia	**n**	**%**
General	1	2.2
Subarachnoid	44	97.8
Intraoperative complications	**n**	**%**
Yes	0	0
Prophylaxis therapy	**n**	**%**
Antibiotic prophylaxis	45	100
Antithrombotic prophylaxis	45	100
Antihemorrhagic prophylaxis	45	100
Cement type	**n**	**%**
DePuy CMW 2	45	100

Table 7 Surgery data of study population in terms of surgical approach, anesthesia, intraoperative complications, prophylaxis therapy and cement type.

Surgery data	**Mean ± SD**	**Min**	**Max**	**Median**
Surgery time (min)	49 ± 11	37	75	44
Blood loss (cc)	227 ± 120	100	500	200

Table 8 Surgery data of study population in terms of surgery time and blood loss.

Bone stock quality of the acetabulum was normal in 55.6% (n = 25) of the patients, porotic in 11.1% (n = 5) and sclerotic in 33.3 % (n = 15). Bone stock quality of the femur was normal in 73.3% (n = 33) of the patients, porotic in 11.1% (n = 5) and sclerotic in 15.6% (n = 7) (**Table 9**). Bone grafting of acetabulum or femur was not necessary for any treated patient.

Bone stock quality - acetabulum	**n**	**%**
Normal	25	55.6
Porotic	5	11.1
Sclerotic	15	33.3
Bone stock quality - femur	**n**	**%**
Normal	33	73.3
Porotic	5	11.1
Sclerotic	7	15.6

Table 9 Bone stock quality of acetabulum and femur of study population.

6.3.1 Implant information

All patients were implanted with the Mueller Cemented cup, of which 71% (n = 32) received the standard version and 29% (n = 13) the protruded one. The most used acetabular cup diameters were 44 mm (28.9%, n = 13) and 46 mm (31.1%, n = 14), followed by 48 mm (20%, n = 9) and 50 mm (15.6%, n = 7). Acetabular cup diameters 40 mm and 52 mm were implanted in 1 case each (2.2%) (**Table 10**).

Acetabular cup type	**n**	**%**
Mueller Cemented cup standard	32	71
Mueller Cemented cup protruded	13	29
Acetabular cup diameter (mm)	**n**	**%**
40	1	2.2
44	13	28.9
46	14	31.1
48	9	20
50	7	15.6
52	1	2.2

Table 10 Implant information related to acetabular cup type and diameter.

In terms of stem type, 44 patients received the Friendly Short femoral stem, of which 88.6% (n = 39) were implanted with the Standard Friendly Short and 11.4% (n = 5) with the Lateralized Friendly Short. The most used femoral stem size was size 1 (43.2%, n = 19), followed by size 0 (36.4%, n = 16), size 3 (11.4%, n = 5) and size 2 (9.1%, n = 4) (**Table 11**).

Femoral stem type	**n**	**%**
Friendly Short Standard	39	88.6
Friendly Short Lateralized	5	11.4
Femoral stem size	**n**	**%**
0	16	36.
1	19	43.2
2	4	9.1
3	5	11.4

Table 11 Implant information related to femoral stem type and size.

All patients were implanted with a Friendly Short plug (with distal centralizer). The most used femoral plug sizes were size 20 (34.1%, n = 15) and 18 (27.3%, n = 12), followed by size 16 (18.2%, n = 8) and 22 (13.6). 3 patients (6.8%) were implanted with femoral plug size 14 (**Table 12**).

Femoral plug type	**n**	**%**
Friendly Short plug (with distal centralizer)	44	100
Femoral plug size	**n**	**%**
14	3	6.8

16	8	18.2
18	12	27.3
20	15	34.1
22	6	13.6

Table 12 Implant information related to femoral plug type and size.

All subjects received a AISI 316/L femoral head taper 12/14 with a diameter of 32 mm. Size M (38.6%, n = 17) and L (45.5%, n = 20) were the most used, followed by S (13.6%, n = 6) and XL (2.3%, n = 1) (**Table 13**).

Femoral head material	**n**	**%**
AISI 316/L	44	100
Femoral head type	**n**	**%**
Head - taper 12/14	44	100
Femoral head diameter (mm)	**n**	**%**
32	44	100
Femoral head size	**n**	**%**
S	6	13.6
M	17	38.6
L	20	45.5
XL	1	2.3

Table 13 Implant information related to femoral head type, diameter and size.

6.4 Efficacy analysis

6.4.1 Clinical results

The primary endpoint of this clinical study is defined as the change in the Harris Hip Score from preoperative to 2 years of follow-up.

