CLINICAL STUDY PROTOCOL

Study ALLOB-DU1

EudraCT number: 2012-005333-36

Protocol Number: 000005/BT

NTC Number: 02020590

A pilot Phase I/IIa, multicentre, open, proof-of-concept study on the efficacy and safety of allogeneic osteoblastic cells (ALLOB®) implantation in non-infected delayed-union fractures

Sponsor

Bone Therapeutics S.A.
Rue Auguste Piccard, 37
B-6041 Gosselies, Belgium

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 Community and national legislation and regulatory requirements

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SPONSOR SIGNATORY APPROVAL

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Protocol Number: *000005/BT*

Title of the protocol:

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Sponsor's representative

Guy Heynen, MD

Chief Clinical and Regulatory Officer

Name and Title	Date	Signature

INVESTIGATOR SIGNATURE AND AGREEMENT WITH THE PROTOCOL

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

Agree:

- That my primary responsibility is to safeguard the rights and well-being of each subject participating in this study, and that the subject'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 subjects prior to their participation in the study and ensure that:
  * Verbal information, adapted to the study participant, has been provided, avoiding direct or indirect coercion, and that the subject has understood the study;
  * The patient information sheet and written informed consent form (dated and numbered version approved by the Ethics Committee) has been provided;
  * The patient has been allowed 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 subjects or their authorised legal representative.
- To acquire the reference ranges for laboratory test performed locally and if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples are retained onsite or elsewhere without the approval of the Sponsor and the express written consent of the subject.
- 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 subject 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 (subject 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

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Principal Investigator

Name and Title Date Signature

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STUDY SYNOPSIS

EudraCT Number: *2012-005333-36*

Protocol Number: *000005/BT*

Protocol Code: ALLOB-DU1

Sponsor or Sponsor's representative in the European Union

Bone Therapeutics S.A., Gosselies, Belgium

Phase of Development

Pilot Phase I/IIa Study

Planned Study Period

Total recruitment period: until maximum 32 patients have been treated

Total study follow-up period: 6 months

[redacted]

Objectives

To evaluate the safety and efficacy of ALLOB®, a proprietary population of allogeneic osteoblastic cells, in the treatment of delayed-union fractures of long bones, given as single percutaneous administration directly into the delayed-union site.

Planned Number of Subjects:

Maximum 35 enrolled patients for maximum 32 treated patients (assuming 10 % drop-out). A minimum of 16 completed patients is required for the Interim Analysis.

Medical Condition, Patient Selection and Inclusion Criteria

Men and women, aged 18 to 80 years old, diagnosed with a non-infected delayed-union fracture of a long bone (femur, tibia, fibula, humerus, ulna and radius) of minimum 3 (± 2 weeks) and maximum 7 months (± 2 weeks) at the time of inclusion.

Test procedure, product, dose and mode of administration

ALLOB® is an allogeneic osteoblastic cell product falling under the EMA classification EMA/486246/2011 as tissue engineered Advanced Therapy Medicinal Products (ATMP).

ALLOB® will be given percutaneously as a single administration into the delayed-union site using a trephine. The volume administered is based on the size of the delayed-union gap and determined as follow:

Fracture interline < 0.5 cm: 2 ml of suspension solution

Fracture interline ≥ 0.5 – ≤ 1 cm: 3 ml of suspension solution

Fracture interline > 1 – ≤ 2.5 cm: 4 ml of suspension solution

In case implantation using 2 surgical sites is judged best approach by the investigator, a total of up to 4 ml may be administered.

Detailed visit schedule

After informed consent is obtained, fulfilment of study inclusion and exclusion criteria will be performed at Visit #1, which will take up to 8 weeks to complete. Visit #2 is scheduled to take place after completion of Visit #1 for baseline clinical assessments and ALLOB® implantation (the baseline of the radiological assessments is Visit #1). At Visit #2, all patients will be hospitalized for 24 or 48 hours after implantation, according to the judgment of the Investigator.

Patients will be followed during 6 months, at 2 weeks, 1, 3, and 6 months (Visit #3 to Visit #6).

[redacted]

Duration of treatment

This is a single dose administration study.

Patient Inclusion Scheme:

In order to maximise patient safety, for the first 16 patients treated, patient recruitment will proceed stepwise by blocks of 4. Full first 2 weeks safety data of the first block of 4 treated patients will be analysed before the first patient of the second block of 4 is treated. First 48 hours safety data of the second block of 4 treated patients will be analysed before treatment of the first patient of the next block. This latter scheme will be repeated until 16 patients have been treated. This review of reported SAE potentially related to the Investigational Medicinal Product (IMP), and especially those related to immunological reactions (severe Adverse Event of Special Consideration (AESC)), will be done by the Safety Monitoring Committee (SMC).

Study Endpoints and Criteria for Evaluation

Safety Criteria

In addition to standard pharmacovigilance requirements, particular attention will be given to AE suggesting immune-mediated reactions, such as: general discomfort, uneasiness, ill feeling, pain or swelling in the implanted area, fever and any inflammatory reactions, flu-like symptoms (e.g., chills, body aches, shortness of breath, cutaneous rashes…). All severe AEs potentially related to the IMP and in particular those potentially related to the allogeneic reactions will be managed by the SMC who will analyse and report these events in a timely manner consistent with the safety of patient recruitment scheme.

Efficacy Criteria

The following clinical and radiological criteria will be used:

- Clinical: Global disease evaluation (GDE) score as assessed by the patient and Investigator using a Visual Analogue Scale (VAS); Pain using a VAS; Weight-bearing score using a Likert Scale
- Radiological healing progression as assessed by CT scan and by conventional X-ray using the Tomographic Union Score (TUS) and modified Radiological Union Score (mRUS), respectively

[redacted]

Evaluation Time Points

Efficacy and safety endpoints will be determined at each scheduled visit over the 6-month follow-up period (at 2 weeks, 1, 3 and 6 months).

The interim report and the decision for continuation will be established on the first 16 assessable patients after 6 months of follow-up and the final Clinical Study Report (CSR) will be established at 6 months (end of study) after treatment for all patients, as applicable.

[redacted]

Interim Analysis

A Data Safety Monitoring Board (DSMB) will be established to analyse and report the safety and the efficacy data when 6-month post-treatment results from the first 16 assessable patients will be available. This Board will recommend whether to continue, modify or stop the study. If success is less than 30% or higher than 70%, patient recruitment will be stopped. If the DSMB recommendation is continuation (with or without changes) of the study, patient recruitment will continue until 32 patients have been treated.

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 reviewed, approved, and signed prior to database lock at the latest.

The safety population will be considered as the primary cohort for analysis of efficacy. It will comprise all treated patients.

Efficacy Endpoints:

The efficacy of ALLOB® will be evaluated at 6 months. The success will be based on the percentage of treated patients (ALLOB®) not failing under treatment. A treated patient will be considered as failed if, at the end of the study (6 months):

- The patient had required a rescue surgery *or*
- The Global Disease Evaluation score as perceived by the patient has not improved by at least 25% *and* the TUS as assessed by CT scan has not increased by at least 2 points.

[redacted]

All safety analyses will be conducted on the safety population and tabulated. For each AE and SAEs reported, the number and percentage of patients will be tabulated based on system organ class and preferred term. Similar tabulations will be performed by severity, relationship to the

study product/procedure, action taken and outcome. The frequency of AEs and SAEs will be assessed using a 95% Confidence Interval.

More details will be given in the SAP.

Ethical considerations

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must review and approve the protocol and the Informed Consent Form (ICF) before any patients are enrolled. Before any protocol-required procedures are performed, the subject must sign and date the IRB/IEC-approved ICF.

Date and Version of the Study Protocol: 02 Feb 2017, V05

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESC	Adverse Event of Special Consideration
AST	Aspartate Amino Transferase (also known as:
(SGOT)	Serum Glutamic-Oxaloacetic Transaminase)
ALT	Alanine aminotransferase (also known as:
(SGPT)	Serum Glutamic-Pyruvic Transaminase)
ATMP	Advanced Therapy Medicinal Product
BMI	Body Mass Index
BP	Blood Pressure
CAs	Competent Authorities
CAT	Committee for Advanced Therapies (EMA)
CBMP	Cell-Based Medicinal Products
CHMP	Committee for Medicinal Product for Human Use (EMA)
CI	Confidence Interval
CMV	Cytomegalovirus
CPMP	Committee for Proprietary Medicinal Products (EMA)
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Application
CU	Clinical Unit
DCF	Data Clarification Form
DSMB	Data Safety Monitoring Board
DMP	Data Management Plan

DU	Delayed-union
EBV	Epstein-Bar Virus
EC	European Commission
ECs	Ethics Committees
EMA	European Medicines Agency
EPCs	Endothelial Progenitor Cells
EU	European Union
EudraCT	European Clinical Trials Database
FA	Full Analysis
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Gr.	Gram
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHV6	Human Herpes Virus Type 6
HIV	Human Immunodeficiency Virus
HSV-1	Herpes Simplex Virus Type 1
HTLV-1	Human T-lymphotropic Virus Type 1
IATA	International Air Transportation Association
IC/EC	Inclusion and Exclusion Criteria
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRB	Institutional Review Board
IRB	Institutional Review Board
LLOQ	Lower Limit of Quantification

LMS	Least Mean Square
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MNC	Mononuclear Cell
MP	Managing Physician
mRUS	Modified Radiographic Union Score
MSC	Mesenchymal Stromal Cell
NU	Non-Union
OECD	Organisation for Economic Co-Operation and Development
PIL	Patient Informed Letter
PK	Pharmacokinetic
PP	Per Protocol
SA	Safety Analysis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SASQE	Serious Adverse Safety/Quality Event
SDV	Source Data Verification
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SSO	Study Safety Officer
SUSAR	Suspected Unexpected Serious Adverse Reaction
TUS	Tomographic Union Score
VAS	Visual Analogue Scale
WHO	World Health Organization
WMA	World Medical Association

DEFINITIONS OF TERMS

- **Adverse Drug Reaction:** 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).Unexpected ADR is an adverse reaction whose nature, severity, specificity, or outcome is not consistent with the applicable product information (e.g., Investigator's Brochure).
- **Adverse Event:** 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 signs (including any abnormal laboratory findings), symptoms, or disease temporally associated with the use of a medicinal product, without any judgment about causality
- **Adverse Event of Special Consideration:** in this study, adverse event which has been identified as potentially related to allogeneic reaction
- **ALLOB®:** is a proprietary allogeneic tissue engineered product (i.e., an advanced therapy medicinal product ATMP, falling under the scope of the European Regulation 1394/2007/EC and the Directive 2001/83/EC), consisting in allogenic osteoblastic cells (ALLOB® cells), manufactured by Bone Therapeutics S.A.
- **Assessable patient:** a patient who completed all scheduled visits up to last scheduled visit (inclusive) or a patient who has been screened (V#1), treated (V#2) and who at least has completed the follow-up visit V#5 or V#6.
- **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
- **Discontinued or withdrawn patient** is a patient who has been enrolled, screened, randomized or treated but has withdrawn from the study before completion of the last scheduled visit

- **Distribution**: transportation and delivery of tissues and cells intended for human applications

- **Delayed-union** (DU): fracture that has not united within a period of time that would be considered adequate for bone healing. In this study, delayed-union is defined at the time of screening as (i) an absence of healing 3 months (± 2 weeks) (and with a maximum of 7 months) after the onset of fracture and (ii) an absence of the progression of healing over the last 4 weeks, as confirmed by clinical and radiological evaluation.

- **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.

- **Eligible patient:** a screened patient who is considered eligible according to selection criteria.

- **Enrolled patient:** patient who has dated and signed the Informed Consent Form (ICF).

- **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

- **Intermediary Structure Tissue Establishment**: is an accredited tissue establishment where the activities of processing, preservation, storage or distribution of human tissues and cells are performed under an agreement with a human tissue bank (Belgian Law of December 19th 2009, the Belgian RD2 of September 28th 2009)

- **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.
- **Managing Physician (or delegate):** 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 Cells:** "plastic-adherent" stem cells, expressing specific surface markers, and giving rise to bone, cartilage, and adipocyte cells.
- **Non-union fracture**: refers to a fracture that will not unite within 6 to 9 months and needs additional surgical or non-surgical intervention
- **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.
- **Osteoprogenitor cells or osteoprogenitors & pre-osteoblasts:** are not-fully differentiated cells committed to the osteoblastic lineage, i.e., precursors of osteoblast displaying limited proliferation capacity.
- **Processing**: all operations involved in the preparation, manipulation, preservation, and packaging of tissues or cells intended for human applications
- **Randomised patient**: 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.
- **Safety Monitoring Committee (SMC)**: a committee established by the Sponsor to analyse, for each block of 4 patients from the first 16 patients, the safety data and make recommendations whether to continue or stop the trial.

- **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**: individual designated to perform the handling, notification, and reporting of safety issues
- **Subject**: an individual who participates in the clinical trial
- **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

- **Tissue Bank**: is the accredited tissue establishment responsible for donation, procurement, testing and release of cells and where activities of processing, preservation, storage or distribution of human tissues and cells can be undertaken. According to Belgian legislation, it can delegate some activities to an accredited Intermediary Structure under an agreement between the parties (Belgian Law of December 19th 2009, the Belgian RD2 of September 28th 2009).

