Clinical Study Protocol
PREOB-ON3
Protocol Number: 000001/BT
EudraCT Number: 2009-012929-11
NTC Number: 01529008

Title

Phase III, Pivotal, Multicentre, Randomised, Double-blind Controlled Study to Evaluate the Efficacy and Safety of Autologous Osteoblastic Cells (PREOB®) Implantation in Early Stage Non Traumatic Osteonecrosis of the Femoral Head

Sponsor
Bone Therapeutics S.A.
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B-6041 Gosselies, Belgium

Sponsor's Representative in the United States of America
Bone Therapeutics USA Inc.
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Boston, MA 02108

Good Clinical Practice (GCP) Statement

This study will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and all applicable legislation and regulatory requirements.

PROTOCOL SPONSOR SIGNATORY APPROVAL

Protocol Number: 000001/BT

Title of the protocol:

Phase III, pivotal, multicentre, randomised, double-blind controlled Study to evaluate the Efficacy and Safety of Autologous Osteoblastic Cells (PREOB®) Implantation in Early Stage Non Traumatic Osteonecrosis of the Femoral Head.

Date of the protocol (Version 6.1): May 15, 2017

Sponsor's representative

Guy Heynen, MD

Chief Clinical and Regulatory Officer

Name and Title	Date	Signature

INVESTIGATOR SIGNATURE AND AGREEMENT WITH THE PROTOCOL

In accordance with all applicable legal and regulatory requirements,

I, the undersigned, agree to conduct this study in compliance with this Protocol and to assume responsibility for the proper conduct of the study at this site.

Agree that the clinical trial will be carried out in accordance with any and all applicable laws, regulations, guidance, guidelines, and principles regarding the:

- Ethical principles for medical research involving human subjects
- Good Clinical Practice as regards conduct of clinical trials and investigational medicinal products for human use
- Clinical safety data management, notification, and reporting
- Advanced Therapy Medicinal Products (According to EMA)
- Sponsor Standard Operating Procedures (SOPs)

Agree:

- That my primary responsibility is to safeguard the rights and well-being of each patient participating in this study, and that the patient's rights and well-being must take precedence over the goals and requirements of the study.
- To ensure the confidentiality and protection of all information obtained from and about the participants.
- To obtain the informed consent of the patients prior to their participation in the study and ensure that:

  * Verbal information, adapted to the patient, has been provided, avoiding direct or indirect coercion;

  * The patient has understood the study;

  * The patient information sheet and written consent form (approved version) has been provided;

  * The patient has been given a reasonable period of reflection (opportunity to inquire about details of the trial and to decide whether or not to participate in the trial).
- To keep the written proof of the informed consent of the patients or their authorised legal representatives.
- To ensure that no clinical samples are retained on site or elsewhere without the approval of the Sponsor and the express written informed consent of the patient.

- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To promptly report any unanticipated problems that involve any risk to patient in research covered under this agreement.
- To ensure the transfer of the information and the data collected for the study (CRF) in a clear, legible way and in conformity with the source documents (patient file).
- To ensure to have the necessary resources (e.g., qualified personnel and material resources) to successfully complete the study with regard to deadlines.

I acknowledge

- That I have been informed that certain Regulatory Authorities require the Sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the Sponsor or the investigational product, and more generally about his/her financial ties with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Principal Investigator

Name and Title Date Signature

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STUDY SYNOPSIS

EudraCT Number *2009-012929-11* **Protocol Number:** *000001/BT* **Protocol Code:** PREOB-ON3	**Phase of Development:** Pivotal Phase III Study
Sponsor in the European Union Bone Therapeutics S.A., Gosselies, Belgium **Sponsor's Representative in the United States of America** Bone Therapeutics USA Inc., Boston, Massachusetts	
Planned Study Period - 12 months recruitment period - 24 months follow-up period - 24 months long term follow-up	
Objectives To determine the efficacy and safety of PREOB®, a proprietary population of autologous osteoblastic cells, in the treatment of early stage non-traumatic osteonecrosis of the femoral head.	
Planned Number of Patients: 118 patients randomised in 1:1 ratio - *59 patients in the control group:* Core decompression/Placebo implantation - *59 patients in the PREOB® group:* Core decompression/PREOB® implantation	
Medical Condition or Disease under Investigation Early stage (ARCO stages I or II) non-traumatic osteonecrosis of the femoral head.	
Patient Selection Men and women, aged 18 to 70 years old, diagnosed with non-fractural (ARCO stages I or II) osteonecrosis of the femoral head, confirmed by conventional X-ray and magnetic resonance imaging (MRI). All patients must be symptomatic, except ARCO stage II patients with a combined coronal and sagittal necrotic angular sum superior to 190°.	
Inclusion Criteria All patients must satisfy ALL the following criteria at study entry: - Men or women between 18 and 70 years (inclusive) with a diagnosis of ARCO Stage I or II non-traumatic osteonecrosis of the femoral head, confirmed by central imaging analysis based on X-ray and MRI - Ability to provide a written, dated, and signed informed consent prior to any study related procedure and to understand and comply with study requirements - Diagnosis of Osteonecrosis: a. ARCO stage I associated with WOMAC® VA3.1 pain score ≥20 mm and necrotic angle sum ≥190° based on sagittal and coronal MRI views or	

b. ARCO stage II associated with WOMAC® VA3.1 pain score ≥20 mm if necrotic angle sum <190° based on sagittal and coronal MRI views

or

c. ARCO stage II associated or not with pain if necrotic angle sum is ≥190° based on sagittal and coronal MRI views

d. Associated with corticosteroid and/or with alcohol abuse and/or idiopathic

- Normal haematology function, defined as leukocytes ≥3000/mm^3, absolute neutrophils count ≥1500/mm^3, platelets ≥140,000/mm^3, and haemoglobin concentration ≥10g/dl (peripheral blood test)

Exclusion Criteria

The following criteria should be checked at the time of study entry. If *any* exclusion criterion applies, the patient must not be included in the study:

Current symptoms and/or signs related to the disease under study

- Exclusively diaphyseal or metaphyseal osteonecrotic lesion
- Traumatic or hyperbaric osteonecrosis, or osteonecrosis associated with haemoglobinopathy or coagulopathy (e.g., thalassemia, sickle cell disease,…), or Gaucher's disease
- Any other focal or diffuse bone marrow lesion
- Osteoarthritis at the hip under evaluation defined as Kellgrens stage ≥2, as assessed by the Central Radiologist
- Patients suffering from any medical conditions interfering with patient's pain evaluation of the hip under evaluation, such as knee arthritis.
- Bone fracture or bone infection at hip under evaluation.
- Patients who are candidates for any predictable joint replacement on the hip under evaluation.

Current or previous diagnoses, signs and/or symptoms

- Blood not qualifying for PREOB® production, including active hepatitis B (defined as positive HBs Ag and/or positive PCR), or active hepatitis C (defined as positive PCR), positive serology for HIV, or Syphilis, or HTLV-1, and any other tests that may be required by the authorities in case of a new disease outbreak that can affect the safety of the physicians and operators at the time of patient screening
- Presence, or previous history, of risks factors for diseases caused by prions, and recipients of grafts of cornea, sclera, and dura mater
- History of blood loss exceeding 450 ml (incl. donations) within 1 month of screening
- Renal impairment, defined by an estimated creatinine clearance value < 30 ml per min, calculated with the Cockcroft-Gault formula
- Hepatic impairment, defined as alanine aminotransferase or aspartate aminotransferase ≥ 3 times the upper limit of normal
- Poorly controlled diabetes mellitus, defined as HbA1C > 9%
- Global sepsis
- Allergy to gentamicin or any substance or device the patient might be exposed to in the context of the study related interventions (*i.e.*, bone marrow harvesting and implantation), as judged by the Investigator
- History of hypersensitivity to human biological material, including blood and blood derived products, documented clinically or by laboratory tests
- Current or past history of solid or haematological neoplasia (except for basal cell carcinoma of the skin and for carcinoma in situ of the cervix that has been treated with no evidence of recurrence)
- History of bone marrow transplantation

- Patients with a life expectancy less than 2 years, as judged by the Investigator

Current or previous treatment

- Patients having participated in another clinical trial within 3 months of screening
- Patients previously treated with PREOB®
- Patients treated by core decompression of the hip under evaluation within 6 months of screening
- Treatment with doses of prednisolone ≥15 mg per day (or equivalent) within 1 month from screening, and patients with anticipated needs of daily corticoid doses ≥15 mg prednisone (or equivalent) in the 6-month period following PREOB/Placebo implantation
- Illicit drug or alcohol abuse interfering with patient's ability to understand and comply with study requirements, as judged by the Investigator

Safety aspects concerning female patients of childbearing potential

- Pregnancy
- Breast-feeding
- Women with childbearing potential not willing or able to use reliable contraceptive method for at least 6 weeks prior to screening and during the whole study period. Reliable contraceptive methods include orally administered hormonal contraceptives, surgical intervention (e.g., tubal ligation), and intrauterine device (IUD).

Other exclusion criteria

- Body Mass Index (BMI) ≥ 35 kg/m^2
- Patients unable to undergo MRI, e.g. patients with pace-maker, intra-ocular or intra-cerebral metallic foreign bodies, and mechanical artificial heart valves
- Patients unable to undergo general anaesthesia or surgical intervention

Test procedure, product, dose and mode of administration

PREOB® Group: Core decompression with a small-diameter trephine and implantation of 5 ml PREOB® suspension into the necrotic lesion.

Control Group: Core decompression with a small-diameter trephine and implantation of 5 ml Placebo solution into the necrotic lesion.

Detailed Visit Schedule

After informed consent is obtained, fulfilment of study inclusion and exclusion criteria and radiological assessment for baseline will be performed at Visit 1.

Visit 2 is scheduled to take place at least 21 days* before Visit 3 for baseline clinical assessments and (sham) bone marrow harvest procedure performed by the Independent Physician.

At Visit 3, the surgical procedure (Core decompression and implantation, PREOB® or Placebo) is performed by the Principal Investigator. Patients will be systematically evaluated 24 hours after the procedure.

Patients will be followed during 24 months, at months 1, 3, 6, 12, 18 and 24 (Visit 4 to Visit 9).

Long term follow-up visits (phone calls) are scheduled at months 36 and 48.

**Visits 2 and 3 will be scheduled in conjunction with the Sponsor's Manufacturing Unit and will take into account the travel time between the Investigating Site and the Sponsor's Manufacturing Unit.*

Duration of Study

Patients will undergo a single administration of PREOB® or Placebo into the necrotic lesion under general anaesthesia. Patients will be considered as having completed the study upon completion of the last scheduled visit of the follow-up period, 24 months after the implantation procedure.

Long term follow-up visits (phone calls) are scheduled at months 36 and 48.

Main Study Objectives and Endpoints

The main objectives of the study are to demonstrate that Core decompression/PREOB® implantation into necrotic lesion is superior to Core decompression/Placebo implantation in relieving hip symptoms and halting (or reverting) radiological progression to fractural stages (ARCO III or higher) in patients with non-traumatic early stage osteonecrosis of the femoral head, *at 24 months*.

Efficacy endpoints

Primary Efficacy Endpoint

- Percentage of treatment responders at Month 24,
  a treatment responder at a studied timepoint being defined as a patient who responded both:
  - Clinically, *i.e.*, if at the studied timepoint, the WOMAC® VA3.1 pain subscale score of the study treated hip improved from baseline by at least the minimal clinically important difference (MCID)[a],
    and
  - Radiologically, *i.e.*, if at the studied timepoint, the study treated hip did not progress to fractural stages (ARCO III or higher), as assessed by conventional X-ray.

[a] *The MCID value is set at 10 mm.*

For patients with a baseline WOMAC® VA3.1 pain subscale score ≥10 mm, the MCID can be used as a threshold value to define a clinically meaningful pain relief. These patients will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip decreased from baseline by at least the MCID.

For patients with a baseline WOMAC® VA3.1 pain subscale score <10 mm, the MCID cannot be used as a threshold value to define a clinically meaningful pain relief. These patients will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip is found in the range [0; 4] (VAS pain range labelled as "no pain").

Secondary Efficacy Endpoint

- Percentage of treatment responders at Month 6, 12 and 18, and over the 24-month follow-up period
- Percentage of clinical responders at Month 1, 3, 6, 12, 18 and 24, and over the 24–month follow-up period; a clinical responder being defined as a patient whom the WOMAC® VA3.1 pain subscale score of the study treated hip improved from baseline by at least the MCID[b] at the studied timepoint
- Percentage of radiological responders at Month 6, 12, 18 and 24, and over the 24–month follow-up period; a radiological responder being defined as a patient whom the study treated hip did not progress to fractural stages (ARCO III or higher), as assessed by conventional X-ray, at the studied timepoint
- Absolute change from baseline in WOMAC® VA3.1 total score and composite pain, stiffness, and function subscale scores of the study treated hip at Month 1, 3, 6, 12, 18 and 24, and over the 24-month follow-up period
- Time to progression to fractural stages (ARCO III or higher) of the study treated hip
- Percentage of patients requiring hip arthroplasty for the study treated hip at Month 1, 3, 6, 12, 18 and 24, and over the 24-month follow-up period
- Time to hip arthroplasty for the study treated hip

[b] *The MCID value is set at 10 mm.*

Patients with a baseline WOMAC® VA3.1 pain subscale score ≥10 mm will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip decreased from baseline by at least the MCID.

Patients with a baseline WOMAC® VA3.1 pain subscale score <10 mm will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip is found in the range [0;4]- (VAS pain range labelled as "no pain").

[redacted]

Safety endpoints

From the beginning to the end of the main study period at Month 24, patients will be systematically assessed for the potential occurrence of any AE or SAE, related to the product or related to the procedure by patient interview, physical examination (including body mass index and vital signs), and laboratory measurements.

Moreover, a long term follow-up will be performed via phone calls (conventional X-ray to be performed only when the patient still feels pain on the treated hip) at 36 and 48 months after IMP implantation. This includes assessment of hip symptoms (pain, stiffness, and function) using WOMAC® LK3.1 (Likert Scale) and the potential occurrence of any AEs and SAEs (patient open questionnaire, including notably any changes in health status and need for total hip arthroplasty).

Statistical Analysis

Statistical methods will be exhaustively described in a Statistical Analysis Plan (SAP), which will constitute the only reference document. The SAP will be generated, reviewed, approved, and signed by the biostatistician and the Sponsor, prior to database lock, at the latest.

Efficacy Analysis

The full analysis set (FAS) consists in an modified Intention-To-Treat population and will be considered as the primary cohort for analysis of efficacy.

The superiority of PREOB® over Placebo will be considered achieved if the percentage of treatment responders is statistically significantly higher in the PREOB® group than in the Placebo group at Month 24. The primary efficacy endpoint will be compared between the two groups by means of a Chi square or a Fisher's exact test (as appropriate). The difference between the two groups will be considered significant if the *p*-value is less than or equal to the Type I error.

Comparison between treatment groups of the secondary binary efficacy endpoints will be performed at each studied timepoint, by means of a Chi square test or a Fisher's exact test (as appropriate). Treatment effect over the 24-month follow-up period will be assessed using a Generalized Estimating Equations (GEE) model taking into account correlations between the repeated measurements within patients.

Comparisons between treatment groups of the secondary continuous efficacy endpoints will be performed at each studied timepoint by means of a parametric Student t-test or a non-parametric Wilcoxon rank-sum test (as

appropriate). Multivariate analyses including analyses over time will also be conducted to assess treatment effect over the 24-month follow-up period.

Distributions of time-to-event variables will be estimated at each timepoint using the Kaplan-Meier product limit method. The log-rank test will be used for treatment group comparison.

The same statistical methods as for the primary and secondary efficacy endpoints will be used to analyse the exploratory efficacy endpoints.

Safety Analysis

The safety set (SAF) will be considered as the primary cohort for analysis of safety.

Safety variables include AEs, SAEs, vital signs, physical examination, laboratory tests and concomitant medications. All safety analyses will be described by treatment group actually received and overall on the SAF.

Date and Version of the Study Protocol: May 15, 2017 - Version 6.1

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
ARCO	Association Research of Circulation Osseous
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ATMP	Advanced Therapy Medicinal Product (according to EMA)
BMC	Bone Marrow Concentrate
BMI	Body Mass Index
BP	Blood Pressure
CAs	Competent Authorities
CAT	Committee for Advanced Therapies (according to EMA)
CBMP	Cell-Based Medicinal Product
CHMP	Committee for Medicinal Product for Human Use (according to EMA)
CI	Confidence Interval
CPMP	Committee for Proprietary Medicinal Products (according to EMA)
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT (scan)	Computed Tomography
CTA	Clinical Trial Application
CU	Clinical Unit
DCF	Data Clarification Form
DSMB	Data Safety Monitoring Board
DMP	Data Management Plan
EC	European Commission
ECs	Ethics Committees
EMA	European Medicines Agency
EPCs	Endothelial Progenitor Cells
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food And Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTLV	Human T-lymphotropic Virus
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier (according to EMA)
IRB	Institutional Review Board
ITT	Intention-To-Treat
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stromal/Stem Cell
OECD	Organisation for Economic Co-Operation and Development
ON	Osteonecrosis
ORA	Office of Regulatory Affairs
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PV-CRO	Pharmacovigilance-CRO
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SASQE	Serious Adverse Safety/Quality Event
SDV	Source Data Verification
SOC	System Organ Class
SOP	Standard Operating Procedure
SPM	Study Procedure Manual
SSO	Study Safety Officer
DCF	DCF
THA	Total Hip Arthroplasty
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization
WOMAC®	Western Ontario McMaster University Score®
WMA	World Medical Association

DEFINITIONS

- **Approval (in relation to ethics committees (ECs):** the affirmative decision of the EC that the clinical trial has been reviewed and may be conducted at the investigating site within the constraints set forth by the EC, the Institution, Good Clinical Practice (GCP, and the applicable regulatory requirements.
- **Autologous:** means that the donor of the human biological material and the recipient of the investigational medicinal product (IMP) is the same individual.
- **Case report form (CRF or eCRF):** a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each trial subject.
- **Clinical study:** is any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational medicinal product and/or to identify any adverse reactions to an investigational medicinal product, and/or to study absorption, distribution, metabolism, and excretion of an investigational medicinal product with the object of ascertaining its safety and/or efficacy - PREOB® in this case.
- **Completed patient:** a patient who completed all scheduled visits up to last scheduled visit (inclusive).
- **Contract Research Organization (CRO):** a person or an organization contracted by the Sponsor to perform one or more of the Sponsor's trial-related duties and functions.
- **Data Safety Monitoring Board (DSMB):** an independent data monitoring committee established by the Sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the Sponsor whether to continue, modify or stop the trial.
- **Discontinued or withdrawn patient:** a patient who has been enrolled, screened, randomised or treated but has withdrawn from the study before completion of the last scheduled visit.
- **Drop out:** a patient who has been randomised but never treated.
- **Distribution:** transportation and delivery of tissues and cells intended for human applications.
- **Eligible patient:** a screened patient who is considered eligible according to selection criteria.
- **Enrolled patient:** a patient who has dated and signed the Informed Consent Form (ICF).
- **Ethics Committee:** a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical trial and is adequately constituted to provide assurance of that protection.
- **Good Clinical Practice (GCP):** set of internationally recognized ethical and scientific requirements and standards as regards the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials, that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, well-being, and confidentiality of trial subjects are protected.
- **Independent Physician:** the unblind physician who will perform both the (sham) bone marrow harvest and blood collection procedures.