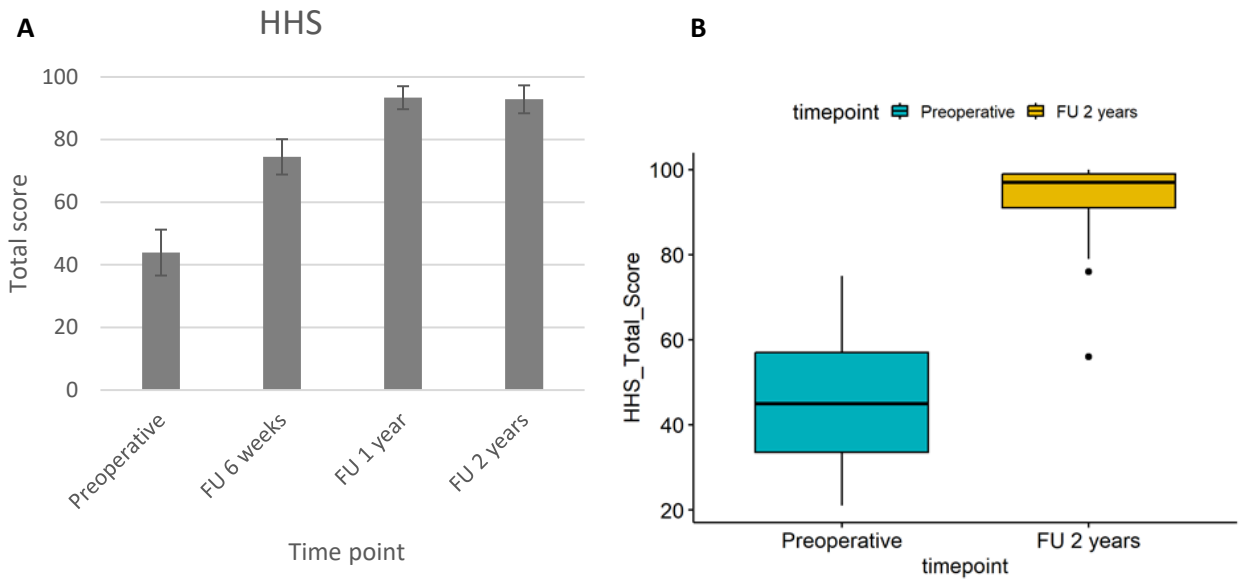

Figure 3 HHS results. (**A**) Graphic representation of total HHS at preoperative (baseline), 6 weeks, 1 year and 2 years after surgery. (**B**) Box plot representation of total HHS results preoperative vs 2 years follow-up.

Time point	Mean ± SD	Min	Max	Median	p-value (vs preoperative)
Preoperative (n = 45)	43.9 ± 14.7	16	75	44	-
6 weeks FU (n = 44)	74.5 ± 11.3	50	99	75.5	<0.001
1 year FU (n = 41)	93.4 ± 7.3	72	100	97	<0.001
2 years FU (n = 40)	92.9 ± 8.9	56	100	97	<0.001

Table 14 Change in total HHS from preoperative (baseline) to 6 weeks, 1 year and 2 years follow-up. p<0.05, p<0.01, p<0.001.

Mean HHS at preoperative (baseline) was 43.9 (± 14.7) and increased to 74.5 (± 11.3) already 6 weeks after surgery. Mean HHS further increased, reaching a mean value of 93.4 (± 7.3) at 1 year follow-up, stabilizing at a final mean value of 92.9 (± 8.9) at 2-year follow-up (**Table 14**).

In terms of descriptive HHS, 89% (n = 41) of the patients reported “very poor” as total score description at preoperative evaluation, and no patients reported “good” or “excellent” descriptions. 6 weeks after surgery, the score description was quite heterogeneous with scores ranging from “very poor” to “excellent”. At this time point, most of the patients reported a “fair” (36%, n = 16) or “good” (25%, n = 11) HHS outcome. 1 year after surgery a significant improvement on HHS values could be observed. Indeed, no patients reported “very poor” or “poor” outcomes, and 78% (n = 32) of the study population reported an “excellent” result. The descriptive outcomes of HHS at 2 years of follow-up remained almost unchanged in comparison to 1 year-follow-up results. However, one patient (pt #84-42) experiences a “very poor” outcome, resulting in a slight decrease in overall HHS from the 93.4 (± 7.3) recorded 1-year postoperatively to 92.9 (± 8.9) at 2 years FU. This patient recorded an “excellent” outcome at the 1-year FU visit, however suffered mobilization of the contralateral cup (which had been implanted before study began) one month prior to the 2-year FU visit. This

condition (detailed in paragraph *6.5.1 Adverse events*) required a revision surgery, which occurred a few weeks after the 2-year FU visit. Therefore, at the time of the visit, the patient's general condition was profoundly compromised, and this was reflected in the outcome of the HHS.

Among the remaining patients, the vast majority (78%, n=31) recorded an "excellent" outcome, while 13% (n=5) reported a "good" and 8% (n=3) a "fair" result (**Table 15**). Among the patients who reported a "fair" result, patients #84-11, #84-20 and #84-44 reported consistent outcomes in terms of HHS and HOOS. The lowest values, in fact, were recorded in terms of the hip functionality, which could be linked to physiological conditions related to the elderly age of patients (respectively, 87, 85 and 79 years old at the time of the last visit).

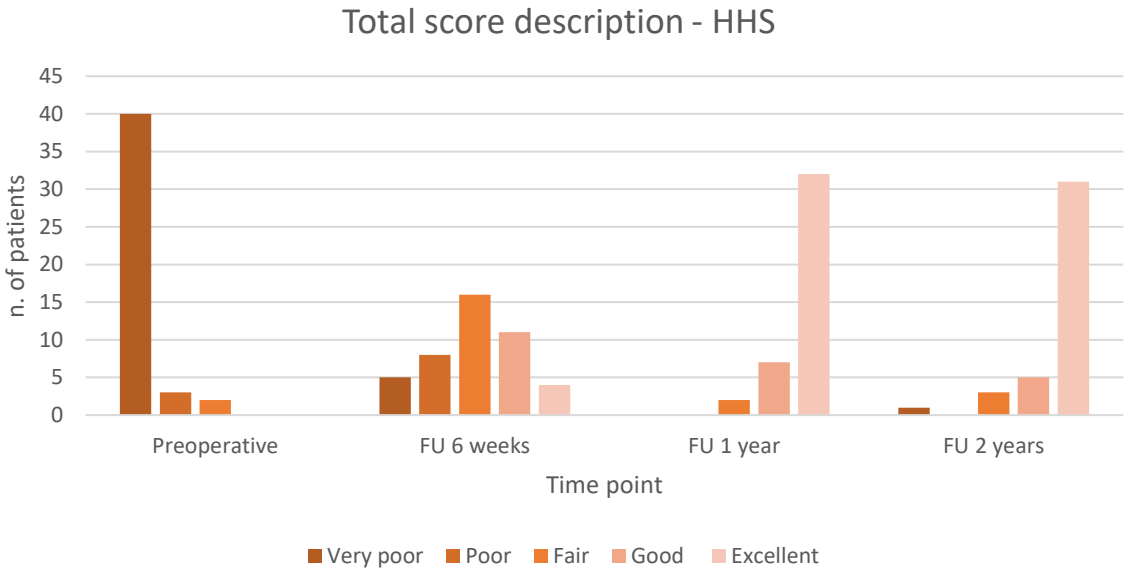

Figure 4 Graphic representation of HHS total score description at preoperative (baseline), 6 weeks, 1 year and 2 years after surgery.

