CLINICAL STUDY PROTOCOL

Study JTA-KOA1

EudraCT number: 2015-002117-30

Protocol Number: 000010/BT

NTC Number: 0274023102740231

Title

A Two-stage 6-month, Multicentre, Randomised, Double-blind, Controlled Study on the Safety and Efficacy of a Single Intra-articular Administration of JTA-004 in Patients with Symptomatic Knee Osteoarthritis

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.

CLINICAL STUDY PROTOCOL

Study JTA-KOA1

EudraCT number: 2015-002117-30

Protocol Number: 000010/BT

Title

A Two-stage 6-month, Multicentre, Randomised, Double-blind, Controlled Study on the Safety and Efficacy of a Single Intra-articular Administration of JTA-004 in Patients with Symptomatic Knee Osteoarthritis

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.

SPONSOR SIGNATORY APPROVAL

EudraCT number: *2015-002117-30*

Protocol Number: *000010/BT*

Title of the protocol:

A two-stage 6-month, Multicentre, Randomised, Double-blind, Controlled Study on the Safety and Efficacy of Single Intra-articular Administration of JTA-004 in Patients with Symptomatic Knee Osteoarthritis

Sponsor's representative

Thomas LIENARD SPRL represented
by its permanent representative Thomas LIENARD
Chief Executive 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 national and Community laws, regulations, guidance, guidelines, and principles regarding:

- Ethical principles for medical research involving human patients
- Good Clinical Practice (GCP) regarding the conduct of clinical trials and investigational medicinal products for human use
- Clinical safety data management, notification, and reporting

Agree:

- That my primary responsibility is to safeguard the rights and well-being of each patient participating in this study, and that the patient's rights and well-being must take precedence over the goals and requirements of the study
- To ensure the confidentiality and protection of all information obtained from and about the patients
- To obtain the informed consent of each patient prior to perform any study-related activity and ensure that:
  * Verbal information, adapted to the patient, has been provided, avoiding direct or indirect pressure, and that the patient 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) before consenting

- To keep the decisions of the ECs and preserve the written proof of the informed consent of the patients or their authorised legal representative
- To ensure that no human biological study sample is retained on site or elsewhere without the approval of the Sponsor and the express written consent of the patient
- To perform no other biological assays on the human biological study sample than those described in the protocol or its amendment(s)
- To promptly report any unanticipated problems in research covered under this agreement that involve any risk to the patients
- To ensure proper study information transfer and study data collection in a clear, legible way and in conformity with the source documents (patient file)
- To ensure adequate resources to successfully complete the study with regard to deadlines, qualified personnel and material

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 medicinal product, and more generally about his/her financial ties with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

Principal Investigator

Name and Title	Date	Signature

STUDY SYNOPSIS

EudraCT Number: *2015-002117-30* **Protocol Number:** *000010/BT* **Protocol Code**: JTA-KOA1	**Test product:** JTA-004 **Reference:** Synvisc-One®
Sponsor: Bone Therapeutics S.A., Rue Auguste Piccard, 37, B-6041 Gosselies, Belgium	
Title: A two-stage 6-month, Multicentre, Randomised, Double-blind, Controlled Study on the Safety and Efficacy of Single Intra-articular Administration of JTA-004 in Patients with Symptomatic Knee Osteoarthritis	
Phase of Development: Two-stage Phase II/Phase III trial	
Number of Centres / Countries: up to 15 centres in Belgium	
Planned Study Period: Total recruitment period: until 164 patients have been included (this number may be adjusted upon sample size reassessment at interim analysis). Total study follow-up period: 6 months	
Study design: This study is a seamless two-stage prospective, randomized, double-blind controlled Phase II/Phase III trial including 3 JTA-004 strengths with 1 reference product. The initial phase of the two-stage design plans for selection of the best JTA-004 strengths for a confirmatory phase testing for superiority compared to a best in class reference treatment.	
Planned Number of Patients: A total of 164 patients are planned.	
Medical Condition under Investigation: symptomatic osteoarthritis of the knee with Kellgren-Lawrence grade II and III.	

Inclusion Criteria:

- Male/female aged between 50 to 79 years
- Diagnosed with primary knee OA, fulfilling the following American College of Rheumatology (ACR) criteria at the target knee:
  - Pain $\geq$ 40 mm on a 0-100 mm VAS during the 3 days preceding the date of the Screening Visit (see Annex 2)
  - Morning stiffness not exceeding 30 minutes
  - Kellgren-Lawrence grade II or III (confirmed by X-ray within the last 6 months)
- Insufficient/failed response to analgesic and/or NSAID

Main Exclusion Criteria

- Concomitant inflammatory disease or other condition affecting the joints (e.g., rheumatoid arthritis, septic arthritis, metabolic bone disease, psoriasis, gout, microcrystalline arthropathies/chondrocalcinosis, Paget's disease…)
- Treatment:
  - Within 6 months prior to Screening: intra-articular hyaluronic acid injections into the target knee
  - Within 2 months prior to Screening: intra-articular glucocorticoids at the target knee
- Current or past history of coagulation disorders, as judged by the Investigator
- Hypersensitivity to any components of HA-based injection products
- Hypersensitivity to human biological material including blood and blood derived products, potential excipients and residues from manufacturing process, documented clinically or by laboratory tests
- Hypersensitivity to avian proteins
- Current anti-hypertensive medication known to be potentiated by a single dose of clonidine

Test Product Strength and Mode of Administration:

Test Product: 3 different strengths of JTA-004 (JTA-004 50 (2ml), JTA-004 100 (2ml) and JTA-004 50 (4ml) and one reference will be tested. All patients will be treated by a single intra-articular administration at visit #2.

Study Visits: There will be 5 visits defined as follows:

- Screening visit (Visit #1)
- Baseline/Treatment visit (Visit #2)
- Follow-up visits at 2 weeks (Visit #3), 3 months (visit #4) and 6 months (visit #5)

Study Endpoints and Criteria for Evaluation:

The WOMAC® VA 3.1 pain subscale scoring at baseline and subsequent assessment time points is the major efficacy criteria

Safety Endpoints

At each follow-up visit, patients will be assessed for the occurrence of any (serious) adverse events using patient open non-directive questionnaire, physical examination (including vital signs), and laboratory measurements. The safety analyses will be based on incidence evaluation of treatment emergent adverse events by preferred term and body system. Laboratory measurements will be compared to the normal laboratory ranges and to laboratory measurements obtained at Baseline Visit.

The final Study Report will be established at Month 6.

Evaluation Time Points

Safety and efficacy endpoints will be evaluated at each of the 3 follow-up visits during the 6-month follow-up period (notably at 2 weeks, 3 months and 6 months after study drug administration).

Statistical Analysis: Full Analysis Set (FAS) will be used for the selection of the most effective strength and for the superiority objective.

Primary Endpoint

The primary endpoint is the change between baseline and Month 6 of the Western Ontario and McMaster Universities (WOMAC® VA3.1 pain subscale (subscale A).

Primary study objectives are (i) the selection of the best JTA-004 strength and (ii) superiority assessment of the best JTA-004 strength efficacy to the reference or (iii) stop the trial at interim analysis for futility. They will be determined as follow:

- For selection of best JTA-004 strength, by comparing the different JTA-004 strengths to the reference with respect to the WOMAC® VA3.1 pain subscale score (mean differences between baseline and Month 3)
- For superiority assessment, by comparing the best JTA-004 strength and reference on the mean differences in WOMAC® VA3.1 pain subscale score between baseline and Month 6, assuming a mean between group difference of 7 mm in favor of the best JTA-004 strength (i.e., difference JTA-004 minus Reference of -7 mm) with a standard deviation of 10 mm.

The following hypothesis is stated to show superiority of JTA-004 to Reference:

H0: The difference in the mean change from baseline at Month 6 between JTA-004 and Reference is superior or equal to 0.

H1: The difference in the mean change from baseline at Month 6 between JTA-004 and Reference is inferior to 0.

The secondary efficacy endpoints are:

- WOMAC® VA3.1 pain subscale (WOMAC® subscale A) at Month 3
- WOMAC® VA3.1 total score over the time

Safety Analysis

All safety analyses will be conducted on the safety population and tabulated by treatment group.

[redacted]

[redacted]

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 Informed Consent Form (ICF) before any patients are enrolled. Before any protocol-required procedures are performed, the patient must sign and date the IRB/IEC-approved ICF.