1 INTRODUCTION

1.1 General Background

1.1.1 Impaired Fracture Healing

Bone has a substantial capacity for repair and regeneration in response to injury or surgical treatment. Both processes involve a complex integration of cells, growth factors and extracellular matrix. Repair simply restores the continuity of the injured tissues without necessarily increasing bone volume, while regeneration involves the differentiation of new cells and the formation of new bone tissue, which results in an overall increase in the volume of new skeletal tissues. Fracture healing is a multistage repair process that involves complex well-orchestrated steps that are initiated in response to injury, resulting eventually in the repair and restoration of function (Al-Aql *et al.,* 2008).

Fractures are now successfully treated in the majority of patients; nevertheless about a third requires some surgical intervention. Among those, delayed-unions or non-unions may necessitate numerous operative procedures, can leave the patient with functional deficits, and are often associated with prolonged morbidity (Wiss and Stetson, 1996).

Fracture healing is considered as a dynamic progressive process. Nowadays, intervention is usually indicated by 3 to 5 months after injury if monthly radiographic studies do not show progression of fracture healing (Wiss and Stetson, 1996).

Typically, delayed-union is a term used for a fracture that has not united within a period of time that would be considered adequate for bone healing. Delayed-union suggests that union is slow but will eventually occur without additional surgical or non-surgical intervention, whereas non-union is defined as the cessation of all reparative process of healing. There is no universally accepted or validated approach to evaluate the progression of fracture healing: definitions of delayed-union or non-union continue to be subject of various interpretations (Bhandari, 2002; Bhandari *et al.,* 2012). The distinction between delayed-union and non-union is based on time: a fracture not healed 3 to 8 months after onset is defined as a delayed-union, whereas a fracture not healed 9 months after onset is defined as non-union (regulatory definition).

However, the timeframe for healing differs according to the fracture sites (e.g., for a tibial diaphyseal fracture, bridging callus and clinical stability should be achieved by 4 months), the initial configuration of the fracture and the individual medical history (Wiss and Stetson, 1996).

1.1.2 Diagnosis of Delayed or Non-unions and Follow-up of the Healing Process

The most common parameters used by surgeons to diagnose delayed- or non-unions are radiological (e.g., cortical continuity) and clinical (e.g., pain on weight bearing) (Bhandari, 2012; Hak *et al.,* 2014). Radiological assessments, by X-ray or CT scan, are made on the union of cortices (3 to 4) and presence/absence of a fracture line. CT scan has been shown to be more accurate than conventional radiography in evaluating fracture healing of long bones (Zimmermann, 2007; Morshed *et al.,* 2008). The radiological evolution can be scored using a modified version of Radiographic Union Scale for Tibial Fracture (RUST) (Kooistra, 2010). Clinical assessments are generally based on pain, weight-bearing, and health related quality of life.

1.1.3 Incidence of Delayed- and Non-Union Fractures

The incidence of impaired healing is estimated to range from 5 to 10% of all long bone fractures (Einhorn, 1995). Incidence varies depending on the type of bones, their vascularisation, and their subcutaneous position.

1.1.4 Aetiology of Delayed- and Non-Union Fractures

The development of delayed/non-union is most closely related to the type and degree of injury, but several other factors may also predispose patients to delayed/non-union. Many of these are related to fracture features, including the degree of fracture comminution, bone loss, and soft tissue injury, as well as the presence of open fracture and displacement (Ellis, 1958; Nicoll, 1964; Bishop *et al.,* 2012). Inadequate reduction of a fracture leading to instability or poor immobilization may be a prime reason for delayed-union and non-union.

Subsequent complications, such as infection and compartment syndrome, have also been shown to play an important role in the occurrence of delayed- and non-union (Court-Brown and McQueen, 1987). The patient profile also contributes to its incidence. For instance, age, smoking and alcohol consumption or medical history such diabetes, anaemia or peripheral

vascular diseases are well documented to increase risks of delayed- or non-union (Schmitz, 1999; Gaston, 2007). The use of non-steroidal anti-inflammatory drugs or corticosteroids can also inhibit bone healing (Giannoudis *et al*., 2000), as well as the nutritional status of the patient and compliance with the post-operative regime (Gaston and Simpson, 2007).

Finally, prompt and appropriate treatment is needed because iatrogenic injury to the soft tissue envelope (i.e., excessive periosteal stripping), distraction across the fracture site, inadequate immobilization or fixation, can promote the development of delayed/non-union (Gaston and Simpson, 2007).

1.1.5 Treatment of Delayed Fractures

Long bone delayed/non-union fractures are treated with debridement of the delayed/non-union site and internal (or external) fixation, with or without application of autogenous or allogeneic cancellous bone graft. New treatments are appearing: grafting of the fracture sites to provide biological stimuli or externally applied systems such as electrical stimulations or low-intensity pulsed ultrasounds, the benefits of which have not been clearly established (Busse, 2002).

Previous analysis have shown that reduced healing times could yield substantial cost savings (included for government agencies) by decreasing the need for secondary procedures and decreasing the amount of time needed by a worker to go back to his activity (Heckman, 1997).

1.1.6 Bone Autograft

Bone autograft still remains the treatment of choice for non-union fractures, particularly for atrophic non-unions, combined or not with intramedullary nailing, plating, and external fixation devices (Kontakis *et al.,* 2006; Soucacos *et al.,* 2006; Crowley *et al.,* 2007; Kanakaris *et al.,* 2007; Sen and Miclau, 2007). Indeed, autologous bone grafting presents excellent osteogenic, osteoconductive and osteoinductive properties, is biocompatible, and avoids any immunogenicity concerns or disease transmission risks (Kanakaris *et al.,* 2007; Sen and Miclau, 2007).

Although considered as the *Gold Standard*, only rare publications on the efficacy of bone autograft in non-union fractures can be found in the literature. Orthopaedic surgeons report that averages of 75% to 85% of non-unions are successfully treated by bone autograft (based on clinical and radiological assessment). This range of efficacy seem confirmed by data from

controlled studies comparing bone autograft with bone morphogenetic proteins in non-union fractures, with reported healing rates of 76% at 8.3 months, clinically, and 77% at 10.9 months, radiologically (Friedlaender *et al.,* 2001; Ronga *et al.,* 2006).

Side-effects of bone autograft are much largely documented and the side effects associated to this procedure are considerable (Soucacos *et al.,* 2006; Sen *et al.,* 2007; Pieske *et al.,* 2009):

a. Major complications in at least 10% of patients such as deep infection, osteomyelitis, haematoma, neurologic injury, vascular injury, iatrogenic wing/SI joint injury, cross contamination, abdomino-lumbar herniation etc…

b. Minor complications such as superficial infection (39%), superficial seroma, small haematoma, persistent short term (40%) or long-term (19%) pain, excessive blood loss, pelvic instability, cosmetic defects, etc…

In the Friedlaender *et al*. (2001) study comparing bone autograft with Osigraft®, osteomyelitis was reported at the fracture site in 21% of patients following treatment with bone autograft, and more than 20% of patients treated with autograft had chronic donor site pain following the procedure. Chronic pain at the harvest site was reported in 41% of patients at 6 months post-surgery and in 33% at 1 year. Finally, in rare circumstances, bone autograft harvesting has been related to an unstable pelvic ring and to ileum fractures (Nocini *et al.,* 2003; Oakley *et al.,* 2007).

1.2 Background of the Study

1.2.1 *General Description of ALLOB®*

ALLOB® is the registered trade name for Bone Therapeutics' human allogeneic cell based medicinal product. The active substance of ALLOB® is human allogeneic osteoblastic cells. Its implantation is intended to produce new bone at the bone defect site of affected patients and to re-establish a healthy bone environment.

ALLOB® is derived from bone marrow mesenchymal stromal cells of healthy adult volunteers. From a bone marrow aspirate (from the healthy donor's iliac crest under local anaesthesia), mesenchymal stromal cells are *ex vivo* cultured under strictly controlled conditions to generate ALLOB® cells. The manufacturing process is conducted in compliance with GMP and follows

procedures that ensure aseptic manufacturing process, full traceability, and quality control. ALLOB® cells are not genetically modified. ALLOB® is not a combined product as the sole active substance is ALLOB® cells in suspension.

ALLOB® cell identity and potency are characterized by the negativity for hematopoietic cell markers, the positivity for mesenchymal stromal cell markers, the positivity for adhesion/osteoblastic cell markers, expression of bone-related genes, absence of immunogenic phenotype, absence of tumourigenic characteristics, bone matrix formation and mineralization properties.

Administration of ALLOB® is done using a minimally invasive technique. The product is administered with a small diameter trephine by percutaneous implantation through a small skin incision, directly into the bone defect site.

For more information concerning the description of ALLOB®, please refer to the Investigator's Brochure.

1.2.2 ALLOB® in Preclinical Studies

Non-clinical *in vivo* and *in vitro* studies have been conducted to assess the pharmacodynamics, safety pharmacology, biodistribution, toxicity, tumourigenicity and immunotoxicity of ALLOB®.

With respect to primary pharmacodynamics, ALLOB® bone formation capacity was assessed in a [redacted] model and in a [redacted] defect model. In both models, radiological and histological analyses confirmed production of new bone after ALLOB® cells administration.

Safety pharmacology was investigated in a [redacted] fracture mouse model after ALLOB® local administration. Safety parameters including clinical observation, body weight follow-up and laboratory physiological parameters (e.g., haematology and blood chemical chemistry parameters) were observed until 6 weeks post-administration. No test items related clinical sign and no test items related laboratory anomaly were observed. Complete necropsy was performed and no macroscopic test item related finding was observed.

The migration of ALLOB® cells after administration at the bone defect site was assessed in the [redacted] fracture mouse model. Radiolabelled cells were administered in the fractured site and

their biodistribution was assessed with high-resolution whole-body quantitative scintigraphy (SPECT/CT imaging). At the different timepoints, the majority of residual radioactivity was retained at the fracture (administration) site suggesting that ALLOB® cells preferentially engrafted at the fracture site and did not migrate and home to the vital organs (heart, lungs, brain, kidney, spleen, liver). The radiolabelling biodistribution study results were consistent with a 6-week PCR biodistribution study after local administration of ALLOB® at the fracture site in femoral fracture mouse model. After euthanasia, organs were excised and processed for analysis. Trace levels of human DNA were transiently detected in heart and lung in 15% to 50% of injected mice during the first 24 hours; after 24 hours, no human DNA was detected in any other organs than bones.

A 24-week long-term GLP toxicity study was conducted in mice after i.v. administration of high doses of ALLOB® (> 50-fold the human dose in order to provide a comfortable safety margin). During the 24-week observation period, ALLOB® administration did not cause excess morbidity or mortality, and the haematological and urine analyses, the macroscopic (during necropsy) and microscopic examinations failed to evidence any test item related anomalies.

In vitro studies have demonstrated that ALLOB® cells have a limited replication capacity and that ALLOB® cells have no tumoural phenotype as cells were unable to grow unattached to a surface. In vivo tumourigenesis studies (*Ph. Eur.* compliant) were conducted in mice to confirm that ALLOB® does not induce tumours. At 3 and 12 weeks post-injection, macroscopic and microscopic examinations failed to reveal any evidence of tumour formation and/or organ invasion (n=20).

In order to assess immunogenic properties of ALLOB®, immunotoxicity studies have been conducted in accordance with the ICH S8 "Immunotoxicity Studies for Human pharmaceutical" guideline. In that respect, peripheral blood mononuclear cells (PBMC) from different unrelated volunteers (recipient PBMC) and ALLOB® cells were co-cultured. The ALLOB®/PBMC co-cultures did not to elicit lymphocytic proliferation in >80% of cases (n=54). In all experiments, pro-inflammatory cytokines production (e.g., INF-γ and TNF-a) were measured on supernatants from ALLOB®/PBMC co-cultures. No production of INF-γ and TNF-α was measured in positive co-cultures, suggesting that positive co-cultures or resulted in incomplete immune response or were unrelated to an immune reaction.

Besides these immunoprivileged characteristics, ALLOB® also display immunosuppressive/ immunomodulatory properties against activated lymphocytes in a dose-dependent manner.

1.2.3 *ALLOB® in Clinical Studies*

The safety and efficacy of ALLOB® is currently evaluated in phase IIa clinical studies in delayed-union fracture, spinal interbody fusion and rescue interbody fusion.

1.2.4 Justification of dose

Preclinical studies on bone formation and bone repair models in mice have demonstrated the efficacy of ALLOB® at the doses up to 50.10^6 cells/ml. To balance between efficacy and safety, the concentration selected for the clinical trial is 25.10^6/ml, since at the maximum injected volume (of 4 ml), this concentration still presents a safety margin of over 90x.

1.3 Assessment of Anticipated Benefits and Risks

Long bone delayed-union fractures are treated with debridement of the delayed-union site and internal (or external) fixation, with or without application of allo/autogenous bone graft. Although the exact pathophysiological mechanism of delayed-union is not known, delayed-union fractures may benefit from redynamisation and/or augmentation to stimulate bone formation, and hence will benefit from the addition of an osteoconductive or osteoinductive stimulus (Wiss *et al.*, 1996). This may be contributed by the local implantation of new ex-vivo cultured cells with osteogenic potential which could replace the defective or missing osteoblastic cells and re-establish a healthy bone environment. In vitro and in vivo experiments have showed that ALLOB® cells have the ability to adhere, synthesize and mineralize new bone matrix without observable toxicity. In addition, biodistribution studies have demonstrated that after local administration (at fracture site), ALLOB® cells do not migrate in non-target organs (heart, lungs, brain, liver, spleen, and kidneys). This supports the potential benefits of the use of ALLOB® in the indication of delayed-union fracture.