	Preoperative (n = 45)		**6 weeks FU** (n = 44)		**1 year FU** (n = 41)		**2 years FU** (n = 40)	
Total score description	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Very poor (0-59)	41	89	5	11	0	0	1	3
Poor (60-69)	3	7	8	18	0	0	0	0
Fair (70-79)	2	4	16	36	2	5	3	8
Good (80-89)	0	0	11	25	7	17	5	13
Excellent (90-100)	0	0	4	9	32	78	31	78

Table 15 Change in total score description of HHS from preoperative (baseline) to 6 weeks, 1 year and 2 years follow-up.

TUG was evaluated preoperatively and at each post-operative timepoint. Mean TUG decreased from 24.1 s (± 24.8) (registered preoperatively) to 8.8 s (± 2.6) at 6-week follow-up. No major changes were observed at 1-year and 2-year follow-up, as TUG value remained overall stable around 8 s (**Table 16**).

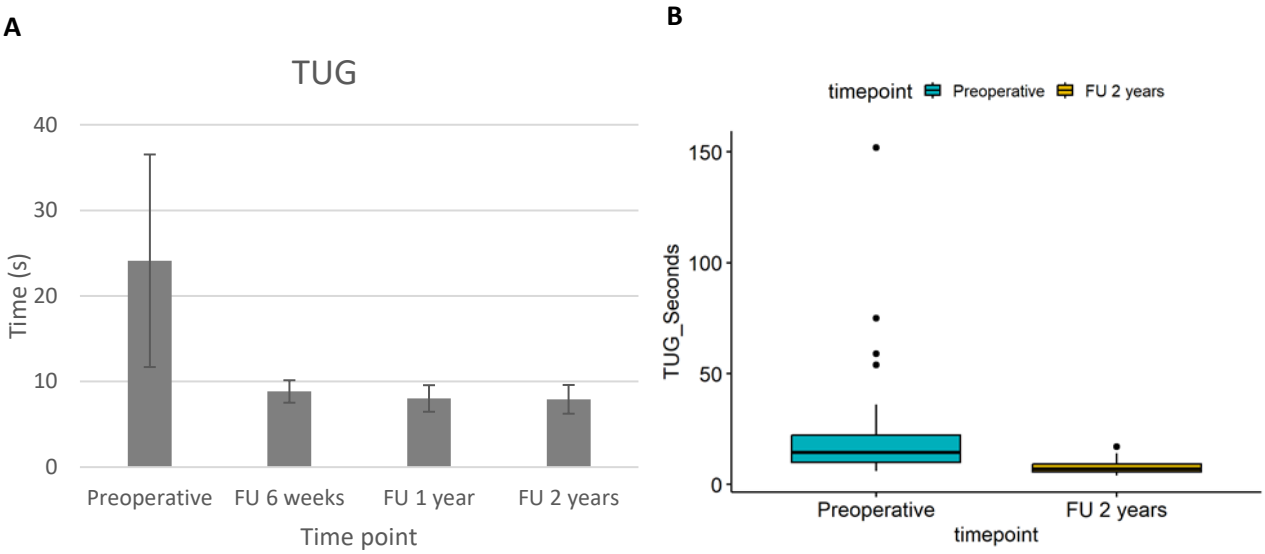

Figure 5 TUG test results. (**A**) Graphic representation of TUG results at preoperative (baseline), 6 weeks, 1 year and 2 years after surgery. (**B**) Box plot representation of TUG results preoperative vs 2 years follow-up.

Time point	Mean (s) ± SD	Min	Max	Median	p-value (vs preoperative)
Preoperative (n = 45)	24.1 ± 24.8	6	152	17	-
6 weeks FU (n = 44)	8.8 ± 2.6	5	18	8	<0.001
1 year FU (n = 41)	8.0 ± 3.1	5	18	7	<0.001
2 years FU (n = 40)	7.9 ± 3.4	4	17	7	<0.001

Table 16 Change in TUG test from preoperative (baseline) to 6 weeks, 1 year and 2 years follow-up. p<0.05, p<0.01, p<0.001.

Table 17 reports the results of HOOS total score at each time point, from preoperative (baseline) to 2 years after surgery. The HOOS total score greatly increased from preoperative (34.9 ± 14.1) to 6-week follow-up (76 ± 13.2). A further improvement could be observed at 1-year follow-up, though not that marked as at the previous time-point (84.8 ± 13.9) while the total score remained almost unchanged at the 2-year follow-up (84.1 ± 17.2).

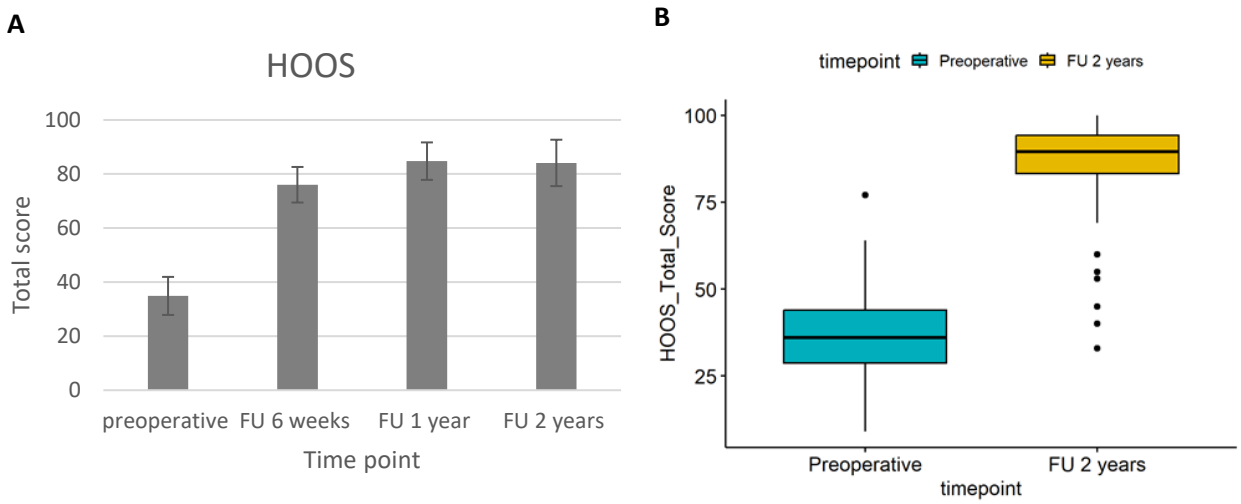

Figure 6 HOOS total score results. (**A**) Graphic representation of HOOS total score at preoperative (baseline), 6 weeks, 1 year and 2 years after surgery. (**B**) Box plot representation of HOOS total score preoperative vs 2 years follow-up.