- **Informed Consent:** a process by which a patient voluntarily confirms his/her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
- **Investigating Site:** any public or private entity or medical facility where clinical trial and trial-related activities are conducted.
- **Investigational Medicinal Product (IMP):** a pharmaceutical form of an active substance or Placebo being tested or used as a reference in a clinical trial.
- **Investigator:** a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator (PI)..
- **Managing Physician:** Managing Physician of Human Biological Material in the Production/Tissue Establishment is a Medical Doctor responsible to guaranty the traceability, the quality and safety of the Human Biological Material, as well as the quality and safety of all operations executed in the Production/Tissue Establishment. He is also responsible for the reporting of Serious Adverse Event and Serious Adverse Reaction related to Human Biological Material. His function can be delegated.
- **Mesenchymal stromal (stem) cells (MSC):** "plastic-adherent" stem cells, expressing specific surface markers, and giving rise to bone, cartilage, and adipocyte cells.
- **Monitor:** refers to Sponsor's authorized CROs and/or CRAs.
- **Multicenter Trial:** a clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.
- **Non-traumatic osteonecrosis:** a bone disease characterized by necrosis of bone and medullary tissues, mainly at bone epiphyseal sites evolving towards articular collapse and joint destruction due to non-traumatic aetiological factors.
- **Osteoblastic cells:** cells belonging to the osteoblastic lineage (bone forming cells) encompassing the osteoprogenitors, the pre-osteoblasts, the osteoblasts, the lining cells and the osteocytes.
- **Patient:** an individual participating in the clinical trial.
- **PREOB®:** a proprietary autologous osteoblastic cells (PREOB® cells) product, *i.e.*, an advanced therapy medicinal product falling under the scope of the European Regulation 1394/2007/EC and the Directive 2001/83/EC manufactured by Bone Therapeutics S.A.
- **Processing:** all operations involved in the preparation, manipulation, preservation, and packaging of tissues or cells intended for human applications.
- **Procurement:** a process by which tissues or cells are made available.
- **Production/Tissue Establishment:** a tissue bank or a unit of a hospital or another body where activities of procurement, testing, processing, preservation, storage, and/or distribution of human tissues and cells are undertaken.
- **Randomised patient:** a patient to whom a randomisation number has been allocated.

- **Screened patient:** a patient who has dated and signed the Informed Consent Form (ICF) (enrolled patient) and who has performed the checking of the selection criteria.
- **Screening failure:** a screened patient who is not eligible for the study after checking the selection criteria.
- **Serious Adverse Event (SAE):** any adverse event (AE) or serious adverse reaction (SAR) that, in the view of the investigator or sponsor, results in any of the following outcomes (ICH E2a): Death, Life-threatening AE, Inpatient hospitalization or prolongation of existing hospitalization, Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, Congenital anomaly/birth defect. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.
- **Serious Adverse Reaction (SAR):** any untoward and unintended responses to an investigational medicinal product related to any dose administered (having a reasonable causal relationship to the product), and that results in death, is life-threatening, requires patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
- **Serious Adverse Safety/Quality Event (SASQE):** any adverse event related to the any operation done on the collected human biological material under the responsibility of the Intermediary Structure (*i.e.*, direct transport and distribution of the human biological material from the harvesting site to the Production/Tissue Establishment of Bone Therapeutics S.A.) that may cause death, be life-threatening, generate disability or incapacity to work to the patient, or that may cause morbidity
- **Storage:** maintenance of the IMP under appropriate controlled conditions until administration.
- **Study Safety Officer:** an individual designated to perform the handling, notification, and reporting of safety issues.
- **Suspected Unexpected Serious Adverse Reaction (SUSAR):** serious adverse reaction, the nature, severity, specificity, or outcome of which is not consistent with applicable product information (e.g., the Investigator's Brochure).
- **Treated patient:** a patient to whom a treatment has been administered.

1 INTRODUCTION

1.1 Background of the Study

1.1.1 Osteonecrosis of the Femoral Head

Non-traumatic osteonecrosis, also known as avascular necrosis, is a bone disease characterized by necrosis of bone and medullary tissues, mainly at bone epiphyseal sites evolving towards articular collapse and joint destruction due to non-traumatic aetiological factors.

Osteonecrosis is a devastating disease with a dramatic natural evolution. Osteonecrosis mainly affects young patients (30-60 years old, with only 20% of patients older than 50 years of age). Natural history of symptomatic osteonecrosis of the femoral head is generally characterized by relentless progression to collapse of the femoral head, ultimately leading to total hip arthroplasty. Based on current practice and available therapeutic options, nearly one-half of patients will require total hip arthroplasty (THA) before the age of 40. Studies have shown that within two years, 93% of stage I and 70% of stage II osteonecrosis in untreated patients will show radiological progression, with a mean progression time of respectively 8 and 14 months, which ultimately leads to femoral head collapse thus requiring total hip arthroplasty (Steinberg *et al.*, 1997; Steinberg *et al.*, 2001).

Non-traumatic osteonecrosis is generally associated with one or more risk factors. In Caucasians, over two thirds of non-traumatic osteonecrosis are associated with past or current corticosteroid therapy and/or alcohol overconsumption. The remaining third includes dysbaric phenomenon, haemoglobinopathies, and coagulopathies. In other rarer medical conditions, the incidence of non-traumatic osteonecrosis is known to be greater than 1%, including organ transplant recipients and patients with systemic lupus erythematosus (Vail & Covington, 1997). Idiopathic cases account for a small proportion of non-traumatic osteonecrosis (<5%).

The exact incidence of osteonecrosis is unknown, but osteonecrosis is the underlying diagnosis in about 5% to 12% of total hip arthroplasty (Lieberman *et al.*, 2003). With an average time to hip arthroplasty of less than two years, the estimated prevalence of osteonecrosis in the OECD countries ranges from 2.5 to 3.1 per 10,000 habitants.

1.1.2 Current Therapeutic Strategies for Osteonecrosis

Several conservative interventions are usually used to halt progression of the disease and stimulate repair, but no treatment has clearly demonstrated efficacy against progression of the lesion towards fractural stages. The best currently available therapeutic option for early stages (I or II) osteonecrosis of the femoral head is core decompression using trephines with a mean

diameter of 8-10 mm This surgical procedure was first described by Phemister (Phemister, 1949), who proposed that core decompression acts to decompress rigid intra-osseous chamber, and thereby improves venous drainage and promotes revascularization of the femoral head.

Interestingly, because of the potential occurrence of various complications with use of this technique, including notably articular cartilage damage and subchondral fractures, several groups developed smaller diameter (3-mm) core decompression method (Mont *et al.*, 2004; Song *et al.*, 2007; Marker *et al.*, 2008; Marker *et al.*, 2008b). This less invasive strategy is reportedly associated with lower morbidity and postoperative complication rates, as compared with those reported with conventional large-diameter method.

However, although core decompression is currently considered as the treatment of choice and has now been in use for many years, it remains controversial because many surgeons have been unable to replicate the high levels of success that have been reported in the initially published series (Camp & Colwell, 1986; Hopson & Siverhus, 1988; Learmonth *et al.*, 1990; Stulberg *et al.*, 1991; Koo *et al.*, 1995). This controversy points to the need to search for more effective conservative therapeutic options in the management of early stage osteonecrosis of the femoral head.

1.1.3 Pathophysiological Mechanisms and Rationale for the Use of PREOB® in Osteonecrosis

It has long been thought that osteonecrosis develops subsequently to a reduction in blood flow to the bone, resulting in local ischemia. Fat embolism (Jones, 1985), retrograde embolization of the marrow fat (Simkin & Downey, 1987), microvascular tamponade of blood vessels of the femoral head by marrow fat (Wang *et al.,* 1977; Wenstrup *et al.*, 2002), and trabecular bone microfracture (Laurent *et al.*, 1973) are amongst the many hypotheses formulated. However, it has been postulated that osteonecrosis of the femoral head may also result from bone and/or mesenchymal cellular deficiency. Indeed, the proliferative activity and the number of mesenchymal stem cells in both the haematopoietic and stromal compartments of bone marrow have been shown to be decreased in patients with osteonecrosis (Gangji *et al.*, 2003). A decrease in the stem cell pool may result in too low number of osteoblasts required for effective bone remodelling during the early stages of the disease (Hernigou & Beaujean, 1997). This decrease in osteoblast proliferative capacity may be indicative of the disruption in the mechanosensory role of the osteocyte-canalicular network and might also explain the observed transition from bone marrow ischemia and oedema to established necrosis.

1.1.3.1 *Previous Trials Treating Osteonecrosis with Cell-Based Products - Bone Marrow Grafts*

Early interventions with bone marrow implantation were reported to be effective in the treatment of osteonecrosis of the humeral head secondary to sickle cell disease (Hernigou *et al.*, 1997). Implanting bone marrow-containing stromal cells after the decompression procedure was also shown to be somehow effective in treating ARCO Stage I and II non-traumatic osteonecrosis of the femoral head in two pilot studies (Hernigou *et al.*, 2002; Gangji *et al.*, 2004). These observations suggested that it may be possible to prevent osteonecrosis damage extension by implantation of bone marrow cells presumably possessing osteogenic potential.

Interestingly, it has been proposed that the effectiveness of previous studies using autologous bone marrow cells for treating osteonecrosis may potentially be explained by the implantation of stem cells with osteogenic potential within the bone lesion (Hernigou *et al.*, 1999; Gangji *et al.*, 2003). It has been postulated that injected bone marrow stromal cells may further act through either the release of angiogenic cytokines, which can lead to an improvement in osteogenesis (Gangji *et al.*, 2004), or the presence of endothelial progenitor cells (EPCs) within the $CD34^+$ fraction (Tateishi-Yuyama *et al.*, 2002). Altogether, the data supports the concept of developing a bone marrow cell derived medicinal product to test its efficacy and safety in patients with osteonecrosis.

1.1.3.2 *PREOB® Phase II Randomised Reference-Controlled Proof-of-Concept Study*

Based on these observations, a proprietary cell population of osteoblastic cells (PREOB®) has been developed and subsequently optimised to solely include the efficacious cell types by Bone Therapeutics S.A. Indeed, using selected and specific osteoblastic cells would allow a more focused, effective, and safe approach to clinical trials. In this respect, a proof-of-concept, randomised, controlled, single-blind, Phase IIb study has documented both the efficacy and safety of a single local implantation of PREOB® in patients with osteonecrosis of the femoral head for up to 5 years, in comparison with an active reference treatment (bone marrow concentrate: BMC).

In this study, subjects (patient's hips) with early stage osteonecrosis of femoral head were randomly assigned to receive Core decompression/PREOB® ([redacted] cells; [redacted] cells/ml) implantation *or* Core decompression/ BMC implantation, with a ratio 1:1. The main efficacy outcome was the proportion of treatment responders – a responder subject being defined as a hip which (i) showed a clinically relevant pain relief and (ii) did not radiologically progress to fractural stages. Results show that 2 years after implantation, there were almost twice as many treatment responders in the PREOB® group (70.0%) than in the BMC group (36.7%) ($p<0.05$; adjusted Chi-Square test). A 33% absolute difference in treatment responder proportions in

favour of PREOB® appeared as soon as 3 months after implantation and was maintained unchanged at all time points up to 3 years after implantation. PREOB® was associated with less radiological progression of the disease to fractural stages: as compared to BMC, PREOB® decreased the risk of hip fracture during the 3 years post-treatment (hazard ratio of 0.370, Cox proportional hazards model). In particular, at 2 years after implantation, the proportions of hips that progressed to fracture in the PREOB® and BMC groups were 20% and 40% respectively, corresponding to a 50% reduction in fracture risk. Consistent with these observations, a lower rate of THA was observed in the PREOB® group (13.3%) compared to the BMC group (36.7%) over the complete study follow-up (*i.e.*, up to 5 years after implantation). PREOB® was also associated with a rapid (within the first 3 months) clinically relevant hip pain relief and function improvement, which lasted for up to 4 years after implantation. In particular, at 2 years after implantation, 76.7% of the PREOB®-treated subjects achieved a clinically relevant (>10 mm) VAS pain relief with a mean reduction of 21.6 mm, versus 50.0% of the BMC-treated subjects with a mean reduction of 4.9 mm.

From a safety perspective, a high number of adverse events (n=578) and serious adverse events (n=128) were reported in the study, as expected with this patient's population (chronic alcoholism and/or long-term corticosteroid use due to transplantation, chronic obstructive bronchitis, refractory asthma or others). Most of SAEs were related to concomitant conditions or to repeated hospitalisations for the treatment of osteonecrosis on other sites than the hip treated in the study (e.g., contralateral hip, knee(s), ankle(s), shoulder(s)), but not related to the PREOB® or BMC treatments.

The sole non-serious adverse event possibly related to study treatment reported was transient fever reported in about 9% of PREOB®-treated subjects – this was comparable to the rate reported in the BMC group and in accordance with the possible risks linked to the study procedures as described in the literature, *i.e.*, core decompression and/or local implantation of a cellular product (such as stem cells or BMC) (Lalu *et al.*, 2012, Liebergal *et al.*, 2013).

Two (2) patients experienced serious adverse events possibly related to PREOB® treatment and requiring prolonged hospitalization: one patient experienced severe pyrexia with altered state of consciousness and hypotension, the two latter being considered as possibly related to the underlying and/or concomitant diseases and treatments; the other patient developed an inflammatory syndrome due to an unknown cause. Still for both patients, a causal relationship with PREOB® treatment could not be excluded. The narratives of these events are further described in the Investigator's Brochure.

In conclusion, data from this Phase IIb clinical trial supports the clinical benefits of PREOB® on pain and function in early stage osteonecrosis patients, as well as on a reduction in

progression to fractural stages, in comparison to Bone Marrow Concentrate. These data form the basis of the clinical Phase III program of PREOB® in osteonecrosis.

1.2 Study Rationale

Primary Efficacy Outcomes

Monitoring of osteonecrosis evolution is usually measured by two parameters:

- Clinical presentation and clinical failure defined as surgical intervention (e.g., hip arthroplasty as a result of intractable pain);
- Radiological progression defined as an advance in Association Research Circulation Osseous (ARCO) stage, mainly to fractural stage III or higher.

Indeed, once fracture occurs, the femoral head evolves towards collapse within 6 to 18 months with the need for total hip arthroplasty. With respect to this dramatic evolution, the objective of the treatment is therefore to delay the evolution towards fractural stage.

Clinical Evaluation

Clinical evaluation of the hip is usually performed using dedicated open questionnaires and/or scores, which have been developed and established in order to assess hip pain, hip stiffness, and/or hip function in patients with osteoarthritis primarily, but also for other hip diseases and following total hip arthroplasty. These include the Merle d'Aubigné, Lequesne, Harris Hip, and WOMAC® Scores.

Although all these scores are frequently used and cited in the literature, the scores of Merle d'Aubigné, Lequesne, and Harris present a number of limitations and pitfalls regarding their use in clinical practice:

- Initially developed and studied to assess pain and function in patients after total hip arthroplasty (d'Aubigné & Postel*.,* 1954), the Merle d'Aubigné Clinical Hip Score has never been systematically evaluated and validated in large trials since its initial description;
- The algofunctional Lequesne's Index for hip and knee osteoarthritis has demonstrated its usefulness and efficacy as an outcome functional measure after hip surgery only (Lequesne, 1997; Stucki *et al.,* 1998; Lequesne & Maheu*,* 2003);
- Finally, the Harris Hip Score has been tested and validated only to study the clinical outcome of total hip arthroplasty (Söderman & Malchau*,* 2001).

By contrast, the Western Ontario and McMaster Universities (WOMAC®) Index, which allows a thorough evaluation of pain, stiffness, and function (through 3 subscales with a total of 24 questions), has been widely validated and used: it has been standardised and tested for reliability, validity, and responsiveness in patients with osteoarthritis of the hip (and/or the

knee) in various clinical settings, including both medical (pharmacological) and surgical management (total hip arthroplasty) of patients (Bellamy *et al.,* 1988; Bellamy 2002; Bellamy 2005; Bellamy 2009).

Moreover, and contrarily to the other hip scores, the WOMAC® Index is available not only in Likert scaled format but also in Visual Analogue Scaled format, which scaling has been suggested to be more reproducible and sensitive as compared to Likert scales (Gerich, 2007).

In this study, the WOMAC® pain subscale has been selected as primary efficacy outcome. Indeed, as illustrated by the questions below, functional hip evaluation inherently implies bilateral hip assessment, making difficult to distinguish one hip function (hip under evaluation) from the other (opposite hip), which may potentially bias the results, either positively or negatively. For example, the function and disease(s) of the non-studied hip could obviously interfere with the evaluation of the studied hip when answering to the following questions: "What degree of difficulty do you have descending or ascending stairs?", "What degree of difficulty do you have walking on a flat surface?", or "What degree of difficulty do you have getting in or out of a car, or getting in or out of a bus?".

Nevertheless, the total WOMAC® Index (including composite pain, stiffness, and function subscales) will be used as a secondary efficacy endpoint.

Finally, in support of WOMAC® against the other hip scores, the additional post study long term follow-up (phone call visits) will be performed using the WOMAC® LK3.1 (Likert) scale, which has also been validated when administered by phone, to assess pain, stiffness, and function (Bellamy *et al.,* 2002).

Radiological Evaluation

Radiologically, patients will be assessed using both conventional X-ray and magnetic resonance imaging (MRI) of the hips, which are well established imaging tools for both the diagnosis and staging (according to ARCO Classification) of femoral head osteonecrosis, achieving excellent sensitivity and specificity. CT scan of the hips will also be performed once during the trial (during the Screening Period only), for additional diagnostic and exploratory purposes.

Detailed description of imaging analysis (performed by a Radiologist from the Central Evaluating Centre, hereafter referred to as the "Central Radiologist"), including diagnosis of femoral head osteonecrosis, presence of perilesional changes, detection of femoral head fracture, staging (according to ARCO staging), quantitative evaluation of the extent of necrotic area, and additional MRI findings, is provided in Annex 2.

Based on existing literature and PREOB® Phase IIb trial data disclosed in Section 1.1.3, (i) pain, as clinically assessed by the WOMAC® VA3.1 pain subscale score (using Visual Analog

Scale), and (ii) radiological progression to fractural stages (ARCO stages III or higher), as assessed by conventional X-ray, are therefore considered to represent valid and robust primary efficacy outcomes to assess the clinical benefits of PREOB® implantation.

Primary Efficacy Endpoint

In the advanced stages of non-traumatic osteonecrosis (ARCO stages III or higher), patients experience severe pain continuously, with negative impact on their day-to-day life (Fine *et al.,* 2011). In these advanced stages, pain not only results from fracture occurrence but also from osteoarthritic degenerative changes of the hip joint (Ficat, 1985; Jagadale *et al.*, 2014; Mont *et al.*, 2015).

In the early stages of the disease (ARCO stages I and II), before the occurrence of fracture or of the osteoarthritic degenerative changes, patients experience mild to moderate pain that may be present before any observable X-ray abnormalities (Koo *et al.*, 1999). In these early stages, pain is therefore rather the consequence of sub-radiological structural changes due to bone ischemia and necrosis (Jagadale *et al.*, 2014, Mwale *et al.*, 2011). The radiological evaluation of the osteonecrotic hips is not suitable - nor validated - to detect microscopic structural improvement of a therapeutic intervention (Trăistaru *et al.,* 2015). Therefore, in early stage osteonecrosis, pain will be the key variable to assess the efficacy of treatment in addition to radiological evaluation.

Accordingly, in early stage osteonecrosis, to be considered effective, a therapeutic intervention must not only delay/stop the progression of the disease to fractural stages but also relieve pain and symptoms if these mainly result from subclinical fractures. Therefore, a composite responder endpoint has been chosen as the primary efficacy endpoint since it is important that improvement in each variable, pain and fracture, occurs at the patient level. This endpoint determines for each patient individually whether s/he has had responded to treatment by taking into account whether s/he had responded to each of the clinical (pain) and radiological efficacy outcomes (described above).

This composite responder approach complies with the regulatory requirements since a single suitable variable is not available and the clinical and radiological components of the composite:

- are the most commonly reported evaluation parameters of osteonecrosis of the femoral head,
- have similar occurrence,
- are unweighted,
- are both dichotomized, and importantly,

- are both taken into consideration to claim a treatment success.

Response threshold for clinical efficacy outcome (WOMAC VA3.1 pain subscale)

The MCID value is set at 10 mm in accordance with the literature for WOMAC® VAS pain subscale (Ehrich *et al.*, 2000; Angst *et al.*, 2001) and with the absolute MCIDs reported in controlled, randomised, parallel group studies that evaluate treatment for hip disorders (Puopolo *et al.*, 2007; Altman *et al.*, 2007; Prior *et al.*, 2014).

For patients with a baseline WOMAC® VA3.1 pain subscale score ≥10 mm, the MCID can be used as a threshold value to define a clinically meaningful pain relief. These patients will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip decreased from baseline by at least the MCID.

For patients with a baseline WOMAC® VA3.1 pain subscale score <10 mm, the MCID cannot be used as a threshold value to define a clinically meaningful pain relief. These patients will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip is found in the range [0; 4]. This definition is based on the literature, which states that any VAS pain rating ≤4 mm is labelled as "no pain" (Jensen *et al.*, 2003).