ALLOB® Manufacturing

Bone marrow starting material is harvested from healthy volunteer donors selected on medical history, physical examination, laboratory parameters and (negative viral) serology according to European directives and national regulations, and raw materials entering the manufacturing

process (medium, factors...) are tested for sterility, endotoxins and mycoplasmas. ALLOB® is manufactured under strict GMP and aseptic conditions. At the end of manufacturing, ALLOB® is controlled (release tests) for quality (identity, potency and absence of immunogenicity) and microbiology (sterility, endotoxins, mycoplasmas).

ALLOB® Toxicity and Immunotoxicity

Long-term toxicity studies have shown that ALLOB® cells even when administered at high doses (over 50-fold the maximal proposed clinical dose) did not cause any excess morbidity or mortality, did not induce any organ toxicity or did not cause ectopic bone formation. Studies have also failed to show tumoural risks at up to 300 times the human therapeutic dose). Similarly, based on preclinical studies, ALLOB® is not expected to induce immunogenic or inflammatory responses.

Patient Benefit

In order to minimise the risk of patient-related treatment failure during this trial, patients will be enrolled based on a strictly controlled medical criteria including classification of the disease, potential compliance with the study protocol and follow-up as well as taking into account concomitant disease and/or treatment not compatible with the ALLOB® treatment. Additionally, patients will be tested for anti-HLA antibodies and other auto-immunity markers in order to monitor the development of immune reaction against ALLOB® or the occurrence of alloreaction.

If available treatments (bone autograft) have shown 76% and 62% of radiological healing and 77% and 81% clinical healing after 9 months respectively, these benefits are counterbalanced by a large number of serious complications (Friedlander *et al.,* 2001; Nocini *et al.,* 2003; Oakley *et al.,* 2007). The minimally invasive implantation approach of ALLOB® intends to avoid the need for open surgery, and hence the related complications. In this pilot study, the test treatment ALLOB® will be provided [redacted] and administered to patients as a single percutaneous administration under anaesthesia at the investigating sites.

In conclusion, taking into account these precautions, the benefit/risk ratio of ALLOB® supports the initiation of its clinical development in delayed-union fractures.

2 INVESTIGATIONAL PLAN

2.1 General Study Design

The present study is a prospective, multicentre, open, non-controlled study to assess the safety and efficacy of allogeneic osteoblastic cells (ALLOB®) implantation in non-infected delayed-union fractures.

After signing the Informed Consent Form (ICF), enrolled patients will enter an up to 8 weeks screening period. Eligible patients (according to the eligibility criteria) will be treated by a single ALLOB® implantation into the delayed-union site. Once treated, patients will be followed up during 6 months with post-treatment assessments performed: at 2 weeks, 1, 3 and 6 months, respectively. During follow-up, non-responding patients (see below and section 3.2.3) could be considered as drop-out and undergo a rescue surgery, according to the judgment of the Investigator.

[redacted]

Experimental design	Prospective, multicentre, open, non-controlled Phase I/IIa study
Duration of study	6 months of follow-up
Delayed-union sites	Femur, tibia, fibula, humerus, ulna, radius
Treatment	ALLOB®
Procedure	Implantation performed under anaesthesia
Study Timepoints	2 weeks, 1 month, 3 months and 6 months after treatment

Self-contained study

Data collection: Case Report Form (CRF)

2.2 Study Objectives

The primary objective is to assess the safety and efficacy of ALLOB® single percutaneous implantation in healing delayed-union fractures at the end of the study period (Month 6).

This also includes a safety and efficacy interim analysis when the 16 first assessable patients will have reached the 6 month follow-up visit.

[redacted]

2.2.1 Safety

From Visit #1 to the end of the main study period at Month 6, subjects will be systematically assessed for the potential occurrence of any AE or SAE, related to the product or related to the procedure, using patient open questionnaires, physical examination, (including vital signs), and laboratory measurements.

2.2.2 Efficacy

The efficacy of ALLOB® will be evaluated at 6 months and based on the percentage of treated patients not failing under treatment.

A patient will be considered as failed under a treatment if, at the end of the study period (at Month 6):

- The patient had a rescue surgery

Or

- The Global Disease Evaluation score (VAS) as perceived by the patient has not improved by at least 25% *and* the TUS as assessed by CT scan has not increased by at least 2 points (versus baseline).

The interim analysis will be performed on same endpoints.

2.2.4 Consideration for Rescue Surgery

During the study follow-up, if judged necessary, the Investigators will have the possibility to withdraw the patient from the study for a rescue treatment such as a bone autograft or any other appropriate surgical or non-surgical treatment. In this case, an early discontinuation visit will be scheduled. Reasons for rescue surgery will be documented.

2.3 Main Study Procedures

2.3.1 Patient Information and Informed Consent

Before any study-related procedure, the Principal Investigator (or a member of the investigating team, designated by the Principal Investigator) 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 notably the following points:

- Purpose, objectives, and nature of the trial (including all performed procedures)
- Conditions under which the trial are conducted
- Consequences and significance of the trial
- Expected benefits
- Inconveniences and risks
- Tests performed
- Right to receive the results of the tests performed
- Rights of the patient to physical, mental, and social integrity, dignity, privacy, confidentiality, and protection of his 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 Community and national laws, regulations, guidance, guidelines, and principles (see reference documents in Section 12)
- Medical confidentiality - recording and protection of patient data

- Access and scrutiny of personal data and information during inspection by the Competent Authorities and any other properly authorized persons, provided that such information is treated as strictly confidential and is not made publicly available
- Right to refuse to participate or 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
- Provision 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, representatives of the Sponsor, and/or the Monitor from liability for negligence.

The patient (or his/her legal representative) will then be provided sufficient time (as needed) and opportunity to inquire about details and ask any questions about the trial to the Principal 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 her/his legal representative) agrees to participate, he/she will be invited to date and sign the ICF. The Principal Investigator (or the person who conducted the Informed Consent discussion) will also sign and date the document on the same day.

One original copy of the ICF signed by the patient (or her/his legal representative) and the Principal Investigator (or the person who conducted the Informed Consent discussion) will be given to the patient (or his/her legal representative), the other original duly signed copy will be kept in the Investigator's Site File at the Investigating Site.

The Principal Investigator will then complete and sign the Case Report Form (Screening and Inclusion Visit pages), thereby attesting and recording that signed ICF has been obtained from the patient.

The study participant will be invited to date and sign any subsequent version of the ICF, as approved by the IEC. The Principal Investigator (or the person who conducted the Informed Consent discussion) will also sign and date the document on the same day.

2.3.2 Procedures

2.3.2.1 *ALLOB® Implantation Procedure*

Patients will undergo under anaesthesia (e.g., general, loco-regional or local as chosen by the Investigators) the implantation of ALLOB® with a trephine into the delayed-union site (single administration).

However, when necessary as per Investigator's judgement, the implantation of ALLOB® into the delayed-union site can be performed using two surgical approaches.

2.3.2.2 *Rescue Surgery Procedure*

When judged necessary, the Principal Investigator can decide to perform a rescue surgery. The patient can be withdrawn from the study for a rescue surgical (e.g., bone autograft, allograft...) or non-surgical treatment according to the standard-of-care procedure of the investigating site.

Reason for rescue surgery, type and date will be recorded.

2.4 Patient Evaluation

2.4.1 Definition of Delayed-union in the Study

In this study, a delayed-union fracture is defined at the time of screening as (i) an absence of healing 3 months (with a maximum of 7 months) ± 2 weeks after the onset of fracture and (ii) an absence of the progression of healing over the last 4 weeks, as confirmed by clinical and radiological evaluation.

2.4.2 *Clinical Evaluation*

In order to avoid bias, clinical evaluation should be the first procedure during a study visit before discussing with the Investigator or the Study Nurse/Coordinator. Indeed, the patient has to complete the questionnaires alone without any outside intervention (Bryant and Fernandes, 2011).

The following clinical assessment will be evaluated:

- Global Disease Evaluation using a Visual Analogue Scale (see details in section 3.2.1 and Annex 1): the Global Disease Evaluation VAS is a 100 mm length horizontal line where 0 means best possible health status ("very well") and 100 the worst possible health status ("extremely bad"). Patients must mark an "X" on the scale to indicate their general health status over the last week. Principal Investigator (or the study nurse) must mark an "X" on the scale to indicate the general health status of the patient as perceived at the time of the visit.
- Pain using a Visual Analogue Scale (see details in Annex 2): the Pain VAS is a 100 mm length horizontal line with endpoints labelled "no pain" (0) and "extreme pain" (100). Patients must mark an "X" on the scale to indicate their pain over the last week. In this study, pain will be evaluated by the patient at rest, during activity and at palpation (performed by the Investigator or the study nurse).
- Weight-Bearing using a Likert scale (see details in Annex 3): in this study, functionality on the affected limb will be assessed using weight-bearing. In this test, the patient will be asked to place only as much weight as he/she feels comfortable (as tolerated) on the injured limb (based on pain feeling) standing. This specific category allows a differential scoring related to pain feeling.

2.4.3 *Radiological Evaluation – TUS and mRUS*

In this study, the modified Radiographic Union Score (mRUS) and Tomographic Union Score (TUS) will be assessed both on conventional X-ray and on CT scan, respectively. CT scan is more sensitive, and three-dimensional reconstruction will allow to have a more global view of the fracture and to improve the assessment (see details in section 3.2.2 and Annex 4).

2.5 Patient inclusion scheme

With the objective of maximum 32 patients treated in the study, and taking into account 10% drop-out, 35 patients will be enrolled.

For the first 16 patients, the patient recruitment will proceed stepwise by blocks of 4. Full first 2 weeks safety data of the first block of 4 patients will be analysed before the first patient of the second block of 4 patients is treated. First 48 hours safety data of the second block of 4 patients will be analysed before treating the first patient of the next block. This latter scheme will be repeated until the first 16 patients have been treated.

A Data Safety Monitoring Board (DSMB) will be established to assess the safety and efficacy when 6-month post treatment results for the first 16 assessable patients will be available (i.e., interim analysis). This Board will recommend to the Sponsor whether to continue, modify or stop the trial. The study can be prematurely stopped:

- For safety concerns
- For futility if less than 4 successes are observed
- For efficacy if 12 or more successes are observed

Additional patients can otherwise be treated in order to reach a total of 32 patients.

2.6 Study Population

2.6.1 Eligibility

Prior to patient inclusion and baseline assessment by the Investigator, a screening period is planned to allow verification of patient eligibility.

Patients will be selected based on the eligibility criteria listed in section 2.6.

Duration of delayed-union

As the trial involves patients diagnosed with delayed-union fractures of a long bone (see 2.4.1) at the time of inclusion, and as the time between screening and implantation could take up to 8 weeks, delayed-union patients could be screened (Visit #1) as from a fracture duration of 3

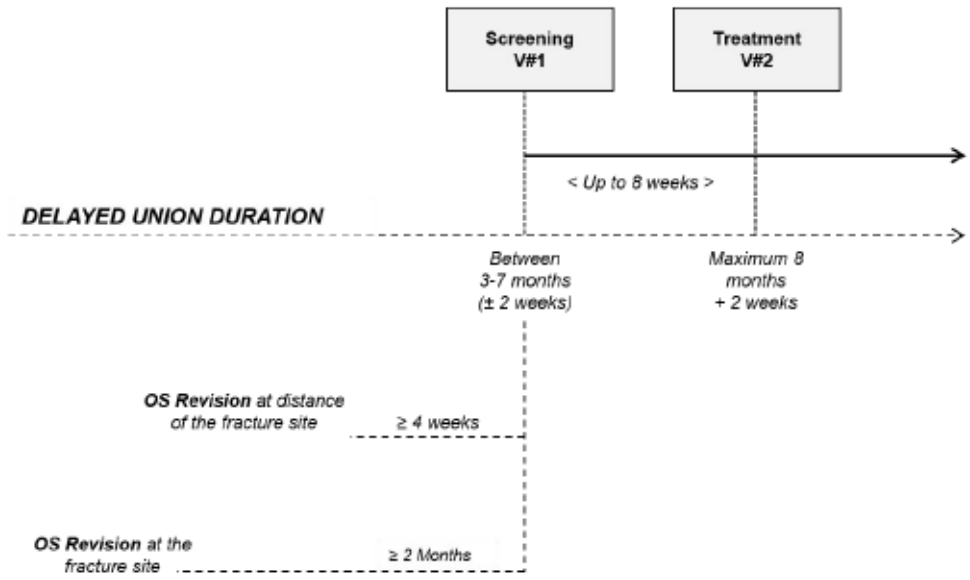
months ± 2 weeks to a maximum of 7 months ± 2 weeks. Patients will be treated up to 8 months + 2 weeks after fracture occurrence.

Revision of osteosynthesis material

Osteosynthesis revision is allowed prior to patient entry into the study:

- With a minimum of 2 months between revision/surgery and screening for revision/surgery performed at the fracture site
- With a minimum of 4 weeks between revision/surgery and screening for revision/surgery outside the fracture site.