Time point	Mean ± SD	Min	Max	Median	p-value (vs preoperative)
Preoperative (n = 45)	34.9 ± 14.1	9	77	33	-
6 weeks FU (n = 44)	76.0 ± 13.2	45	93	78	<0.001
1 year FU (n = 41)	84.8 ± 13.9	51	100	90	<0.001
2 years FU (n = 40)	84.1 ± 17.2	33	100	89.5	<0.001

Table 17 Change in HOOS Total score from preoperative (baseline) to 6 weeks, 1 year and 2 years follow-up. p<0.05, p<0.01, p<0.001.

HOOS results have been further analyzed for the five subdomains, i.e. symptoms stiffness, pain, daily functionality, sport functionality and quality of life. A graphic representation is reported in **Figure 7**, which shows the mean values of the HOOS subdomains at the different timepoints (**Table 18**). The figure shows that each subdomain recorded a notable increase from the preoperative visit and the 6-weeks FU and a further (but limited) one at 1-year FU. For all the subdomains, the results remained almost unchanged at the 2 years FU, except for a minor deflection. According to the Principal Investigator, this is due to the patients' ageing, particularly relevant considering that their mean age at surgery was equal to 79.9, and a consequent worsening of their general conditions.

Among the subdomains, quality of life recorded the greatest increase throughout the observation period, from a preoperative score of 20.4 (± 16.1) to the value of 82.3 (± 22.6) at 2 years FU.

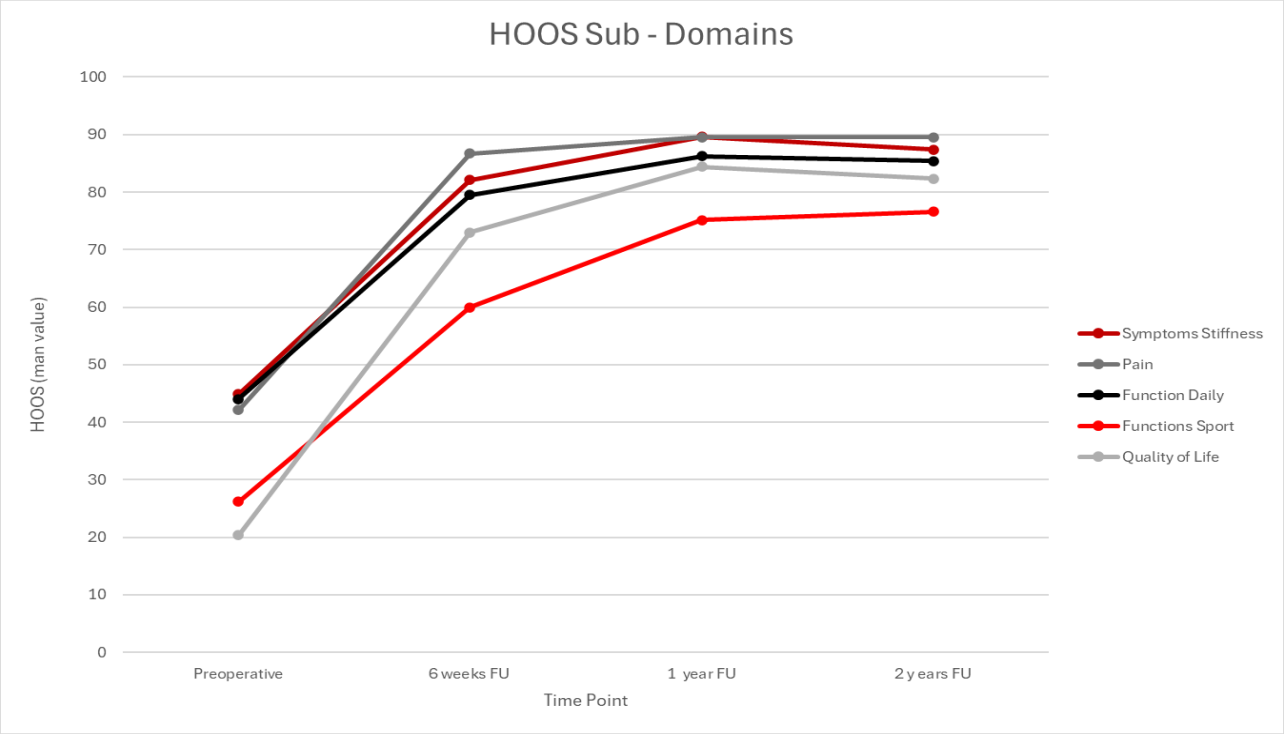

Figure 7 Graphic representation of the mean value of the HOOS sub-domains at preoperative (baseline), 6 weeks, 1 year, 2 years after surgery.

Time point	Symptoms stiffness	Pain	Function daily	Function sports	Quality of life
Preoperative (n = 45)					
Mean ± SD	44.9 ± 16.1	42.1 ± 13.7	44 ± 18.6	26 ± 16.9	20.4 ± 16.1
Median	45	43.5	41.5	25	25
6 weeks FU (n = 44)					
Mean ± SD	82.1 ± 12.1	86.7 ± 11.2	79.5 ± 14.1	60 ± 21.1	73 ± 23.0
Median	80	90	83	62	75
p-value (vs preoperative)	<0.001	<0.001	<0.001	<0.001	<0.001
1 year FU (n = 41)					
Mean ± SD	89.6 ± 11.4	89.5 ± 11.2	86.2 ± 15.2	75.1 ± 24.0	84.4 ± 18.1
Median	95	94	92	81	87
p-value (vs preoperative)	<0.001	<0.001	<0.001	<0.001	<0.001
2 years FU (n = 40)					
Mean ± SD	87.4 ± 13.5	89.2 ± 15.9	85.4 ± 18.8	76.6 ± 22.1	82.3 ± 22.6
Median	23.5	95	92.5	81	89
p-value (vs preoperative)	<0.001	<0.001	<0.001	<0.001	<0.001

Table 18 Change in HOOS sub-domains at preoperative (baseline), 6 weeks, 1 year and 2 years after surgery. p<0.05, p<0.01, p<0.001.