Date and Version of the Study Protocol: September 23th, 2016 – Version 03

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event
BMI	Body Mass Index
bpm	Beats per minute
CE	Conformité Européenne
COMP	Cartilage Oligomeric Matrix Protein
eCRF	electronic Case Report Form
DCF	Data Clarification Form
DMP	Data Management Plan
EC(s)	Ethics Committee(s)
FAS	Full Analysis Set
G	Gauge
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Hyaluronic Acid
HCl	Hydrochloride
IA	Intra-articular
IB	Investigator's Brochure
ICF	Informed Consent Form
ISF	Investigator Site File
IUD	Intrauterine device
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MW	Molecular weight
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs

OA	Osteoarthritis
PP	Per Protocol
SA	Safety Analysis
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDV	Source Data Verification
SPM	Study Procedure Manual
SSO	Study Safety Officer
SOPs	Standard Operating Procedures
TMF	Trial Master File
VAS	Visual Analogue Scale
WHO	World Health Organisation
WOCF	Worst Observation Carried Forward
WOMAC®	Western Ontario McMaster University Score

DEFINITIONS OF TERMS

- **Case Report Form (eCRF):** a printed, optical or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each trial subject
- **Completed Patient:** a patient who completed all scheduled visits up to last scheduled visit (inclusive)
- **Contract Research Organisation (Monitor):** a person or an organisation contracted by the Sponsor to perform one or more of the Sponsor's trial-related duties and functions
- **Coordinating Investigator:** Investigator who is appointed by the Sponsor to coordinate work in a multicentre clinical study
- **Discontinued or withdrawn patient:** a patient who has been enrolled, screened, randomised, or treated but has withdrawn from the study before completion of the last scheduled visit
- **Double-blinding:** double-blinding is a procedure in which the patient, the Investigator, the monitor, and data analyst are kept unaware of the treatment assignments
- **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
- **Endpoint(s):** indicator(s) used for assessing the primary hypothesis of a study
- **Eligible patient:** screened patient (having signed and dated the informed consent form) who is considered eligible according to selection criteria
- **Enrolled patient:** patient who has dated and signed the Informed Consent Form
- **Ethics Committee (EC):** A review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical trial and is adequately constituted to provide assurance of that protection
- **Good Clinical Practice (GCP):** set of internationally recognized ethical and scientific requirements and standards as regards to 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 patients are protected

- **Informed consent:** process by which a patient voluntarily confirms his/her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form
- **Investigation Site:** any public or private entity or hospital 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.
- **Investigator's Brochure (IB):** compilation of the clinical and non-clinical data on the investigational medicinal product which are relevant to the study of the product in human subjects
- **JTA-004:** reconstituted JTA-004 finished product to be administered (2 ml or 4 ml) to osteoarthritic patients and combining high molecular weight hyaluronic acid and two active medicinal substances
- **Legally authorized representative:** individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial
- **Monitor:** While ICH GCP uses the term "Monitor" instead of Clinical Research Associate (CRA), the two terms are considered to be synonymous. A Monitor is a person employed by a Sponsor, or by a Contract Research Organization (Monitor) acting on a Sponsor's behalf, who monitors the progress of a clinical trial and ensures that is conducted, recorded, and reported in accordance with the protocol, written procedures, and the applicable regulatory requirements.

- **Patient:** an individual who participates in a clinical trial, either as a recipient of the investigational medicinal product or a member of the reference group
- **Randomisation:** process of assigning patients to the investigational medicinal product or reference groups using an established recognized statistical methodology to determine the assignment in order to reduce bias
- **Reference (treatment):** an investigational or marketed product (e.g., active control), placebo, used in the reference in a clinical trial
- **Screened patient:** patient who has dated and signed the informed consent form (enrolled patient) and who has performed the checking of the selection criteria
- **Screening failure:** screened patient but who is not eligible for the study after checking the selection criteria
- **Serious Adverse Event (SAE)**: any untoward medical occurrence or effect in a patient or clinical trial patient administered a medicinal product, which does not necessarily have a causal relationship with this treatment, and that, at any dose, 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 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.
- **Source data:** all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical trial, necessary for the reconstruction and evaluation of the trial
- **Source document:** printed, optical or electronic document containing source data
- **Sponsor:** individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial

- **Storage:** maintenance of the investigational medicinal product under appropriate controlled conditions until administration
- **Study Protocol:** document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical trial
- **Study Report**: document describing the design, execution, statistical analysis and results of a trial
- **Study Safety Officer (SSO)**: individual designated to perform the handling, notification, and reporting of safety issues
- **Suspected Unexpected Serious Adverse Reaction (SUSAR):** serious adverse reaction, the nature, severity, specificity, or outcome of which is not consistent with applicable product information (e.g., the Investigator's Brochure)
- **Treated patient:** patient to whom a treatment has been administered

1 INTRODUCTION

1.1 Osteoarthritis

The most common type of arthritis is osteoarthritis (OA) also known as degenerative joint disease. OA is a chronic, progressive musculoskeletal disorder characterized by focal areas of fibrillation, fissures, ulceration and full thickness loss of articular cartilage within synovial joints, associated with hypertrophy of bone (osteophytes and subchondral bone sclerosis) and thickening of the capsule. OA can affect any joint, but is most common and more painful in weight-bearing joints such as the knees and hips, but can also affect the hand, the spine, and more rarely the wrist, elbow, and shoulder joints (Manek and Lane, 2000). Clinically, the condition is characterized by joint pain, tenderness, limitation of movement, crepitus (grating, cracking or popping sounds in the joint), and stiffness after immobility and limitation of movement with occasional effusion and variable degrees of local inflammation. The pathological change, when severe, results in radiological changes (loss of joint space, subchondral sclerosis, cysts and osteophytes) (Manek and Lane, 2000).

1.1.1 Incidence of Knee Osteoarthritis

Worldwide, OA is the most common joint disorder. The incidence of OA increases with age. Men are affected more often than women among those aged below 45 years, whereas women are affected more frequently among those aged above 45 years (Petersson *et al.*, 2002). In developed countries, the prevalence of symptomatic knee OA is approximately 10% in men and 13% in women among adults 60 years of age or older (Zhang and Jordan, 2010). The prevalence of OA is expected to increase in the coming years as risk factors, such as an aging population and obesity, become more prevalent.

1.1.2 Aetiology of Osteoarthritis

The development of OA involves multiple systemic and local factors. Systemic factors include advanced age, female gender, and family history. Genetic factors are also thought to play a role in the development of OA, and different genes may be implicated in different types of arthritis. Local factors comprise overweight and obesity, joint injury, repetitive use of joints at work, participation in certain sports, joint laxity, abnormal anatomic alignment, muscle weakness and

atrophy (Felson *et al.*, 2000; Zhang and Jordan, 2010). Among all these factors, obesity and joint injury appear to be the strongest risk factors that have the potential for substantial impact on a population level.

1.1.3 Pathophysiology of Osteoarthritis

OA can be categorized into two main types of OA, which have differing causes: primary (idiopathic) OA or secondary OA. Primary OA is the most common type, has no identifiable cause and may be localized (involving only one or two sites) or generalized (affecting at least three sites) (Lajeunesse *et al.,* 2003). Secondary OA is caused by an underlying condition such as a joint injury, accumulation of calcium inside the joint, rheumatoid or other arthritis, metabolic or endocrine disorders, or congenital factors.

OA has previously been considered as a disease resulting from wear and tear of the joints; however, it can be more exactly described as a disorder resulting from several biochemical, biomechanical, inflammatory and immunologic factors (Lajeunesse *et al.,* 2003).

In healthy cartilage, there is a continual process of natural breaking down and repair of the cartilage extracellular matrix in joints. This process becomes disrupted in OA, leading to an abnormal repair response. The smooth surface of the cartilage begins to deteriorate and to become worn causing friction between the bones. If the cartilage wears down completely, the result will be bone to bone contact. As pieces of cartilage break off, the bones thicken and broaden, causing inflammation. This inflammation may stimulate new bone outgrowths called osteophytes to form around the joints. As the bones thicken and broaden, joints become stiff, painful, and may be difficult to move. Fluid may also build up in the joints.

The reason this normal repair process is disrupted is not known but collagenolytic enzymes are thought to contribute to the breakdown of cartilage. Cytokines and growth factors are thought to play a role in the pathophysiology of the OA. Interleukin-1 and Tumour Necrosis Factor-α may function to activate enzymes involved in proteolytic digestion of cartilage (Pelletier *et al.,* 1993). Growth factors such as Tissue Growth Factor-β and Insulin Growth Factor-1 may play a role in the body's attempts to repair cartilage through cartilage synthesis (Iannone and Lapadula, 2003).

1.2 Treatment Options for Osteoarthritis

There is currently no cure for OA. Treatment for OA focuses on relieving and controlling pain and symptoms, preventing disease progression, minimizing disability, and improving quality of life. Management of OA includes varied techniques and principles, both non-pharmacologic and pharmacologic in nature.

Most treatments consist of a combination of the following methods: education, weight loss, exercise, joint protection, physical and occupational therapy. A large number of drugs are also prescribed for patients with OA, typically used to reduce the inflammation, which in turn decreases pain and stiffness. These drugs include acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, topical analgesics, narcotic analgesics, glucosamine and chondroitin, tramadol and intra-articular (IA) corticosteroids (Manek and Lane, 2000). Although effective in reducing symptoms, NSAIDs are often associated with side effects sometimes described as costly for society. The primary safety concern with NSAIDs is the increase in gastrointestinal problems, including ulceration, haemorrhage, and perforation (Roth, 2011). Compared to traditional NSAIDs, COX-2 inhibitors claim to be more selective in their mode of action, with reduced gastrointestinal complications. However, an increased risk of cardiovascular complications has recently been attributed to various NSAIDs including COX-2 inhibitors (McGettigan and Henry, 2006). IA steroids are effective but usually have quite short duration of effect (Godwin and Dawes, 2004).