Study Population

As previously described, non-traumatic osteonecrosis is generally associated with one or more risk factors. In Caucasians, it is considered that about two thirds of non-traumatic osteonecrosis are related to corticosteroid therapy and/or alcohol abuse. The remaining third includes a heterogeneous group of diseases, notably dysbaric phenomenon, haemoglobinopathies, coagulopathies, and other rare medical conditions such as organ transplant recipients and systemic lupus erythematosus (Vail & Covington, 1997). Finally, idiopathic cases occur for a small proportion (<5%) of non-traumatic osteonecrosis.

In order to address the question of both sample size and heterogeneity of patients across the variety of osteonecrosis aetiologies, the proposed Phase III study has been designed to include a relatively homogeneous patient population, focusing on the most frequent aetiologies of the disease, *i.e.*, corticosteroid and alcohol associated osteonecrosis, as well as the idiopathic forms of osteonecrosis. It will therefore exclude others aetiologies such as trauma, sickle cell disease, other haemoglobinopathies, and dysbaric osteonecrosis.

Besides, it is interesting to note that, even if the exact pathophysiological mechanisms involved in osteonecrosis have yet to be fully elucidated, it is increasingly recognized that osteonecrosis of the femoral head is a disease of bone and/or MSCs (Hernigou & Beaujean, 1997; Gangji *et*

al., 2003). Indeed, the number and levels of activity of mesenchymal stem cells in both the haematopoietic and stromal compartments of bone marrow have been shown to be depressed in patients with osteonecrosis of the femoral head (Hernigou *et al.,* 1999) as well as the proliferative capacity of osteoblastic cells, as measured by cell population doubling time (Gangji *et al.,* 2003). Moreover, this decreased proliferative capacity was found not only in glucocorticoid-induced osteonecrosis (Weinstein *et al.*, 2000), but also in osteonecrosis due to other risk factors (Gangji *et al.,* 2003).

Hernigou *et al.* have also reported a decrease in the number and activity of fibroblast colony-forming units (CFU-F; reflecting the number of MSCs that could potentially give rise to mature osteoblasts) in the proximal femur of patients with osteonecrosis (Hernigou *et al.,* 1997; Hernigou *et al.,* 1999). The same group further showed that patients with osteonecrosis due to different aetiological factors, including steroids, alcohol abuse, and transplantation, disclosed comparable decrease in the number of CFU-F and similar response to treatment (Hernigou *et al.,* 2002). This strongly suggests common pathophysiological pathways across the various aetiologies of the disease (except sickle cell disease).

Finally, our own experiments revealed no significant differences in both yield and identity of PREOB® cultures from osteonecrosis patients according to aetiologies (corticosteroid *versus* alcoholic *versus* idiopathic patients, unpublished observations).

Study blindness

In order to ensure the blindness of both patient and Investigator, both treatment groups will undergo the same procedures: (i) patients randomised in the PREOB® group will undergo a bone marrow harvesting and a core decompression procedure with PREOB® implantation into the necrotic lesion, and (ii) patients randomised in the Placebo group will undergo a sham bone marrow harvesting and a core decompression procedure with Placebo implantation into the necrotic lesion.

The only patient procedure that can identify group assignment will be the Bone Marrow Harvest. This procedure will therefore be performed by an Independent Physician who will not be involved in patient selection, treatment, and follow-up.

The Investigational Medicinal Product (IMP), PREOB® and Placebo, will be supplied in identical packaging conditions, and will be blind to the Investigator.

Core decompression is the most commonly proposed treatment for ARCO stage I and II osteonecrosis of the femoral head. As standard of care, 8 to 10-mm trephines are commonly used (over 1500 cases published, Arlet & Ficat, 1964; Ficat 1999; Aaron, 2001; Marker *et al.,* 2008). However, such large-diameter trephines cannot be used to perform the core

decompression when cell implantation, such as PREOB®, is contemplated because of an increased risk of product leakage. An increasing number of groups - both in the US with the group of Marker and Mont, and elsewhere in the world with the group of Song and Kim - have recently published data using smaller diameter trephines. Indeed, use of multiple small-diameter trephines has been shown to decrease the occurrence of postoperative complications, such as articular cartilage damage and subchondral fractures, and was associated with lower morbidity together with comparable clinical benefits as compared to conventional large-diameter method (Mont *et al.,* 2004; Marker *et al.,* 2008; Marker *et al.,* 2008b; Song *et al.,* 2007).

A detailed description of methods and procedures to ensure a correct blinding is provided in Section 2.3.

1.3 Risks and Benefit Assessment

PREOB® is a cell-based medicinal product (CBMP), consisting in human autologous bone marrow-derived osteoblastic cells.

Characterization studies have shown that PREOB® cells express and exhibit features of "trabecular osteoblasts", including the expression of typical cell surface marker profile and bone matrix proteins, expression of bone enzymes and related osteogenic biological activity such as alkaline phosphatase, as well as bone matrix synthesis and mineralization capacity.

Non clinical studies *in vitro* have further demonstrated that PREOB® cells have the ability to adhere, multiply, produce bone matrix, and mineralized new bone matrix. PREOB® engraftment at lesion site and PREOB® bone formation capacity have been confirmed *in vivo* in femoral fracture model and a calvaria bone formation model in immunodeficient mice. Taken together, these results show the ability of PREOB® cells to produce new bone at the bone defect site as well as to re-establish a healthy bone environment, and hence support its use in patients affected by osteonecrosis of the femoral head.

No *in vivo* toxicity has been observed. PREOB® cells, when administered locally at the fracture site (in a femoral fracture mouse model), persisted at the fracture site and did not invade non-bone organs (*i.e.*, brain, heart, lungs, kidneys, liver and spleen). PREOB® appeared to be safe and devoid from toxicity even at very high doses. A long-term (26 weeks) GLP toxicity study performed in immunodeficient nude mice showed that PREOB® administered intravenously at the dose of [redacted] cells (> 100 times the clinical human intended dose) did not cause any excess mortality, or morbidity and did not induce any organ toxicity or ectopic bone formation. Moreover, karyotype analyses have shown no relevant chromosomal abnormalities, and *in vitro* tumourigenesis studies revealed no abnormal proliferation and no tumoural characteristics (anchorage independent growth). Results of the *in vivo* tumourigenic study confirms the

absence of tumourigenic potential of PREOB® cells at a dose largely >100 times the clinical human intended dose. As such, there are no non-intended effects or unwanted biological activities expected from PREOB® administration to patients, and no expected toxicity.

Finally, the human proof-of-concept Phase IIb study documents both the efficacy and safety of a single local implantation of PREOB® in patients with early stage ONFH for up to 5 years, in comparison with a reference active treatment (bone marrow concentrate: BMC). Study efficacy data analyses reveal a better efficiency of PREOB® over BMC in relieving clinical hip pain and delaying radiological progression to fractural stages. The primary efficacy variable analysis at 24 months after implantation shows that the proportion of treatment responders was statistically significantly higher in the PREOB® group (70.0%) than in the BMC group (36.7%) ($p<0.05$, adjusted Chi-square).

Taken together, non-clinical and clinical results (exposed in sections 1.3 and 1.1.3.2) demonstrate the favourable benefit-risk profile of PREOB®, and strongly support the proposed pivotal Phase III study to evaluate the efficacy and safety of the association of core decompression and PREOB® (total dose [redacted] cells) implantation into necrotic lesion in patients with early stage non-traumatic osteonecrosis of the femoral head.

2 INVESTIGATIONAL PLAN

2.1 Overall Study Design

The present study is a 24-month prospective, multicentre, randomised, double-blind, controlled, pivotal Phase III trial comparing the efficacy and safety of Core decompression/PREOB® implantation (PREOB® Group; 1 dose, [redacted] cells) to Core decompression/Placebo implantation (Control Group) in patients with non-traumatic early stage (ARCO I or II) osteonecrosis of the femoral head, as diagnosed by conventional bilateral X-ray and bilateral MRI of the hips.

An additional long term follow-up at 36 and 48 months will assess some selected efficacy and safety data.

2.2 Main Study Objectives and Endpoints

The study objectives are to demonstrate that Core decompression/PREOB® implantation is superior to Core decompression/Placebo implantation in relieving clinical hip symptoms and halting (or reverting) radiological progression to fractural stages (ARCO III or higher) in patients with non-traumatic early stage osteonecrosis of the femoral head, *at 24 months*.

Patients will be assessed using the Western Ontario and McMaster Universities (WOMAC®) index. Central Radiological evaluation will include conventional bilateral X-ray and bilateral MRI of the hips to assess the ARCO staging and to measure the sum of the coronal and sagittal necrotic angles.

2.2.1 Follow-up Period

Efficacy endpoints

Primary Efficacy Endpoint

- Percentage of treatment responders at Month 24,

  a treatment responder at a studied timepoint being defined as a patient who responded both:

  - Clinically, *i.e.*, if at the studied timepoint, the WOMAC® VA3.1 pain subscale score of the study treated hip improved from baseline by at least the minimal clinically important difference (MCID)[a],

    and

  - Radiologically, *i.e.,* if at the studied timepoint, the study treated hip did not progress to fractural stages (ARCO III or higher), as assessed by conventional X-ray.

[a] The MCID value is set at 10 mm in accordance with the literature for WOMAC® VAS pain subscale (Ehrich *et al*., 2000; Angst *et al*., 2001) and with the absolute MCIDs reported in controlled, randomised, parallel group studies that evaluate treatment for hip disorders (Puopolo *et al*., 2007; Altman *et al.*, 2007; Prior *et al.*, 2014).

For patients with a baseline WOMAC® VA3.1 pain subscale score ≥10 mm, the MCID can be used as a threshold value to define a clinically meaningful pain relief. These patients will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip decreased from baseline by at least the MCID.

For patients with a baseline WOMAC® VA3.1 pain subscale score <10 mm, the MCID cannot be used as a threshold value to define a clinically meaningful pain relief. These patients will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip is found in the range [0; 4]. This definition is based on the literature, which states that any VAS pain rating ≤4 mm is labelled as "no pain" (Jensen *et al.*, 2003).

Secondary Efficacy Endpoint

- Percentage of treatment responders at Month 6, 12 and 18, and over the 24-month follow-up period
- Percentage of clinical responders at Month 1, 3, 6, 12, 18 and 24, and over the 24–month follow-up period; a clinical responder being defined as a patient whom the WOMAC® VA3.1 pain subscale score of the study treated hip improved from baseline by at least the MCID[b] at the studied timepoint
- Percentage of radiological responders at Month 6, 12, 18 and 24, and over the 24–month follow-up period; a radiological responder being defined as a patient whom the study treated hip did not progress to fractural stages (ARCO III or higher), as assessed by conventional X-ray, at the studied timepoint
- Absolute change from baseline in WOMAC® VA3.1 total score and composite pain, stiffness, and function subscale scores of the study treated hip at Month 1, 3, 6, 12, 18 and 24, and over the 24-month follow-up period
- Time to progression to fractural stages (ARCO III or higher) of the study treated hip
- Percentage of patients requiring hip arthroplasty for the study treated hip at Month 1, 3, 6, 12, 18 and 24, and over the 24-month follow-up period
- Time to hip arthroplasty for the study treated hip

[b] The MCID value is set at 10 mm.

Patients with a baseline WOMAC® VA3.1 pain subscale score ≥10 mm will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip decreased from baseline by at least the MCID.

Patients with a baseline WOMAC® VA3.1 pain subscale score <10 mm will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip is found in the range [0;4] (VAS pain range labelled as "no pain").

[redacted]

Safety endpoints

From the beginning till the end of the main study period at Month 24, patients will be systematically assessed for the potential occurrence of any AE or SAE, related to the product or related to the procedure by patient interview, physical examination (including body mass index and vital signs) and laboratory measurements.

2.2.2 Long Term Follow-up

A long-term follow-up will be performed via phone calls at 36 and 48 months after IMP implantation. This includes assessment of hip symptoms (pain, stiffness, and function) using WOMAC® LK3.1 (Likert Scale), radiological progression (conventional X-ray to be performed only when the patient still feels pain on the treated hip), and the potential occurrence of any AEs and SAEs (patient open questionnaire, including notably any changes in health status and need for total hip arthroplasty).

2.2.3 Clinical Study Report

The Final Clinical Study Report will be established based on the efficacy and safety data collected up to Month 24. The long-term follow-up data will be analysed and reported as Annexes and Supplementary Data to the Final Clinical Study Report.

2.3 Main Study Plan and Procedures

2.3.1 Patient Information and Informed Consent

Before any study-related procedure, the Principal Investigator (or delegate) will give detailed and comprehensive information regarding all aspects of the trial to the patient (or, when the patient is not capable of giving informed consent, his/her legal representative), including:

- Purpose, objectives, and nature of the trial (including all performed procedures)
- Conditions under which the trial and procurement of blood/bone marrow are conducted
- Expected benefits for the patient and for the research
- Inconveniences and risks
- Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- Trial treatments and the probability for random assignment to each treatment arm
- Right to receive the results of the tests performed, excluding those that could lead to potential unblinding
- Rights of the patient to physical, mental, and social integrity, dignity, privacy, confidentiality, and protection of his/her personal data and medical records, in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996), with amendments, and any other applicable laws, regulations, guidance, guidelines, and principles
- Right to refuse to participate or right to withdraw from the clinical trial, at any time, without any resulting detriment, penalty or loss of benefits to which the patient is otherwise entitled, notably in terms of medical care, follow-up, and patient-physician relationship
- Medical confidentiality - Recording and protection of patient data
- Access and scrutiny of personal data and information during inspection by the CAs and any other properly authorized persons, provided that such information is treated as strictly confidential and is not made publicly available
- Provision has been made for insurance or indemnity to cover the liability of both the Sponsor and Investigator (including all members of the investigating team and any other participants to the trial)

This detailed information will be given in both oral and written forms (Subject Information Sheet and Informed Consent Form (ICF)), in appropriate and clear manner, worded in the patient's mother tongue, using non-technical and practical language and terms that are easily understood by the patient (or his/her legal representative). The information provided will not include any term or sentence that appears to waive any of the patient's legal rights, or appears to release the Investigator, Institution/Investigating Site, Sponsor, or any representative of the Sponsor, from liability for negligence.

The patient (or his/her legal representative) will then be given sufficient time (as needed) and opportunity to inquire about details and ask any questions about the trial to the Investigator (or the person who conducts the Informed Consent discussion) and to decide whether or not to participate to the trial. All questions about the trial will be answered to the satisfaction of the patient (or his/her legal representative).

If the patient (or his/her legal representative) agrees to participate, he/she will be invited to date and sign two copies of the ICF. The Investigator (or the person who conducted the Informed Consent discussion) will also sign and date the document on the same day. One original signed copy will be given to the patient (or his/her legal representative), the other original signed copy will be kept in the Investigator's Site File.

The Investigator will then complete the patient's records, thereby attesting and recording that signed ICF has been obtained from the patient.

2.3.2 Inclusion and Exclusion Criteria

Inclusion criteria

To be eligible for the study, patients **must** satisfy **ALL** the following criteria:

1. Men or women between 18 and 70 years (inclusive) with a diagnosis of ARCO Stage I or II non-traumatic osteonecrosis of the femoral head, confirmed by central imaging analysis based on X-ray and MRI
2. Ability to provide a written, dated, and signed informed consent prior to any study related procedure and to understand and comply with study requirements
3. Diagnosis of osteonecrosis:
    a. ARCO stage I associated with WOMAC® VA3.1 pain score ≥20 mm and necrotic angle sum ≥190° based on sagittal and coronal MRI views

    or

b. ARCO stage II associated with WOMAC® VA3.1 pain score ≥20 mm if necrotic angle sum <190° based on sagittal and coronal MRI views

or

c. ARCO stage II associated or not with pain if necrotic angle sum is ≥190° based on sagittal and coronal MRI views

d. Associated with corticosteroid and/or with alcohol abuse and/or idiopathic.

Table 1: *Inclusion Criteria: Osteonecrosis Diagnosis*

ARCO Stage	Necrotic Angles*	Pain**
Stage I	≥ 190°	≥ 20 mm
Stage II	< 190°	≥ 20 mm
Stage II	≥ 190°	-

** Sum of coronal and sagittal necrotic angles*

*** WOMAC® VA3.1 pain during the 48 hours before screening*

4. Normal haematology function, defined as leukocytes ≥3000/mm^3, absolute neutrophils count ≥1500/mm^3, platelets ≥140,000/mm^3, and haemoglobin concentration ≥10g/dl (peripheral blood test)

Exclusion criteria

To be eligible for the study, patients **must NOT** present any of the following criteria:

Current symptoms and/or signs related to the disease under study

1. Exclusively diaphyseal or metaphyseal osteonecrotic lesion
2. Traumatic or hyperbaric osteonecrosis, or osteonecrosis associated with haemoglobinopathy or coagulopathy (e.g., thalassemia, sickle cell disease,…), or Gaucher's disease
3. Any other focal or diffuse bone marrow lesion
4. Osteoarthritis at the hip under evaluation defined as Kellgrens stage ≥2, as assessed by the Central Radiologist
5. Patients suffering from any medical conditions interfering with patient's pain evaluation of the hip under evaluation, such as knee arthritis.

6. Bone fracture or bone infection at hip under evaluation.
7. Patients who are candidates for any predictable joint replacement on the hip under evaluation

Current or previous diagnoses, signs and/or symptoms

8. Blood not qualifying for PREOB® production, including active hepatitis B (defined as positive HBs Ag and/or positive PCR), active hepatitis C (defined as positive PCR), positive serology for HIV[1], or Syphilis[1], or HTLV-1[1], and any other tests that may be required by the authorities in case of a new disease outbreak that can affect the safety of the physicians and operators at the time of patient screening
9. Presence, or previous history, of risks factors for diseases caused by prions, and recipients of grafts of cornea, sclera, and dura mater
10. History of blood loss exceeding 450 ml (incl. donations) within 1 month of screening
11. Renal impairment defined by an estimated creatinine clearance value < 30 ml per min, calculated with the Cockcroft-Gault formula
12. Hepatic impairment, defined as alanine aminotransferase or aspartate aminotransferase ≥ 3 times the upper limit of normal
13. Poorly controlled diabetes mellitus, defined as HbA1C > 9%
14. Global sepsis
15. Allergy to gentamicin or any substance or device the patient might be exposed to in the context of the study related interventions (*i.e.*, bone marrow harvesting and implantation), as judged by the Investigator
16. History of hypersensitivity to human biological material, including blood and blood derived products, documented clinically or by laboratory tests
17. Current or past history of solid or haematological neoplasia (except for basal cell carcinoma of the skin and for carcinoma in situ of the cervix that has been treated with no evidence of recurrence)
18. History of bone marrow transplantation
19. Patients with a life expectancy less than 2 years, as judged by the Investigator

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[1] *For patients whose seropositivity is revealed from the study procedures, the Investigator should ensure that adequate medical care will be provided to the patient and that his/her confidentiality will be preserved.*

Current or previous treatment

20. Patients having participated in another clinical trial within 3 months of screening
21. Patients previously treated with PREOB®
22. Patients treated by core decompression of the hip under evaluation within 6 months of screening
23. Treatment with doses of prednisolone ≥15 mg per day (or equivalent) within 1 month from screening, and patients with anticipated needs of daily corticoid doses ≥15 mg prednisone (or equivalent) in the 6-month period following PREOB/Placebo implantation
24. Illicit drug or alcohol abuse interfering with patient's ability to understand and comply with study requirements, as judged by the Investigator

Safety aspects concerning female patients of childbearing potential

25. Pregnancy
26. Breast-feeding
27. Women with childbearing potential not willing or able to use reliable contraceptive method for at least 6 weeks prior to screening and during the whole study period. Reliable contraceptive methods include orally administered hormonal contraceptives, surgical intervention (e.g., tubal ligation), and intrauterine device (IUD).

Other exclusion criteria

28. Body Mass Index (BMI) ≥ 35 kg/m^2
29. Patients unable to undergo MRI, e.g. patients with pace-maker, intra-ocular or intra-cerebral metallic foreign bodies, and mechanical artificial heart valves

    Patients unable to undergo general anaesthesia or surgical intervention

2.3.3 Randomisation

Eligible patients will be randomly assigned to one of the two study treatments, PREOB® or Placebo, in a 1:1 ratio.