Before implantation, the absence of signs of radiological healing (due to the osteosynthesis revision performed before the study) will be confirmed by the Independent Radiologist. This will be done by comparing the images from conventional X-Ray (and/or CT scan) performed at Visit #1 with the X-Ray (and/or CT scan) performed before the study (a minimum of 4 weeks between the images is required).



Patient Information

Apart from inclusion and exclusion criteria detailed in section 2.6.2 and 2.6.3, the following clinical information and data will also be collected and recorded:

- Past and current relevant medical (and surgical) history

- Alcohol consumption (including the number of drinks per day)
- Smoking habits (including the number of cigarettes, cigars, and/or pipes per day)

Patients will not be selected according to their gender, since there are no known or expected gender differences in pharmacokinetics, efficacy, and/or safety profile of the test product, no subgroup analysis with sex as a variable is planned (random sex distribution).

2.6.2 Inclusion Criteria

All subjects must satisfy ALL the following criteria at study entry:

- Patient aged 18 to 80 years inclusive
- Patient diagnosed with a non-infected delayed-union fracture of a long bone (femur, tibia, fibula, humerus, ulna, radius) of minimum 3 months and maximum 7 months (± 2 weeks)without signs of healing over the last 4 weeks at the time of screening
- Modified Radiographic Union Score (mRUS)[1] < 10
- Global Disease Evaluation Score as assessed by the patient ≥ 20 mm on a Visual Analogue Scale
- Patient (or patient's legally acceptable representative) capable to provide a written, dated, and signed informed consent prior to any study procedure.

2.6.3 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

- Fracture interline > 2.5 cm, as defined by the Independent Radiologist
- Insufficient reduction of the fracture

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[1] In case the mRUS is not assessable, the Tomographic Union Score (TUS) could be used instead (judged by the Independent Reader)

- Insufficient fracture stability defined as osteolysis at the level of the nails/screws and/or defect and/or mobility of the osteosynthesis material at physical examination, as assessed by the Investigator
- Osteosynthesis material revision or surgery (i) performed less than 2 months from the screening visit at the fracture site *or* (ii) performed less than 4 weeks from the screening visit at distance of the fracture site.
- Active bone infection (at site)
- Femoral neck fracture, if the femur is the target bone of the study
- Multifocal fracture (e.g., more than one fracture site on the studied bone)
- Symptomatic delayed/non-union fracture on the neighbouring bone , as judged by the Investigator
- Severe nerve damage and/or neuropathic/neuropathic-like pain at fracture site, that may interfere with assessment during the study, as appreciated by the Investigator
- Severe tendon lesion (e.g., rupture or enthesopathy) at fracture site, that may interfere with assessment during the study, as appreciated by the Investigator

Current or previous diagnoses, signs and/or symptoms

- Positive serology for HIV (defined as positive Anti-HIV 1 and/or 2 and/or positive PCR)
- Active hepatitis B (defined as positive HBs Ag and/or positive PCR)
- Active hepatitis C (defined as positive Anti-HCV and/or positive PCR)
- Global sepsis
- Renal impairment, defined as serum creatinine >2 mg/dl or 176 µmol/L
- Hepatic impairment, defined as alanine aminotransferase or aspartate aminotransferase ≥ 3 times the upper normal limit
- Poorly controlled diabetes mellitus (defined as HbA1C >8%)
- Known allergy to gentamicin
- 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
- History of organ or bone marrow transplantation
- Active auto-immune disease (e.g., sclerodermia, Sjögren syndrome, lupus,...)
- Any concomitant disease that could interfere with the evaluation of efficacy, as judged by the Investigator, including but not limited to local or metabolic bone diseases
- Life expectancy less than 6 months

Current or previous treatment

- Patients who have previously been treated with ALLOB®
- Participation in another clinical study involving a pharmacological treatment within 3 months prior to screening
- Current (or within 1 month of screening) treatment with calcitonin, raloxifen, teriparatide, and/or strontium ralenate
- Current (or within 6 months of screening) illicit drug abuse (as per local law)

Safety aspects concerning female subjects of childbearing potential

- Pregnancy
- Breast-feeding
- Woman not willing or able to use a 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)
- Woman with positive urine pregnancy tests at Visits #1 and/or #2

Other exclusion criteria

- Body Mass Index (BMI) of 35 kg/m^2 or greater
- Unable to undergo general anaesthesia or a surgical intervention

3 RATIONAL FOR THE STUDY DESIGN

3.1 Types and Sites of Delayed and Non-Union Fractures

In this study, patients with delayed-union fractures of long bones will be enrolled. All long bones have a longitudinal axis consisting of a body or shaft (the diaphysis) and an expanded portion (the epiphysis) at each end that is usually articular. According to the AO classification by Müller (1990), four different groups of fractures are similarly distinguished for all long bones and the tendency of evolving towards non-unions appears to be grossly similar among them (Calori *et al.,* 2007).

To avoid evaluation bias, patients with multifocal fractures will be excluded from the study. In such cases, it will be difficult to evaluate the treated fractures independently from the other untreated fracture.

3.2 Clinical and Radiological Evaluation Tools

3.2.1 Clinical Evaluation

To assess fracture healing, orthopaedic surgeons perform both a clinical and a radiological evaluation (Megas, 2005; Corrales *et al.*, 2008). Clinical criteria used to assess fracture union are the absence of pain or tenderness during weight bearing, the absence of pain or tenderness on palpation and the ability to bear weight (Corrales *et al.*, 2008). This clinical assessment is usually combined with radiological examinations including plain radiographic measures such as cortical continuity, presence of fracture line and callus formation (Corrales *et al.*, 2008).

Visual Analogue Scales

The usual tool to assess pain is the Visual Analogue Scale (VAS). This one-dimensional tool allows reliable assessment of symptoms (Breivick et *al.*, 2008). A VAS is a measurement instrument dedicated to the evaluation of characteristics, attitudes or symptoms that is believed to range across a continuum of values and cannot easily be directly measured (e.g., pain or global health status in this particular study). In VAS, the symptom that a patient feels ranges across a continuum from no symptom (0 mm) to extreme symptom (100 mm) on a horizontal

line of 100 mm in length. The patient marks on the line the point that he/she feels represents his/her perception of his/her current status of symptom. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks.

Pain (VAS)

In pain VAS, the pain that a patient feels ranges across a continuum from none (0 mm) to extreme (100 mm) on a horizontal line of 100 mm in length (see Annex 2). This VAS has been shown to allow reliable assessment of pain both at rest, during activities and at palpation (Breivik *et al.,* 2008). The patients with VAS pain scores of 30 mm or less would be categorised as having mild pain, those with scores of 70 mm or more are categorised as having severe pain, and those from 31 to 69 mm, moderate pain (Kelly, 2001). The time frame over which the patients should consider the severity of their pain is the last 24 hours (Breivik *et al.,* 2008). In this study, pain will be assessed at rest, during activity and at palpation.

Measurement of the intensity of pain and determination of the extent to which pain affects an individual is not simple as pain is a complex and multidimensional phenomenon. Indeed, pain can be generated by different mechanisms including tissue ischemia, muscle contraction, and direct tissue damage from trauma. In addition, the peripheral and central nervous systems not only passively carry the nociceptive signal for cognitive processing but also actively modify it along the way. Interpretation of this signal includes psychological, physiological, emotional and behavioural dimensions. Because of these characteristics, the perception of and the response to pain can vary greatly (Kendall *et al.*, 1996; Knox, 1996).

The data derived from this measurement can be analysed using parametric statistical techniques (Kelly, 2001). A minimal clinically significant difference (minimally important difference MID) in Pain as measured by VAS score has been determined and is generally reported to range between 9 to 15 mm (Kelly, 1998, 2001; Pope *et al.,* 2009; Kwok and Pope, 2010; George and Pope, 2011).

To take into account this variability, other questionnaires are available to obtain a better overview of the global disease and health quality of life, such as the Short-Form health survey SF-36 questionnaire, the Health Assessment Questionnaire (HAQ), Oswestry Disability Index (ODI), Weight-Bearing score (for more instances, see Shearer and Morshed, 2011).

Assessing the global disease evaluation enable to avoid some bias associated with the evaluation of pain or the function of the fractured site. Indeed, another fracture nearby the target fracture, multiple fractures at the same site, nerve damages or previous surgical interventions may negatively impact the patient ability to distinguish between pain from those collateral symptoms and pain caused at the treated fracture site.

Global Disease Evaluation (VAS)

Response (general disease improvement) to treatment can be assessed by a Global Disease Evaluation score (visual analogue scale), which is commonly used for joint diseases (Felson *et al.,* 1997). The patient's global assessment of disease activity is a standardized and validated measure of disease (activity) status developed by the American College of Rheumatology in order to provide a simple, generic measure of health for clinical appraisal and response to treatment (ACR, Vol.57, N2, 2007; EMA, CPM/EWP/422/04, 2006).

The Global Disease Evaluation VAS defines the general health patient status corresponding at the Question "How do you feel (on a score of 0 – 100 mm where 0 mm is as good as you can feel and 100 mm extremely bad) over the last week regarding your disease (i.e., delayed-union fracture), please indicate by an "X" (between 0 mm to 100 mm) your general health status on the horizontal scale line". This information is used as a quantitative measure of health as judged by the individual respondents. The patient is asked to simply mark an "X" on the scale to indicate his/her health today (see Annex 1). The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks.

The data derived from this measurement can be analysed, as for pain, using parametric statistical techniques (Kelly, 2001). However, clinical and statistical significance are not necessarily the same, and the clinical impact on the patient and on the medical practice is a crucial factor. Therefore, a minimal clinically significant difference (minimally important difference MID) in Global Disease Evaluation as measured by VAS score has also been determined and is generally reported to range between 8 to 12 mm (Kwok and Pope, 2010; George and Pope, 2011).

Weight-Bearing Score

The functional evaluation using weight bearing limits or restrictions is based on a semi-quantitative score on the following categories (e.g., University of Pittsburgh, Medical Center info for patients, 2004):

- Non weight bearing (score of 0): no weight on injured arm/ leg in allowed. While the patient stand or walk he/she must hold injured leg/arm off the floor/table.
- Toe-touch or finger-touch weight bearing or touchdown weight bearing (score of 1): when the patient stand or walk, he/she may only touch the floor/table for balance. No body weight can be placed on the leg/arm.
- Partial weight bearing (score of 2): the patient may place some of his/her body weight on the injured leg/arm when he/she stand or walk.
- Full weight bearing (score of 3)

This scoring can be done "unrestricted" or "as tolerated". In the latter, the patient can place only as much weight as he/she feels comfortable on the injured limb (based on pain feeling). The patient places less weight on the affected limb if he/she feels pain. This specific category allows a differential scoring related to pain feeling (see Annex 3). There is no weight-bearing assessment based on a visual analogue scale.

Unfortunately, weight bearing scoring does not allow the use of validated assessment tools, and the current existing scoring method cannot avoid room for subjective patient and physician interpretation. [redacted]

3.2.2 *Radiological Evaluation*

Diagnosis and treatment evaluation (healing) of impaired fracture healing is based on clinical symptoms as well as on radiological signs appearing during the course of treatment. The radiological signs depend on the type of delayed-unions but generally included the absence or presence of bridging between the bone fragments, persistence or not of fracture lines, absence or presence of bone callus (Megas, 2005).

Based on a systematic review of published clinical outcomes pertaining to long bone fracture healing, the most common radiographic definitions of fracture healing in studies appear to be a bridging of the fracture site by callus, trabeculae, or bone (53% of the studies), bridging of the fracture site at 3 cortices (27% of the studies), and obliteration of the fracture line or cortical continuity (18% of the studies) (Corrales *et al.*, 2008).

More recently, in an attempt to improve the reliability of radiographic assessment of healing, studies have explored a novel radiographic assessment for tibial shaft fractures, the Radiographic Union Scale for Tibial Fractures (RUST). RUST was developed as a standard measurement of fracture healing in patients with tibial fractures (Whelan *et al.,* 2002; Kooistra *et al.,* 2010; Whelan *et al.,* 2010). The RUST assesses the presence of bridging callus and of a fracture line on each of four cortices (seen on anterior, posterior, medial, and lateral views). Each of the four cortices is evaluated according to a range from 1 to 3. The individual scores are added to provide an overall total ranging from 4 (none of the cortices bridged) to 12 (bridged at all four cortices with no presence of the fracture line) (see Annex 4). The Tomographic Union Score (TUS) and modified Radiological Union Score (mRUS) are being used in this study (from 2 to 16) in order to take into account the case when the fracture line is absent on at least 2 views of the scan after a recent fracture (Score 0), and the case when callus is totally absent on each view of the scan after bone reparation (Score 4).

The development of the RUST highlights the first attempt at creating a validated system for determining healing in tibial fractures and may serve as an example for the development of other scoring systems, particularly those in which hardware or casting material may obscure visualization on X-ray (Axelrad and Einhorn, 2011; Vannabouathong *et al.,* 2011). This scoring system has demonstrated higher inter-rater reliability when compared with surgeon's general impression (Whelan *et al.,* 2010). In an attempt to improve the reliability of radiographic assessment of healing as well as the standardization of the observations, and based on the literature review (Corrales *et al.,* 2008), the radiological evaluation of fracture healing will be done according to a modified version of the RUST (i.e., mRUS and TUS) in this study.