In severe cases, when the therapies above do not work, surgery may be considered as a last-resort effort to manage OA symptoms. Surgical interventions include total joint arthroplasty and joint lavage and debridement. There is no evidence demonstrating that lavage or debridement is more effective in relieving pain or improving function than non-surgical treatment (Moseley *et al.,* 2002). Arthroplasty has significantly reduced knee pain and increased functionality in patients who were severely incapacitated before surgery (Pendleton *et al.*, 2000). Prosthesis loosening and infection are among the complications that can occur.

1.2.1 Viscosupplementation

Although there are several non-surgical treatments available for the treatment of knee OA, their long-term use and their safety have not been systematically monitored. Viscosupplementation has been used in the treatment of symptoms associated with knee OA with a favourable safety

profile (Pagnano and Westrich, 2005). Viscosupplementation is an IA therapeutic technique for the treatment of knee OA based on the physiologic importance of hyaluronic acid (HA) in synovial joints. Its therapeutic goal is to address the cause of pain and to improve mobility of the joint by replacing the low elastoviscous osteoarthritic synovial fluid with high elastoviscous solutions of HA or its derivatives.

There are several different strengths of viscosupplements of widely different molecular weights. This difference of molecular weight (MW) is thought to be of importance with respect to the volume/amount and number of injections, the residue time in the joint and biologic effects (Huang *et al.,* 2010).

Based on many analyses, viscosupplementation is an effective alternative treatment for knee OA with beneficial effects on pain, function and patient global assessment. Moreover, it was shown that viscosupplements have more prolonged effects than IA corticosteroids (Bellamy *et al.,* 2009).

2 BACKGROUND OF THE STUDY

2.1 General Description of JTA-004

JTA-004 is a single administration enhanced viscosupplement developed for the treatment of knee OA. It is composed of three active substances:

Hyaluronic acid (HA), [redacted]. HA is a natural polysaccharide (glycosaminoglycan). The naturally occurring HA, as found synovial fluid for example, show highly elastoviscous properties and have protective, lubricating, shock absorbing, and structure-stabilizing effects. Since the elasticity and viscosity of synovial fluid are directly proportional to the content and integrity of HA, an IA injection of HA represents a rational approach for the management of knee OA. IA injection of JTA-004 is therefore intended to reproduce the natural composition of synovial fluid, and thus, to improve pain and joint function.

N-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine has known antalgic and anti-inflammatory properties (Sun *et al.*, 2013, Romero-Sandoval *et al.*, 2007, Zhang *et al.*, 2011; see section 2.2 Non-clinical Data) and human plasma provide gelification properties. These two active substances are expected to enhance the JTA-004 action.

For further information concerning the description of JTA-004, please refer to the Investigator's Brochure (IB).

2.2 Non-clinical Data

2.2.1 Anti-inflammatory properties of JTA-004

The anti-inflammatory properties of JTA-004 were shown [redacted] in three independent experiments.

[redacted]

[redacted]

[redacted]

2.3 Clinical Data

JTA-004 has not yet been administered to humans. However, clinical evaluation of similar products can be found in the IB.

2.4 Assessment of Anticipated Benefits and Risks

Based on the experience from other HA-based preparations, reasonably foreseeable risks linked to the product and the administration procedure can be identified. In particular, anticipated adverse drug effects are summarized in Section 8 of this protocol. Most of these effects are mild to moderate in nature, transient and can be avoided or limited by simple bedside procedures (e.g., applying ice on the injection site to limit local reactions).

Risks linked to Manufacturing

JTA-004 is manufactured according to the Good Manufacturing Practise (Eudralex Vol 4, annexes 1 and 13). The whole manufacturing process is also environmentally controlled. The finished product is controlled for sterility and identity.

Risks linked to the Administration Procedure

Reasonably foreseeable risks linked to the administration procedure (i.e., intra-articular injection) can be identified. Misuses or use errors, such as periarticular injection, may occur and are not different from the ones expected with commercially available HA preparations. Their occurrence, however, is expected to be very low since the product will only be administered by trained and experienced Independent Physician.

Risks linked to the Investigational Medicinal Product

JTA-004 contains three active substances: the hyaluronic acid, the human plasma and a α_2 adrenoreceptor agonist[1]. Most of the reported HA-related adverse effects, such as pain at the injection site and local joint swelling, are mild to moderate in nature, transient and can be avoided or limited by simple bedside procedures (e.g., applying ice on the injection site to limit local reactions). Hypersensitivity to HA has been reported; therefore patients with known hypersensitivity to HA will be excluded from the study at Screening.

Given the pharmacological effects of α_2 adrenoreceptor agonists, it is possible that administration of any of the tested JTA-004 strengths could induce transient hypotensive episode. "Instructions for Use" will therefore include protective measures such as monitoring the patient at the Investigation Site for 45 minutes post-injection. Preclinical toxicity studies have shown that JTA-004, up to 10 times the human injected dose, does not cause any toxicity, but only transient mild to moderate effects that disappeared 6 hours after injection. These effects were not considered as adverse effects due to their nature (Lewis *et al.,* 2002).
Residual risks have to be further estimated during the study.

Patient Benefit

During this trial, patients can receive either JTA-004 or the commercially available viscosupplement, Synvisc-One®. There is evidence that one single IA injection of Synvisc-One® reduces joint pain and improves function in patients with knee OA over a period of at least 6 months (Chevalier *et al., 2010*). JTA-004 is a HA-based preparation expected to act by the same mechanism as the currently available viscosupplements. However, compared to other HA-based preparations, JTA-004 contains active substances with gelification properties which has shown to stabilize HA and antalgic and anti-inflammatory properties. The clinical benefits expected from JTA-004 single IA injection are therefore a prolonged relief of OA symptoms. In conclusion, with the data collected to date, the anticipated benefits-risks balance of JTA-004 is favourable. A more precise estimate of this balance will be obtained after clinical trials.

[1] the alpha-2 adrenergic receptor agonist 2,6-Dichloro-N-2-imidazolidinylidenebenzenamine hydrochloride

3 INVESTIGATIONAL PLAN

3.1 General Study Design

The present study is a two-stage, prospective, multicentre, randomised, double-blind, controlled study comparing the safety and efficacy of JTA-004 single IA administration in patients with symptomatic knee OA to a reference HA preparation having shown superiority to placebo.

The main objectives of the study is to select the best among 3 different JTA strengths and demonstrate its superiority to a reference treatment with respect to knee pain at Month 6.

After signing the Informed Consent Form (ICF), patients, if eligible (according to the eligibility criteria, cf. Section 3.5), will be randomised on a 1:1:1:1 ratio into the JTA-004 or the reference groups. Treated patients will be followed up during 6 months with post-treatment assessments performed at 2 weeks, 3 months and 6 months.

Experimental design	Prospective, multicentre, double-blind, reference-controlled study
Number of centres	up to 15
Countries	Belgium
Number of Patients	116 patients (incl. 10% drop-out) for the interim analysis where sample size will be re-estimated based on first 3 months of follow-up data. 164 patients (incl. 10% drop-out) for the whole study.
Duration of Study	6 months of follow-up
Osteoarthritis Site	Knee
Osteoarthritis Type	Kellgren-Lawrence grade II and III
Treatment	JTA-004 50 (2 ml), JTA-004 50 (4 ml) & JTA-004 100 (2 ml) Reference (6 ml)
Procedures	JTA-004 and reference single IA administration performed ambulatory
Patient Allocation	1:1:1:1 randomisation schedule
Study Time Points	2 weeks, 3 months and 6 months after administration

Self-contained study

Data collection: Case Report Form (eCRF)

3.2 Study Objective

The objective of this study is to assess the safety and efficacy of JTA-004 single IA administration in patients suffering from symptomatic OA of the knee at the end of the study period (at Month 6).

This study is a prospective, randomized, double-blind controlled two-stage Phase II/Phase III trial including 3 test and 1 reference products to select the best test product and demonstrate its superiority compared to the reference treatment.

[redacted]

3.2.1 Primary Endpoint

The primary endpoint is the Western Ontario and McMaster Universities (WOMAC® VA3.1 pain subscale (subscale A): the individual changes in WOMAC® VA3.1 pain subscale score between baseline and Month 6 will be calculated and compared to the reference group.

3.2.2 Secondary Endpoints

The secondary efficacy endpoints are:

- WOMAC® VA3.1 pain subscale (WOMAC® subscale A) at Month 3
- WOMAC® VA3.1 total score over time

3.2.3 Exploratory Endpoints

[redacted]

[redacted]

3.2.4 Safety Endpoints

From the treatment visit to the end of the study period at Month 6, patients will be systematically assessed for the potential occurrence of any adverse events (AEs) and serious adverse events (SAE), related or not to the product or the procedure, using patient open questionnaire, physical examination (including vital signs), and laboratory measurements.

The final Study Report will therefore be established at Month 6.

3.3 Main Study Procedures

3.3.1 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 his/her legally authorized representative), including notably the following points:

- Purpose, objectives, and nature of the trial (including all performed procedures)
- Conditions under which the investigation are conducted
- Consequences and significance of the investigation
- Expected benefits and inconveniences and risks
- Treatments and probability for random assignment to each treatment
- Tests performed
- Right to receive the confirmed results of the tests performed, clearly explained

- 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 Patients, 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
- Medical confidentiality - Recording and protection of patient data
- Access and scrutiny of personal data and information during inspection by the Agencies and any other properly authorised 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 Principal Investigator (including all members of the his/her team and any other participants to the trial)

This detailed information will be given in both oral and written forms (Patient Information Letter and 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 legally authorized 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/Investigation Site, Sponsor, Sponsor's representatives, and/or the Monitor from liability for negligence.