Patients will be allocated a Patient Randomisation Number via the randomisation process (through the eCRF). Stratification according to ARCO Stage I or Stage II will automatically be made at the time of randomisation.

2.3.4 Blinding

The study will be conducted double-blind with reference to the evaluation of trial results.

Briefly:

- The only physician to know patient group assignment is the Independent Physician, performing the (sham) bone marrow harvesting procedure.
- Investigators and Patients are blind to treatment assignment. Both patient groups undergo a bone marrow harvest, real or sham, performed by the Independent Physician, and a Core decompression/Implantation procedure performed by the Investigator, following identical procedures.
- The Investigational Medicinal Product, PREOB® and Placebo, are supplied in identical packaging conditions. The final product is packaged in a blind ready to use syringe.
- Radiologists are blind to the group assignment. All images (conventional X-ray, MRI and CT) will be processed to ensure blinding, notably coding and masking of posterior iliac crest through a Centralized Medical Imaging System. Processed images (*i.e.* blind) will be analysed by a single reader (Central Radiologist).
- To ensure the blinding of the study, imaging data should not be distributed to the patient and/or to the blinded study staff. However, if distribution is required (for any reasons), the imaging data should be masked at the harvesting region (iliac crest) prior to distribution, or depending on local Hospital policy.
- Blinding will only be lifted after completion of all study visits from all patients.

2.3.5 Bone Marrow Harvest and Blood Collection Procedures

Bone marrow harvest will be performed by the Independent Physician, under local anaesthesia, at least 21 days[2] before the IMP implantation procedure. However, if the patient has signs of

[2] *The bone marrow harvest and the core decompression procedure will be scheduled in conjunction with the Sponsor's Manufacturing Unit and will take into account the travel time between the Investigating Site and the Sponsor's Manufacturing Unit.*

acute or chronic infection, the harvesting procedure should be postponed until the infection is resolved, as judged by the Investigator.

- In the PREOB® Group, bone marrow harvest will consist of a 50 ml bone marrow aspiration from the posterior iliac crest.
- In the Control Group, bone marrow harvest will consist of a sham procedure in order to ensure blindness of the patient to the group assignment.
- In both groups, peripheral blood will be collected for IMP production and research in the PREOB®, and Placebo Group, respectively.

2.3.6 Core decompression and Implantation Procedures

All patients will undergo a core decompression performed by the Investigator (or delegate) (with a small diameter trephine) under general anaesthesia combined with the implantation of 5 ml of either PREOB® ([redacted] cells) or Placebo into the necrotic lesion (single administration).

2.3.7 Follow-up Period

Efficacy and safety endpoints will be determined in all patients at each scheduled visit over the 24-month follow-up period (planned at 1, 3, 6, 12, 18, and 24 months).

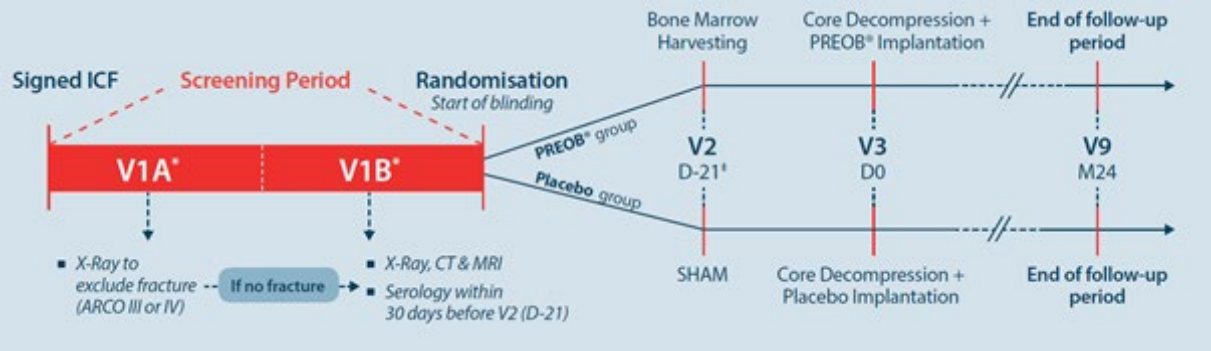
2.4 Long -Term Follow-up

A long-term follow-up will be performed via phone calls at 36 and 48 months after IMP implantation. This includes assessment of hip symptoms (pain, stiffness, and function) using WOMAC® LK3.1 (Likert Scale), radiological progression (conventional X-ray to be performed only when the patient still feels pain on the treated hip) and the potential occurrence of any AEs and SAEs (patient open questionnaire, including notably any changes in health status and need for total hip arthroplasty).

3 DETAILED SCHEDULE OF VISITS AND PROCEDURES

An overview of the study assessments and procedures is given in the Flow Chart below. Study procedures are described separately for the PREOB® study and the long term follow-up in table 2 and table 3 respectively. These Tables show how efficacy and safety endpoints relate to the study objectives, and describe involvement of the Investigator (in white), Independent Physician (in red), and Central Radiologist (in blue).

Figure 1: *Study Flow-Chart*



**In case V1A and V1B are performed separately: X-ray shall be performed during visit 1A. If >4weeks have elapsed between the 2 visits, X-Ray must be repeated at V1B, only.*

‡Procedure performed by the Independent Physician (UNBLIND). Principal Investigator and other staff members are BLIND.

Table 2: Follow-up Period: *Schedule of visits and procedures*

	Screening Period (Visit 1)[1]		(Sham) Bone Marrow Harvest	Core decompression/ Product Implantation	Follow-up Visits					
					Month 1	Month 3	Month 6	Month 12	Month 18	Month 24**
Visits	**Visit 1A**	**Visit 1B***	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
[redacted]										

[redacted]

Table 3: Long Term Follow-up*: schedule of phone calls and procedures*

	Long term follow-up	
	Month 36	**Month 48**
Visits	**Visit 10**	**Visit 11**

[redacted]

[redacted]

3.1 Screening Period (Visit 1)

Visit 1 (Screening Period) will include the following procedures, which can either be performed in one single visit (if the site can arrange to perform all the assessment on the same day) or split into Visit 1a and Visit 1b

The first visit day of the Screening Period (Visit 1a) includes:

If the screening visit was split into Visit 1a and Visit 1b and the patient does not meet any exclusion criteria after Visit 1a, the second visit of the Screening Period (Visit 1b) will be performed and will include:

[redacted]

If the time period between Visit 1b and Visit 2 exceeds 6 weeks, WOMAC® VA3.1 questionnaire and conventional X-ray of the hips should be re-performed and will be considered as clinical and radiological baselines.

Prior to patient randomisation, radiological eligibility must be confirmed by the central radiologist. Subsequently full eligibility will be confirmed by the PI (or delegate) through the eligibility form in the eCRF.

3.2 Randomisation

In case of patient eligibility,

- Randomisation is performed by the Principal Investigator (or delegate) through the eCRF.
- The eCRF will automatically allocate a unique Randomisation Number for the patient.
- Upon randomisation, the eCRF will automatically inform the study team that a new patient has been randomised.

[redacted]

- Both the unblind Independent Physician and the Sponsor's Managing Physician must log into the eCRF system to obtain the patient's treatment allocation.

3.3 (Sham) Bone Marrow Harvest and Blood Collection (Visit 2, Day -21)

The (sham) bone marrow harvest and blood collection (Visit 2, Day -21) will be performed at least **21 days**[4] before the Core decompression/implantation procedure (Visit 3, Day 0).

Before the actual (sham) bone marrow harvest and blood collection procedures, the following evaluations must be performed either by the Independent Physician or by the Principal Investigator (or delegate):

[redacted]

The (sham) bone marrow harvest and blood collection procedures must be conducted by the Independent Physician exclusively:

(Sham) Bone Marrow Harvest procedure (see detailed description in Section 4.1) will be performed by the Independent Physician. (Sham) bone marrow and blood samples will then be immediately labelled and packed by the Independent Physician *himself*, and immediately shipped to the Sponsor's Manufacturing Unit for further processing (see detailed description of packaging, labelling, and shipment procedures in Study Procedure Manual (SPM) for IP).

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[4] *The bone marrow harvest and the core decompression procedure will be scheduled in conjunction with the Sponsor's Manufacturing Unit and will take into account the travel time between the Investigating Site and the Sponsor's Manufacturing Unit.*

Patients will then be allowed to leave the Clinic on the same day, following thorough clinical evaluation and documentation of any potential AEs or SAEs.

3.4 Product Implantation (Visit 3, Day 0 and Day +1)

Day 0

The patient will be admitted to the Clinic on Day 0. The following examinations and procedures will then be performed by the Investigator:

[redacted]

On the same day, the shipping box containing the Investigational Medicinal Product (PREOB® or Placebo) will be shipped by the Manufacturer to the Pharmacy Department of the Investigating Site.

If the IMP is not useable due to a technical problem that occurred during the production process, the Managing Physician will immediately notify the CAs and SSO, and record relevant information in the eCRF. Once completed, the eCRF will automatically send e-mail alerts to the Study Safety Officer (SSO), and PI.

In case the IMP is not available for the implantation, the PI will inform the patient about the cancellation of the latter procedure. In this case, the patient will be considered as drop out, but the Investigator is however allowed to re-include the patient after 2 months (novel inclusion procedure).

Upon IMP receipt the Pharmacist will check if all the conditions listed on the Release Form for the Hospital - Hospital Pharmacist Section - [redacted] are met, and subsequently release the IMP and immediately inform the Principal Investigator (and/or delegate) (see detailed description of related procedures in the SPM for Pharmacist). If released by the pharmacist, the IMP will be transferred to the Operating Room.

In the Operating Room, the Principal investigator will check if all the conditions listed on the Release Form for the Hospital - Principal Investigator Section - are met, and subsequently release the IMP and perform the surgical procedure (core decompression and implantation, PREOB® or Placebo) (see detailed procedures in Section 4.2 and in the SPM for PI).

After implantation, the empty PREOB® or Placebo syringe will be kept and stored by the Investigator (or a member of the investigating team designated by the Investigator) until the next Monitoring visit.

Day +1

Patients will be systematically evaluated 24 hours after the core decompression/implantation procedure, and will then be discharged from the Clinic after the following examinations:

[redacted]

3.5 Follow-up Visits - *up to Month 24*

Following the IMP implantation (Visit 3), 6 follow-up visits will be performed at the investigating site at Month 1, 3, 6, 12, 18 and 24.

However, if a treated patient is withdrawn/discontinued from the study any time before visit 9 at Month 24, he/she will no longer be asked to come for the remaining follow-up visits. In this case, an early discontinuation visit/Exit visit will be completed at the time of discontinuation and a follow-up visit will be performed at Month 24 (via phone call). The reason for withdrawal/discontinuation must be documented clinically and/or by the central radiologist if applicable.

3.5.1 Follow-up Visit 4 [redacted] and Visit 5 [redacted]

Patients will be evaluated as follows:

[redacted]

[redacted]

3.5.2 *Follow-up Visit 6* [redacted] *and Visit 7* [redacted]

Patients will be evaluated as follows:

[redacted]

3.5.3 *Follow-up Visit 8* [redacted]

Patients will be evaluated as follows:

[redacted]

[redacted]

3.5.4 Follow-up Visit [redacted]

Patients will be evaluated as follows:

[redacted]

End-of-period examination: This 24-month visit corresponds to the end of study examinations at the Investigating Site.

3.6 Long Term Follow-up (Months 36 and 48 [redacted])

For all treated patients (*i.e.,* even for patients who have been withdrawn/discontinued from the study before the end of the 24-month follow-up period), phone call "visits" will be performed by the Investigator at 36 months [redacted] (Visit 10) and 48 months [redacted] (Visit 11) after IMP implantation, to evaluate the following safety data:

- Assessment of any changes in health status
- Review of concomitant medication
- Documentation of SAE (notably in case of THA)

Patients who have completed all the follow-up visits (*i.e.* up to Month 24 included) will also be evaluated for the following clinical variables:

[redacted]

4 DETAILED DESCRIPTION OF THE PROCEDURES AND INVESTIGATIONAL MEDICINAL PRODUCT

Site staff will be trained on the trial-related procedures and Standard Operating Procedures, including step-by-step instructions during the Site Initiation Visit (SIV) at the latest.

Table 4: *Summary of Procedures Performed in the PREOB® and Placebo Groups*

Procedures	***Timepoints***	**PREOB® Group**	**Placebo Group**
Bone Marrow Harvest	Day-21	Yes [redacted]	Yes [redacted]
Peripheral Blood Sampling	Day-21	Yes [redacted]	Yes [redacted]
Core decompression (using a 5mm trephine)	Day 0	Yes	Yes
Intra-osseous Implantation (blind vials)	Day 0	Yes	Yes

4.1 Bone Marrow Harvest and Blood Collection Procedures (performed by the Independent Physician)

PREOB® Group - Bone Marrow Harvest Procedure

At least twenty-one days[5] before the surgical procedure (Implantation Visit, Visit 3), the patient will be admitted to the hospital in order to undergo a bone marrow aspiration (Visit 2). In the operating room or another aseptic environment, the patient will be placed on the left or right side (on the target hip side or not, as judged by the Independent Physician), and local anaesthesia of the skin, muscles, and periosteum of the right or left posterior iliac crest will be performed using 5-10 ml of a local anaesthetic (e.g., lidocaïn hydrochloride). Sedation can be administered as per Independent Physician judgement. After 5 to 10 minutes, a 5-mm incision will be made at the level of the posterior iliac crest, the bone marrow aspiration needle is introduced into the iliac crest, and [redacted] bone marrow is aspirated and used for the culture of PREOB®. If the bone marrow harvesting is difficult or insufficient, the orientation of the needle within the same incision can be modified according to the need. The patient will then be placed in a supine position and [redacted] peripheral blood will be taken. The patient will be

[5] *The bone marrow harvest and the core decompression procedure should be scheduled in conjunction with the Sponsor's Manufacturing Unit and should take into account the travel time between the Investigating Site and the Sponsor's Manufacturing Unit.*

allowed to leave the hospital 30 minutes after vital signs have been checked (see detailed procedures in the SPM for the Independent Physician).

Control Group - Sham Bone Marrow Harvest Procedure

At least twenty-one days[6] before the surgical procedure (Implantation Visit, Visit 3), the patient will be admitted to the hospital in order to undergo a sham bone marrow aspiration (Visit 2). In the operating room or another aseptic environment, the patient will be placed on the left or right side (on the target hip side or not, as judged by the Independent Physician), and local anaesthesia of the skin, muscles, and periosteum of the right or left posterior iliac crest will be performed using 5-10 ml of a local anaesthetic (e.g., lidocaïn hydrochloride). Sedation can be administered as per Independent Physician judgement. After 5 to 10 minutes, a 5-mm incision will be made at the level of the posterior iliac crest, and the bone marrow aspiration needle is placed in contact with the iliac crest for 5 minutes without penetration of the bone. There will be no bone marrow aspiration. The patient will then be placed in a supine position for 10 minutes and [redacted] peripheral blood will be taken. The patient will be allowed to leave the hospital 30 minutes after vital signs are checked (see detailed procedures in the SPM for the Independent Physician).

4.2 Core Decompression and Implantation Procedures

4.2.1 Control of the Investigational Medicinal Product Quality

On the core decompression and IMP (PREOB® or Placebo) implantation day, the shipping box, containing the IMP will be shipped to the Pharmacy Department of the Investigating Site by the Manufacturer.

Upon reception, the Pharmacist will check the external product package and, if all the conditions listed on the Release Form for the Hospital – Hospital Pharmacist Section are met, subsequently release the IMP. The pharmacist immediately informs the Principal Investigator (and/or delegate) of the IMP release status (see detailed description of related procedures in SPM for the Pharmacist). If released by the pharmacist, the IMP will be transferred to the Operating Room.

In the Operating Room, the Principal Investigator will check the internal product package, IMP syringe, and labelling (including Patient Identification Number, name and surname) *himself* and

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[6] *The bone marrow harvest and the core decompression procedure will be scheduled in conjunction with the Sponsor's Manufacturing Unit and will take into account the travel time between the Investigating Site and the Sponsor's Manufacturing Unit.*

complete the Release Form for the Hospital – Principal Investigator Section (see detailed description of procedures in the SPM for Principal Investigator). If any problem occurred and the IMP is not released by the Principal Investigator (*i.e.* the Patient cannot be treated), the Investigator completes the eCRF, and the IMP will be labelled with "Medication return - to be destroyed" label and shipped to the Manufacturer within 72 hours of receipt together with the « Medication Return Form » duly completed and signed by the Investigator.

If the IMP is not released due to any problem linked to the production process, the Managing Physician will notify the Competent Authorities (CA) and Study Safety Officer (SSO), and record relevant information in the eCRF. Once completed, the eCRF will automatically send e-mail alerts to the SSO and the Investigator.

In case the IMP is not available for the implantation, the Investigator will inform the patient about the cancellation of the procedure. In this case, the patient will be considered as drop out, but the Investigator is however allowed to re-include the patient after 2 months (novel inclusion procedure).

4.2.2 Core decompression/Investigational Medicinal Product implantation (PREOB® or Placebo)

A C-arm fluoroscope is draped with a sterile sleeve and is positioned over the hip region to allow an antero-posterior view and, after flexion of the knee and abduction of the hip, a frog leg lateral view of the proximal part of the femur. A 5 to 10 mm incision is then made laterally through the skin and the fascia at the level or just under the great trochanter and a drill hole is made manually in the lateral femoral cortex (mechanical drill is allowed until reaching the intertrochanteric region using the same diameter trephine, followed by manual drill with the provided core decompression material). Under fluoroscopic control, the external trephine is then drilled further manually through the neck and head of the femur to reach the necrotic lesion, usually located below the articular cartilage. In doing so, the direction of the trephine must be adjusted in both planes so that it is pointing towards the necrotic zone. The position of the trephine will be checked in both antero-posterior and lateral fluoroscopic views; the tip of the external trephine should be placed inside the necrotic zone. The internal trephine is then introduced into the external trephine in order to perform the core decompression, as previously described (Hauzeur *et al.,* 1986). For this purpose, the tip of the internal trephine is drilled up to a few mm distance from the chondral plate.

After core decompression, the internal trephine is removed and a 3-waystopcock is connected at the extremity of the external trephine and set in a closed position. The blind syringe is gently tapped and rolled between hands to properly re-suspend its content, and is then connected to

the 3-waystopcock. The 3-waystopcock is then opened and the content of the syringe [redacted] is fully pushed through the trephine into the necrotic lesion. The injection is performed slowly for approximately 1 to 2 minutes. In case of resistance during the injection, it is recommended to pause and close the 3-waystopcock for 1 or 2 minutes and then re-open it to continue and finalize the injection into the necrotic area.

Finally, the trephine is washed with a rinse solution (NaCl 0.9%) to ensure that the entire IMP (5ml) was injected into the necrotic lesion. The syringe is then removed and the 3-waystopcock is closed. The 3-waystopcock is removed and gel foam (Gelfoam®, Pfizer) or equivalent is pushed through the external trephine towards the necrotic lesion to allow clotting and closing of the hole made by the trephine in the necrotic lesion. The external trephine is removed and stitches are applied to close the skin.

4.2.3 Peri-operative antibiotic therapy and other medications

All patients will receive a single intravenous infusion of Cefazolin (2 g) or any standard-of-care antibiotic therapy used at the Investigating Site at induction. In case of allergy to Cefazolin or Penicillin, intravenous administration of Clindamycin (3 × 600 mg a day) during 24 hours can be performed. Drugs used during anaesthesia will not be systematically recorded in the eCRF, except if an Adverse Event should have occurred.

Postoperative Management

Following the core decompression and implantation procedure, all patients will remain non-weight-bearing on the operated leg for 1 to 3 weeks. Following this period of time, total weight bearing will be permitted. No specific rehabilitation procedure will be conducted (either immediately or on a long-term basis). More specifically, patients will be allowed to progressively mobilise the hip without any physiotherapy management. Stitches (if any) will be removed 7 to 14 days after surgery as per standard of care.