6.4.2 Radiographic results

6.4.2.1 Preoperative evaluation

Prior to surgery, patients underwent a radiographic assessment to define the main anatomical parameters of the study population. The radiographic analysis underlined an average leg-length discrepancy of 7 mm (±

12) (**Table 19**). Most of the subjects (68.2%, n = 39) showed no varus/valgus deformity of the affected hip, while 13.6% (n = 6) had a valgus deformity and 18.2% (n = 8) a varus deformity (**Table 20**).

Biomechanical feature	Mean ± SD	Min	Max	Median
Leg length discrepancy (mm)	7 ± 12	0	35	0

Table 19 Preoperative assessment of leg-length discrepancy in study population.

Varus/valgus deformity	n	%
Neutral	30	68.2
Valgus	6	13.6
Varus	8	18.2

Table 20 Preoperative assessment of varus/valgus deformity in study population.

Furthermore, in the preoperative analysis osteophytes were denoted in 97.7% (n = 43) of the patients. Herein, 61.4% of the subjects (n = 27) reported osteophytes in 3 of the DeLee-Charneley zones, 9.1% (n = 4) in 2 zones, 27.3% (n = 12) in 1 one zone while only 1 subject presented no osteophytes (**Table 21**).

Presence of osteophytes	n	%
yes	43	97.7
no	1	2.3
Number of zones involved	**n**	**%**
0	1	2.3
1	12	27.3
2	4	9.1
3	27	61.4

Table 21 Preoperative assessment of presence and location of osteophytes.

Regarding the presence of cysts, 61.4% (n = 27) of the subjects reported no cysts, 9.1% (n = 4) presented cysts in 1 zone, 13.6% (n = 4) in 2 zones, 13.6% (n = 6) in 2 zones and 15.9% (n = 7) in 3 zones (**Table 22**).

Presence of cysts	n	%
yes	17	38.6
no	27	61.4
Number of zones involved	**n**	**%**
0	27	61.4
1	4	9.1
2	6	13.6
3	7	15.9

Table 22 Preoperative assessment of presence and location of cysts.

6.4.2.2 Postoperative evaluation

Postoperative radiographic evaluation was performed at immediate postoperative (baseline), 6 weeks, 1 year and 2 years of follow-up. Acetabular radiographic analysis focused on the assessment of acetabular abduction angle, heterotopic ossification as well as presence of radiolucent lines.

Average acetabular abduction angle was measured to be 44.1° (± 4.2) postoperatively and remained constant over time (**Table 23**).

Time point	Mean (°) ± SD	Min	Max	Median
Postoperative (n = 44)	44.1 ± 4.2	30	55	45
6 weeks FU (n = 44)	44.1 ± 4.2	30	55	45
1 year FU (n = 41)	44.1 ± 4.3	30	55	45
2 years **FU (n = 40)**	44.1 ± 4.3	30	55	45

Table 23 Postoperative assessment of acetabular abduction angle at immediate postoperative, 6 weeks, 1 year and 2 years follow up.

No heterotopic ossification on the acetabular side was observed at immediate postoperative and 6 weeks after surgery, though it was identified in a few patients starting from 1 year after surgery. More in detail, heterotopic ossification was absent in 78% of the subjects (n = 32) at 1-year FU, while class I and class II heterotopic ossifications were found in 17.1% (n = 7) and 4.9% (n = 2) of the subjects, respectively. The presence of heterotopic ossification remained almost unchanged at 2 years FU, except for one patient (#84-16) who was previously diagnosed with Class I, but presented no ossifications at 2 years FU (**Table 24**). The appearance of heterotopic ossification is physiologic during the first year after total hip arthroplasty (Willburger et al., 2022), since it is caused by a cicatricial reaction occurring during the first months after surgery and it usually stabilizes within 1 year. It depends both on factors related to the surgical intervention (i.e. the surgical technique) and on the genetic predisposition of patients. A renowned and universally accepted guideline to prevent heterotopic ossifications is not available. They are generally not painful, particularly in case of grade I and II. Indeed, all patients presenting heterotopic ossifications in this study reported good clinical outcomes, both at 1- and 2-year of follow up.

	Postop (n = 44)		6 weeks FU (n = 44)		1 year FU (n = 41)		2 years FU (n= 40)	
Grade	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Absent	44	100	44	100	32	78	32	80
Class I	0	0	0	0	7	17.1	6	15
Class II	0	0	0	0	2	4.9	2	5

Table 24 Postoperative assessment of acetabular heterotopic ossification at immediate postoperative, 6 weeks, 1 year and 2 years after surgery.

The presence of radiolucent lines on the acetabular side was evaluated at immediate postoperative, 6-weeks, 1-year and 2-year follow-up. No radiolucent lines were detected for any patient at immediate post-op nor at

6-week follow-up. At 1-year follow-up, 27% (n = 11) of the subjects presented 1 mm radiolucency in zone 1, 2% (n =1) in zone 2, while no radiolucency was detected in zone 3. A slight increase of radiolucent lines has been detected 2 years after surgery: 30% (n = 12) of the patients presented 1 mm radiolucency in zone 1, 5% (n = 2) in zone 2 (**Table 25**). Two subjects, #84-07 and #84-09, presented 1 mm radiolucency both in zone 1 and in zone 2.

Radiolucency is a quite common occurrence in cemented prosthesis (Vanrusselt et al., 2015), it usually arises in zone 1 and it is due to the generation of fibrotic tissue concomitantly to bone resorption at the interface between bone and cement. A non-progressive radiolucent line in zone 1 or 2 is not meaningful and it is generally completely asymptomatic.