The patient (or his/her legally authorized representative) will then be provided ample time 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 process), and to decide whether or not to participate in the trial. All questions about the trial will be answered to the satisfaction of the patient (or his/her legally authorized representative).

If the patient (or his/her legally authorized representative) agrees to participate, he/she will be invited to date and sign the ICF. One original copy of the ICF signed by the patient (or his/her legally authorized representative) and by the Principal Investigator (or the person who conducted the informed consent process) will be given to the patient (or his/her legally authorized representative). The other original copy duly signed will be kept in the Investigator Site File (ISF) at the Investigation Site.

The Principal Investigator will then complete and sign the eCRF, thereby attesting and recording that signed ICF has been obtained from the patient.

As soon as the ICF has been signed by the patient and the Principal Investigator, the "Patient Card" will be completed and given to the patient.

Note: The Sponsor has prepared a template of the ICF which embodies the ICH GCP required elements and any local relevant regulations to be disclosed for the consent to be legally effective. The Principal Investigator has the final responsibility for the final presentation of the ICF. The final version of the protocol and the Patient Information Sheet and ICF will previously be notified to the relevant Agencies and submitted to and approved and/or provided a favourable opinion in writing by the relevant ECs before the beginning of the trial. These documents (and the IB) may also need to be subsequently revised during the course of the investigation, 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 first be notified to the relevant Agencies and submitted to and approved by the ECs prior to any submission to the patients (and all concerned Principal Investigators and Investigating Sites) except when it is necessary to eliminate apparent immediate hazards to patients. The Investigator may not perform a procedure on a patient without new signed ICF if the procedure was not mentioned in the original ICF.

3.3.2 Randomisation and Blinding Procedures

Randomisation and Blinded Treatment Allocation

Patients will be randomised in a 1:1:1:1 ratio to JTA-004 groups or Reference group [redacted] according to a randomisation scheme through Interactive Web Response System

(IWRS). The IWRS will only be accessible through a secure website to authorised users with valid login and password.

Once the eligibility and participation of the patient has been confirmed:

- The IWRS will determine the treatment group of the patient and allocate a treatment number to the patient in order to associate a specific treatment (IMP or Reference) to a specific patient.
- A notification of the treatment number without reference to the nature of the treatment (blinded notification) will be sent to the Principal Investigator and Sponsor's representative.
- A notification of the treatment number with the nature of the treatment (unblinded notification) will be sent to the Sponsor's Production Manager in order to label the treatment with the treatment number but also to the local Pharmacist and the Independent Physician.

Treatment Preparation, Patient Treatment and Blinding of the Study

Not later than the day before the treatment Visit #2, the kit containing the treatment (IMP or reference product) labelled with the treatment number will be shipped to the Hospital Pharmacy. The IMP will be reconstituted by the pharmacist of the hospital at the request of the Independent Physician. The reference product does not need reconstitution but the Independent Physician must also require the preparation by the local. Before the injection time, the Study Nurse will pick up the reconstituted IMP or the reference product at the Hospital Pharmacy and bring it, into a blinding transfer box, to the Independent Physician.

Although shipping packages will be identical, JTA-004 and reference products will not be provided in the same primary packaging.

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

- The Investigators will be blind to treatment assignments with respect to the patient evaluation. They will recruit, include and assess patients during the whole study follow-up period, but will not treat the patients. Investigators will therefore not be aware of treatment assignment.

- Patients will be blind to treatment assignment, as the four patient groups will undergo the same intra-articular injection (performed by the Independent Physician). As the appearance of the resuspended JTA-004 is different from the reference, appropriate measures must be taken to ensure that the patient is unable to see the injected treatment during the injection procedure. The injection procedure will be identical in all patients.
- Only the Independent Physician and the local Pharmacist will not be blind to treatment assignments, as they will perform the reconstitution or the intra-articular administration of the IMP.

Unblinding is restricted to emergency situations and should only be used under circumstances in which knowledge of the treatment given during the trial is necessary for the proper treatment and medical care of the patient. In the case of medical emergency, decoding will be done for a patient by choosing the "Unblinding" option of the IWRS that allows the user to learn the nature of the treatment taken by a patient in. Under normal circumstances, this option is only available to Principal Investigators/Co-Investigators. In addition, the date of unblinding must be recorded in the appropriate place in the eCRF and signed by the Principal Investigator.

3.3.3 Procedures per Treatment Group

Patients will undergo during Baseline/Treatment visit (Visit #2) a single 2 ml or 4 ml IA administration of JTA-004 or 6 ml of reference treatment into the knee joint. The recommended needle size is a 21-gauge needle (or alternatively a 19-gauge needle) but the choice of the needle size is at the Independent Physician's discretion. The size of the needle must be recorded in the appropriate place in the eCRF.

After administration, the patient will be asked to remain at the Investigation Site for 45 minutes. For more information regarding the administration procedure of investigational medicinal products, please refer to Section 6 of this protocol.

3.4 Patient Evaluation

3.4.1 Clinical Evaluation

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

The following clinical assessments will be evaluated:

- WOMAC® VA3.1 (see details in section 5.3.1 and Annex 1): at each follow-up visit from the baseline/treatment visit to the end of the study follow up at Month 6, patients will be assessed using the WOMAC® Index for knee OA severity and symptoms. To this end, each Investigating Site will receive validated WOMAC® Indexes in the language of the patient and the WOMAC® Index User Guide in English.

- [redacted]

3.4.2 Biological Evaluation

At baseline/treatment, and 3 and 6 months after treatment, the effects of the investigational medicinal products on knee OA severity will also be explored [redacted] This method may be thus an opportunity to gather more information on the mode of action and efficacy of JTA-004.

3.4.3 Radiological Evaluation

The Principal Investigator or the radiologist must grade the severity of OA according to Kellgren-Lawrence Radiographic Score. For the purpose of this study, radiographic assessment is only required on the target knee [redacted]

3.5 Study Population and Selection

3.5.1 Eligibility

Prior to patient inclusion and randomisation, a Screening period is planned to allow verification of patient eligibility.

[redacted]

There is a random gender distribution in this study. The patients will not be selected according to their gender but according to inclusion and exclusion criteria as set out in this protocol. Since there are no known or expected gender differences in efficacy, and/or safety profile of the study products, no subgroup analysis with gender as a variable is planned.

Once randomised (allocation to either JTA-004 or reference group), patients will receive appointment for the single IA injection.

3.5.2 Inclusion Criteria

All patients must satisfy **ALL** the following criteria at study entry:

- Male/female aged between 50 to 79 years.

- Ambulatory (able to walk unassisted, the use of a crutch or a walking stick is allowed)
- Diagnosed with primary knee OA, fulfilling the following American College of Rheumatology (ACR) criteria at the target knee:
  - Pain ≥ 40 mm on a 0-100 mm VAS during the 3 days preceding the date of the Screening Visit (see Annex 2)
  - Morning stiffness not exceeding 30 minutes
  - Kellgren-Lawrence grade II or III (confirmed by X-ray within the last 6 months)
- Insufficient/failed response to analgesics and/or NSAID
- Willing and able to abstain from physical therapy of the knee and knee braces for the entire duration of study
- Capable to understand and comply with study requirements and to provide a written, dated, and signed informed consent prior to any study procedure for participation in the study and transmission of personal "anonymized" data

3.5.3 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

- Isolated symptomatic femoropatellar OA of the target knee
- History of trauma or surgery or arthroscopy at the target knee within 6 months before inclusion
- Concomitant inflammatory disease or other condition affecting the joints (e.g., rheumatoid arthritis, septic arthritis, inflammatory joint disease, metabolic bone disease, psoriasis, gout, microcrystalline arthropathies/chondrocalcinosis, Paget's disease)
- Any musculoskeletal condition (such as hip osteoarthritis, amputation, neurologic disorder) that would impede measurement of efficacy at target knee
- Target knee prosthesis planned within 12 months after the Screening Visit

Current or previous diagnoses, signs and/or symptoms

- Uncontrolled diabetes mellitus, end-stage hepatic or renal disease documented in the patient's file
- Current (or within the last 5 years prior to entering the study) history of solid or haematological neoplasia or bone marrow transplantation (except for basal cell carcinoma and completely excised squamous cell carcinoma)
- Other severe acute or chronic medical or psychiatric conditions or pre-dispositions or laboratory abnormalities, as judged by the Investigator
- Current or past history of coagulation disorders, as judged by the Investigator
- Hypersensitivity to any components of HA-based injection products
- History of hypersensitivity to human biological material including blood and blood derived products, potential excipients and residues from manufacturing process, documented clinically or by laboratory tests
- Hypersensitivity to avian proteins
- Life expectancy less than 6 months

Current or previous treatment

- Participation in another clinical study within 6 months prior to Screening
- Patients previously treated with JTA-004
- Treatment:
  - Within 6 months prior to Screening: intra-articular hyaluronic acid injection at the target knee
  - Within 2 months prior to Screening: intra-articular glucocorticoids at the target knee
- Current chemo-, radio- or immuno-cancer-therapy or immunosuppressive therapy
- Current anti-hypertensive medication the effects of which are known to be potentiated by a single dose of clonidine
- Current (or within 6 months prior to Screening) illicit drug abuse

Safety aspects concerning female subjects of childbearing potential

- Females who are pregnant, lactating or woman with childbearing potential (last menstrual bleeding less than 12 months ago) unwilling to use medically acceptable contraception, or women with childbearing potential unwilling to perform a pregnancy test before administration of study treatment.