5 INVESTIGATIONAL PRODUCT AND STARTING MATERIALS

5.1 Investigational Medicinal Products

Table 5: *Identity of Investigational Medicinal Products*

	PREOB®	***Placebo***
CBMP	Human autologous bone marrow-derived osteoblastic cells	N.A.
Cellular concentration	[redacted] cells/ml - 5 ml suspension solution	N.A. – 5 ml solution
Container	Blind ready-to-use syringe	Blind ready-to-use syringe
Batch number	Provided on the label	Provided on the label
Expiry date	Provided on the label	Provided on the label
Manufacturer	Bone Therapeutics S.A.	Bone Therapeutics S.A.
Trade name	PREOB®	N.A.
Storage requirements	Provided on the label	Provided on the label

Treatment administered

Each patient will receive a single dose of:

- PREOB® ([redacted] cells)

or

- Placebo

Table 6: *Administration of the Investigational Medicinal Product*

	PREOB®	***Placebo***
Procedure/ Route of administration	Core decompression and intra-osseous implantation with trephines	Core decompression and intra-osseous implantation with trephines
Single dose	5 ml – [redacted] cells	5 ml
Dosage schedule	One single dose per patient on Visit 3 (Day 0)	One single dose per patient on Visit 3 (Day 0)

5.2 Investigational Medicinal Product Post-administration Sterility Testing

PREOB®, due to its nature as a cell product with limited shelf life, will conditionally be released for clinical use. The compendial sterility and mycoplasma tests to be performed on the Investigational Medicinal Product usually require at least 14 days to be completed. Conditional release of the final product is thus done on the basis of alternative rapid tests, without having the final results available (conditional release - first step). The IMP Final Release Certificate will be sent to the Investigating Site about 30 days post-implantation, upon completion of compendial sterility and mycoplasma testing (final release - second step).

This procedure therefore bears the possibility that the IMP could be "refused" after administration if the post-administration sterility tests are positive. Once a post-administration sterility test is reported positive, an investigation will be started in order to verify that sterility results are valid. If confirmed, the Manufacturer will immediately inform the Principal Investigator through the eCRF (eCRF completion automatically triggers e-mail notifications). Additional microbiological analyses and antibiogram will be conducted to identify the micro-organism(s) involved. The result of these tests will be reported to the Investigator as soon as available in order to allow immediate and appropriate therapeutic measures (including the need for adequate antibiotic therapy). In all cases, blinding will be maintained, unless unblinding is required for patient safety issues.

5.3 Tracking, Traceability, and Accountability of Investigational Medicinal Product

A coding tracking system allowing complete traceability of both the Starting Materials and the IMP at all stages will be established and maintained (by Sponsor, Manufacturer, Managing Physician of the Production/Tissue Establishment, Investigator, Independent Physician, and Monitor). This tracking system will ensure that:

- The Starting Materials and IMP (PREOB® and Placebo), are tracked and traced during the whole process, from harvest to implantation, each procedure and step being described in Standard Operating Procedures, and systematically collected, verified, and recorded using specific Forms and Receipts (and in the eCRF).
- The patient is implanted with an autologous batch of PREOB® or Placebo
- Data from the Quality Control tests of each batch (and documentation of completion of each step in batch production and testing records) are accurately tracked and recorded.
- A unique identification code (Patient Identification Number) is allocated by the CRF system upon registration performed during patient screening (and will be associated to both the Starting Materials and IMP, at all stages and steps of the process and trial). The link between the identity of the patient and the identification code will be protected and kept strictly confidential. This information will be known, (identity of the patient (*i.e.* name and surname)), collected, and recorded *only* by the Investigator and his/her team and the Managing Physician of the Production/Tissue Establishment (and will be kept and recorded in restricted access files: Investigator's Site File at Investigating Site and a register maintained for the purpose at the Manufacturer (Production/Tissue Establishment), respectively).
- Used syringes (without needles) will be kept and stored in each Investigating Site until Monitor's verification visits, and destroyed after drug accountability and reconciliation.

Finally, data and records required for full traceability will be kept by the Sponsor, Managing Physician of the Production/Tissue Establishment, Manufacturer, and Investigator for a minimum of 30 years after clinical use.

6 LABORATORY ASSESSMENT

6.1 Blood for Laboratory Testing

Table 7: *Blood collected*

Type of sample and volume collected	***Assay***	***Visits***	***Laboratory***
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

* *if applicable*

** *other tests may be done if required by the authorities in case of a new disease outbreak that can affect the safety of the physicians and operators at the time of patient screening*

Blood testing for biochemistry, haematology, and serology will be done at the Investigating Site's laboratories. The Sponsor will obtain a copy of the Certification of these laboratories as well as up-to-date normal ranges.

When applicable, in order to assess potential changes of systemic biomarkers of the patients enrolled in the study, the levels of biomarkers will be measured [redacted].

The total amount of blood collected is expected not to exceed [redacted].

6.2 Storage of collected Blood and exceeding Starting Materials

All collected samples or excess of Starting Materials will be stored for up to 2 years after last patient's last visit unless local rules, regulations or guidelines require different timeframes or different procedures.

6.3 Use of exceeding Bone Marrow, Peripheral Blood, and PREOB® product

If excess of Starting Materials (bone marrow and peripheral blood) or PREOB® cells is available, these materials can be used for additional research experiments within the context of this study (genotyping excluded).

7 SAFETY: TOLERABILITY MEASUREMENTS AND ENDPOINTS

7.1 Overview of Safety Parameters and Endpoints

The treatment safety and tolerability will be systematically investigated throughout the study period. Patients will be evaluated at each follow-up visit for the potential occurrence of any AE or SAE, related to either the product or any study procedures (see Section 8 for Definitions of AE/SAE).

Table 8 below shows how the safety endpoints of this study relate to the study objectives. Assessments and measurements will be carried out at the timepoints specified in the main study schedule of visits and procedures (Table 2).

Table 8: *Overview of Safety Parameters and Endpoints*

Objectives	***Variables***	***Visits***
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

7.1.1 Vital Signs

- Blood pressure (BP) will be assessed in all patients on site by standardised cuff measurements. Preferably, the same person should do all the measurements on the same patient.

- Heart rate will be measured, in beats per minutes (bpm) after the patient has been in a resting state (seated) for at least 5 minutes. Heart rate will be counted for 30 seconds, multiplied by 2 and recorded in bpm.
- The Body temperature and Respiratory rate will also be recorded.
- Results of measurements should only be reported as AE if, in the Investigator's opinion, they are outside of "expected values or variations". Also they must be considered as SAE if they fulfil the SAE definition.

7.1.2 Physical Examination

- Physical examination, including assessment of general appearance, skin, head, and neck (including eyes, ears, nose, and throat), lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, lungs, abdomen, and neurological status will be performed preferably by the same person.
- Height will be measured in centimetres (cm). Weight will be measured in kilograms (kg) using a scale. Body Mass Index (BMI) will be calculated as follows: Weight (Kg)/Height^2 (m) = BMI.

7.1.3 Laboratory Safety Measurements

Serology testing [redacted] will have to be performed [redacted].

Blood will be sampled [redacted]

The following parameters will be analysed for the safety measurements:

- Haematology: red blood cell count, haematocrit, haemoglobin, leukocyte, neutrophil, lymphocyte, monocyte, basophil, eosinophil, and platelet counts.
- Biochemistry: creatinine, urea nitrogen, uric acid, sodium, potassium, calcium, phosphorus, albumin, total proteins, CPK, alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT), total bilirubin, gammaglutamyltransferase, alkaline phosphatase, LDH, amylases, glucose, HbA1C, C-reactive protein (both "standard" CRP and *hs* CRP, highly sensitive CRP), lipids (total cholesterol, LDL cholesterol, and triglycerides), and coagulation parameters (including PT and APTT).

7.2 Other Safety Measurements

7.2.1 Women with childbearing potential

Women with childbearing potential must use a reliable method of contraception for at least 6 weeks prior to Screening Period and during the whole study period. Reliable contraceptive methods include orally administered hormonal contraceptives, surgical intervention (e.g., tubal ligation), and intrauterine device (IUD).

Moreover, women with childbearing potential will systematically undergo urine pregnancy test at each visit performed (from Screening Period up to Month 24). Pregnancy test kits will be provided by the Sponsor, performed on site according to manufacturer's instructions, and results will be recorded in the eCRF.

7.2.2 Additional safety examinations and procedures

If any unclear clinical event, including symptoms, signs, or other observations or abnormalities, should occur, the Investigator, or any other physician in charge, may perform additional clinical examinations and procedures (other than outlined in this protocol), including any clinical, laboratory, imaging and/or technical testing, in order to clarify and establish the aetiology and diagnosis of this clinical event.

8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1 Definitions

Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject who has been administered a pharmaceutical product and/or any investigational medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including any abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal product, without any judgment about causality (ICH E2a).

Adverse events will be graded with respect to intensity and classified as either serious or non-serious according to the World Health Organisation Classification.

Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as any AE or suspected adverse reaction (SAR) that, in the view of the Investigator or Sponsor, results in any of the following outcomes (ICH E2a and ICHE6):

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Table 9: *Classification of Adverse Events*

Intensity	*Mild*	Some awareness of symptoms or signs that does not interfere with the patient's usual activities or is transient, easily tolerated and resolved without treatment and with no sequelae
	Moderate	Symptoms or signs causing enough discomfort to interfere with the patient's usual activities, and/or requires symptomatic treatment
	Severe	Incapacitating event, including symptoms or signs, causing severe discomfort and inability to work or to perform usual activities, and requires treatment
Seriousness	*Serious (SAE)*	Any untoward medical occurrence that at any dose: – Results in death, or – Is life-threatening, or – Requires patient hospitalization or prolongation of existing hospitalization, or – Results in persistent or significant disability/incapacity, or – Is a congenital anomaly / birth defect or – Is medically important
	Non-serious	Any other adverse event

Notes

1. The term "life-threatening" in the definition of SAE refers to an event that in the view of the Investigator places the patient at immediate risk of death at the time of the event; it does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. The term "life-threatening" does not imply a possible future course which might or might not have happened, but was prevented due to adequate physician's action. For example, a simple bacterial wound infection can potentially lead to gangrene, sepsis, and eventually death; while sepsis is usually regarded as a SAE because of known high mortality, the primary wound infection itself is usually not regarded as a SAE. In analogy, a newly diagnosed malignant disease is usually regarded as a SAE because malignant diseases usually have a high mortality rate and are therefore life-threatening.

2. To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following clarification is provided: the term

"severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself however may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to the patient's life or functioning.

3. In addition, events that may not meet the criteria indicated above, but which the Investigator finds very unusual and/or potentially serious, will be reported as SAE. Indeed, medical and scientific judgments should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also usually be considered as SAEs. Examples of such events include intensive treatment in the Emergency Room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not results in hospitalization, and/or development of drug dependency or drug abuse.

4. A hospitalization planned by the patient prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure occurs as planned, the record in the patient's medical history is considered complete. However, complications or other events that may occur during hospitalization will be considered as AEs or SAEs and will be captured accordingly.

Causal relationship with the Investigational Medicinal Product

The term "causality" describes the degree of attributability (causality) between an investigational medicinal product and an event. Causality assessment of AEs is the structured and standardised assessment of individual patients / case reports for the likelihood of involvement of suspected drug in causing a particular event in a given patient.

The drug-event causal relationship will be assessed using the following criteria, approved by the WHO Collaborating Centre for International Drug Monitoring (Edwards & Biriell, 1994). It should be noted that, for classification, all criteria of a category have to be met.

Table 10: *Assessment of drug-event causal relationship*

Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure, if necessary.

Probable/Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Conditional/Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
Not assessable/Unclassifiable	A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

In practice, determination of the causal relationship between an AE/SAE and the trial medication must be made by the Investigator by answering the following question: "Is the causal relationship between the medicinal product and this AE/SAE reasonably possible"?

- Yes: related
- No: not related

Indeed, causality assessment is a clinical decision based on all available information at the time of and after the occurrence of the event. The factors which may be considered when evaluating the causal relationship of an AE/SAE to the IMP administration include the followings:

- Underlying, concomitant, and/or intercurrent diseases: each report should be evaluated in the context of the natural history and course of the disease being treated and any other diseases the patient may have had prior to, or developed during the course of the study
- Concomitant medication or treatment: other drugs the patient is taking or treatment the patient is receiving at the time of the event should be examined to determine whether any of them may be recognized to cause the event in question
- Known response pattern for this class of drug

- The pharmacology and pharmacokinetic of the IMP: absorption, distribution, metabolism, and excretion of the IMP or other medications the patient is receiving coupled with the pharmacodynamic responses should be considered when evaluating an event

Adverse Drug Reaction (ADR)

An Adverse Drug reaction (ADR) is any untoward and unintended responses to an investigational medicinal product related to any dose administered (having a reasonable causal relationship to the product, the term "reasonable causal relationship" meaning that there is evidence or arguments to suggest a causal relationship).

Serious Adverse Reaction (SAR)

A Serious Adverse Reaction (SAR) is any untoward and unintended responses to an investigational medicinal product related to any dose administered (having a reasonable causal relationship to the product), and that results in death, is life-threatening, requires patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect or is medically important.

Serious Adverse Safety/Quality Event (SASQE)

A Serious Adverse Safety/Quality Event (SASQE) is any adverse event related to any operation done on the collected human biological material under the responsibility of the Intermediary Structure (*i.e.*, direct transport and distribution of the human biological material from the harvesting site to the Production/Tissue Establishment of Bone Therapeutics S.A.) that may cause death, be life-threatening, generate disability or incapacity to work to the patient, or that may cause morbidity.

Expectedness

An (S)AE or ADR/SAR is considered unexpected if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described elsewhere (for example, approved prescribing information).

The Reference Safety Information for this study is in Section entitled "Reference Safety Information" of the current Investigator's Brochure.

8.2 Assessment of Adverse Events

The occurrence of AE/SAE (drug- or procedure or study-related) will be assessed by non-directive questioning of the patient since the beginning of the study at the screening Period, and

each follow-up visit searching for any changes in health status (e.g., "Have any Adverse events or Serious adverse events occurred since the last visit?"). Furthermore, AE/SAE spontaneously reported by the patient during or between the follow-up visits, or detected through observation, physical examination (including body mass index and vital signs), laboratory testing, or other clinical procedures during the observation period will be documented. Patients will be instructed that they must immediately report any adverse events, subjective complaints, or objective changes in their wellbeing to the investigator or the Investigating Site's personnel, regardless of the perceived relationship between the event and the test product.

If it is determined that an AE/SAE has occurred, the Investigator should obtain all the information required to complete the corresponding AE or SAE Form of the eCRF, and establish potential causality relationship with the product or study procedures, including the bone marrow harvesting, the blood sampling and the product implantation (core decompression, implantation surgery, and general anaesthesia).

8.2.1 Observation period for the occurrence of AEs and SAEs

Table 11 below defines the observation period for the occurrence of AE and SAE during both the follow-up period (up to 24 months) and the long term follow-up (at 36 and 48 months). These safety observation periods must be respected for all treated patients (*i.e.*, regardless of the patient's outcome in the study, whether the patient has been withdrawn/discontinued early or not).

Table 11: *Observation period for the occurrence of AEs and SAEs*

Follow-up: AE/SAE Observation Period	From Screening Period up to 24 months after implantation (Visit 3)
Long term follow-up: AE/ SAE Observation Period	At 36 and 48 months after implantation (Visit 3)

If the investigator learns of any SAE, including a death, any time after the two defined observation period for the occurrence of AEs and SAEs (Table 11), and considers the event reasonably related to the Investigational Medicinal Product, the investigator will promptly notify the Study contact for reporting SAEs.

8.2.2 Summary of Possible Risks related to the Procedures

Table 12: *Summary of Possible Risks related to the Procedures*

	AE	***SAE (Fatal and Non-Fatal)***
Bone Marrow Harvest	Pain at the aspiration site Local haematoma	-
Bone Marrow Concentrate/Mesenchymal Stromal Cells Implantation	Fever	-
Core Decompression and Implantation Procedure	*Surgery* Pain at the implantation site Local haematoma Infectious complications *General anaesthesia* Transient hypotension Nausea and vomiting	*Surgery* Femoral neck fracture Femoral head blow-up Haemorrhage Sepsis Shock *General anaesthesia* Cardiac complications • Myocardial infarction • Cardiopulmonary arrest • Ventricular tachycardia Neurological complications • Stroke Pulmonary complications • Inhalation pneumonia • Pulmonary embolism Anaphylactic shock
Blood Sampling	Pain at the sampling site Local haematoma Superficial vein thrombosis Transient hypotension/lypothymia	Syncope

8.2.3 Summary of Observed Adverse Events (AE) and Serious Adverse Events (SAE) possibly related to Study Treatment in Osteonecrosis

Table 13: *Summary of Observed Adverse Events (AE) and Serious Adverse Events (SAE) possibly related to Study Treatment (i.e., PREOB® and/or to the Implantation Procedure) (33 subjects (hips)*)*

Non-Serious AE		***SAE (Non-Fatal)***	
Total	**9.1%**	**Total**	**6.1%**
Fever	9.1%	Systemic inflammatory response syndrome	3.0%
		Pancytopenia**	3.0%
		Pyrexia**	3.0%
		Altered status of consciousness**	3.0%
		Hypotension**	

** Based on the Phase IIb study with the product under investigation in osteonecrosis. For more detailed information, see the Investigator's Brochure. AEs and SAEs were limited to treatment emergent adverse events (TEAEs) and serious treatment emergent adverse events (STEAEs) and reported per Preferred Term (PT) (MedDRA coding), along with their frequency of occurrence in subjects. Subjects were counted once for each PT. An AE/SAE was considered as treatment-emergent if it occurred on or after the date of the IMP implantation. In case of missing start date, the AE was considered as treatment-emergent*

*** 4 SAEs were reported in the same patient.*

8.3 Management of Safety Issues

- In the event of an AE/SAE, the Investigator will immediately initiate appropriate therapy and management according to his/her medical judgment and will decide whether to withdraw the patient from the study.
- The patient must be followed-up by additional examinations according to the medical judgment of the Investigator, until the AE/SAE and/or abnormal condition is resolved or the Investigator deems further observations or examinations are no longer medically indicated.

8.3.1 Safety Data Notification Reporting, and Monitoring

8.3.1.1 *Reporting of Adverse Events (AEs)*

All AEs will be recorded on the appropriate and corresponding AE Form of the eCRF by the Investigator. All AEs must be reported whether or not considered causally related to the IMP or any related study procedures. For every AE, the Investigator will provide an assessment of

the severity and causal relationship to the IMP or any related study procedures and document all actions taken with regard to the IMP, and any other treatment modalities for the AE. Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the patient's eCRF.

If the outcome of an AE is not available at the time of the initial report or at study exit (premature or not), follow-up will proceed until outcome is known. All collected data will be recorded in source documents.

8.3.1.2 *Notification and reporting of Serious Adverse Events (SAEs)*

Any SAE, whether deemed drug/procedure-related or not, must be recorded on the corresponding eCRF Form (SAE form), which will, upon completion, be automatically followed by e-mail alerts to Pharmacovigilance-CRO (PV-CRO), Investigator (if completed by Independent Physician), Monitor, Sponsor, and Managing Physician of the Production/Tissue Establishment. In case of technical problem with the eCRF, a paper version of the Form will be sent by fax to the SSO **(+[redacted])** who will immediately inform the Managing Physician of the safety event occurrence, and the eCRF will be completed (by the Investigator or Independent Physician) thereafter as soon as possible.

In the event of any SAE, occurring from the Screening Period up to the end of the long term follow-up (48 months after Product Implantation (Visit 3)), the Investigator (or Independent Physician for visit 2) will **within 24 hours of event occurrence or awareness**:

1. the Study Safety Officer (SSO) by phone: Safety Events Phone Number, 24/7 cover: [redacted]
2. Record the SAE on the corresponding eCRF Form (SAE form) or send it by fax [redacted]) or per email ([redacted]) to the SSO who will immediately inform the Sponsor of the safety event occurrence

   The eCRF will be completed (by the Investigator or Independent Physician) thereafter as soon as possible.