		Zone 1		Zone 2		Zone 3	
	Radiolucent lines	**n**	**%**	**n**	**%**	**n**	**%**
Post-op (n = 44)	None	44	100	44	100	44	100
	1 mm	0	0	0	0	0	0
	2 mm	0	0	0	0	0	0
	> 2 mm	0	0	0	0	0	0
6 weeks FU (n = 44)	None	44	100	44	100	44	100
	1 mm	0	0	0	0	0	0
	2 mm	0	0	0	0	0	0
	> 2 mm	0	0	0	0	0	0
1 year FU (n = 41)	None	30	73	40	98	41	100
	1 mm	11	27	1	2	0	0
	2 mm	0	0	0	0	0	0
	> 2 mm	0	0	0	0	0	0
2 years FU (n = 40)	None	28	70	38	95	40	100
	1 mm	12	30	2	5	0	0
	2 mm	0	0	0	0	0	0
	> 2 mm	0	0	0	0	0	0

Table 25 Postoperative evaluation of cup regarding presence of radiolucent lines at immediate postoperative, 6 weeks, 1 year and 2 years follow-up.

The angle between diaphyseal axis and stem axis was measured postoperatively. The average angle corresponded to 1.5° (± 2.7), ranging from 0° to 10°. This variety is due to the shortness of the Friendly Short stem, which enters only for 6 cm within the femoral canal. The angle is therefore influenced by the morphology of the proximal femur and can be adjusted intraoperatively by the surgeon. The angle remained consistent over time (**Table 26**).

It should be noted that stem radiographical evaluation at 2 years FU was performed on 39 patients out of the 40 evaluated at this timepoint. One patient (pt #84-02) underwent a partial revision of the stem after a

traumatic event (see paragraph *6.5.1 Adverse events*), receiving a competitor product. Therefore, radiographic analysis does not include the evaluation of this stem.

Time point	Mean (°) ± SD	Min	Max	Median
Postoperative (n = 44)	1.5 ± 2.7	0	10	0
6 weeks FU (n = 44)	1.3 ± 2.7	0	10	0
1 year FU (n = 41)	1.4 ± 2.8	0	10	0
2 anni FU (n = 39)	1.5 ± 2.8	0	10	0

Table 26 Postoperative evaluation of diaphyseal axis - stem axis angle at immediate postoperative, 6 weeks, 1 year and 2 years follow-up.

The presence of radiolucent lines on the stem was evaluated for each Gruen zone. No radiolucent lines were observed for any patient up to 2 -ears follow-up (**Table 27**).

	Radiolucent lines	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7
Post-op (n = 44)	None	44	44	44	44	44	44	44
	1 mm	0	0	0	0	0	0	0
	2 mm	0	0	0	0	0	0	0
	> 2 mm	0	0	0	0	0	0	0
6-week FU (n = 44)	None	44	44	44	44	44	44	44
	1 mm	0	0	0	0	0	0	0
	2 mm	0	0	0	0	0	0	0
	> 2 mm	0	0	0	0	0	0	0
1-year FU (n = 41)	None	41	41	41	41	41	41	41
	1 mm	0	0	0	0	0	0	0
	2 mm	0	0	0	0	0	0	0
	> 2 mm	0	0	0	0	0	0	0
2-year FU (n = 39)	None	39	39	39	39	39	39	39
	1 mm	0	0	0	0	0	0	0
	2 mm	0	0	0	0	0	0	0
	> 2 mm	0	0	0	0	0	0	0

Table 27 Postoperative evaluation of stem regarding presence of radiolucent lines at immediate postoperative, 6 weeks, 1 year and 2 years of follow-up.

Osteolysis around the stem was analyzed for each Gruen zone. No osteolysis was detected for any patient up to 2 years follow-up (**Table 28**).

	Osteolysis	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7
Post-op (n = 44)	None	44	44	44	44	44	44	44
	1 cm	0	0	0	0	0	0	0
	2 cm	0	0	0	0	0	0	0
	> 2 cm	0	0	0	0	0	0	0
6-week FU (n = 44)	None	44	44	44	44	44	44	44
	1 cm	0	0	0	0	0	0	0
	2 cm	0	0	0	0	0	0	0

	> 2 cm	0	0	0	0	0	0	0
1-year FU (n = 41)	None	41	41	41	41	41	41	41
	1 cm	0	0	0	0	0	0	0
	2 cm	0	0	0	0	0	0	0
	> 2 cm	0	0	0	0	0	0	0
2-year FU (n = 39)	None	39	39	39	39	39	39	39
	1 cm	0	0	0	0	0	0	0
	2 cm	0	0	0	0	0	0	0
	> 2 cm	0	0	0	0	0	0	0

Table 28 Postoperative evaluation of stem regarding presence of osteolysis at immediate postoperative, 6 weeks, 1 year and 2 years of follow-up.

Implant stability was assessed over time in terms of loosening, subsidence, cement cracks as well as any possible other features. No signs of implant instability were observed for any patient up to 2 years follow-up. 1 mm subsidence was registered in 2 cases at 1 year follow-up, and in 4 cases at 2 years follow-up (**Table 29**). Small-scale subsidence (<5 mm) usually appears within the first months after surgery and it does not correlate with the worsening of clinical outcomes (Hasler et al., 2021). A subsidence of a few mm might be related to a proper integration process of the prosthetic implant, as a result of the cement mantle plastic deformation due to compressive forces transferred upon the insertion of a conic shape femoral stem (Siepen et al., 2016) (Howell et al., 2005).

Implant stability	Postop	6 weeks FU	1 year FU	2 years FU
Loosening	0	0	0	0
Subsidence	0	0	2	4
Cement cracks	0	0	0	0
Other features	0	0	0	0

Table 29 Evaluation of overall implant stability at immediate postoperative, 6 weeks, 1 year and 2 years of follow-up.

6.5 Safety analysis

6.5.1 Adverse events reporting

The occurrence of adverse events was monitored throughout the study period for all enrolled subjects. **Table 30** summarizes the adverse events registered in terms of seriousness, severity, causality with the investigational device and the study procedure, the actions taken to treat the adverse event and outcome of the event. **Table 31** reports the adverse events categorization.