Other exclusion criteria

- Body Mass Index (BMI) of 35 kg/m^2 or greater

3.7 General Overview of Visits and Procedures

An overview of the study assessments and procedures is given in Table 1 below. Study procedures are described for JTA-004 products and reference.

Table 1: *Detailed Schedule of Visits and Procedures – Double-blind phase*

[redacted]

[redacted]

4 DETAILED SCHEDULE OF VISITS AND PROCEDURES

Before any study-related procedure, the Principal Investigator (or a member of his/her team) will give, both in oral and written, detailed and comprehensive information regarding all aspects of the trial to the patient (including the Patient Information Sheet and ICF). After signing the ICF, the patient will be given a unique Patient Identification Number.

4.1 Screening Period (Visit #1)

Visit #1 will include the following procedures to be performed:

[redacted]

4.2 Randomisation/Baseline/Treatment Visit (Visit #2)

Baseline/Treatment (Day 0) Visit #2 [redacted] y. Before randomisation, the investigator or the study nurse will call the patient to confirm his/her participation to the study. Promptly after patient participation confirmed, the patient will be given a unique Randomisation Number and will be allocated to one of the four study arms (JTA-004 50 2ml or 4 ml, JTA-004 100 2 ml, or Reference) through IWRS platform.

During Visit #2, the following procedures will be performed:

[redacted]

During the whole study follow-up after IA of JTA or reference product, patients must not receive any IA treatment in the target knee (either hyaluronic acid or corticoids injection). If such IA injection is performed, reasons must be documented in the concomitant medications section and the patient must be withdrawn from study. The "Early Termination Form" must be completed in such case.

4.3 Follow-up Visit #3 (Week 2 [redacted])

During this visit, the following procedures will be performed:

[redacted]

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

4.4 Follow-up Visit #4 (Month 3 [redacted])

During this visit, the following procedures will be performed:

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

4.5 Follow-up Visit #5 (Month 6 [redacted])

During this visit, the following procedures will be performed:

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

5 RATIONALE FOR THE STUDY DESIGN

5.1 Study Rationale

Bone Therapeutics S.A. has developed an enhanced HA-based viscosupplement (JTA-004) with stabilising effects on the joint mechanical integrity. Compared to other HA-based preparations, the novelty of JTA-004 lies in its composition and formulation expected to extend its action, as JTA-004 includes active substances[6] with gelification properties and antalgic and anti-inflammatory properties. Single injection of JTA-004 is therefore intended to provide prolonged relief of OA symptoms.

The overall goal of JTA-KOA1 is to determine JTA-004 safety, select the best strength in terms of efficacy and compare it to an approved viscosupplement.

5.2 Types of Osteoarthritis

Knee OA is classified in four severity grades, from doubtful to severe, according to the Kellgren-Lawrence grading system. This categorical scale incorporates important radiographic features of OA (see Annex 5).

In order to have a study population as homogenous as possible and to avoid patients with doubtful and severe OA, the study will only include patients with Grade II and Grade III symptomatic knee OA.

5.3 Clinical and Biological Evaluation Tools

5.3.1 Clinical Evaluation

The usual tool to assess pain is the VAS. This 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 general health status in this particular study). In VAS, the symptom that a patient feels ranges across a continuum from no symptom

---

6 Human plasma and the alpha-2 adrenergic receptor agonist 2,6-Dichloro-N-2-imidazolidinylidenebenzenamine hydrochloride

(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 (see Annex 2).

WOMAC®

Clinical evaluation of the knee is usually performed using dedicated open questionnaires and/or scores, which have been developed and established in order to assess knee pain, knee stiffness, and/or knee function (physical disability) in patients with primary OA, but also for other knee diseases. These include the Lequesne and WOMAC® Scores.

Patients will be assessed using the WOMAC® Index. The WOMAC® Osteoarthritis Index is a tri-dimensional, self-administered, patient-centred health status questionnaire for knee disease severity and osteonecrosis symptoms (see Annex 1).

Although the Lequesne score is frequently used and cited in the literature, it presents a number of limitations and pitfalls regarding its use in clinical practice. Indeed, it has demonstrated its usefulness and efficacy as an outcome functional measure after hip surgery only (Lequesne *et al.,* 2003; Stucki *et al.,* 1998). By contrast, the WOMAC® Index, which allows a thorough evaluation of pain, stiffness, and function (through 3 subscales with a total of 24 questions), has been widely validated and used: it has been standardised and tested for reliability, validity, and responsiveness in patients with knee OA in various clinical settings, including both medical (pharmacological) and surgical management (total hip replacement) of patients (Bellamy, 2002; Bellamy, 2005; Bellamy *et al.,* 1988).

Moreover, and contrarily to the other knee scores, the WOMAC® Index is available not only in Likert scale format but also in VAS format. Indeed, VAS has been suggested to be more reproducible and sensitive compared to Likert scales (Gerich *et al.,* 2007).

As for primary endpoint, the WOMAC® Index pain subscale will be used.

However, the WOMAC® Index total score, stiffness and function subscales will be used as secondary endpoints.

The minimal clinically important difference (MCID) represent the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management

(Beaton *et al.,* 2002). For the WOMAC® Index pain subscale, the MCID, expressed in a percentage of the baseline is defined in the literature as a difference of 20% or 10 mm of the baseline (Ehrich *et al.,* 2000; Bellamy *et al*, 2005).

[redacted]

5.4 Rationale for Choice of Reference Group

Active comparators should be chosen with care. An example of a suitable active comparator would be a widely used therapy whose efficacy in the relevant indication has been clearly established and quantified in well designed and well documented superiority trial(s) and which can be reliably expected to exhibit similar efficacy in the contemplated active control trial (ICH E9). Optimally, this is demonstrated by finding that the active treatment intended for use as the active control was reliably found superior to placebo.

For these reasons, among the several commercially available HA preparations, Synvisc-one® was selected as reference in this clinical trial. Indeed, Synvisc-One® is an approved and well-established treatment of knee OA in Europe and USA. Three clinical trials have shown that Synvisc-One® is safe and effective by providing statistically significant and clinically relevant pain relief in patients suffering from knee OA. The first study (Conrozier et al., 2009) demonstrated that a single 6 ml intra-articular injection of Synvisc-One® is as safe and effective that multiple injection (2 ml, three time, one week apart) in providing statically significant, clinically relevant pain relief, as measured by WOMAC® A pain scores at 24 weeks. A change from baseline at 24 weeks of -34.9 mm (corresponding to a mean percentage change in pain from baseline of 54.7 %). The second study (Chevalier et al., 2010), a controlled randomised, multicenter, double-blind study, compares a single (6 ml) IA injection of Synvisc-One® to a placebo (PBS). This study demonstrated that a single 6 ml intra-articular injection of Synvisc-One® provides statically significant, clinically relevant pain relief, as measured by WOMAC® A pain scores over 26 weeks, with a modest difference compared with placebo (-3,0 mm, SEM 1,52, p = 0.047). An estimated change from baseline over 26 weeks of -21 mm (corresponding to a mean percentage change in pain from baseline of 36 %) is observed for Synvisc-One® versus an estimated change from baseline of -17,25 mm (corresponding to a mean percentage change in pain from baseline of 29 %) observed for placebo demonstrating that Synvisc-One® is reliably superior to placebo. The last study (Drieser et al., 2015) compared a high molecular weight hyaluronan (Ostenil®Plus) to Synvisc-One®. In this randomised, double-blind study, an estimated change from baseline after 26 weeks of -34.3 mm (corresponding to a mean percentage change in pain from baseline of 58.9 %) is observed for Ostenil®Plus versus an estimated change from baseline of -36.2 mm (corresponding to a mean percentage change in pain from baseline of 62.5 %) observed for Synvisc-One® demonstrating that both treatments provide statistically significant and clinically relevant pain relief.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND REFERENCE TREATMENT

6.1 Treatments Administered

6.1.1 Investigational Medicinal Products

The investigational medicinal products (3 different strengths: JTA-004 50 (2ml), JTA-004 50 (4ml) and JTA-004 100 (2ml)) will be provided [redacted]

6.1.2 Reference

The reference treatment, Synvisc-One®, is a sterile viscoelastic solution provided in a ready-to-use syringe. The six millilitre solution contains 48 mg sodium hyaluronate.

6.2 Treatment with Investigational medicinal products and reference

6.2.1 Reconstitution Procedure

[redacted] The reference product is provided in a ready-to-use syringe and does not need reconstitution.

6.2.2 Injection Procedure

[redacted]

[redacted]. The injection is accomplished following puncture through the skin and into the joint space. If resistance is encountered, redirection of the needle may be necessary. The use of local anaesthesia with lidocaine prior to the IA injection is at the discretion of the Independent Physician.