Generally, mRUS is performed on X-rays, but can be done on both X-ray and CT scan (TUS). In the present study, TUS on CT scan has been chosen as a primary endpoint, because CT scan is a more sensitive method, and the three-dimensional reconstruction will allow to get a more

global view of the fracture and will improve the assessment. Numerous studies have expounded the benefits of computed tomography in providing a more accurate assessment of healing and a higher correlation with fracture rigidity (Morshed et *al.*, 2008). One study showed good reliability and diagnostic accuracy of CT for tibial non-union fractures (kappa = 0.67, $p < 0.0001$; sensitivity = 100%, specificity = 62%), versus plain radiography (kappa = 0.14, $p = 0.36$; sensitivity = 54%, specificity = 62%) (Bhattacharyya *et al.*, 2006).

In this pilot phase I/IIa study, the primary target for TUS as assessed by CT scan will be an improvement of at least 2 points at Month 6, as an improvement by two points of TUS means:

- There is a total consolidation of one cortices, or
- There is a bone union on two cortices (even if the fracture interline is still visible), or
- The disappearance of the fracture interlines on two cortices in bone union.

3.2.3 Rationale for the Choice of Clinical and Radiological Improvement Levels

In their daily practice, orthopaedic surgeons take the decision of a new surgical intervention if signs of both clinical and radiological improvements are observed (i.e., signs of favourable evolution). This is because clinical and radiological improvements are not always correlated. This has been observed in other studies where some patients showed significant clinical improvement with limited radiological improvement or vice versa. In the present study, the same strategy of a combined clinical and radiological evaluation will help determining if a rescue surgery will be required or not.

Based on the efficacy of the treatment, Investigators will have the opportunity to switch to rescue surgery from Month 3 if the patient has not improved by at least 15% his/her global disease evaluation score (VAS) as perceived by the patient and his/her TUS or mRUS (as available) has not improved by at least 1 point.

The levels of improvements have been calculated as based on other similar impaired fracture healing trials (e.g., PREOB® on non-union fracture) and take into account standard deviation and patient variability.

4 DETAILED SCHEDULE OF VISITS

4.1 General Overview of Visits and Procedures

Study Flow Chart

An overview of the study assessments and procedures is given in the Flow Chart below. Study procedures are described separately for the ALLOB® study, the [redacted] and the [redacted] in Table 1, [redacted].

[redacted]

	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	■							
[redacted]	■	■						
[redacted]	■							
[redacted]	■	■	■	■	■	■	■	■
[redacted]	■	■	■	■	■	■	■	■
[redacted]	■	■	■	■	■	■	■	■
[redacted]	■							
[redacted]	■	■			■	■	■	■
[redacted]	■							■
[redacted]	■							■
[redacted]	■						■	■
[redacted]	■					■	■	■
[redacted]	■	■			■	■	■	■
[redacted]		■			■	■	■	■
[redacted]		■				■	■	■
[redacted]	■	■	■	■	■	■	■	■
[redacted]		■						
[redacted]		■						
[redacted]	■	■	■	■	■	■	■	■

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]						[redacted]	[redacted]	[redacted]	[redacted]
[redacted]											
[redacted]			[redacted]								
[redacted]			[redacted]								
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]											
[redacted]		[redacted]								[redacted]	[redacted]
[redacted]		[redacted]								[redacted]	[redacted]

4.2 Screening (Visit #1)

Before any study-related procedure, the Principal Investigator (or a member of the investigating team, designated by the Investigator) will give, both in oral and written, detailed and comprehensive information regarding all aspects of the trial to the patient (including the Patient Information Letter and Informed Consent Form). The screening period will last up to 8 weeks.

Visit #1 will include the following procedures to be performed after ICF has been signed:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted] **Treatment/ALLOB® Implantation Visit (Visit #2)**

Before ALLOB® implantation, the following procedures will be performed:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

4.4 Follow-up Visit #3 (2 weeks ± 2 days)

During this visit, the following procedures will be performed:

[redacted]

- [redacted]

4.5 Follow-up Visit #4 (Month 1: 4 weeks ± 1 week)

During this visit, the following procedures will be performed:

- [redacted]

4.6 Follow-up Visit #5 (Month 3: 12 weeks ± 2 weeks)

The following procedures will be performed:

- [redacted]

[redacted]

4.7 Follow-up Visit #6 (Month 6: 24 weeks ± 3 weeks)

The following procedures will be performed:

[redacted]

[redacted]

4.8 [redacted]

[redacted]

5 DETAILED DESCRIPTION OF THE PROCEDURES

5.1 Revision Procedure prior to the Trial

Osteosynthesis revision or surgery of the delayed-union under study is allowed prior to entry into the study:

- If there is a minimum of 2 months between the revision/surgery and the screening if the revision/surgery has been performed at the fracture site
- If there is a minimum of 4 weeks between the revision/surgery and the screening if the revision/surgery has been performed outside the fracture site.

At screening (Visit #1), the absence of signs of radiological healing (due to the osteosynthesis revision performed before the study) will be confirmed by the Independent Radiologist. This will be done by comparing conventional X-Ray (and/or CT scan) performed at screening Visit #1 with the X-Ray (and/or CT scan) performed before the study (min. time of 4 weeks).

Upon the Independent Radiologist or the Principal Investigator's judgement as needed (e.g., absence or poor quality of pre-study images, pre-study images whose dates are to close from the dates of the fractures…), a second set of X-ray can be performed during screening period (i.e., 4 weeks after the first set of X-rays), in order to assess the evolution of the fracture: absence of fracture healing over the last 4 weeks at time of inclusion (inclusion criterion, section 2.6.2).

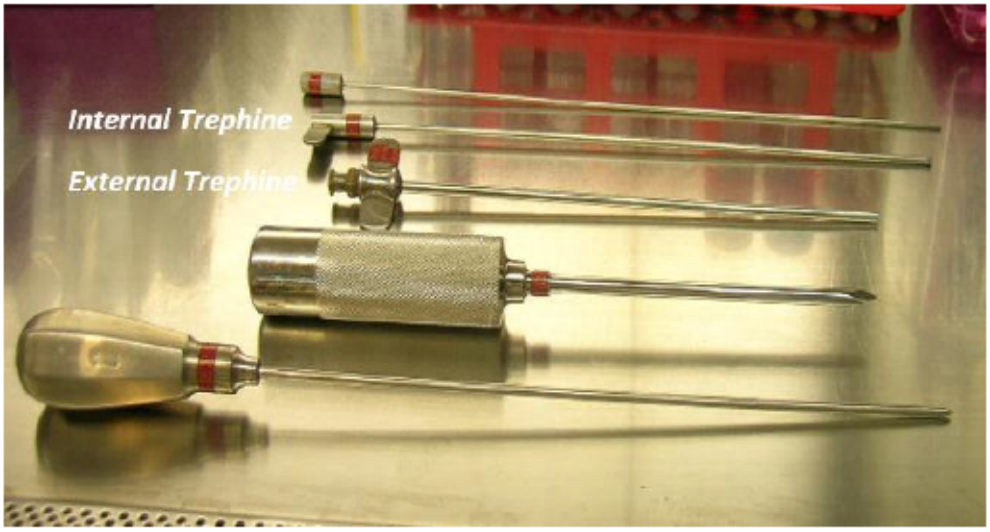
However, all efforts must be done to collect the images performed at the time of revision.

5.2 ALLOB® Implantation Procedure

In the operating room, the C-arm fluoroscope (or equivalent) will be draped with a sterile sleeve and positioned over the delayed-union region to allow an antero-posterior view and lateral view of the lesion. Under anaesthesia, a 5 to 10 mm incision is then made laterally through the skin and the fascia at the level of the delayed-union site. [redacted]

[redacted]. The injection of the suspension is performed slowly for approximately 1 to 2 minutes. Finally the trephine is washed with a rinse solution (NaCl 0.9%) to ensure that the entire suspension has been injected into the delayed-union lesion. The syringe is then removed [redacted]. The [redacted] (e.g., Gelfoam®, Upjohn, USA) is pushed through the external trephine to allow clotting and closing of the hole made by the trephine. The trephine is removed and stitches are applied to close the skin.

Implantation trephine (external and internal trephines)



If judged necessary, the IMP ALLOB® (i.e., same syringe) can be administered into the delayed-union site from two different surgical approaches, using the same procedure.

5.3 Peri-operative antibiotic therapy and other medication

All patients will receive a single intravenous infusion of cefazolin (2g) or any standard-of-care antibiotic therapy used at the investigating site at induction. Besides, drugs used during anaesthesia will not be systematically recorded in the CRF, except if an Adverse Event should have occurred.

Patients will be hospitalized for 24 or 48 hours, upon Investigator's judgement ([redacted]). If patients are hospitalized for 24 hours, they must return to the Investigating Site for the Visit #2 – 48h post-implantation visit.

5.4 Post-operative Management

Following the implantation procedure and the hospital stay, immobilization and unloading of the treated bone will be requested and all patients will remain non-weight-bearing on the operated limb as long as judged necessary by the Investigator. Progressive mobilization and load bearing will be allowed thereafter.

[redacted] (at Visit #3).

5.5 Revision Procedure during the Trial

Simple osteosynthesis revision (defined as second intervention anywhere but at the fracture site) can be performed in case of osteosynthesis material instability as from Month 3 after treatment.

5.6 Rescue Surgery Procedure

Rescue surgery (when judged necessary, as from Month 3 after treatment) will be performed according to standard-of-care procedure of the investigating site.

5.7 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6 INVESTIGATIONAL PRODUCT

6.1 Investigational Medicinal Product

Table 4: Characteristics of the Investigational Medicinal Product

	ALLOB®
CBMP	allogeneic bone marrow-derived osteoblastic cells
Cellular Concentration	[redacted] cells/ml
Volume	[redacted] ml
Container	[redacted]
Batch number(s)	Provided on the label
Expiry date	Provided on the label
Manufacturer	Bone Therapeutics S.A.
Trade name	ALLOB®
Storage requirements	[redacted]

Treatment administered

The ALLOB® dose to be used in this study will depend upon the size of fracture interline and the surgical approach (from [redacted] at a concentration of [redacted] cells/ml). Therefore, ALLOB® volume will be determined on a case-by case basis.

Table 5: *Administration of the Test Product*

	ALLOB® Product Procedure
Product	ALLOB®
Procedure/Route of administration	Percutaneous administration via a trephine
Single dose	[redacted] cells/ml ([redacted] depending on the delayed-union size)
Dosage schedule	1 single dose per subject at implantation visit (#2)

Regarding the packaging, labelling, shipment of the Investigational Medicinal Product (IMP), Standard Operating Procedures, including step-by-step instructions and detailed descriptions, will be provided to the Principal Investigator before the beginning of the trial. Complete information will be provided in the Study Procedure Manual and training of the healthcare professionals involved will also be conducted during the Site Initiation Visits and at the Investigator's Meeting.

6.2 [redacted]

[redacted]

[redacted]

6.3 Tracking, Traceability, and Accountability of Investigational Medicinal Product

A tracking system allowing complete traceability of both the Starting Materials (e.g., bone marrow) and IMP (i.e., ALLOB®) at all stages will be established and maintained (by Sponsor, Manufacturer, Managing Physician of the "Intermediary Structure", Investigator and CRO). This tracking system would ensure that:

- The Starting Materials and IMP are tracked and traced during the whole process, from the eligibility and selection of the donor, through the donation, procurement, testing, processing, storage, preservation, labelling, packaging, release, transport, distribution, and delivery, to the implantation to the patient, each procedure and step being described in Standard Operating Procedures, and systematically collected, verified, and recorded using specific Forms and Receipts (and in the CRF).
- Production data of each batch are accurately tracked and recorded.
- There is also an accurate system in place to notify, report, investigate, register, and transmit information about any Serious Adverse Safety/Quality Events which may influence the quality and safety of the product, and which may be attributed to the procurement of starting material, testing, processing, storage, preservation, delivery, and distribution (see detailed description in Section 8).

In addition, it should be noted that all used syringes (without needles) will be kept and stored in each investigating site until monitor's verification visits, and destroyed after the monitoring visit on site and once the accountability is performed.

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

7 SAFETY AND TOLERABILITY MEASUREMENTS AND ENDPOINTS

7.1 Overview of Safety Parameters and Endpoints

The safety and tolerability of the test product (ALLOB®) 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 the study procedures. Definitions of AE/SAE are in Section 8.

For the first 16 patients, recruitment will proceed stepwise by blocks of 4. Full first 2 weeks safety data of the first block of 4 patients will be analysed before the first patient of the second block will be treated. First 48 hours safety data of the second block of 4 patients will be analysed before treating the first patient of the next block. This latter scheme will be repeated until the 16th patient has been treated.

Table 6 below shows how the safety endpoints of this study relate to the study objectives. Assessments and measurements will be carried out at the times specified in the study Flow Chart (see above).

Table 6: Overview of Safety Parameters and Timepoints

Variables	*Time Points*
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[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 will do all the measurements on the same patient.

Results of measurements should only be reported as AE if, in the Investigator's opinion, it is outside of "expected values or variations". Also they must be considered as SAE if it fulfils the SAE definition.

Heart rate will be measured once, 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 systematically measured.

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 as well as the fractured limb and the administration site will be performed preferably by the same person (Principal Investigator).

Height (without shoes) will be measured in centimetres (cm). Weight (without shoes) will be measured in kilograms using a scale. Historical patient information and/or patients reports must not be used.

Body Mass Index (BMI) will be calculated as follows: Weight (Kg)/Height^2 (m) = BMI.