Adverse events						**N=17**
Seriousness	**n**	**(%)**	**Seriousness type**			**n (%)**
Serious	7	(41)	Death			2 (29)
			Life-threatening			0 (0)
			Hospitalization or prolonged hospitalization			3 (43)
			Permanent impairment			1 (14)
			Medical or surgical intervention to prevent one of the above			1 (14)
Not serious	10	(59)	-			-
Severity				**n**	**(%)**	
Mild				10	(59)	
Moderate				3	(18)	
Severe				4	(24)	
Causality: relationship to study medical device				**n**	**(%)**	
Causal relationship (related)				0		
Probable				0		
Possible				0		
Not related				17	(100)	
Causality: relationship to study procedure				**n**	**(%)**	
Causal relationship (related)				4	(31)	
Probable				1	(6)	
Possible				3	(18)	
Not related				9	(53)	
Action taken			**n**	**(%)**	**Detailed action**	**n**	**(%)**
None			5	(38)	-	-	-
Not Pharmacological			7	(41)	Hemotransfusion	3	(44)
					Closed reduction	1	(14)
					Revision surgery	1	(14)
					Contralateral revision surgery	1	(14)

			Contralateral THA	1	(14)
Pharmacological	2	(12)	Pain killers	1	(50)
			Beta blockers	1	(50)
Both	0	(0)	-		
Unknown	1	(8)	-		
Outcome	**n**	**(%)**			
Recovered	9	(53)			
Recovered with residual effect	1	(6)			
Ongoing	5	(29)			
Fatal	2	(12)			
Unknown	0	(0)			

Table 30. Adverse events occurred (seriousness, severity, causal relationship with the study medical device and with the procedure, actions, outcome)

AE/SAE general category	n	(%)	Specific category	n	(%)
Injury, poisoning and procedural complications	4	(23)	Trauma	1	(25)
			Post-op anemia	3	(75)
Cardiac disease	3	(18)	Heart failure	1	(33)
			Post-op alteration of the rhythm	1	(33)
			Atrial fibrillation	1	(33)
Musculoskeletal disorder	7	(41)	Osteoarthritis	1	(14)
			Trochanteritis	2	(29)
			Arthrosis	1	(14)
			Mobilization of a contralateral implant	1	(14)
			Degenerative flat foot	1	(14)
			Post-op dislocation	1	(14)
Tumor	1	(6)	-	-	-
Nervous system disorder	1	(6)	-	-	-
Not known	1	(6)	-	-	-

Table 311. Adverse events/serious adverse events categorization

A total number of 17 adverse events have been registered. Among these, 7 were defined serious.

- **SAE pt. #84-17**: this is the only SAE that was defined related to the study procedure (SADE). A post-operative hip dislocation occurred to patient #84-17, which was treated the day after surgery through a closed reduction. Prosthesis dislocation is a possible adverse effect of total hip arthroplasty

and it is one of the most common complications of this procedure (Kurtz et al., 2016). Therefore, the event was defined as anticipated by the Principal Investigator.

- **SAE pt. #84-32**: the patient was affected by endometrial cancer (diagnosed prior to the enrolment) which worsened during the course of the study and led to premature patient's death, after the 6-weeks follow up visit.
- **SAE pt #84-02**: the subject was exposed to a high energy trauma while performing intense sporting activity (skiing) 9 months after surgery, which resulted in a periprosthetic femoral fracture that required a revision surgery of the Friendly Short femoral stem. A longer stem and cerclages were implanted to restore articular functionality. Mueller cemented cup was not impacted and remained stable, thus it was not replaced. The event was considered not related to the device nor to the procedure by the Principal Investigator. Since the investigational device was not revised, this patient continued to participate in the study.
- **SAE pt. #84-03**: this SAE led to the death of patient #84-03 at the age of 87 years, two years after THA. Sub-I explained that, due to privacy reasons, the informatic system did not allow to retrieve information on the death reason. PI declared this event definitely not related to the investigational device nor to the study procedure, based on the clinical evidence collected at the 1-year follow-up visit, which was very positive from both a radiographic, clinical and subjective point of view.
- **SAE pt. #84-28**: this patient presented a severe contralateral coxarthrosis (on the left side), which required a THA 1.5 years after right total hip arthroplasty. This event was considered not related to the investigational device nor to the study procedure.
- **SAE pt. #84-42**: this subject began experiencing right lumbosciatic and hip pain during weight-bearing and walking 1.5 years after surgery. This was due to the mobilization of a cemented cup implanted in 2016 on the contralateral (right) hip, which was then revised. The event was considered not related to the investigational device nor to the procedure by the Principal Investigator.
- **SAE pt. #84-45**: the subjected suffered a progressive cognitive impairment which occurred approximately 2 years after surgery and caused him to be unable to walk. This patient could not leave the house, so he missed the 2-year FU visit. Patient's family reported no complications to the treated hip. This event was considered not related to the investigational device nor to the procedure.

Among the 17 events registered, the severity was considered mild in 10 cases (59%), moderate in 3 cases (18%) and severe in 4 cases (24%).

In 5 cases (29%) the adverse events did not require any action.

In 7 cases (41% of the total) the adverse events were not treated pharmacologically. Among these, three required hospitalization and consequent surgical intervention (as detailed above, revision surgery after trauma for pt. #84-02, contralateral THA for pt. #84-28 and contralateral revision surgery for pt. #84-28). One patient (pt. #84-17) was treated with a closed reduction after hip dislocation. The remaining three events treated with not pharmacological interventions were all postoperative anemia (with no further symptoms), which required blood transfusion. These events were related to the procedure, intraoperative blood loss, but are considered ordinary, especially in elderly patients who are particularly impacted by anemia (Patel et al., 2023) (Song et al., 2017).

In two cases (12%), the intervention was pharmacological. Pt. #84-11 received pain killers to be relieved from degenerative osteoarthritis affecting the contralateral knee. Pt. #84-09 was treated with Beta blockers to counteract post-operative atrial fibrillation with troponin alteration. This subject had previous history of stroke and hypertension (registered in the preoperative phase) and suffered from another heart failure after the 6-week follow-up visit, which prevented the patient from attending the 1-year FU visit.