The injections will be performed by an Independent Physician who are very well experienced with this type of administration to limit the risk of periarticular administration. Products should be injected in the synovial space only and not into blood vessels, extra-articularly, or in the synovial tissue or capsule. If the whole volume of Investigation Medicinal Product cannot be injected, the reason must be documented in the eCRF.

The products are intended for single use and strict aseptic administration technique must be followed. For the reference, the syringe containing the HA solution should be used immediately [redacted] in order to guaranteed the sterility of the product.

If effusion is found in the knee upon needle placement in the joint space, it must be removed before lidocaine and JTA-004 or reference product is injected. [redacted]

The administration procedure is summarised in the Table 2 below:

Table 2: *Administration of the Investigational medicinal product*

	JTA-004	**Reference**
Product	JTA-004 50 & 100	Synvisc-One®
Route of administration	(Percutaneous) intra-articular administration	(Percutaneous) intra-articular administration
Single dose	2 or 4 ml	6 ml
Dosage schedule	One single dose per patient on Study Day 0 (Visit #2)	One single dose per patient on Study Day 0 (Visit #2)

6.2.3 Post-injection Procedures

After withdrawing the needle from the joint space, light pressure should be applied to the injection site, followed by application of a simple adhesive bandage. The patient will be asked to remain at the Investigation Site for 45 minutes post-injection under clinical and blood pressure monitoring. During this period, the blood pressure is monitored [redacted] after intra-articular injection. The blood pressure will be performed when the patient is sitting and one minute after standing up to control for hypotensive effect during the acute phase following the injection. The patient will leave the hospital if no clinical signs of hypotension are present.

The patient should be encouraged to rest the injected joint for 24 to 48 hours. Patients will be advised to wait the next day before returning to normal activities, drive a car or manage a machine. Typically there could be pain associated with the procedure. For post-administration pain management, it is recommended that patients rest and ice the injection site.

All AEs and clinical findings prior, during, and post-injection must be recorded. Patients experiencing pain and swelling at the target joint or any other AE will be instructed to contact the study staff.

6.2.4 Concomitant Medications

Throughout the clinical trial, the Investigator may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the exclusion criteria. If they are required, the patient will have to be withdrawn from the study.

Any medication will be recorded in the eCRF.

6.3 Study Follow-up

Safety and efficacy endpoints will be determined in all patients at each scheduled visit over the whole follow-up period.

6.4 Packaging and Labelling

Label text will be prepared to meet the requirements of the European Directive (2003/94/EC) and the local regulation, and to maintain the double-blind. All products will be labelled "For Investigational Use Only."

Regarding the packaging and labelling of investigational medicinal product, a study procedure manual (SPM) for the Principal Investigator including step-by-step instructions and detailed descriptions will be provided to each Investigator before the beginning of the clinical trial. Complete information and training of the participating healthcare professionals will also be conducted during the Site Initiation Visit.

Please refer to the SPM for the Principal Investigator for more details.

6.5 Storage

JTA-004 products are manufactured by Bone Therapeutics S.A., Gosselies, Belgium. [redacted]

[redacted]

[redacted]Opened or damaged packages or vials should not be used.

Synvisc-One®, manufactured by Genzyme Corporation, New Jersey, USA are provided in a syringe (no-needle co-packed with it) and should be stored below 30 °C and protected from sunlight and freezing. Opened or damaged packages or syringes should not be used.

6.6 Summary of Investigational medicinal products and Reference

A description of investigational medicinal products and reference is summarised in Table 3 below:

Table 3: *Identity of JTA-004 Investigational medicinal products and Reference*

	JTA-004	Reference
Active substances	Sodium hyaluronate [redacted] *N*-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine Human plasma	Sodium hyaluronate 48 mg
Volume	2 or 4 ml	6 ml
Strength	50 or 100	NA
Container	Vial	Ready-to-use syringe
Lot number(s)	Provided on the label	Provided on the label
Expiry date	Provided on the label	Provided on the label
Treatment Number	Provided on the label	Provided on the label
Manufacturer	Bone Therapeutics S.A.	Genzyme Corporation
Trade name	NA	Synvisc-One®
Storage requirements	[redacted]	below 30 °C

6.7 Tracking, Traceability and Accountability of Investigational medicinal products and reference

A tracking system allowing complete traceability of the (JTA-004 and reference) products at all stages will be established and maintained by the Sponsor, Investigator and Monitor.

The Sponsor will keep records to document the physical location of all products from shipment of products to the Investigation Sites until return or disposal.

The Principal Investigator (or authorized designee) must keep accountability records which shall include:

- the date of receipt
- identification of each investigational medicinal product or reference (lot number/serial number)
- the date of use
- patient identification
- the date of return of unused, expired or malfunctioning investigational medicinal products or reference

This tracking system would ensure that investigational medicinal products and reference are tracked and traced during from the order to patient administration, each step being systematically collected, verified, and recorded using specific Forms and Receipts.

The pharmacist of the hospital must ensure that the investigational medicinal products and reference are kept under secure conditions, with access limited to those authorised by the Investigator.

Products accidentally damaged during shipment or at an Investigation Site should be accounted for and documented. It should be noted that all empty vials of JTA-004 and syringes of reference will be kept and stored at each Investigation Site until Monitor verification visits and returned to the Sponsor for destruction once the accountability is performed. Disposal of hazardous material, i.e., syringes and needles, must be conform to applicable laws and regulations. The products must not be used outside the trial.

When the study is completed, all unused products at each Investigation Site will be returned to the Sponsor for destruction.

Finally, data and records required for full traceability will be kept by the Sponsor and Investigator for a minimum of 20 years after clinical use.

7 SAFETY ASSESSMENTS

7.1 Overview of Safety Parameters and Endpoints

The safety and tolerability of investigational medicinal products will be systematically investigated throughout the whole study period. AEs will be collected and reported from the time the patient signs the informed consent until study completion. Patients will be evaluated at each visit for the potential occurrence of any AE/SAE using the following safety criteria listed in the table below. Definitions of AE and SAE are given in Section 8.1.

Table 4 below shows how the safety endpoints of this study are related to the study objectives. Assessments and measurements will be carried out at the times specified in the study Flow Chart (see Section 3.6).

Table 4: *Overview of Safety Parameters and Time Points*

[redacted]

7.1.1 Medical History and Demographics

Medical history must be obtained at Screening. The information will be recorded on the eCRF relating to any prior or existing medical conditions/surgical procedures.

The patient will be asked to provide his/her medical history with specific dates. Those conditions reported will be compared to the inclusion and exclusion criteria for the study. Specific attention will be paid to the patient's previous history with respect to exclusionary conditions, procedures, and surgeries.

7.1.2 Vital Signs

Vital signs [redacted] will be measured [redacted].

[redacted]

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

7.1.3 Physical Examination

[redacted]

[redacted]

[redacted].

7.1.4 Laboratory Safety Measurements

Any sample testing will be done in line with the consent of the individual patient.

[redacted]

[redacted]

[redacted]

Table 5: *Overview of Collected Volumes for Blood Analyses*

[redacted]

7.2 Other Safety Measurements

7.2.1 Pregnancy Test

Women with childbearing potential will undergo a urine pregnancy test at Visit #1 and #2. Pregnancy tests will be provided by the Sponsor, performed on site according to manufacturer's instructions, and results will be recorded in the eCRF.

Patients will be carefully screened to ensure that all women with childbearing potential have used a reliable method of contraception for at least 6 weeks prior to study inclusion (Screening Visit) and will use the reliable method of contraception during the whole study period. Reliable contraceptive methods include orally administered hormonal contraceptives, surgical intervention (e.g., tubal ligation), and IUD. Women who cannot comply will not be enrolled in the study. Women of non-childbearing potential must confirm that they are surgically sterile, or have been postmenopausal for at least 1 year prior to study treatment.

These information will be recorded on the Medical History page of the eCRF.

7.2.2 Additional Safety Examinations and Procedures

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

8 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject who has been administered a pharmaceutical product and/or any investigational medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended signs (including any abnormal laboratory findings), symptoms, or disease temporally associated with the use of a medicinal product, without any judgment about causality. Adverse events will be graded with respect to intensity and classified as either serious or non-serious according to the World Health Organisation Classification.

All disease signs and symptoms experienced by the patient will be recorded on the eCRF from the time of the patient signs the ICF until completion of the final study visit.

If clinically significant worsening of the patients' physical condition is noted, the changes will be documented as AE on the AE Page of the eCRF. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care.

8.1.2 Serious Adverse Event (SAE)

An SAE is defined as any AE or 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 hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Notes

Life-threatening means that 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.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Congenital anomaly means any physiological or physical defect observed in a child born from a mother who participated in the current study and who became pregnant during the course of this study.

8.1.3 Severity and Seriousness

AEs will be graded with respect to their severity and seriousness according to the World Health Organisation Classification.

Table 6: *Classification of Adverse Events*

Severity	*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 adverse event that led to: – death, – serious deterioration in health of the patient, that either resulted in 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function, or 3. in-patient or prolonged hospitalisation, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, – foetal distress, foetal death or a congenital abnormality or birth defect
	Non-serious	Any other adverse event

To avoid 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 severity (intensity) 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.