Briefly, the SAE Form (and the related Follow-up Forms if needed) will include the following information and differentiated assessment:

- Patient identification: Patient Identification Number, age, and sex
- SAE diagnosis and description, start and end dates, concomitant drugs and history

- Outcome (recovery with or without sequelae, unchanged, improvement, worsening, death, or other) and action taken (none, patient discontinuation and withdrawal from the study, change in concomitant medication(s) and/or new medication(s), other treatment(s) and/or therapeutic procedure(s) (*i.e.* invasive procedures, surgery, or unknown)
- Criteria for seriousness (death, life-threatening, persistent or significant disability or incapacity, new or prolonged hospitalization, congenital abnormality or birth defect, important medical event), severity (mild, moderate, severe), and frequency (intermittent, continuous, or other)
- Causal relationship with the IMP (assessment of drug-event causal relationship and consistency with applicable product information, e.g., the Investigator's Brochure and evaluated as certain, probable or likely, possible, unlikely, unrelated, unknown or not assessable)
- Causal relationship with the trial procedures, including the bone marrow harvesting and blood sampling, and the product implantation (core decompression, implantation surgery, and general anaesthesia)
- Relationship with the study disease and/or underlying, concomitant, and/or intercurrent diseases, relationship with concomitant medication or treatment, and/or drug interactions
- Suspected or confirmed cases of infection
- Suspected or confirmed cases of ectopic calcification or myositis ossificans
- Unexpected reactions (e.g., hypersensitivity, allergic, immunogenic, autoimmune, and/or toxic)

In Europe

Based on data and information available in both the SAE Form and in the Investigation and Conclusion Report (see below) (and additional queries, if needed), the SSO will notify the occurrence of SUSAR, SAR, and/or SAE related to the trial procedures to both EudraVigilance database and Ethics Committees (all Member States concerned), and to all concerned Investigators and Sponsor in agreement with all applicable legislation.

This notification will be sent by the unblinded SSO to both Eudravigilance database and Ethics Committees while blinding will be preserved for both the Investigators and Sponsor.

In the United States of America

Based on data and information available in both the SAE Form and in the Investigation and Conclusion Report (see below) (and additional queries, if needed), the Sponsor will notify the

FDA and all participating investigators in an IND safety report of potential serious risks, including any suspected adverse reaction that is both serious and unexpected.

This notification will be sent by the SSO to the FDA and Investigators.

The Sponsor or designee (PV-CRO) must submit a written summary of the clinical course of any life-threatening SAE and related patient information to the FDA within 15 days. Serious and unexpected ADRs that are not-life-threatening must be reported to the FDA within 15 calendar days. Any serious and unexpected AE (including all deaths) must also be reported to the IRB by the Investigator according to IRB reporting requirements (where applicable) and documentation of this report sent to the Sponsor and designee (PV-CRO).

All SAEs will be followed to resolution, defined as patient's health has returned to his/her baseline status or all variables have returned to normal). If the Investigator does not expect any further improvement or worsening of the event the SAE is followed until stabilization of the event. The event is otherwise explained regard less of whether the patient is still participating in the study.

8.3.1.3 *Notification and Reporting of Serious Adverse Safety/Quality Events (SASQE)*

Based on the information available in the eCRF SAE Form, the Managing Physician will immediately investigate. If the investigation indicates that the safety event is actually related to the procurement, testing, processing, storage, labelling and packaging, delivery, transport, and/or distribution of Investigational Medicinal Product, and/or to the quality and safety of the product the event will then be considered as a serious and unexpected adverse reaction to the product, or SAE related to the trial procedures, and the Managing Physician will within 24 hours of the event occurrence or awareness notify (through an Immediate Notification Report) the CAs and SSO (the Investigator, Monitor, and Sponsor will also be notified via an automatic e-mail alert generated from the eCRF page completed by the Managing Physician).

An Investigation and Conclusion Report - prepared by the Managing Physician - will be sent to the CAs and SSO (with a blind copy sent to the Investigator and Sponsor) as soon as possible and no later than 5 calendar days after knowledge of event for the initial report (or for the additional follow-up reports if needed). The SSO will record this event in the Eudravigilance database.

If the SASQE has occurred during the harvest or implantation procedure in Investigating Site, or between reception of the IMP at the Investigating Site and IMP implantation, the Independent Physician or the Investigator, respectively, will immediately record the relevant information in the corresponding eCRF Form (completion of this Form will be followed by automatic e-mail

alerts to the Managing Physician, SSO, Investigator (in case of completion by Independent Physician), Monitor, and Sponsor).

If a serious safety issue is identified, either upon receipt of an individual case report or upon review of aggregate data, the Sponsor will issue a communication to all Investigators as soon as possible. A safety issue that impacts upon the course of the trial, including suspension of the trial, safety-related amendments to the Study Protocol, change or update of Subject Information Sheet and Informed Consent Form or Investigator's Brochure, will also be reported to the Investigators (after prior submission and approval by the CAs and ECs).

8.3.2 Annual Safety Reports – Development Safety Update reports (DSURs)

EU Annual Safety Reports

In addition to the expedited reporting, the SSO will provide annual development safety update reports (DSUR) to CAs, ECs, and Sponsor, including but not limited to all SARs, and/or SAEs related to the trial procedures, together with an overview of all other SAEs, AEs, and SARs that have occurred during the reporting period (in all sites and countries). The report will be provided in the format laid down in Guideline ICH topic E2 F.

IND Annual Safety Reports

In addition to the expedited reporting, the SSO will provide annual development safety update reports for submission to the FDA according to 21 CFR 312.33, including but not limited to all IND safety letters, SARs, and/or SAEs related to the trial procedures, together with an overview of all other SAEs, AEs, and SASQEs that have occurred during the reporting period (in all sites and countries). The report will be provided in the format laid down in Guideline ICH E2 F.

8.3.3 Safety Data Monitoring

The occurrence of AEs, SAEs, and SASQEs will be monitored during the whole study period (from Screening Period) on an ongoing basis by the Study Safety Officer, the Managing Physician of the Production/Tissue Establishment, and the Sponsor. The Sponsor will also receive from the Study Safety Officer a regular detailed updated listing of all AEs, SAEs, and SASQEs.

8.3.4 Data Safety Monitoring Board

An independent data-monitoring committee will be established to assess at intervals the progress of the study, the safety data and the critical efficacy endpoints. This board will

recommend to the Sponsor whether to continue, modify or stop the trial. The members of the board will be unblind for the study while the Sponsor and Investigators will remain blind.

8.4 Procedure in Case of Pregnancy

Women included in the study must be post-menopausal (defined as at least 12 months post cessation of menses), surgically sterile or, for women with childbearing potential, using a reliable method of contraception for at least 6 weeks prior to study entry (Screening Period, Visit 1) and during the whole study period. Women with childbearing potential will undergo pregnancy tests at all study visits, and at the last visit to the clinic in case of premature discontinuation. However, if a female patient becomes pregnant during the trial, she will be followed as per study procedure but will **NOT** undergo bilateral X-ray and MRI of the hip.

Any pregnancy will be systematically followed and reported within 24 hours of diagnosis to the Study Safety Officer and Monitor (Pregnancy Form will be immediately completed in the eCRF, with subsequent urgent notification), and their outcomes will be reported to the Study Safety Officer and Monitor.

Any pregnancy will be handled as an SAE regardless the relationship between the Investigational Medicinal Product and the event. Any complication arising during pregnancy will be recorded as an AE and will constitute a SAE if it fulfils any of the specified criteria for a SAE.

At the end of the pregnancy, whether that be full-term or premature, information on the status of the mother and child will be forwarded to Study Safety Officer.

If the outcome of pregnancy is:

- Elective abortions without complications, they will be recorded, documented and reported to the Study Safety Officer and Monitor, but they should not be handled as AEs;
- Any spontaneous miscarriages or abortions for medical reasons, or congenital abnormalities or birth defects, will be recorded, documented, reported, and handled as SAEs and full details will be requested.

8.5 Emergency Procedures

8.5.1 Emergency Contact Procedure

- In case of SAE or any other safety event or medical concern, the following contact will be available (24/7 cover) for continuous support and assistance (Study Safety Officer):

Emergency and Safety Events Phone Number: [redacted]

The Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. Each patient will receive a Patient Study Card with the name and surname, the Patient Identification Number, Title and Number of the study, type of treatment received (cell product), and Name of the Sponsor. This card will also record the name, surname, full address, and phone number of the Investigator, the address and phone number of the Emergency Room of the Investigating Site, and the Emergency and Safety Events Phone Number (24/7 cover). The aim of this card is to inform any physician having to deal with a patient in an emergency situation that the patient is in a clinical trial and that he/she can contact the trial investigator for more relevant information. Patients will be instructed to carry this card around at any time during the study.

- For any other questions or study information, the following contact will be available (office hours) for continuous support and assistance:

[redacted]

[redacted]

8.5.2 Methods for Breaking the Blind

The treatment code must not be broken. However, the Investigator can unblind the patient's treatment assignment in case of medical emergency of safety concerns *if knowledge of the treatment allocation is able to improve or modify the management of the patient*. However, it is important to note that the unblinding procedure should not been used in order to assess the causality of an AE or SAE. The code may also have to be broken if someone not in the study received the IMP or if pregnancy of a randomised patient occurs. Once the decision taken, the Investigator will promptly inform the Study Safety Officer and document the reasons for the premature unblinding.

The unblinding/decoding process will be performed by the Investigator via the eCRF system. Additionally, a progress note summarising these events should be documented as part of the patient's study file, with clarification as to patient SAE outcome.

Investigators must always keep in mind that unblinding procedures will have a serious impact on the validity and analysis of the data.

8.6 Long-Term Pharmacovigilance System

Finally, during the course of the trial, the Sponsor plans to design, develop, and submit to the relevant CAs if needed, a detailed long-term follow-up strategy, under Pharmacovigilance Plan in line with Guideline ICH Topic E2 E.

9 PREMATURE REMOVAL FROM THE STUDY

9.1 Reasons for Early Discontinuation

Notification of patient study discontinuation (and reasons for discontinuation) will be communicated by the Investigator as soon as possible. The Investigator will document the circumstances for premature discontinuation in the patient's electronic Case Report Form as follows:

- ***Violation of eligibility criteria***

Patients will be withdrawn if incorrectly randomised (*i.e.*, not in compliance with one or more eligibility criteria). The Investigator may contact the Monitor in order to discuss the potential continuation of wrongly included patients if judged that is in the interest of the patient to continue the study.

In any case, and especially if the patient is withdrawn for safety reasons, the explanation for this discontinuation due to violation of eligibility criteria should be documented in the patient's eCRF.

- ***Adverse Events / Serious Adverse Events***

Any patients may be withdrawn from the study at the Investigator's discretion in case of a safety concern. However, patients can be withdrawn from the study for AEs or SAEs **only** if the Investigator has clearly determined that the patient's withdrawal would reduce the safety risks. In this case, the eCRF AE/SAE Form must be completed, explaining the rationale for withdrawal. In addition, the Investigator should ensure that adequate medical care and management will be provided to the patient.

- ***Withdrawn consent***

Participation in the study is strictly voluntary. A patient has the right to withdraw his/her consent from the study at any time, and for any reason, without prejudice to further treatment, care, and patient-physician relationship. Under these circumstances, an adequate standard of care will always be adopted by the Investigator. The reason(s) for withdrawing consent will also be documented in source documentation and the eCRF.

- ***Lack of patient compliance to the protocol***

- ***Study termination***

The Sponsor has the right to terminate the study at any time.

- ***Lost to follow-up***

Intensive efforts will be made to re-contact patients who do not return for scheduled visits in order to, at minimum, determine health status and the potential occurrence of AE and/or SAE. All efforts to re-contact will be documented in the source documentation and the eCRF.

- ***Reaching of endpoint***

Severe pain and/or femoral head fracture of the treated hip are the composites of the primary efficacy responder endpoint of this study. These events must carefully be documented either clinically for pain (WOMAC® VA 3.1) or radiologically for fracture (central radiologist assessment) before a patient is discontinued from the study. If severe enough to justify or warrant THA, these events will also be reported as SAE.

These events will be reported as study endpoints *via* the eCRF.

- ***Other reasons***

If no above-mentioned reasons are applicable in case of early discontinuation, the other reason(s) will be clearly documented and explained in the eCRF and source documents.

9.2 Procedure for Early Discontinuation

In case of early discontinuation and whenever possible, Investigators will ask patients to perform Visit 9 (Exit Visit) as the Premature Discontinuation Visit. At the end of the Exit visit, the Investigator will declare early discontinuation in the eCRF. However, the Investigator will continue to follow the patient (via phone calls) for the occurrence of any AEs and SAEs at Month 24, 36 and 48 post-treatment (See Table 11).

All collected data, during the visits and phone calls, should be recorded in the source documents and eCRF.

9.3 Replacement of Patients

As evaluation of the patient number to be randomised in the study took into account the percentage of discontinued patients, patients withdrawn from the study will not be replaced.

10 STATISTICAL CONSIDERATIONS AND METHODS OF ANALYSIS

A Statistical Analysis Plan (SAP) exhaustively detailing statistical methods will be generated, reviewed, approved, and signed by the biostatistician and the Sponsor, prior to database lock, at the latest. This document will be the main reference document as far as statistical analyses are concerned and therefore the description provided in this Study Protocol will not be exhaustive.

10.1 Collection and Derivation of Efficacy Assessments

10.1.1 Primary Efficacy Endpoint

Efficacy will be assessed by the following primary endpoint:

- Percentage of treatment responders at Month 24,

  a treatment responder at a studied timepoint being defined as a patient who responded both:

  - Clinically, *i.e.*, if at the studied timepoint, the WOMAC® VA3.1 pain subscale score of the study treated hip improved from baseline by at least the minimal clinically important difference (MCID)[a],

    and

  - Radiologically, *i.e.*, if at the studied timepoint, the study treated hip did not progress to fractural stages (ARCO III or higher), as assessed by conventional X-ray.

[a]The MCID value is set at 10 mm in accordance with the literature for WOMAC® VAS pain subscale (Ehrich *et al.*, 2000; Angst *et al.*, 2001) and with the absolute MCIDs reported in controlled, randomised, parallel group studies that evaluate treatment for hip disorders (Puopolo *et al.*, 2007; Altman *et al.*, 2007; Prior *et al.*, 2014).

For patients with a baseline WOMAC® VA3.1 pain subscale score ≥10 mm, the MCID can be used as a threshold value to define a clinically meaningful pain relief. These patients will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip decreased from baseline by at least the MCID.

For patients with a baseline WOMAC® VA3.1 pain subscale score <10 mm, the MCID cannot be used as a threshold value to define a clinically meaningful pain relief. These patients will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip is found in the range [0; 4]. This definition is based on the literature, which states that any VAS pain rating ≤4 mm is labelled as “no pain” (Jensen *et al.*, 2003).

10.1.2 Secondary Efficacy Endpoints

Efficacy will be assessed by the following secondary endpoints:

- Percentage of treatment responders at Month 6, 12 and 18, and over the 24-month follow-up period
- Percentage of clinical responders at Month 1, 3, 6, 12, 18 and 24, and over the 24-month follow-up period; a clinical responder being defined as a patient whom the WOMAC® VA3.1 pain subscale score of the study treated hip improved from baseline by at least the MCID[b] at the studied timepoint
- Percentage of radiological responders at Month 6, 12, 18 and 24, and over the 24-month follow-up period; a radiological responder being defined as a patient whom the study treated hip did not progress to fractural stages (ARCO III or higher), as assessed by conventional X-ray, at the studied timepoint
- Absolute change from baseline in WOMAC® VA3.1 total score and composite pain, stiffness, and function subscale scores of the study treated hip at Month 1, 3, 6, 12, 18 and 24, and over the 24-month follow-up period
- Time to progression to fractural stages (ARCO III or higher) of the study treated hip
- Percentage of patients requiring hip arthroplasty for the study treated hip at Month 1, 3, 6, 12, 18 and 24, and over the 24-month follow-up period
- Time to hip arthroplasty for the study treated hip

[b] The MCID value is set at 10 mm.

Patients with a baseline WOMAC® VA3.1 pain subscale score ≥10 mm will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip decreased from baseline by at least the MCID.

Patients with a baseline WOMAC® VA3.1 pain subscale score <10 mm will be considered, at the studied timepoint, as a clinical responder if the WOMAC® VA3.1 pain subscale score of the study treated hip is found in the range [0;4] (VAS pain range labelled as “no pain”).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.2 Collection and Derivation of Safety Assessments

Safety will be assessed using the following variables:

- Adverse events (AEs) occurring throughout the study period
- Serious adverse events (SAEs) occurring throughout the study period
- Occurrence of any abnormality at physical examination at Month 1, 3, 6, 12, 18 and 24
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate) evaluations and absolute change from baseline at Month 1, 3, 6, 12, 18 and 24
- Body Mass Index and absolute change from baseline at Month 1, 3, 6, 12, 18 and 24
- Hematologic and biochemical values and absolute change from baseline at Month 1, 3, 6, 12, 18 and 24
- Hematologic and biochemical values outside the normal ranges at Month 1, 3, 6, 12, 18 and 24
- Concomitant medications throughout the study period

10.3 Statistical Considerations

10.3.1 General Considerations

Continuous data will be summarized using the number of observations, mean, 95% confidence interval of the mean (unless specified otherwise), standard deviation, median, 25% (Q1) and 75% (Q3) percentiles, minimum and maximum.

Categorical data will be presented in contingency tables along with number of patients, percentages and their 95% confidence interval (unless specified otherwise).

Statistical tests will be two-sided at 5% significance level. Adjustment to control the type I error for multiplicity will be performed as described in Section 10.7 on interim analysis. Except for the adjustment made for the interim analysis, no additional adjustments for multiple comparisons will be done in this study.

AEs, SAEs and medical history terms will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the most recent version of the WHO drug dictionary.

Statistical analyses will be performed using the SAS® software (SAS Institute, Cary, NC, USA) version 9.2 or higher.

The Final Clinical Study Report will be established based on the efficacy and safety data collected up to 24 months. The long-term follow-up data (collected at 36 and 48 months after IMP implantation) will be analysed and reported as Annexes and Supplementary Data to the Final Clinical Study Report.

10.3.2 Statistical Hypotheses for the Primary Endpoint

The superiority of PREOB® over Placebo will be considered achieved if the percentage of treatment responders is statistically significantly higher in the PREOB® group than in the Placebo group at Month 24 (primary endpoint).

- H0 (null hypothesis): the difference in percentages between PREOB® and Placebo is equal to 0,
- H1 (alternative two-sided hypothesis): the difference in percentages between PREOB® and Placebo is different from 0 (with percentage PREOB® ≥ percentage Placebo).

Superiority will be proven if the *p*-value of the statistical test comparing the percentages of treatment responders between PREOB® and Placebo is less than or equal to the Type I error (two-sided) as defined in Section 10.7 in which case the null hypothesis H0 will be rejected in favor of the alternative hypothesis H1.

10.4 Sample Size

The single sample size test is planned with a two-sided 5% significance level and a power of 90% assuming the use of Chi-square test (see Table 14). The proportion of treatment responders

is assumed to be equal to 63% for the PREOB® group and 30% for the Placebo group. Theses hypotheses have been estimated on the basis of the Phase IIb data set.

Table 14: *Sample size estimation - Chi-square test*

Test?	Chi-square
Test significance level, α	0.05
1 or 2-sided test?	2
Group 1, PREOB® proportion, π1	0.63
Group 2, Placebo proportion, π2	0.30
Power (%)	90
N per arm	46

A Chi-square test with a 5% two-sided significance level will have 90% power to detect the difference between a Group 1 proportion, π1, of 0.63 and a Group 2 proportion, π2, of 0.30 when the overall sample size is 92 patients (46 patients in the PREOB® group and 46 patients in the Placebo group).

As an interim analysis is planned in the study using a group sequential design approach, the maximum sample size must be increased to achieve the desired power of 90% at final analysis. The increase in sample size depends on the overall significance level, the statistical power, the number of interim analyses and the type of boundaries being used (See section 10.7). Thus, the maximum sample size is obtained by multiplying the above fixed sample size by a constant determined by these parameters. For the current study, the maximum sample size is 110 patients (1.19 * 92 patients).

Taking into account a drop out and lost to follow-up rate of 7.5%, the overall sample size should be of 118 patients (59 patients in the PREOB® group and 59 patients in the Placebo group) to ensure around 110 evaluable patients at Month 24.

Sample size was computed using the procedure seqdesign of SAS® software version 9.2.

Additional considerations for sample size estimation

Although no claim is intended for the comparison of efficacy endpoints other than the primary endpoint, sample size calculations have been conducted to ensure that such comparisons may be performed with sufficient power to provide additional characterization of the treatment effect and yield supportive evidence related to the primary objective.