7.1.3 Laboratory Safety Measurements

The blood collected for biochemistry, haematology, and serological testing will be done at the Investigator's laboratories.

The total amount of blood collected [redacted] during the whole study is expected not to exceed 300 ml.

Table 7: Overview of Blood Collection

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Serology

[redacted]

For this analysis, 9 ml of blood will be collected and the analysis will be performed at the local laboratory.

Safety

Laboratory tests will be performed [redacted]

The following parameters will be analysed as safety measurements:

[redacted]

For these analyses, 11 ml of blood will be collected at each visit.

These analyses will be performed at the local laboratory.

Other exploratory Analyses: [redacted]

In order to assess the effects of treatment [redacted]

[redacted]

For these analyses, 29 ml of peripheral blood will be collected in 4 different blood collection tubes (3×9 ml and 1×2 ml) [redacted]

[redacted]

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 study inclusion (screening visit) 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 testing at each visit performed at the Investigating site (from Screening up to month 6). Pregnancy test kits will be provided by the Sponsor, performed on site according to manufacturer's instructions, and results will be recorded in the CRF.

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.

X-ray of the thorax and liver Ultra Sound will be performed at 6 months after treatment [redacted] in order to confirm absence of any ectopic mineralization.

8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event (AE) and Serious Adverse Event (SAE)

- An adverse event (AE) is 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 signs (including any abnormal laboratory findings), symptoms, or disease temporally associated with the use of a medicinal product, without any judgment about causality.

- All AEs will be reported from the time a signed and dated ICF is obtained until completion of the subject's last visit.

- Events related to pre-existing conditions should be reported as AE, upon Investigator's judgement, justified by an increase in frequency or intensity of signs or symptoms.

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

Table 8: 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 subject hospitalization or prolongation of existing hospitalization, or – Results in persistent or significant disability/incapacity, or – Is a congenital anomaly / birth defect – Is medically important (see note 3)
	Non-serious	Any other adverse event

Notes

1. The term "life-threatening" in the definition of SAE refers to an event in which the patient is at immediate risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe or had continued untreated. 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. Some medical events may jeopardise the subject or may require an intervention to prevent one of the characteristics/consequences described in the SAE definition (Section 8.1). Such events (referred as "important medical events") should also be considered as "serious" in accordance with the definition.

5. Elective procedures requiring hospitalization will not be considered as SAEs if they were pre-planned prior to signing ICF (as documented in source documents). However, complications or other events that may occur during hospitalization will be considered as AEs or SAEs and will be captured accordingly.

8.1.2 Causal relationship with the Investigational Medicinal Product

Causality shall be determined according to the definition of an adverse reaction (Section 8.1).

All adverse events judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse

reactions. The causality assessment given by the Investigator should not be downgraded by the Sponsor. If the Sponsor disagrees with the Investigator's causality assessment, both, the opinion of the Investigator and the Sponsor should be provided with the report.

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

- Yes: Certain
- Likely
- Unlikely
- No: Not related
- Unknown/ Not assessable

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 disease(s): 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

8.1.3 Adverse Drug Reaction (ADR)

Adverse Drug Reaction (ADR): 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).

Unexpected ADR: an adverse reaction whose nature, severity, specificity, or outcome is not consistent with the applicable product information (e.g., Investigator's Brochure)

8.1.4 Serious Adverse Reaction (SAR)

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, the term "reasonable causal relationship" meaning that there is evidence or arguments to suggest a causal relationship), 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.

8.1.5 Serious Adverse Safety/Quality Event (SASQE)

An 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.

8.2 Reporting of Adverse Events

The occurrence of AE/SAE (drug- or procedure- or study-related) will be assessed by non-directive questioning of the subject since the beginning of the study at the screening visit, 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 volunteered 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 well-being to the Investigator or site 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 CRF, and establish potential causality relationship with the product or the surgical procedure.

8.2.1 Observation period for the occurrence of AEs and SAEs

Table 9: *Observation Period for the Occurrence of AEs and SAEs*

Start of Study AE/SAE Observation Period	At ICF signature
End of Study AE/SAE Observation Period	6 months after Implantation
[redacted]	[redacted]

[redacted]

8.2.2 *Summary of Possible Risks related to the Procedures*

Table 10: *Summary of Possible Risks related to the Procedures*

	AE	*SAE (Fatal and Non-Fatal)*
ALLOB® Implantation	*Surgery* Pain at the implantation site Local haematoma Infectious complications *Anaesthesia* Haematoma Irritation Infection Lipothymia Paraesthesia Transient hypotension Nausea and vomiting	*Surgery* Haemorrhage Sepsis Shock Infectious complications *Anaesthesia* Allergy Infection Systemic toxicity Respiratory arrest 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	Syncope

8.2.3 Summary of Adverse Drug Reactions and Possible Risks related to the Product and/ or to the Procedures

There is no reported ADR with ALLOB® at this stage.

However, PREOB®, an autologous osteoblastic cell product, has been administered in humans in phase I/IIa and IIb studies. A summary of observed adverse events possibly related to study treatment (i.e., PREOB® and/or the implantation procedure) is listed in Table 11.

Table 11: *Summary of Observed Adverse Events (AE) and Serious Adverse Events (SAE) possibly related to Study Treatment (i.e., PREOB® and/or the Implantation Procedure)*

Non-Serious AE		*SAE (Non-Fatal)*	
Total	**27.0%**	**Total**	**3.2%**
Pyrexia	7.9%	Systemic inflammatory response syndrome	1.6%
Pain	17.5%		
Pain (general disorders)	*6.3%*	Pancytopenia**	1.6%
Procedural Pain	*4.8%*	Pyrexia**	1.6%
Musculoskeletal Pain	*3.2%*	Altered status of consciousness**	1.6%
Arthralgia	*1.6%*	Hypotension**	1.6%
Pain in extremity	*1.6%*		
Urinary retention	1.6%		
Post-procedural haematoma	1.6%		
Post-procedural bleeding	1.6%		

** AEs and SAEs were limited to TEAEs and 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.*

8.2.4 Assessment of the Safety Monitoring Committee

A review of all the reported SAE potentially related to the IMP, and especially those related to immunological reactions (severe AESCs), will be done by the Safety Monitoring Committee

(SMC) after the inclusion of each block of 4 patients until the inclusion of the first 16 patients. This review will cover all SAE potentially related to the IMP from the day of treatment to the first 15 days of follow-up for the first block of 4 patients and from the day of treatment to the end of hospitalization period for the second, third and fourth blocks of 4 patients.

The main conclusions and decisions will be communicated to all Investigators 48 hours after each meeting. A report will subsequently be prepared and its summary submitted to the IECs and CAs. The SMC will be composed by a Safety Consultant and one medically qualified member of the Sponsor. This committee will decide whether the study can be continued as planned. If the decision is to stop or modify the study, it will be communicated by the Sponsor to the Investigators of all centres within 48 hours, the IECs and CAs.

After the review of the fourth block of 4 patients, the recruitment will continue (up to maximum 32 treated patients) and no more safety committee will be performed for all the subsequent treated patients. The safety of all patients will be monitored regularly as described in the study protocol and documented as appropriate.

8.3 Reporting of Safety Issues

In the event of an AE/SAE, the Investigator will immediately initiate appropriate therapy and management according to her/his medical judgment and will decide whether to withdraw the subject from the study.

The subject 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 CRF by the Investigator. All AEs must be reported whether or not considered causally related to IMP. For every AE, the Investigator will provide an assessment of the severity and causal relationship to

the IMP and document all actions taken with regard to the IMP, and any other treatment modalities for the AE. Treatment of any adverse event 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 CRF.

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)*

Expedited Reports – Individual Case Safety Reports

In the event of any SAE related or not to trial procedure or treatment and/or any other event or relevant information which require a re-evaluation of the benefit-risk ratio, occurring from Screening Visit up to the end of the post-study open follow-up period (24 months after the end of the study), the Principal Investigator will **within 24 hours of event occurrence or awareness**:

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

The CRF will be completed (by the PI) 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:

- Subject 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(s) taken (none, subject 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, likely, unlikely, unrelated, unknown or inassessable)
- Causal relationship with the trial procedures, including blood sampling and the product implantation (implantation , surgery, anaesthesia)
- Relationship with the study disease and/or underlying, concomitant, and/or intercurrent diseases, relationship with concomitant medication or treatment, and/or drug interactions
- Any other relevant information

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 ECs (all Member States concerned), and to all concerned PIs and Sponsor in agreement with all applicable national legislation.

This notification will be sent by the SSO to the ECs and Eudravigilance database, while blinding will be preserved for both the PIs and Sponsor.

SUSARs that are fatal or life-threatening are recorded and reported within 7 days of awareness. Other SUSARs are recorded and reported within 15 days of awareness.

8.3.1.3 *Notification and Reporting of Serious Adverse Reaction related to the Human Biological Material*

In the case a reported SAE (including SUSAR and SAR) is identified by the Sponsor as being potentially related to the use of human biological material for the manufacturing of ALLOB®, the Managing Physician (MP) of the Intermediary Structure will be immediately informed. The Managing Physician will initially report this SAE potentially related to the use of Human

Biological Material to the Belgian CA (Biovigilance) and the Tissue Bank with 24 hours of the event occurrence or awareness in line with the Belgian law of the December 19, 2008 on the used human biological material and applicable Royal Decree.

Then, based on the information available in the CRF SAE Form, the Managing Physician will start on investigating to confirm if the safety event is related to the procurement, collection, testing, processing, storage, labelling and packaging, delivery, transport, and/or distribution of the tissues and cells, and/or to the quality and safety of the Biological Material. The Investigation and Conclusion Report have to be submitted to the Belgium CA of Biovigilance and the Tissue Bank within 5 days of awareness by the MP. In parallel, investigating conclusion reports are communicated by the MP to the SSO (who will notify Investigator, CRA, and Sponsor) and if applicable complete the information that has been communicated via the Eudravigilance system.

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 Principal 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 Principal Investigators (after prior submission and approval by the CAs and ECs).

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

In addition to the expedited reporting, the SSO will provide annual development safety update reports (DSUR) to CAs, ECs, and Sponsor, including all SUSARs, SARs, and/or SAEs related to the trial procedures, together with an overview of all other SAEs, AEs, and SAR that have occurred during the reporting period (in all sites and countries).

The DSUR should be submitted no later than 60 calendar days from the DSUR data lock point; based on the date of the Sponsor's first authorisation to conduct the clinical study in any country in line with the ICH Topic E2 F.

8.3.3 Safety Data Monitoring

The occurrence of AEs, SAEs, and SAR will be monitored during the whole study period on an on-going basis by the Study Safety Officer, the Managing Physician of the Intermediary Structure, and the Sponsor. The Sponsor will also receive from the Study Safety Officer a regular detailed updated listing of all AEs, SAEs, and SAR.

8.3.4 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established to assess the safety data and the efficacy endpoints when 6-month post treatment results for the first 16 assessable patients are available. The safety and efficacy data of the supplementary patients enrolled after the first 16 treated patients will be also analysed.

This board will recommend to the Sponsor whether to continue, modify or stop the trial based on:

- the efficacy data of the first 16 assessable patients (primary endpoints at Month 6)
- all the available safety data of all the treated patients.

A guidance document (DSMB chart) will be established to ensure proper monitoring of the data.

8.4 Management of Safety Issue

8.4.1 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 (Visit #1) and during the whole study period. Women with childbearing potential will further undergo a pregnancy test at all study visits, and at the last visit to the clinic in case of premature discontinuation.

If a female patient becomes pregnant during the trial, after the treatment with ALLOB®, the patient must immediately inform the investigator. These patients will not be excluded and will

be followed-up as foreseen by the Clinical Study Protocol for safety, clinical and laboratory parameters but not for radiological examinations (Chest X-Ray, CT-scan and X-ray of the fracture).

Any pregnancy will be handled as an SAE regardless the relationship between the IMP 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 is 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 CRO, 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.

8.4.2 Emergency Procedures

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 and the Patient Identification Number, Title and EudraCT Number of the study, type of treatment received (Advanced Therapy Medicinal Product (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 08:00 to 17:00) for continuous support and assistance:

Hotline - Phone Number: [redacted]

Hotline - E-mail: [redacted]

8.5 Long-Term Pharmacovigilance System

Finally, during the course of the trial, the Sponsor plans to design, develop, and submit to the relevant CAs, a detailed strategy for long-term patient follow-up, under Pharmacovigilance Plan in line with the 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 to the Sponsor by the Investigator as soon as possible. The Investigator will document the circumstances for premature discontinuation in the subject's Case Report Form as follows:

- ***Violation of eligibility criteria***

Patients will be withdrawn if incorrectly included (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 CRF.

- ***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 (including notably clinical and/or laboratory events) only if the Investigator has clearly determined that the patient's withdrawal would reduce the safety risks. In this case, the CRF AE 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 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 reviewed with

the patient and documented in source documentation and the CRF. Particularly, the patient must be carefully questioned for the possible occurrence of any AE or SAE.

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

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 CRF.

- ***Lack of efficacy***

Early discontinuation for lack of efficacy will not be considered as an AE but as a treatment failure. The reason of the lack of efficacy will be documented in the CRF and source documents.

- ***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 CRF and source documents.