8.1.4 Causal Relationship towards the Investigational Medicinal Product

In practice, determination of the causal relationship between an AE and the investigational medicinal product must be made by the Investigator by answering the following questions:

"Do you consider that there is a reasonable possibility that the event may have been caused by the investigational medicinal product?"

according to the following definitions:

- Yes: the relationship of the AE and the use of the product can be definitely established.
- Possible: there is no clear relationship between the AE and the use of the study product; however, one cannot definitely conclude that there is no relationship.
- No: there is no relationship between the AE and the use of the investigational medicinal product. This may include but is not limited to the incident being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the patient experienced.
- Unknown: the relationship of the AE and the use of the product is not assessable

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.

8.1.5 Outcome of Adverse Events

The Investigator will be asked to indicate the outcome of the AE using the following categories: Resolved without sequelae, Resolved with sequelae, Death, or Ongoing. The Investigator should use medical judgment to compare the reported AE to similar type events observed in clinical practice.

Below are the applicable guidelines for outcome assessment:

- Resolved without sequelae: the AE has resolved without residual symptoms
- Resolved with sequelae: the AE has resolved, however, residual consequences will persist
- Death: the AE ended with death
- Ongoing: the AE is not resolved yet

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.

8.1.6 Adverse Drug Reaction (ADR)

Adverse Drug Reaction (ADR): any untoward and unintended response 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)

8.1.7 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.

8.2 Identifying Adverse Events

The occurrence of AE/SAE (related or not to product or study procedure) will be assessed by non-directive questioning of the patient from Visit #1, and each other visit searching for any changes in health status (e.g., "Have any adverse events, serious adverse events occurred since the last visit?") (see Table 7 below).

***Table** 7: Observation Period for the Occurrence of AE and SAE*

Start of Study AE/SAE Observation Period	Visit #1 (ICF signature)
End of Study AE/SAE Observation Period	6 months after treatment (Study completion)

Furthermore, any events volunteered by the patient during or between the follow-up visits, or detected through observation, physical examination (including 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 AEs, complaints, or objective changes in their well-being to the Investigator or clinic personnel, regardless of the perceived relationship between the event and the investigational medicinal product.

In the event of an AE/SAE, the Investigator will immediately initiate appropriate therapy and management according to his/her medical judgment, and current good medical practice and will decide whether the patient must be withdrawn from the study or not. The patient must be followed up by additional examinations according to the medical judgment of the Investigator, until the AE/SAE and/or abnormal condition is resolved or the Investigator deems further observations or examinations are no longer medically indicated. Any medication administered for the treatment of an AE should be recorded in the patient's eCRF.

8.3 List of Foreseeable Adverse Events and Anticipated Adverse Drug Effects

There are no known adverse events related to the use of JTA-004 products at this stage as the products have not yet been administered to humans. However, based on experiences from other HA preparations for knee OA, foreseeable adverse events related either to the product or to the procedures can be determined. A summary of foreseeable adverse events and their likely incidence based on clinical data from other HA-based viscosupplements is given in the Table 8 below:

Table 8: *Summary of Foreseeable Adverse Events*

	AE	**Likely Incidence***
Local AE	Arthralgia	1/10
	Joint stiffness	1/100
	Joint effusion	1/100
	Joint swelling	1/100
	Injection site pain	1/100
	Joint warmth	1/100
	Local haematoma	1/100
	Infectious complications	1/100
	Local skin reaction	1/100
	Pseudosepsis	1/10 000
	Injection site haemorrhage	1/10 000
Systemic AE	Back pain	1/100
	Cold symptoms (stuffy nose, sneezing, sore throat)	1/100
	Nausea	1/100
	Fatigue	1/100
	Paraesthesia	1/100
	Headache	1/1000
	Allergic reactions	1/10 000
	Transient hypotension	Unknown

** Based on clinical data from other HA-based viscosupplements.*

8.4 Reporting of Safety Issues

8.4.1 Reporting Events to the SSO by the Principal Investigator

All the following events are considered reportable events:

- any SAE
- new findings/updates in relation to already reported events

All reportable events must be notified by the Investigator to the Study Safety Officer (SSO).

SAEs will be documented on the SAE Report containing a detailed written description of the event.

SAE Reports Forms should be completed, signed and sent by the Investigator not later than **within 24 hours of event occurrence or awareness** to the SSO by e-mail [redacted] who will inform the Sponsor of the safety event occurrence.

Briefly, the SAE Report Form will include the following information and differentiated assessment:

- Patient Identification Number
- Investigation site and country
- Event: organ system
- SAE status and description
- Date of event onset and event resolution
- Outcome (recovery with or without sequelae, ongoing, death)
- Action taken (none, patient discontinuation and withdrawal from the study, change in concomitant medication(s) and/or new medication(s), inpatient hospitalisation or prolongation of existing inpatient hospitalisation, non-drug therapy given, other)
- Criteria for seriousness (death, life-threatening, medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure, permanent impairment of a body structure or a body function, new or prolonged hospitalisation, congenital abnormality or birth defect), and severity (mild, moderate, severe)
- Assessment of relationship to the investigational medicinal product (evaluated as yes, possibly, no)
- Assessment of relationship to procedures, including the treatment injection and blood sampling (evaluated as yes, possibly, no)

8.4.2 Reporting Events to ECs and Agencies by the SSO

The SSO is responsible for reporting SAEs received from Investigators to the ECs and Agencies, while blinding will be preserved for both Principal Investigators and Sponsor unless it is considered necessary in the interest of research patient safety.

Any SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients, users or other persons or a new finding are to be recorded and reported immediately, **but not later than 7 calendar days** after awareness by the SSO.

Any other reportable event as described above is to be recorded and reported immediately, **but not later than 15 calendar days** following the date of awareness by the SSO. The report must be provided to all Agencies relevant to all states in which the trial is taking place.

8.4.3 Serious Adverse Event Stopping Rule

In case of SAE occurs, which have not been identified in nature, severity or frequency in this protocol or in the IB and, which are thought to be possibly related to investigational medicinal products and are considered to be a health risk for all participating patients, Bone Therapeutics S.A. may decide in consultation with the Investigators to postpone treatment of newly included patients until the Investigators and Bone Therapeutics S.A. have thoroughly investigated the event(s) and conclude that continuation of the trial is justified.

8.4.4 Safety Data Monitoring

The occurrence of AEs and SAEs will be monitored during the whole study period on an ongoing basis by the SSO and the Sponsor. The Sponsor will also receive from the SSO a regular detailed updated listing of all AEs and SAEs.

8.4.5 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established to assess the safety and efficacy data endpoints at intervals. This board will recommend to the Sponsor whether to continue, modify or stop the trial. Further information concerning the DSMB can be found in the SAP.

8.5 Management of Safety Issues

8.5.1 Procedure in Case of Pregnancy

All pregnancies occurring during the trial (including both patient pregnancy and patient's partner pregnancy) will be systematically reported within 24 hours of diagnosis to the SSO and Monitor (a Pregnancy Form will be immediately completed, with subsequent urgent notification).

If there is a pregnancy during the study period, the patient must be followed and the outcome of pregnancy must be reported to the SSO and Monitor. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Any pregnancy will be handled as an SAE regardless the relationship between the treatment and the event. Any complication arising during pregnancy will be recorded as an AE/ADE 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 SSO.

If the outcome of pregnancy is:

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

8.5.2 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 (SSO):

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 Card" with the

name and surname and the Patient Identification Number, Title and EudraCT Number of the study, type of treatment received 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 Investigation 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 involved in a clinical trial and that he/she can contact the Investigator for more relevant information. Patients will be instructed to carry this card around at any time during the study.

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

Hotline - Phone Number: [redacted]

Hotline - E-mail: [redacted]

8.6 Long-Term Safety Reporting 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 Patient Premature Discontinuation

Notification of patient study discontinuation (and reasons for discontinuation) will be communicated to the Monitor and/or the Sponsor by the Investigator as soon as possible. The Investigator will document the circumstances for premature discontinuation in the patient's eCRF 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 it 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 eCRF.

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

Any patients may be withdrawn from the study at the Investigator's discretion in case of a safety concern. However, patients can be withdrawn from the study for AE/SAE (including notably clinical and/or laboratory events) only if the Investigator has clearly determined that the patient's withdrawal would reduce safety risks. In this case, the AE Page in the eCRF 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 eCRF. Particularly, the patient must be carefully questioned for the possible occurrence of any AE/SAE.

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

The Investigator or the Sponsor can terminate the study at any time for non-compliant patients.

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

Efforts must 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/SAE. All efforts to re-contact patients will be documented in the source documentation and the eCRF.

- ***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 eCRF 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 eCRF and source documents.

9.2 Procedure for Patient Premature Discontinuation

In case of premature discontinuation and whenever possible, Investigators will ask patients to perform Visit #5 (Exit Visit) as the Premature Discontinuation Visit. At the end of the Exit Visit, the Investigator will declare premature discontinuation in the eCRF. If study participation is terminated due to an AE possibly related to the study treatment or trial-related procedures, the patient 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 eCRF.

9.3 Replacement of Patients

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

9.4 Premature Termination of the Clinical Trial

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

- Safety issues
- Following a decision of the Sponsor
- Following a decision of the Agencies or the ECs

For the first three options, the ECs and Agencies must be informed.