10.5 Analysis Sets

Three different sets of population will be used in the analysis of this study: a safety set (SAF), a full analysis set (FAS), and a per-protocol set (PP).

The safety set (SAF) will include all treated patients, *i.e.*, patients with both (i) core decompression and (ii) PREOB® or Placebo implantation. Analyses on the SAF will be performed according to the IMP actually received.

The full analysis set (FAS) consists in a modified Intention-To-Treat population and will include all randomised and treated patients, with a baseline value available of both the ARCO stage and the WOMAC® pain subscale score, and at least one post-baseline value available of both the ARCO stage and the WOMAC® pain subscale score. Analyses on the FAS will be performed according to the randomisation group regardless of the IMP actually received.

The per-protocol set (PP) will be a subset of the FAS including all randomised and treated patients who had no major protocol deviations during the study. Analyses on the PP will be performed if the PP differs by more than 10% from the FAS.

10.6 Statistical Methods

10.6.1 Primary Efficacy Endpoint Analyses

The primary endpoint is the percentage of treatment responders at Month 24.

Main analysis of primary endpoint

The percentage of patients fulfilling the criteria for treatment response (primary efficacy endpoint), as obtained after applying the rules for replacement of post-baseline missing data detailed in the SAP, will be presented by treatment group.

The primary efficacy endpoint will be compared between the two treatment groups by means of a Chi square test or a Fisher's exact test (as appropriate). The relative risk (PREOB® vs. Placebo) will be reported along with the associated confidence interval. The difference between the two groups will be considered significant if the *p*-value is lower than the significance level as defined in Section 10.7.

10.6.2 Secondary Efficacy Endpoint Analyses

Detailed statistical methodology for the analysis of secondary efficacy endpoints will be provided in the SAP. Secondary endpoints will be tested at a 0.05 significance level The significance of *p*-values lower than 0.05 will be considered for exploratory purpose only.

Comparison between treatment groups of the secondary efficacy binary endpoints will be performed at each studied timepoint using the same analyses as for the primary endpoint, *i.e.* by means of a Chi square test or a Fisher's exact test (as appropriate). Treatment effect over the 24-month follow-up period will be assessed using a Generalized Estimating Equations (GEE) model taking into account correlations between the repeated measurements within patients.

Comparisons between treatment groups of the secondary efficacy continuous endpoints will be performed at each studied timepoint by means of a parametric Student t-test or a non-parametric Wilcoxon rank-sum test (as appropriate). Multivariate analyses including analyses over time will also be conducted to assess treatment effect over the 24-month follow-up period.

Distributions of time-to-event variables will be estimated at each studied timepoint using the Kaplan-Meier product limit method. The log rank test will be used for treatment group comparison.

[redacted]

10.6.4 Safety Endpoint Analyses

Detailed statistical methodology for the safety analyses will be provided in the SAP.

Safety variables include AEs, SAEs, vital signs, physical examination, laboratory tests and concomitant medications. All safety analyses will be described by treatment group actually received and overall on the SAF. No replacement of missing safety data will be performed.

For each AE reported, the number and percentage of patients will be tabulated based on the MedDRA system organ class and preferred term. Similar tabulations will be performed by

relationship to treatment and by severity. AEs will be distinguished between treatment-emergent AEs and non-emergent AEs (*i.e.*, AEs pre-implantation and AEs post-implantation).

Standard summary statistics of clinical and laboratory values, as well as shift tables presenting incidence of physical and laboratory abnormalities will also be provided by treatment group.

10.7 Interim Analysis

A Data Safety Monitoring Board (DSMB) will be responsible for reviewing accumulated safety and efficacy data at intervals throughout the study.

In particular, the DSMB will evaluate the results of a formal pre-planned interim efficacy analysis in order to assess the efficacy effect of PREOB® versus Placebo with the intent to stop the study early if there is overwhelming evidence of treatment benefit or futility. The DSMB will recommend to the Sponsor whether to continue, modify or stop the clinical trial based on efficacy or futility but also on safety issues or other considerations not related to efficacy or safety.

The interim analysis will be performed after approximately 40% of required patients have been included in the study with available efficacy data at 12 months. A group-sequential stopping boundary will be used to preserve the overall Type I error rate at 5%.

The Lan-DeMets (Lan *et al.*, 1983) alpha-spending approach will be applied with Pocock (Pocock *et al.*, 1977) stopping boundaries to evaluate the difference in proportions of treatment responders between the treatment groups. A significance level of 0.01341 on the upper and lower boundaries will be used for the interim analysis to support early termination for efficacy. The significance level at the final analysis is expected to be of the order of 0.01341 on each of the upper and lower tails. Significance levels may be adjusted depending on the exact number of patients evaluated at the interim analysis. Futility will be assessed with conditional power (Lachin *et al.*, 2005), *i.e.,* probability of success at the end of the trial given the interim results.

To provide the DSMB with supporting data for recommendation following review of results of the interim analysis, the DSMB may request the analysis results for main secondary endpoints. If the study is stopped based on the recommendation of the DSMB, then all planned analyses will be performed according to what is described for the final analysis in this protocol and the SAP.

The Sponsor and other trial personnel will receive the DSMB recommendations only. No analysis results on the interim results will be communicated.

The specific activities of the DSMB as well as statistical procedures and rules for interim and final analyses are further described in the SAP and the DSMB charter.

11 STUDY MANAGEMENT

11.1 Monitoring

Before study initiation, the Monitor will visit Investigating Sites to evaluate feasibility of participation in the study (e.g., patient recruitment, staff availability, facilities, equipment), initiate site staff, train site staff on the Study Protocol and trial-related procedures, and verify good understanding of GCP (e.g., Investigator's and Sponsor's responsibilities) as well as any other applicable legal and regulatory requirements, notably as regards standards of quality and safety for the procurement (including patient selection and inclusion), testing, distribution, administration, and traceability of human tissues and cells, as well as notification and reporting of any SAE.

Very shortly after the first patient inclusion, an on-site monitoring visit will take place in order to verify the adherence to the protocol and study procedures, and thus avoiding any miscompliance in the future inclusions, if applicable.

During the course of the study, on-site monitoring visits and regular contacts with Investigating Sites will be conducted by a monitor in order to provide detailed information and support the Investigator(s), and to assess that the study is performed in strict compliance and accordance to the Study Protocol, ICH-GCP, and all applicable regulatory requirements.

For instance, the following aspects will be closely verified:

- Procurement of signed and dated Informed Consent
- Patient rights, including as regards protection of privacy and confidentiality of personal data and medical records, welfare, and safety
- Patient recruitment, eligibility, selection, and inclusion
- Study procedures
- IMP receipt, verification, and final delivery by the Pharmacist
- IMP receipt and verification by the Investigator
- IMP administration to the patient by the Investigator
- IMP accountability and traceability
- Blinding process, including the respective roles of the Investigator and Independent Physician
- SAE notification and reporting

- Emergency and pregnancy procedures
- Data generation and collection processes
- Accuracy of data collected and recorded in the eCRF
- Investigator's Trial Master File (and other on-site source documentation)

Any detected non-compliance with the approved Study Protocol, GCP, or any other applicable legal and regulatory requirements, as well as notification and reporting of any SAE will be fully documented by the monitor with the explanation provided by the Investigator on a deviation log.

During monitoring visits, the Investigator and clinical study staff should be available for questions, verification of data from the source documentation, and possible corrections to the eCRF.

Following each monitoring visit, the Investigator will be sent a follow-up letter detailing any actions required by either the Investigating Site staff or the monitor. Any actions must, wherever possible, be addressed immediately, or by the next scheduled monitoring visit.

The monitor will continuously be reachable and available between visits if the Investigator(s), or other study staff at the Investigating site, needs additional information and/or advice.

11.2 Source Documents

Each Investigating Site will maintain and archive all appropriate medical and research records related to the trial, in compliance with Guideline ICH topic E6 - Section 4.9., and regulatory and institutional requirements for the protection of patient confidentiality.

Source data are all information, original records of clinical findings, observations, or other documents in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source documents may include, but are not limited to, a patient's medical records, hospital charts if any, clinic charts if any, the Investigator's patient study files, pharmacy dispensing records, recorded data from automated instruments, as well as the results of diagnostic tests, such as radiographs, laboratory and urine pregnancy tests.

The following information should be entered into the patient's medical record:

- Patient name, surname and date of birth
- Patient's contact information
- Medical chart (e.g., hospital source document tracking number), if any

- A statement that ICF was obtained with the date of ICF collection and a documentation on the person who conducted the Informed Consent discussion
- Dates of initial screening and all patient visits
- The patient identification number obtained at Visit 1 (Screening Period)
- The study title and/or the protocol number of the study and the name of the Sponsor
- Medical/surgical history and physical examination (including weight and height)
- Results of BP, heart rate, respiratory rate and body temperature
- Results of urine pregnancy tests (only for female with childbearing potential)
- Smoking habits (including the number of cigarettes, cigars, and/or pipes per day)
- Evidence of risk factors for HTLV-1 infection, including patients living in, or originating from, high-incidence areas
- Alcohol consumption (including the number of drinks per day)
- Results of radiographs, MRI, and CT Scan
- Laboratory results reports
- All concomitant medications and concurrent procedures (list all prescription and non-prescription medications being taken at the time of entry in the Screening Period of the study. At each subsequent visit, changes to the list of medications will be recorded.)
- Occurrence and status of any AE and SAE
- The date the patient exited the study, and a notation as to whether the patient completed the study or the reason for discontinuation

The WOMAC® subscales are to be completed directly by the patient. The original pages, considered as source data, will be kept and filed on site (in the Investigator's Trial Master File).

11.3 Source Data Verification

To ensure that data in the eCRF are accurate and complete, and in accordance with patient source documents and other source data (e.g., laboratory results forms), 100% of source data verification (SDV) will be performed by the Monitor on all data and eCRFs including SAE and pregnancy-related documents, consisting in a comparison of the source documentation data with the eCRFs and other records relevant to the study. This will require direct access to all original records for each patient.

For WOMAC® VA 3.1 pain subscale questionnaires, 100% SDV will be performed by the Monitor on site. Following this SDV, any errors (discrepancies) greater than 1 mm discovered during independent verification by/on behalf of the Sponsor (e.g., audits) must trigger appropriate corrective actions to ensure exactness of all WOMAC® VA 3.1 pain subscale values in the study.

The process of obtaining IC and the presence on file of the signed and dated ICF will be verified for all patients screened, whether or not they were randomised into the study.

The back-transcription of data from the eCRF into source documents is not allowed, including when discrepancies/omissions are detected by SDV.

As some data will be directly entered into the eCRF, the eCRF will be considered as source document for these data. The “Source Data Location List” will be completed confirming the location of the source data.

11.4 Completion of Electronic Case Report Forms, Signing, and Filing

The patients will be monitored throughout the course of the trial and all results of evaluations will be recorded in the eCRF.

Electronic CRFs will be completed for each patient screened in the trial, including screening failure patients. They will be completed as soon as possible after the patient visit. All eCRFs will be checked for consistency, accuracy, and completeness, and will be dated and signed on an ongoing basis by the Investigator. This will be done as soon as possible after each patient study visit.

In addition, a personal log, detailing each site staff member working on the trial, will be kept up to date in the Investigator File. This log will record examples of each individual's handwriting, signature/initials and job title as well as the tasks the Investigator has delegated to his staff (with date of delegation). The Investigator must sign this log to indicate his/her authorisation.

The Investigator will be responsible for the punctuality, completeness, consistency, and accuracy of eCRFs. Electronic CRFs and related source data will be made available by the Investigator for data verification at each scheduled monitoring visit.

Completed eCRF and SAE/Pregnancy-related documents will be collected by the monitor for analysis and filing. A copy of all these documents will be stored in the Investigator's archives after completion or discontinuation of the trial for of 30 years duration according to Sponsor’s SOP and Guideline ICH topic E6.

11.5 Data Management

The study Data Management Plan (DMP) will describe methods used to collect, check, and process clinical data, as well as the procedure to follow for database lock. The DMP will be developed by the data manager and approved by the Sponsor. It will also list the roles and responsibilities of the personnel (with the corresponding functions) involved in data management process.

The database lock will be possible after approval by at least 2 authorised representatives of the Sponsor.

11.6 Audits and Inspections

Authorised representatives of the Sponsor, Monitor, CAs, and/or ECs may visit the Investigating site at any time during or after the study to perform audits and/or inspections, including SDV. The purpose of such audit or inspection is to systematically and independently examine all study-related procedures and documents and to determine whether these data and procedures were conducted, collected, recorded, analysed, and reported accurately and in accordance with the approved Study Protocol, GCP, and all applicable legal and regulatory requirements (see reference documents in Section 12.1).

The Investigator must immediately inform the Monitor if contacted by the CAs and/or ECs about an inspection at his/ her site.

The presence of the Monitor on the Investigating site is mandatory in case of visit/audit (at least for the SDV audit and Debriefing with the Investigator) by any authorised representative of the Sponsor.

During these audits and inspections, protection of the patient rights and privacy, and confidentiality of the patient personnel data and medical records, will be strictly respected, and patients will be informed that authorised representatives from the Sponsor, CAs and/or ECs may wish to inspect their medical records.

Any results and information arising from the inspections by the CAs and/or ECs will be immediately communicated by the Investigator to the Monitor (and Sponsor).

The Investigator should take all the corrective actions for any issue or problem identified and raised during audit/inspections.

11.7 Access to Source Data

Authorised representatives of the Monitor, Sponsor, CAs and/or ECs will be allowed to have full and direct access to the various records relating to the trial (*i.e.* paper Medical Records and other patient data records, including laboratory results reports and radiographs) to verify adherence to the Study Protocol, GCP, and any applicable legislation and regulatory requirements, and the completeness, consistency, and accuracy of the data being reported.

11.8 Training of Staff

The Investigator will maintain records of all individuals involved in the study conduct (medical, nursing, and other staff). The Investigator will ensure that appropriate information relevant to the study is given to the study staff, and that any new information of relevance to the performance of the study will be provided to the staff involved. The Investigator must inform the monitor, in a timely manner, of any change in the study site staff.

11.9 Changes to the Protocol

The Investigator cannot implement any deviation from or changes to the Study Protocol without prior approval by the Sponsor and prior submission, review and documented approval/favourable opinion from the CAs and ECs (except when necessary to eliminate immediate hazards to study patients, or when changes involve only logistical or administrative aspects of the study, e.g., changes in monitors or phone numbers). Any deviation from the Study Protocol will be identified, reviewed, and reported by the Monitor with an explanation provided by the Investigator, when applicable.

If it is necessary for the Study Protocol to be amended, the amendment or a new version of the Study Protocol will be submitted to and approved by the CAs and ECs before implementation.

If a protocol amendment requires a change to a particular site's ICF, the Monitor, Sponsor, and site's CA will be notified. Approval of the revised ICF by the, Sponsor, and concerned CAs and ECs, if applicable, is required before the revised form is used.

The Monitor (under the supervision of the Sponsor) will distribute amendments and new versions of the Study Protocol to each Investigator for review and approval, and to the site staff. The distribution of these documents to the CAs and ECs will be handled according to local practice.

Amendments to the trial are regarded as “substantial” if they are likely to have a significant impact on:

- The safety, physical health, and mental integrity of the patients;

- The scientific value of the trial;
- The conduct or management of the trial;
- The quality and/or safety of any IMP used in the trial.

If any new event occurs or any information becomes available regarding either conduct of the trial or development of the IMP, which may impact safety of the patient population or evaluation of the risk-benefit ratio for the clinical trial, the Sponsor will immediately inform the Investigators, and appropriate safety measures will be taken to protect patients against any immediate hazard. The Study Safety Officer (under the supervision of the Sponsor) will also immediately inform CAs and ECs of these events and/or data, and the measures taken.

Detailed description of the notification, reporting, investigation, and implications of safety events for the conduct of the clinical trial, including suspension of the trial, safety-related amendments to the Study Protocol, change or update of the Subject Information Sheet and ICF, and/or Investigator's Brochure, is provided in Section 8.

12 ADMINISTRATIVE, LEGAL, AND ETHICAL ASPECTS

12.1 Ethical Principles and Conduct of the Trial

The trial will be conducted in accordance with all applicable laws, regulations, guidance, guidelines, and principles regarding:

- Protection of the rights, safety, privacy, and welfare of human subjects
- Ethical principles for medical research involving human subjects
- Good Clinical Practice as regards conduct of clinical trials and investigational medicinal products for human use
- Clinical safety data management, notification, and reporting within the context of clinical trials
- Advanced Therapy Medicinal Products
- Requirements and standards of quality and safety for donation, procurement, testing, processing, preservation, storage, traceability, and distribution of human tissues and cells
- Good Manufacturing Practice and quality requirements for manufacture of investigational medicinal products for human use
- Standard Operating Procedures (SOPs) of the relevant institutions

This includes notably the followings reference documents:

- World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research involving Human Subjects (with amendments)
- Charter of Fundamental Rights of the European Union (2000/C 364/01)
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
- Standards for Privacy of Individually Identifiable Health Information - 45 CFR Parts 160 and 164 (August 14, 2002, Privacy Rule, United States Department of Health and Human Services)
- Health Insurance Portability and Accountability Act of 1996, Public Law 104-91 (August, 21, 1996, 104th Congress, United States of America)

- ICH Topic E2 A - Clinical Safety Data Management : Definitions and Standards for Expedited Reporting - Note for Guidance (June 1995, European Medicines Agency, CPMP/ICH/377/95)
- ICH Topic E2 F - Development Safety Update Report - Note for Guidance (September 2011, European Medicines Agency, EMA/CHMP/ICH/309348/2008)
- ICH Topic E3 – Structure and Content of Clinical Study Reports – Note for Guidance (July 1996, European Medicines Agency, CPMP/ICH/137/95)
- ICH Topic E6 (R1) - Guideline for Good Clinical Practice - Note for Guidance (July 2002, European Medicines Agency, CPMP/ICH/135/95)
- ICH Topic E8 - General Considerations for Clinical Trials - Note for Guidance (March 1998, European Medicines Agency, CPMP/ICH/291/95)
- ICH Topic E9 - Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)
- ICH Topic E10 - Choice of Control Group and Related issues in Clinical Trials- ICH harmonized tripartite guidelines (July 2000)
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- Detailed Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products - European Commission (2009, ENTR/F/2/SF/dn D)
- Guideline on Human Cell-Based Medicinal Products (21 May 2008, European Medicines Agency, Committee for Medicinal Product for Human Use, EMEA/CHMP/410869/2006)
- Reflection Paper on Stem Cell-Based Medicinal Products (14 January 2011, European Medicines Agency, Committee for Advanced Therapies, EMA/CAT/571134/2009)

- Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports arising from Clinical Trials on Medicinal Products for Human Use - European Commission (April 2006, ENTR/CT3)
- Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance, Clinical Trial Module) - European Commission (April 2004, ENTR/CT4)
- Guideline on Safety and Efficacy Follow-up Risk Management of Advanced Therapy Medicinal Products (20 November, 2008, European Medicines Agency, Committee for Medical Products for Human Use (CHMP), EMEA/149995/2008)
- Guideline on the Risk-Based Approach according to Annex I, Part IV of Directive 2001/83/EC Applied to Advanced Therapy Medicinal Products (11 February 2013, European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), EMA/CAT/CPWP/686637/2011)
- Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells
- Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC of the European Parliament and of the Council as regards certain technical requirements for the testing of human tissues and cells
- Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells
- Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

- Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) 726/2004
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- European Union Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use - Investigational Medicinal Products (Rules Governing Products in the European Union, Eudralex Volume 4, Annexe 13, February 2010, ENTR/F/2/AM/an D (2010) 3374)
- Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials - (31 March 2006, European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), CHMP/QWP/185401/2004)
- Guidance on Investigational Medicinal Products (IMPs) and other Medicinal Products used in Clinical Trials - European Commission (Eudralex Volume 10 - Clinical Trials, Notice to Applicants)
- Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products (31 May 2001, European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP), CPMP/BWP/41450/98)
- Code of Federal Regulation Title 21 part 312: Investigational New Drug Application

12.2 Health Authorities and Independent Ethics Committees/Institutional Review Board

Before the beginning of the trial:

- The Clinical Trial Application (CTA) will be submitted to and approved/authorized by the CAs
- The relevant ECs will approve and/or provide favourable opinion on the clinical trial, based on a comprehensive file, including the Study Protocol (with amendments), written Subject Information Sheet and Informed Consent Form, other written information to be provided to patients (such as the Patient Study Card), patient recruitment procedures, Investigator's Brochure, available safety information, information about payments and compensation available to patients, the investigators current curriculum vitae and/or

other documentation evidencing qualifications, a list of involved ECs and attendees, and any other documents that the ECs may need to fulfil its responsibilities, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The Investigator and Investigating Site will not initiate nor apply any study procedure or deliver IMP until approvals have been obtained from the CAs and ECs. Copies of any correspondence between the Investigator and the CAs and/or ECs will be given to the Monitor.