In three cases (18%) the information on the intervention undertaken was unknown.

No adverse events related to the investigational device were registered.

6.5.2 Device deficiency

No device deficiencies were reported.

6.5.3 Device survivorship

Revision of the acetabular component for any reason is considered as the endpoint of the implant survivorship analysis. No acetabular component revision has been registered up to 2 years after surgery. Therefore, the survivorship of Mueller cemented cup is 100%.

The revision of the femoral component has been registered in 1 case out of the 40 active at 2-year FU, so the survivorship of Friendly Short femoral stem and of the AISI 316/L femoral heads is equal to 97.9% (95% confidence interval from 93.3% to 100%). **Figure 8** shows Kaplan-Meier survival curve of the femoral stem.

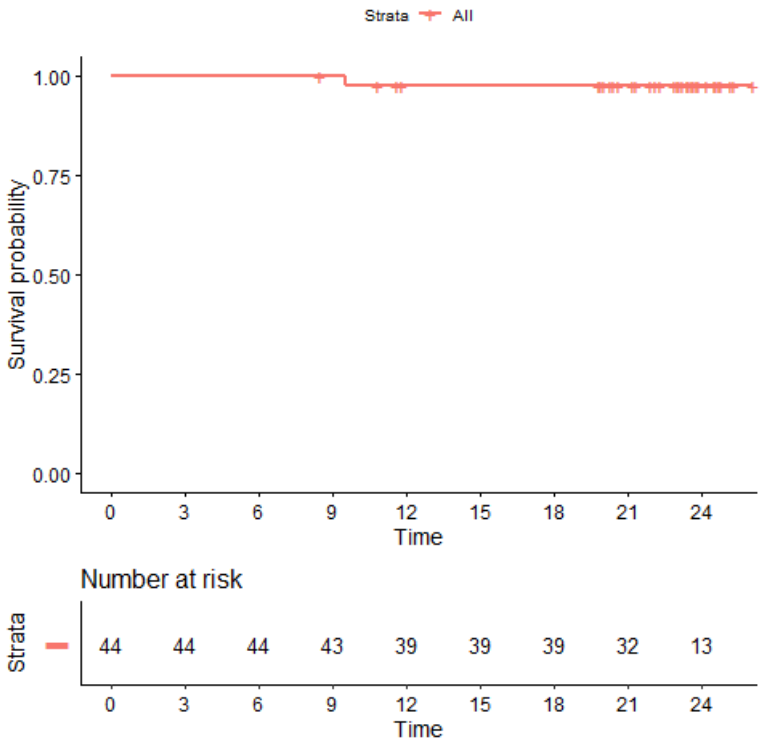

Figure 8. Kaplan-Meier survival curve of femoral side components

6.6 Protocol deviation

Subject ID	Date of deviation	Category of deviation	Description	Reason for deviation and corrective measure
84-25	05-Jul-2021	Major	Investigational device used off-label.	Intraoperative necessity. Patient withdrawn from the study.

Table 32. Protocol deviation list.

One protocol deviation was registered in the study (**Table 33**).

Perioperatively, the Principal Investigator decided to implant Mueller acetabular cup in combination with a femoral stem from another manufacturer (S-ROM stem, Depuy-Synthes), since this device was considered more suitable to the patient's conditions (the decision was taken independently from the clinical study).

H-31 clinical investigation plan establishes that Mueller cup must be implanted according to the standard surgical technique, which exclusively allows the coupling of the cup with other Limacorporate devices. For this reason, the enrolment of patient 84-25 within H-31 trial was considered a major protocol violation and the patient was eventually withdrawn.

The patient has been followed up according to the Institution standard of care. Ethics Committee has been informed about the deviation occurred and the corrective action taken.

7.0 DISCUSSION

Evidence was collected on clinical, radiographic and safety outcomes on 40 patients treated with Mueller cemented cups in combination with Friendly Short stem, up to 2 years after surgery. Therefore, the population observed at 2 years of FU exceeded the 36 patients necessary to reach a statistical power of 90%. In terms of primary endpoint, a functional change in Harris Hip Score of 49 points was detected between preoperative and 2-year FU visit, greater than the difference defined as moderate improvement (40 points) (Singh et al., 2016).

The analysis of 2-year FU clinical and patient-reported outcomes of patients included in this study highlighted excellent results. Evident signs of improvement of patients' conditions were detected starting from the 6-week follow-up visit, and an even more marked increase was recorded between the preoperative and the 1 year after surgery visits. The results remained unchanged up to the 2-year FU.

Radiographically, the implant showed stability and good integration within the entire observation timeframe, no complications, osteolysis or cement cracks were detected. No radiolucent lines were detected around the femoral stem, while only a few cases of 1 mm radiolucency were registered, though with no further symptoms related.

No significant complications or adverse events related to the investigational devices were recorded.

Clinical, patient-reported and radiographic outcomes highlighted excellent performance and safety of Mueller cemented cups in total hip prosthesis up to 2 years after surgery.

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Clinical Investigation Report (CIR) Approval Form

Clinical Investigation Information:

Title “A Prospective Clinical Study Evaluating Clinical, Radiographic And Patient-Reported Outcomes Of THA With Cemented Acetabular Cups”

Version n° 2.0

Date August 2020

All the functions participating to the CIR preparation have to be listed below:

Approval			
Function/Role	**Name and Surname**	**Date**	**Signature**
RMCL/CMCL	Fabiana Pavan		
Statistician	Luca Dozza		
Medical Expert	Dr. Luca Marega		
Medical Writer	Domizia Baldassi		

Clinical Investigation Report (CIR) Signature Page

Clinical Investigation Code/Name of product:

n°H-31 CEMENTED CUP

COODINATING INVESTIGATOR
AND LIMACORPORATE'S REPRESENTATIVE SIGNATURE

Clinical Investigation Title

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the investigation

Coordinating Investigator: _____ **Date**_____
Dr. Luca Marega **Signature**

Authorized LimaCorporate Representative Signature

Signature: _____ **Date:** _____
Fabiana Pavan
Clinical Trial Lead