9.2 Procedure for Early Discontinuation

In case of early discontinuation and whenever possible, Investigators will ask patients to perform [redacted] Exit Visit as the Premature Discontinuation Visit. At the end of the Exit visit, the Investigator will declare early discontinuation in the CRF. If study participation is terminated due to an AE possibly related to the study medication or trial-related procedures, the subject will however be followed by additional examinations according to the medical judgment of the Investigator until the AE is resolved or the Investigator deems further observations or examinations to be no longer medically indicated. All collected data should be recorded in the source documents and CRF.

9.3 Replacement of Subjects

Patients withdrawn from the study will not be replaced.

9.4 Suspension of the Trial

Overall, the study or the study treatment can be prematurely interrupted in certain circumstances. The Sponsor can stop or interrupt the study for the following reasons:

- ALLOB® is ineffective
- ALLOB® is effective
- Safety issues
- Following a decision of the Competent Authorities or the Ethics Committee.

10 STATISTICAL CONSIDERATIONS AND METHODS OF ANALYSIS

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

10.1 Analysis Populations

Two analysis sets will be defined:

- The safety population that will include all treated patients. (Treated patients will be defined as patients implanted with ALLOB®). As the study is not randomized and only one study group will be studied, the safety set will be used also to analyse the whole efficacy data.
- The Per-Protocol (PP) efficacy population will include all patients of the safety population without any major protocol deviation.

The definition of the populations will be finalised prior to database lock. The safety population will be considered as the primary cohort for the analysis of safety, efficacy, demographics, and baseline characteristics. Efficacy variables will be analysed using the safety population. Primary criteria and corresponding variables will be analysed in the PP population.

The patients screened will be described in the summary table presenting the disposition of patients.

10.2 Efficacy Endpoints

The efficacy of ALLOB® will be evaluated at Month 6. The success of the study will be based on the percentage of treated patients (ALLOB®) not failing under treatment.

A patient will be considered as failed under treatment if, at Month 6:

- He/she had a rescue surgery

Or

- The Global Disease Evaluation score (VAS) as perceived by the patient has not improved by at least 25% *and* the TUS as assessed by CT scan has not increased by at least two points (versus baseline).

An interim report will be established based on the efficacy and safety results from the first 16 assessable patients at 6 months of follow-up. The interim report will also include the safety and efficacy data of the supplementary patients enrolled after the first 16 treated patients.

10.4 Safety

Safety will be assessed using the following variables:

- AEs
- SAEs
- Vital signs: heart rate and blood pressure
- Physical examination
- Laboratory analyses (haematology and biochemistry)

10.5 Statistical Analysis

10.5.1 Generality

10.5.1.1 *Descriptive statistics*

Continuous variables will be described using the number of observed values, mean, standard deviation (SD), median, first quartile, third quartile, minimum and maximum values, and number of missing data.

Categorical data will be presented using counts (number and number of non-missing data) and percentages (%). The number of missing data will also be presented. The percentages will be calculated taking into account the non-missing data.

No adjustment on centres is planned.

10.5.1.2 *Type 1 error rate, significance tests*

In this study, two sided tests will be performed at a 5% level of significance except for efficacy analyses.

According to the Schoenfeld approach (Schoenfeld *et al.,* 1980), for the efficacy analysis, the type I error rate will be increased from the usual 5% to the 10% rate. Indeed, in this pilot single arm "proof of concept" study, it is appropriate to maintain the power and increase the type I error rate. This increases the risk of erroneously concluding that the treatment is worthy of further investigation, but does not increase the risk of missing an efficacious treatment. So in

this phase II study, since the trial will be followed by further testings, a type II error may be more serious than a type I error.

10.5.1.3 *Patient dispositions*

All screened and eligible patients will be accounted for. All post-inclusion discontinuations will be summarised and reason for discontinuation. The number of patients screened and not eligible will be presented with the main reason for their non-eligibility.

Patient disposition will be based on the patients screened and tabulated for the following categories:

- Total number of patients enrolled
- Total number of patients eligible
- Number (percentage) of patients completing the study
- Number (percentage) of patients prematurely discontinuing from study
- Primary reason for premature discontinuation
- Number of patients in the safety population
- Number of patients in the PP population

For each population, reasons for exclusion from the population will be carefully described.

10.5.2 Demographics and patients characteristics

10.5.2.1 *Demographics and other characteristics*

Descriptive statistics of demographics, and other baseline characteristics as well as medical history will be presented for all eligible patients.

10.5.2.2 *Viral serology*

Viral serology recorded at screening visit will be tabulated.

10.5.2.3 *Fracture characteristics*

Descriptive analysis will be conducted on the Safety and the Per-Protocol population.

The time from fracture to screening, the time from delayed-union diagnosis to screening, fractured bone, fracture side, fracture level, whether the fracture at onset was open, type of fracture, cause of fracture, whether any tendon or nerve was damaged at the fracture site and measure of fracture interline will be summarized.

Time from osteosynthesis to screening, type of osteosynthesis, time from last osteosynthesis revision to screening, and type of osteosynthesis revision will also be presented.

Location of neighbouring bone fracture(s), type of osteosynthesis on the neighbouring bone, whether neighbouring fracture healed and whether a delayed/non-union fracture is on the neighbouring bone will be tabulated.

10.5.2.4 *Medical history*

Medical history will be summarised safety population, and frequency of pathologies will be summarised using descriptive statistics. Frequencies will be given by system organ and preferred term according to the MedDRA Dictionary (last available version).

10.5.2.5 *Previous and concomitant medications*

Previous and concomitant medications will be summarised for the safety population.

Frequency of medication will be summarised using descriptive statistics:

- frequency of patients with at least one previous medication
- frequency of patients with at least one concomitant medication

Frequency will be given by ATC term according to the WHO Drug Dictionary (WHO DD) (last available version) used for drugs coding. Each frequency table will be sorted by descending frequency of ATC term and then within each ATC by descending frequency of WHO Drug name (all treatment groups).

10.5.3 Protocol deviations

All the protocol deviations will be identified and acted as major or minor deviations during a data review meeting occurring close to the database lock.

The protocol deviations will be as follows:

- No implantation with ALLOB®

- Violation of inclusion/exclusion criteria
- At least one post-inclusion protocol violation (e.g., taking of a forbidden treatment, no evaluation of major efficacy parameters)
- At least one deviation with respect to the study procedure

Frequency and percentages of patients with protocol deviations will be tabulated.

Patients presenting major deviation will be excluded from the PP population.

10.5.4 Implantation procedure

The whole procedures used for ALLOB® implantation will be summarized descriptively on the all enrolled patients.

These procedures concern:

- If the patient was able to undergo the implantation procedure;
- If the patient had any changes in health occurred since the last visit before implantation;
- If the IMP was released by the sponsor, the pharmacist or the investigator;
- If the implantation was performed;
- the duration of implantation operation;
- In case of a non-implantation, the reasons ;
- The prescribed dose,
- The administered dose and the reason if the prescribed dose was not totally administered;
- If fluoroscopy images were taken;
- If the IMP implantation was performed by the use of 2 different surgical approaches and if yes, the description of the 2 approaches;
- If operative blood loss with the description of the amount;
- Type of anaesthesia;
- Any relevant peri-procedural events.

During the 24 hours post-administration follow-up, number of patients having experienced AE/SAE or having done any changes in the concomitant medications will be described.

10.5.5 Extent of exposure

Extent of exposure will be summarised by descriptive statistics for the duration of treatment, calculated in days as follows:

Duration of treatment = (Date of last visit or date of rescue surgery – Date of ALLOB® implantation)

The extent of exposure summary will be presented for the safety and PP populations.

10.5.6 Efficacy analysis

10.5.6.1 *Primary efficacy criteria*

The primary efficacy criteria will be analysed in the safety population and in the PP population, the safety population corresponding to the main efficacy population.

Percentage of responder patients will be calculated as the percentage of patients who will not be considered as failed under treatment at Month 6.

A patient will be considered as failed under a treatment if, at Month 6:

- He/she had a rescue surgery

  Or

- The Global Disease Evaluation score (VAS) as perceived by the patient has not improved by at least 25% *and* the TUS as assessed by CT scan has not increased by at least two points (versus baseline).

[redacted]

[redacted]

10.5.7 Safety analysis

Safety will be analysed in the safety population, with all centres pooled. The statistical analysis will be mainly descriptive. For qualitative variables, 95% CI of percentages will be computed, and for quantitative variables, 95% CI of means will be computed.

10.5.7.1 *AEs and SAEs*

AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each AE reported, the number and percentage of patients will be tabulated based on system organ class and preferred term. Similar tabulations will be performed by severity, relationship to the study product/procedure, action taken and outcome. The number and percentage of patients who experienced an AE as defined in the pre-defined subsets of events will also be tabulated.

The frequency of AEs and SAEs will be estimated by using the 95% CI.

An analysis of following parameters will also be performed:

- Treatment-emergent (S)AE (occurring or worsening after ALLOB® implantation)
- (S)AE leading to premature withdrawal

10.5.7.2 *Other safety variables*

For blood pressure, standard summary statistics will be provided at baseline and each follow-up visit, including mean values and mean changes from baseline. Heart rate measurements will be summarised for the mean values and the mean changes from baseline at each follow-up visit using standard summary statistics. Shift tables [low (<50 bpm), normal (between 50 bpm and 120 bpm), and high (>120 bpm)] showing each individual patient's baseline value and follow-up visits will be performed.

[redacted]

Standard summary statistics of laboratory values and shift tables presenting incidence of laboratory abnormalities will also be provided. The frequency of normal / abnormal examination will be tabulated for each time point.

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

10.5.8 Interim data analysis

10.5.8.1 *Efficacy Assessment*

At Month 6, the efficacy assessment will be based on:

- The patient had a rescue surgery

  Or

- The Global Disease Evaluation score (VAS) as perceived by the patient has not improved by at least 25% *and* the TUS as assessed by CT scan has not increased by at least 2 points (versus baseline).

For rescue surgery, based on the efficacy of the treatment, Investigators will have the opportunity to switch to rescue surgery from Month 3 if the patient has not improved by at least 15% his/her global disease evaluation score (VAS) as perceived by the patient and his/her mRUS or TUS, as available, has not improved by 1 point.

The levels of improvements have been calculated as based on other similar impaired fracture healing trials (e.g., PREOB® on non-union fracture) and take into account standard deviation and patient variability.

10.5.8.2 *Presentation of the 2-stage design*

The main objective of this phase I/II-a non-comparative sequential design is to assess the interest presented by this new treatment without performing a comparative study that allows identifying only small differences of efficacy between the new treatment and a control, what requires a relatively high number of subjects. The principle of a sequential design is to perform the study in two or more stages in order to minimize the number of patients exposed to an ineffective treatment to conclude in a more premature way.

The most appropriate sequential method for this study is the 2–stage Fleming plan. In this design, the efficacy criterion is a binary criteria of "success/failure" type, with p0 as the superior limit of ineffectiveness (maximum value below which the new treatment is considered as being ineffective) and p1 as the inferior limit of efficacy (minimum value above which the new treatment is considered as being effective). The null and alternative test hypotheses are the following:

- H_0: $p \leq p0$
- H_1: $p \geq p1$

Using α = the type I error and β = the type II error

The tested hypotheses are as follows:

- H_0 : a success rate ≤ 30% is uninteresting (p0=0.30)
- H_1: a success rate of at least 70% is expected (p1=0.70)

Using $\alpha = 0.05$ and $\beta = 0.20$

In the case of a two-stages Fleming plans, the study can be stopped for ineffectiveness (if the number of successes is lower than a computed limit) or for efficacy (if the number of successes is ≥ a computed limit).

10.5.8.3 *Results of the computing*

According to the 2 stages Fleming method, 20 treated patients are required (type I error rate α of 5% and a statistical power of 80%). Taking into account that patients are enrolled by cohort of 4 and considering the potential heterogeneity of the population, 32 patients in total will be enrolled and treated in the study.

Step	Nb. of patients/step	Cumulated Nb. of patients	Treatment ineffective if Π < 0.30	Treatment effective if Π > 0.70
1	16 (assessable)	-	Number of successes ≤ 4	Number of successes ≥12
2	Up to 16 (assessable)	32	n.a.	n.a.

For the first 16 assessable patients, an interim analysis will be performed at the end of the 6 months follow-up (Visit #6).

The study will be prematurely stopped for:

- Safety concerns

- Ineffectiveness, if less than 4 successes are observed
- Efficacy, if 12 or more successes are observed

Otherwise, additional patients will be treated in order to reach a total of 32 patients.

10.5.9 Post-treatment data analysis

The final CSR including assessment of both efficacy and safety endpoints, will be established at 6 months.

[redacted]

10.6 Randomisation

There is no randomisation in the study.

10.7 Sample size estimation

Using the 2 stages Fleming method, a maximum of 32 treated patients are required. Assuming a rate of 10 % of non-assessable patients, a total of 35 patients will have to be enrolled.

10.8 Handling of missing values

For all efficacy criteria, the imputation approach will incorporate the pattern of missing values as follows:

- Missing data due to treatment-related AE leading to study withdrawal will be replaced by the Worst Observation Carried Forward (WOCF) method from scheduled or unscheduled visits: for each patient dropping out due to treatment related AE, his/her worst observation will be used to replace his/her missing values.

- Missing data due to any reason other than treatment-related AE leading to study withdrawal will be imputed using last observation carried forward (LOCF) from previous visit (scheduled or unscheduled visit).
- Missing values in-between two measured values will be extrapolated using linear mixed models.