The Investigator will immediately notify the Study Safety Officer and/or the Managing Physician of the Production/Tissue Establishment (Manufacturer) about the occurrence of any SAE and other relevant Serious Adverse Safety/Quality Events, in order to allow proper notification and reporting of these events to the CAs, ECs, and Investigators involved in the trial. Detailed description of Safety Data Notification, Reporting, and Management procedures is provided in Section 8.3).

The Sponsor (with support from the Monitor) is responsible for submitting to the CAs and ECs any amendment to the Study Protocol, and any changes to the Subject Information Sheet and Informed Consent and/or Investigator's Brochure, for approval prior to implementation.

The Investigator will prepare and submit (with support from the Monitor) the "Annual Progress Reports" to the CAs and ECs, and according to local regulations and guidelines. The Investigator (with support from the Study Safety Officer) must also provide the CAs and ECs with any reports of SAEs from the Investigating site, as dictated by the CAs and ECs requirements.

12.3 Patient Data Protection and Confidentiality

The confidentiality of data and records that could identify patients will be protected in order to respect privacy and confidentiality rules, in accordance with all applicable legislation and regulatory requirements (see the reference documents in Section 12.1).

A report of the results of the study may be published or sent to the appropriate CAs in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor (or any authorized representatives, including the Monitor) or the CAs, during inspections of trial records and data. Appropriate precautions will always be taken to maintain confidentiality of medical records and personal information.

By the way of the ICF, written authorisation will be obtained from each patient prior to entry into the study, in accordance with applicable legislation and regulatory requirements (see the

reference documents in Section 12.1). The patients will be informed that the results will be kept and analysed in a computer but that nothing apart from what has been recorded in the eCRF will be registered. They will also be informed that their data will only be available to the above-mentioned entities.

The written ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with all applicable legislation and regulatory requirements. The patient‘s names will not be recorded in this database. The written ICF will also explain that, for data verification purposes, authorised representatives of the Sponsor (or any authorized representatives, including the Monitor), CAs, and/or ECs may require direct access to parts of the Hospital or practice records relevant to the study, including patients' medical history.

Finally, in order to ensure proper identification of the patient and verification of the patient identity (as required for the production process of a cell therapy product), and traceability of Starting Materials and the IMP, together with the requirements as regards protection of privacy and confidentiality of personal data and medical records, a unique identification code (Patient Identification Number) will be allocated during screening of the patient. The link between the identity of the patient and the identification code will be protected and kept strictly confidential. This information will be known (identity of the patient (name and surname) will appear on the labels of the bone marrow, blood, and IMP), collected, and recorded by the Investigator and the Managing Physician of the Production/Tissue Establishment (and will be kept and recorded in restricted access files).

12.4 Insurance

The Sponsor liabilities in connection with the study will be covered by an insurance policy, including any event, damage, injury, or death of the patient, occurring during the course of the study and being or not, directly or indirectly, linked to the study, and in accordance with any applicable legislation and regulatory requirements.

The Sponsor insurance will also cover all individuals participating to and/or intervening in the study, independently from the nature of the existing link between the Sponsor, participant, and patient.

12.5 Financial aspects

Financial details regarding performance of the study will be specified in an Investigational Study Agreement signed by the Sponsor and the Investigator before start of the study (each party will receive an original signed copy).

The Investigator at each Investigating site must comply with all the terms, conditions, and obligations of the Investigational Study Agreement.

12.6 Archiving at the End of the Study

After the close-out visit at each Investigating site, a copy of the following documentation (non-exhaustive list) will be stored in the Investigator's archives for a period of time of 30 years according to Sponsor's SOP and ICH-GCP guideline. Archiving responsibilities cannot be transferred to the Sponsor.

- Investigator's Trial Master Site File with the final Protocol and current Investigator Brochure
- Copy of completed eCRFs, SAE, and Pregnancy Forms
- Signed ICFs
- Patient screening/randomisation log and Patient Identification Code List
- Source documentation
- All required regulatory documents required by ICH-GCP, and any other applicable laws and regulations

All study-related documentation must be stored in a secure manner and must remain available upon request from the Sponsor or any CAs and/or ECs.

Before or at the end of the archiving period, the Sponsor can request an extension of the storage of all materials, or part of them, for a further period. An appropriate agreement will be drawn up accordingly. If an extension of the storage is not required, it is the responsibility of the Investigator to decide to destroy or keep these study-related materials after this archiving period.

It is the responsibility of the Sponsor to inform the sites when archiving is no longer needed.

13 REPORTING AND PUBLICATIONS POLICY

13.1 Clinical Study Report

When all completed eCRFs and Data Clarification Forms (DCFs) have been collected, and data have been analysed, a draft of the Clinical Study Report (CSR) will be produced by the Medical Writer, and sent to both the Investigators (designated prior to writing) and Sponsor, for review and comments. When agreement on the contents has been reached, the report will be signed by all parties.

The CSR will include the "Individual Patient Data Listing" (16.4 of CSR according to the ICH). The results will be tabulated, evaluated, and issued as a complete final Clinical Study Report by the Monitor according to the Guideline ICH topic E3. This report will be written in English.

The Sponsor will send a summary of this Clinical Study Report to both the CAs and ECs within one year after the end of the trial.

13.2 Publications and Posters

Any and all Sponsor Confidential Information, including but not limited to scientific, technical, clinical, medical and/or regulatory information, documents, data and databases, basic and/or clinical research results, product information and methods, materials, patents and patent applications, knowledge, know-how, ideas, concepts, design, algorithms, trade secrets, research and development activities, projects, and plans, strategic orientations, society structure, organization and collaborations, contracts and agreements, business, financial and/or marketing plans and information, whether in oral, written (including but not limited to written documents, memorandum, minutes, correspondence, reports), graphic (including but not limited to drawings, figures, schema or other material) or computer-readable form, will remain the sole property of the Sponsor.

Any and all Study data, databases, results, materials, analysis, information, documents, and reports (including but not limited to eCRFs), collected, generated, created, written, and/or otherwise obtained during (or in connection with) the Study under the Study Protocol (except for Study patient's medical records), whether in oral, written (including but not limited to documents, memorandum, minutes, reports, correspondence), graphic (including but not limited to drawings, figures, schema or other material) or computer-readable form, will become the property of the Sponsor.

The Investigator will retain any information or data of any kind pertaining to the Study, including but not limited to Study results from individual Study sites, as well as any Sponsor Confidential Information for the purpose of the Study, whether in any and all intangible and/or

tangible expressions, in any media, in strict confidence, and shall not directly or indirectly publish, communicate, disseminate, display, deliver, distribute, reproduce, disclose, or otherwise make available such information and/or data to any third party prior written approval from the Sponsor.

Publication, communication (including but not limited to abstracts and posters), disclosure, release, or dissemination of any information or data of any kind pertaining to the study, including study results from individual study sites, is however possible in mutual agreement between the Investigator and the Sponsor, provided that:

- Any proposed communication (including, but not limited to abstracts and posters) or publication will be submitted to the Sponsor prior to any submission; and
- Any proposed communication or publication will reflect the collaboration and respective roles of the Investigators, Investigating Sites, and Sponsor' personnel; and
- The Sponsor shall be given thirty (30) days to review communications (abstracts and posters), and sixty (60) days to review publications; and
- In the event that the Sponsor does not object to the proposed communication or publication within thirty (30) days or sixty (60) days of its receipt, as the case may be, it will be deemed to have been approved; and
- In the event that the Sponsor objects to the proposed communication or publication for reasons relating to the patentability of an invention or the protection of any other forms of intellectual property rights that would be disclosed by such proposed communication or publication, then submission of the communication or publication will be delayed for a maximum of six (6) months to enable the Sponsor to protect its rights; and
- In the event that the Sponsor reasonably objects to the proposed communication or publication as conflicting with or compromising Sponsor' intellectual property rights or interests, the proposed communication or publication shall be modified in order to fully address Sponsor' concerns and requests of modifications (including, but not limited to deletion of any Sponsor Confidential Information from the proposed communication or publication), and such modified communication or publication may not be submitted, published, disclosed, or disseminated until the Sponsor has confirmed its agreement in writing; and
- Any objection/requested modification made by the Sponsor concerning a proposed communication or publication shall be with due regards of the importance of scientific dissemination of the study results.

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ANNEXES

Annex 1 : *WOMAC® Index*

See the documents attached

Annex 2 : Imaging Data Analysis

1. Diagnosis of Femoral Head Osteonecrosis (based on MRI)

Lesion Definition

The diagnosis of osteonecrosis of the femoral head is based on analysis of SE T1-weighted images (bilateral hip evaluation). It is defined as the presence of a femoral head marrow lesion surrounded by a rim or a band of low signal intensity. The signal of the lesion is variable but a component with high signal intensity (fat-like) must be present, at least in some areas of the lesions.

Lesion Topography

The lesion must involve the epiphysis of the proximal femur (the so-called femoral head) which is delimited by subchondral bone plate and the physeal scar. The lesion may also extend in the femoral neck but its centre should be located above the physeal scar. If centre of the lesion is located below the physeal scar, it is considered to be a femoral neck lesion (to be excluded).

Perilesional Changes

- Presence (or absence) of marrow oedema in adjacent marrow defined by the presence of decreased signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images with ill-delimited margins (large transitional zone towards normal adjacent marrow)
- Presence (or absence) of fluid in the articular space defined by the presence of a high signal intensity component within the articular space on T2-weighted images. A small amount of fluid located inferior to the femoral head with preservation of acetabular fat pad is considered to be normal.

2. Diagnosis of Fracture in Femoral Head Osteonecrosis (based on MRI and Radiographs)

Lesion Definition

- On Radiographs
  1. Focal loss of femoral head sphericity (does not include chronic and often bilateral changes in sphericity)
  2. Subchondral fracture cleft (crescent sign)
- On MRI
  1. Focal loss of femoral head sphericity
  2. Subchondral fracture cleft (hyperintense line on T2-weighted images in lesion)

3. Crescent-shaped area of low signal intensity on T1- and T2-weighted images

Flow Chart for the Detection of Fracture

In visits in which both MRI and conventional X-ray are obtained ([redacted]), the reader will focus first on MRI studies for detection of femoral head fracture. Fracture will be diagnosed if obvious signs of fracture are present (overt fracture - *i.e.*, obvious lack of sphericity or obvious line of high signal intensity). Oedema at periphery of the lesion will not be considered as a definite sign for fracture. Oedema-like changes involving the bone marrow, synovium, or periarticular muscles will be mentioned but not used in staging. If MRI is considered to be equivocal or not contributive for accurate demonstration of fracture, conventional X-ray will then be analysed, alone (during the Screening Period) or in comparison with previous imaging studies. In this case, any alteration of femoral head contour or cleft sign will be considered as fracture.

In visits in which conventional X-ray are obtained only ([redacted]), the reader will analyse conventional X-ray in comparison with previous X-ray studies. Any alteration of femoral head contour or cleft sign will be considered as fracture.

3. Staging of Femoral Head Osteonecrosis (based on MRI and Radiographs)

- Stage 0 - Negative radiographs and negative MRI
- Stage I - Negative radiographs and positive MRI
- Stage II - Positive radiographs and MRI without femoral head deformity or subchondral bone fracture. Normal joint space.
- Stage III - Positive radiographs and MRI with subchondral bone fracture (crescent sign) but without deformity of the femoral head
- Stage IV - Positive radiographs and MRI with deformity of the femoral head without osteoarthritic changes
- Stage V - Positive radiographs and MRI with deformity of the femoral head and osteoarthritic changes.
- Stage VI - Complete joint destruction

Femoral Head Osteononecrosis Staging

Adapted from ARCO Staging (Enneking, 1997)

	Conventional X-ray			***MRI***
Stage	***Femoral Head Contour***	***Bone Structure***	***Joint Space***	
0	Normal	Normal	Normal	Normal or equivocal
I	Normal	Normal or equivocal	Normal	Osteonecrosis without fracture
II	Normal	Bone sclerosis or mixed changes	Normal	Osteonecrosis without fracture
III	Subchondral bone fracture	Bone sclerosis or mixed changes Crescent sign	Normal	Osteonecrosis with fracture and femoral head deformity
IV	Subchondral bone fracture Femoral head deformity	Any bone changes	Normal joint space	Osteonecrosis with fracture and abnormal cartilage
V	Subchondral bone fracture Femoral head deformity	Any bone changes	Abnormal joint space	Osteonecrosis with fracture and femoral head deformity and abnormal cartilage
VI	Massive femoral head destruction	Any bone changes	Abnormal joint space	

The stage 0 will never be used as no biopsy of the femoral head lesion will be performed at inclusion.

4. Additional MRI Findings

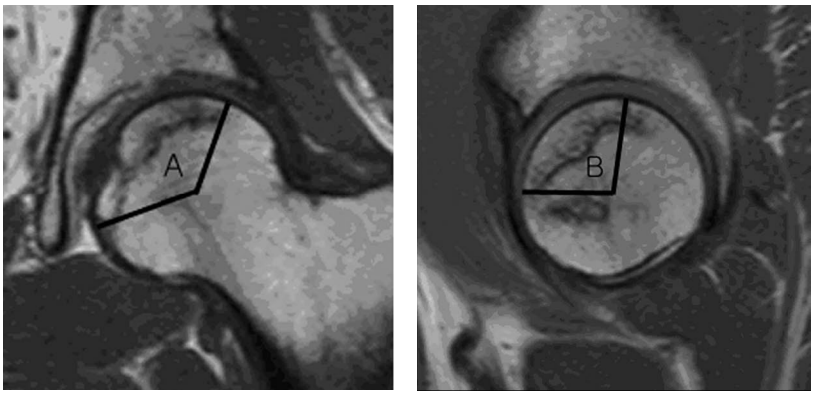
- Presence (or absence) of marrow oedema in adjacent marrow defined by the presence of decreased signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images with ill-delimited margins (large transitional zone towards normal adjacent marrow)
- Presence (or absence) of fluid in the articular space defined by the presence of a high signal intensity component within the articular space on T2-weighted images. A small amount of fluid located inferior to the femoral head with preservation of acetabular fat pad is considered to be normal.
- Labral cyst and/or tears (expressed in mm determined on coronal T2-weighted SE images) (presence or absence)
- Adjacent muscle oedema (presence or absence)
- Focal femoral and/or acetabular cartilage changes with normal conventional X-ray (Noyes grading system; < 50%, > 50% and < 100%, 100%). Limited femoral and acetabular cartilage defect (less than 50% loss of cartilage thickness) will be recorded and quantified as < 50% or > 50% head, < 50% or > 50% acetabulum)
- Subchondral cyst in acetabular roof (largest axis in mm on coronal T2-weighted SE images)
- Hamstring or gluteus muscle tendon lesions (presence or absence), defined as thickening of tendons with moderate increase in signal intensity on T2-weighted SE images

5. Quantitative Analysis of MR Imaging Data - Evaluation of the Extent of the Necrotic Area

Combined Necrotic Angle (Ha, 2006)

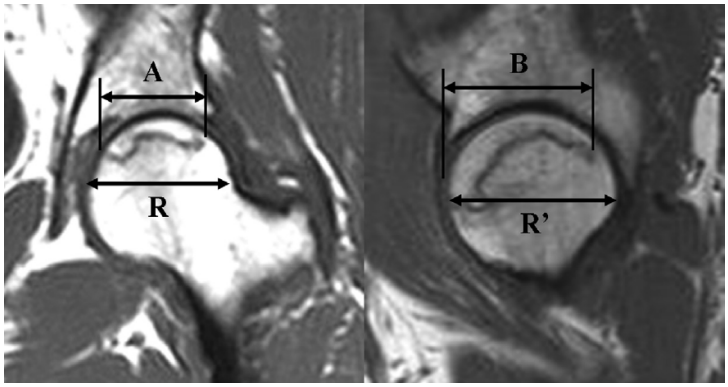
The combined necrotic angle takes into account the arc of the femoral articular surface reached by the necrotic area on coronal (angle A) and sagittal (angle B) MR images passing through the mid-plane of the femoral head (all images will be archived, including lines and values of angles measured). The necrotic angle corresponds to the sum of angles A and B.

Lesions with a necrotic angle > 190 ° will be included. ARCO stage I (and asymptomatic stage II, see Inclusion/Exclusion Criteria) lesions with a necrotic angle < 190° will be excluded.



Percent Necrotic Area (Nam, 2008)

The percent necrotic area takes into account the length of the infarct / maximum diameter of femoral head on mid-coronal (value A / value R) and mid-sagittal (value B /value R') MR images (all images will be archived, including lines and values of angles measured). The percentage of femoral head involved by necrosis corresponds to the ratio between the products of these values: (A × B) / (R × R') × 100. The lesions with a percentage of necrotic surface > 30% are included.



6. Qualitative analysis of MRI, CT scan and X-ray images

During the Screening Period, each hip will be classified by an independent musculoskeletal radiologist (Central Reader), according to the ARCO staging system. The Central Reader's results will be encoded in the eCRF.

In order to evaluate the interobserver reliability and reproducibility of ARCO staging for MRI, CT scan and Radiographs images, a second independent musculoskeletal radiologist will separately classify the hips treated in this study.

The reproducibility evaluation will be performed before database lock. If any discrepancies are revealed, they shall be discussed between the two independent radiologists. If no consensus is reached by the two readers, the patient will not be considered for the final analysis.

7. Overview of Radiological Criteria

Exclusion Criteria

- Normal MRI

  Fat-like signal intensity marrow in the femoral head; physeal scar not to be confused with the infarct margin

- Osteonecrosis ARCO stage I with necrotic angle sum <190°
- Osteonecrosis ARCO stage II with necrotic angle sum <190° and with WOMAC® VA3.1 pain score <20 mm during the 48 hours preceding the screening
- Osteonecrosis ARCO stage I or II located either in the femoral neck or femoral head but without contact with the subchondral bone plate
- Osteonecrosis ARCO stage III or higher
- Osteoarthritis defined as Kellgrens stage II or above on conventional X-ray. On MRI, presence of limited cartilage changes (more than 50% of loss of cartilage thickness) in femoral head or acetabular cartilage.
- Any other focal or diffuse bone marrow lesion
- Bone fracture(s) that may interfere with the study evaluation procedures

Incidental findings on conventional X-ray (compact bone islands, herniation pits, acetabular ossicle or calcification, healed fractures, Paget's disease) will not be considered as radiological exclusion criteria and will be recorded in an open fashion. They will not be used in data analysis.

The percentage of necrotic area will be calculated and recorded at each evaluation but will not be considered as an inclusion criteria.

Annex 3: Overview of Patient Data Protection, Confidentiality, and Blinding

	Access to Patient Personal Data/Identity and to the Link with the Identification Code*	***Access to Patient Identification Code***	***Blinding to Treatment Allocation***
Patient	-	-	Yes
Principal Investigator	Yes	Yes	Yes
Independent Physician	Yes	Yes	No
Pharmacist (Investigating Site)	No	Yes	Yes
Radiologist (Central Evaluating Centre)	No	Yes**	Yes
Managing Physician (Production/Tissue Establ.)	Yes	Yes	No
Manufacturer	No	Yes	No
Sponsor	No	Yes	Yes
Monitor (blind)	Yes	Yes	Yes
Study Safety Officer	No	Yes	No***

** Restricted access - Personal data and medical records, as well as the link between the Identification Code and the identity of the Patient, will be kept protected and strictly confidential.*

*** The Radiologist of the Central Evaluating Centre will have an access code number for the Patient identification number.*

**** For the management of SAEs and SUSARs, and their reporting and notification to the ECs and CAs.*