10.9 Safety Follow-up

For the first 16 patients, patients will be treated in the study by sub-group (block) of 4. Before starting the treatment of a new block of 4 patients, a safety review at the end of the Visit #3 for the first block (48 hours of hospitalization and first follow-up visit at 2 weeks after implantation) and at the end of Visit #2 (48 hours hospitalisation or on-site visit) for the other blocks will be conducted. If from this review, 3 or more patients have not experienced SAE potentially related to the IMP, including severe AESC, and resulting in death, life-threatening, resulting in persistent or significant disability/incapacity, requiring intervention to prevent permanent impairment or damage, the next block of 4 patients will be allowed for treatment (Visit #2).

The members of the SMC will perform this safety monitoring analysis.

After inclusion of the first 16 assessable patients and based on 6-month treatment follow-up, a safety and efficacy interim analysis will be planned.

10.10 Interim Analysis

For the interim analysis, a DSMB will be established by the Sponsor. The DSMB will assess the safety data and the efficacy endpoints when 6-month post treatment results for the first 16 assessable patients are available. The board will also assess the available safety and efficacy data of supplementary enrolled patients.

The DSMB may decide in accordance with the Sponsor to decrease the sample size, to modify the design of the study, to continue or to stop the clinical trial.

11 STUDY MANAGEMENT

11.1 Monitoring

Before study initiation, the CRA will visit the Investigating Sites to evaluate the feasibility of participating to the study (e.g., patient recruitment, staff availability, facilities, equipment). During the Study Initiation Visit, the CRA will initiate the Principal Investigator and the site staff in order to train the PI and the site staff on the Study Protocol and trial-related procedures, and verify good understanding of GCP (e.g., Investigator's responsibilities) and any other applicable Community and national 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 and/or Serious Adverse Safety/Quality Events.

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 the Investigating Sites will be conducted by a monitor or the Sponsor in order to provide detailed information and support the Investigator(s), and to assess that the study is performed in compliance and accordance to the Study Protocol, ICH-GCP, and all applicable Community and national 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, including laboratory and urine tests, trial-related procedures and imaging procedures
- IMP receipt, verification, and final delivery by the Pharmacist

- IMP receipt and verification by the Investigator
- IMP accountability and traceability
- SAE Serious Adverse Safety/Quality Events notification and reporting
- Emergency and pregnancy procedures
- Data generation and collection processes
- Accuracy of data collected and recorded in the CRF
- Facilities and Investigating Site staff
- Investigator's Trial Master File (and other on-site source documentation)

Any detected non-compliance with the Study Protocol, GCP, or any other applicable Community and national legal and regulatory requirements will be fully documented by the monitor with the explanation provided by the Investigator on a deviation log.

During the 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 CRF.

Following each monitoring visit, the Investigator will receive 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 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 ICH E6 GCP 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
- The study title and/or the protocol number and the name of the Sponsor
- Medical/surgical history and physical examination
- Results of blood pressure, heart rate, respiratory rate and body temperature
- Results of urine pregnancy tests (only for female with childbearing potential)
- Results of radiographs and CT Scan
- Laboratory results reports
- All concomitant medications and concurrent procedures (list of all prescription and non-prescription medications being taken at the time of entry/screening 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 questionnaires are to be completed directly by the patient (except for the Global Disease Evaluation as perceived by the physician). 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 CRF 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 on site by the monitor such as CRA on all data and CRFs including but not limited to patient questionnaire, SAE and pregnancy-related documents, consisting in a comparison of the source documentation data with the CRFs and other records relevant to the study. This will require direct access to all original records for each patient.

Following this SDV, any errors (discrepancies) greater than 3 mm noticed on a VAS during independent verification by/on behalf of the Sponsor (e.g., audits) must trigger appropriate corrective actions to ensure exactness of all VAS 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 considered eligible for the study.

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

As some data will be directly entered into the CRF, the CRF 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 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 CRF.

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 CRFs 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 CRFs. CRFs and related source data will be made available by the Investigator for data verification at each scheduled monitoring visit.

Completed CRF 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 a duration of 30 years according to Sponsor's SOP and European Directive.

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 CRO and/or the Sponsor 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 (including at least the Director of Clinical Development).

11.6 Audits and Inspections

Authorised representatives of the Sponsor, CRO, CRA, CAs, and/or ECs may visit the 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 Community and national legal and regulatory requirements (see reference documents in Section 12.1).

The Investigator must immediately inform the CRA and/or the CRO and/or the Sponsor if contacted by a CA and/or EC about an inspection at his or her site.

The presence of the CRA on the 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. Nevertheless, when justified, the CRA may be represented by another representative involved in the study.

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 CRO and/or 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 CRA, CRO, CAs and/or ECs will be allowed to have full and direct access to the various records relating to the trial to verify adherence to the Study Protocol, GCP, and any applicable Community and national 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 CRA 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 CRA, CRO, Sponsor, and site's CA will be notified. Approval of the revised ICF by the CRA, CRO, Sponsor, and concerned CAs and ECs, if applicable, is required before the revised form is used.

The CRA or CRO (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 subjects;
- 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 subjects 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 Sections 7 & 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 Community and national 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 (2010/C23/02)
- 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 (April 03, 2003, 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 E6 (R1) - Guideline for Good Clinical Practice - (July 1996, European Medicines Agency, CPMP/ICH/135/95)
- ICH Topic E8 - General Considerations for Clinical Trials - (March 1998, European Medicines Agency, CPMP/ICH/291/95)
- ICH Topic E9 – Note for guidance on statistical principles for clinical trials (March 1992, European Medicine Agency, CPMP/ICH/363/96)
- 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 (03 December 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)
- ICH Topic E2 A - Clinical Safety Data Management : Definitions and Standards for Expedited Reporting - (June 1995, European Medicines Agency, CPMP/ICH/377/95)

- 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)
- Draft Guideline on the Risk-Based Approach according to Annex I, Part IV of Directive 2001/83/EC Applied to Advanced Therapy Medicinal Products (19 January 2012, 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
- Commission 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, 03 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 - Committee for Medicinal Products for Human Use (CHMP) European Medicines Agency (31 March 2006, CHMP/QWP/185401/2004)
- Guidance on Investigational Medicinal Products (IMPs) and 'non investigational medicinal products' (NIMPs) - European Commission (18 March 2011, Eudralex Volume 10 - Clinical Trials, Notice to Applicants, SANCO/C/8/SF/cg/a.5.001(2011)332855)
- 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)
- And any other applicable and relevant national laws and regulations

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 (as required) the Study Protocol (with amendments), written Subject Information Sheet and Informed Consent Form, other written information to be provided to subjects (such as the Patient Study Card), subject recruitment procedures, Investigator's Brochure, available safety information, information about payments and compensation available to subjects, 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 above-mentioned documents may also need to be subsequently revised during the course of the trial, for instance whenever important new information that may be relevant to the patients' safety and/or re-evaluation of the risk/benefit ratio becomes available. In this case, any change, update, and/or amendments to these documents will always be first submitted to and approved by the CAs and ECs prior to any submission to the patients (and all concerned Investigators and Investigating Sites).
- The Sponsor has prepared a template of the ICF, which embodies the ICH GCP required elements and includes any local regulations to be disclosed for the consent to be legally effective.

The final version of the Study Protocol, the Subject Information Sheet and ICF, will be submitted to and approved and/or provided a favourable opinion in writing by the relevant CAs and ECs before the beginning of the trial. These documents (and the Investigator Brochure) may also need to be subsequently revised during the course of the trial, whenever important new information that may be relevant to the patients' safety and/or re-evaluation of the risk/benefit ratio becomes available. In this case, any change, update, and/or amendments to

these documents will always be first submitted to and approved by the CAs and ECs prior to any submission to the patients (and all concerned Investigators and Investigating Sites).

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 CRO or the Sponsor.

The Investigator will immediately notify the Study Safety Officer and/or the Sponsor 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 the other Investigators involved in the trial. Detailed description of Safety Data Notification, Reporting, and Management procedures is provided in Section 7).

The Sponsor (with or without the support from the CRO) 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 or without the support from the CRO) annual 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 study site, as dictated by the CAs and ECs requirements.

The CAs and ECs will be notified by the Sponsor about the end of the trial within 90 days. If the trial is terminated earlier, the CAs will be notified within 15 days. A report summarising the study results will be sent to the CAs within one year after the end of the trial.

12.3 Subject 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 Community and national 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 CRA 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 Community and national 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 CRF 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 Community and national 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 (including CRA, CRO), 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, 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 and recorded *only* by the Investigator and will be kept and recorded in restricted access files: the Investigator's Site File at the Investigating Site.

12.4 Insurance

The Sponsor's 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 Community and national 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 Investigator's Agreement signed by the Sponsor and the Investigator (and related parties if needed) before start of the study.

The Investigator at each site must comply with all the terms, conditions, and obligations of the Investigator's Agreement.

12.6 Archiving at the End of the Study

After the close-out visit at each 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 European directives, national laws and Sponsor's SOP. 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 CRFs, SAE, and Pregnancy Forms
- Signed ICFs
- Patient screening/inclusion log and Patient/Subject Identification Code List
- Source documentation
- All required regulatory documents required by ICH-GCP, and any other applicable Community and/or national 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 CRFs and all Data Clarification Forms (DCFs) will have been collected, and when all collected data will have been analysed, a draft of the Clinical Study Report (CSR) will be produced and sent to the Principal Investigators (designated prior to writing), for review and comments.

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 according to the ICH-E3 "Note for guidance on structure and content of clinical study reports". 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, 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 CRFs) generated, created, written, and/or otherwise collected or 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, who will have 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, 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's 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 respectively, 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 Bone Therapeutics reasonably objects to the proposed communication or publication as conflicting with or compromising the Sponsor's intellectual property rights or interests, the proposed communication or publication shall be modified in order to fully address the Sponsor's 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 implemented.

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15 ANNEXES

15.2 ANNEX 1: VISUAL ANALOGUE SCALE OF GLOBAL DISEASE EVALUATION

In the patient's and Investigator's questionnaires, the Visual Analogue Scale for Global Disease Evaluation is presented as follows:

"Considering (over the last week*) all the way your disease (i.e., delayed-union fracture) affects you, please indicate by an X on this horizontal line how well you are doing with the worst possible general health (100) and best possible general health (0)."

**Or as perceived by the Investigator during the visit*

15.3 ANNEX 2: VISUAL ANALOGUE SCALE OF PAIN

In the patient's questionnaires, the Visual Analogue Scale for pain is presented as follows:

"The horizontal line below represents extreme pain (100) and no pain (0). Please indicate on this horizontal line the position reflecting the best your answer to the below question by a X"

15.3.1 Pain at rest

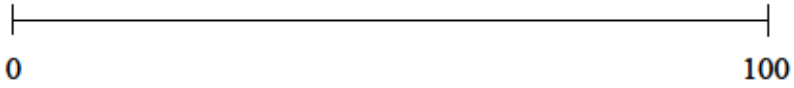
On average, how would you qualify your pain at rest over the last week?

15.3.2 Pain during activities

On average, how would you qualify your pain during daily life activities over the last week?

15.3.3 Pain at palpation (performed by the Investigator or the nurse)

How would you qualify the pain at palpation?



15.4 ANNEX 3: WEIGHT BEARING SCORE

For a delayed-union fracture of a lower extremity, the patient will be requested to stand or walk.

For a delayed-union fracture of an upper extremity, the patient will be requested, while standing, to push with the injured arm on a table.

The test will be done "as tolerated" by the patient who will complete the questionnaire below according to the fracture site.

Fracture site:

Score	Lower Extremity Long Bones ☐	Upper Extremity Long bones ☐
0 ☐	No weight on injured leg is allowed. While the patient stands or walks, he/she must hold leg off the floor.	No weight on injured arm is allowed. While the patient stands, he/she must hold injured arm off the table.
1 ☐	When the patient stands or walks, he/she may only touch the floor for balance. No body weight can be placed on the leg.	When the patient stands, he/she may only touch the table. No body weight can be placed on the arm.
2 ☐	The patient may place some of his/her body weight on the injured leg when he/she stands or walks.	The patient may place some of his/her body weight on the injured arm when he/she stands and leans on the table.
3 ☐	Full weight bearing.	Full weight bearing.

15.5 ANNEX 4: RADIOLOGICAL EVALUATION: MODIFIED RUS /TUS

The radiological evaluation will be done using conventional X-ray (incl. antero-posterior, latero-lateral) and CT Scan.

The scores used in the imaging interpretation are:

- Score 0 = Callus is Absent and Fracture line is Absent; Fracture is recent (<6 weeks)
- Score 1 = Callus is Absent and Fracture line is Visible
- Score 2 = Callus is Present and Fracture line is Visible
- Score 3 = Callus is Present and Fracture line is Invisible
- Score 4 = Callus is Absent and Fracture line is Absent; Fracture is not recent (>6 weeks)

The minimum mRUS/TUS score is 2 (presence of a fracture line at least on 2 views), maximum is 16 (bone is totally repaired).

mRUS/TUS SCORE: Individual cortical score (Lateral, Medial, Anterior and Posterior Cortex)

Modified RUS/TUS					
Lateral Cortex	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Medial Cortex	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Anterior Cortex	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Posterior Cortex	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

The total mRUS/TUS score (2– 16) is the addition of the individual scores (Lateral, Medial, Anterior and Posterior Cortex)