10 STATISTICAL CONSIDERATIONS AND METHODS OF ANALYSIS

[redacted]

10.1 Analysis Populations

Four treatment groups including the reference and JTA-004 groups will be studied and compared. Comparisons with respect to reference will be performed in a superiority design.

Patient populations are defined as followed:

- The safety set (SAF) will include all treated patients.
- The Full Analysis Set (FAS) will include all randomised and treated patients.
- The Per-Protocol (PP) set will include all patients of the FAS without any major protocol deviation.

Demographics, baseline characteristics and efficacy variables will be analysed using the FAS. These analyses will be performed as randomised and treated.

The FAS will be considered as primary cohort for the selection of the best JTA-004 product and for the superiority analysis. Primary criterion and corresponding variables will be analysed in the FAS and in the PP.

All safety variables will be analysed on an as-treated basis using the SAF.

10.2 Study Objectives

Primary study objectives are (i) the selection of the best JTA-004 strength and (ii) the superiority assessment of the best JTA-004 strength efficacy to the reference. They will be determined as follow:

- For selection of best JTA-004 strength, by comparing the different JTA-004 groups to each other with respect to the WOMAC® VA3.1 pain subscale score (mean differences between baseline and Month 3) based on the point estimates and the 90% confidence intervals,
- For superiority assessment, by comparing the best JTA-004 strength and reference on the mean differences in WOMAC® VA3.1 pain subscale score between baseline and Month 6.

10.3 Primary Endpoint

The primary endpoint is the change between baseline and Month 6 of the Western Ontario and McMaster Universities (WOMAC® VA3.1 pain subscale (subscale A)).

The WOMAC® Index pain subscale is a standardised and validated methodology for assessing pain associated with OA and is often used as a primary endpoint in studies for treatment of this disease (Bellamy *et al.*, 1988).

10.4 Secondary Endpoints

The secondary efficacy endpoints are:

- WOMAC® VA3.1 pain subscale (WOMAC® subscale A) at Month 3
- WOMAC® VA3.1 total score over time

10.5 Exploratory Endpoints

[redacted]

[redacted]

10.6 Safety

From inclusion (signing of ICF) to the end of the study follow up at Month 6, patients will be systematically assessed for the potential occurrence of any (serious) product or procedure related adverse events using patient open questionnaire, physical examination and laboratory measurements.

Safety will be assessed using the following variables:

- AE and SAE
- Vital signs and physical examination
- Laboratory analyses
- Concomitant medications

The final Study Report, including assessment of both safety and efficacy endpoints, will be established at Month 6.

10.7 Statistical Analysis

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

Categorical data will be presented using counts (number and number of non-missing data) and percentages.

All tests will be conducted at a 5% two-sided alpha level of significance unless otherwise stated.

10.7.1 Patients Dispositions

All enrolled patients will be accounted for. All post-inclusion discontinuations will be summarised by time of, and reason for, discontinuation. The number of patients screened and not included will be presented with the main reason for their non-inclusion.

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

- Total number of patients enrolled

- Number (percentage) of patients completing the study
- Number (percentage) of patients prematurely discontinued from study
- Primary reason for premature discontinuation
- Number of patients in the SAF
- Number of patients in the FAS
- Number of patients in the PP

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

10.7.2 Protocol Deviations

Patients presenting major deviation will be excluded from the PP. Major protocol deviations will be as follows:

- Violation of inclusion/exclusion criteria
- Missing WOMAC® subscale A score at baseline and/or at Month 6

Major and minor protocol violation will be precisely defined. Frequency and percentages of patients with protocol deviations will be tabulated.

10.7.3 Demographics and other Baseline Characteristics

Descriptive statistics of demographics, and other baseline characteristics as well as medical history will be presented for all included patients. In addition, a summary of demographic and baseline characteristics will be presented by Investigation Site.

10.7.4 Medical History, Concomitant Medications

Previous and concomitant medications will be summarised for all enrolled patients.

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 preferred term according to the WHO Drug Dictionary (WHO DD) 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). Medical history will be summarised for all included patients, 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.

10.7.5 Primary Endpoint

The mean change in the WOMAC® VA3.1 pain subscale score of JTA-004-treated patients between baseline and Month 6 will be compared to the mean change in the WOMAC® VA3.1 pain subscale score of the reference-treated patients between baseline and Month 6.

The following hypothesis is stated to show superiority of JTA-004 to Reference:

H0: The difference in the mean change from baseline at Month 6 between JTA-004 and Reference is superior or equal to 0.

H1: The difference in the mean change from baseline at Month 6 between JTA-004 and Reference is inferior to 0.

This hypothesis is expressed mathematically by:

H0: $\text{Mean}_{\text{JTA-004}} - \text{Mean}_{\text{Reference}} \geq 0$ versus

H1: $\text{Mean}_{\text{JTA-004}} - \text{Mean}_{\text{Reference}} < 0$

10.7.6 Secondary [redacted] Endpoints

For the analysis of the secondary endpoints,

- WOMAC® VA3.1 pain subscale (WOMAC® subscale A) at Month 3
- WOMAC® VA3.1 total score over time

groups will be compared using a parametric or non-parametric ANCOVA (according to the normality of data and the homogeneity of the variances) with the following factors: baseline value and group. Repeated measures analyses will be performed on longitudinal data.

In each group separately, the evolution of each parameter between baseline and each time point will be described using the number of observed values, mean, standard deviation (SD) 95%-confidence intervals.

[redacted]

Categorical data will be presented using counts (number and number of non-missing data) and percentages.

10.7.7 *Safety Analysis*

All safety analyses will be conducted on the SAF and tabulated by treatment group.

AE/SAE

AE/SAE will be coded using the 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 AE/SAE will be compared between the groups using chi-square or Fisher's exact tests (as appropriate).

An analysis of following parameters will also be performed:

- Treatment-emergent (S)AE (occurring or worsening after treatment)
- (S)AE leading to premature withdrawal

Other safety variables

[redacted]

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

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

10.8 Randomisation

Patients will be randomised in one of the three JTA-004 groups or in the reference group according to a 1:1:1:1 ratio using IWRS.

10.9 Sample Size Estimation

The sample size calculation for the superiority trial for the primary endpoint – change in WOMAC® VA3.1 pain subscale from baseline to Month 6 - is based the following assumptions:

- The mean pain difference of patients treated with the JTA-004 and those treated with the reference treatment is assumed to be -7 mm (i.e. the mean JTA-004 treatment is 7 mm better than the reference). The absolute mean difference is set to 7 mm which is below the accepted MCID of the WOMAC® VA3.1 pain subscale, which is 10 mm (Ehrich *et al.*, 2000; Bellamy *et al.*, 2001);
- The standard deviation of the mean pain difference between the two treatments, estimated from the Borrás-Verdera *et al.*, 2012 and Pavelka and Uebelhart., 2011 data, are in the range of 4.7 to 6.6 mm for sample sizes between 48 and 24, respectively. To ensure maximal power, a standard deviation value of 10.5 was used for sample size estimation.);

Under the scenario of a mean between group difference of -7 mm (i.e., JTA-004 is better than control by a mean of 7 mm) with a standard deviation of 10.5 mm, thirty-seven (37) patients per group are required for analysis, reaching a power of 80% to test for superiority, keeping the type I error at 0.05 (two-sided). This would allow collecting enough efficacy data per group while avoiding exposing too many patients.

The level of drop-out is estimated to 10%. Thus 41 patients per group have to be included.

As recruitment will continue in all 4 treatment groups until the final analysis, the maximum total number of included patients will be 164 (4 x 41).

10.10 Methods to Be Used to Handle Missing Values

The following imputation will be made in case of missing data:

- Missing data due to treatment-related AE leading to study withdrawal will be handled using the Worst Observation Carried Forward (WOCF) method: the patient's worst observation from scheduled or unscheduled visits will be used to replace his/her missing values after study withdrawal.
- Missing data due to any reason other than treatment-related AE leading to study withdrawal will be handled using the Last Observation Carried Forward (LOCF) method: the patient's last observed value from scheduled or unscheduled visit will be used to replace his/her missing values after study withdrawal.
- Missing data in-between two adjacent non-missing values will be handled using the mean-in-between method: the mean of the two (before and after) adjacent values will be used to replace his/her missing value.
- If there are more than one missing values in-between, the LOCF approach will be used: the patient's last observed value from scheduled or unscheduled visit will be used to replace his/her missing values.

10.11 Multiplicity

This is a 2-stage design with an interim analysis. In order to guarantee the experiment-wise error probability of 5%, the p-values of the test will be adjusted according to the Dunnett method (Koenig *et al.,* 2008;). With two groups in the final superiority analysis the confidence intervals will be calculated using the Dunnett-corrected t-value, which is 1.99 instead of the unadjusted t-value of 1.96.

The multiplicity for the secondary endpoints will be controlled using Hochberg's step-up-method (Hochber, 1988).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.13 Independent Data Monitoring Committee

10.13.1 Members

The IDMC will consist of 2 persons who are not involved in any kind in the study. One person will be a statistician and one person will be a Rheumatologist.

10.13.2 Responsibilities

The members of the IDMC are responsible for the data analysis and medical interpretation concerning clinical relevance and toxicity of the interim analysis. They will summarize the results and give a written report to the sponsor.

10.13.3 Study Data to be sent to the IDMC

[redacted]

[redacted]

[redacted]

10.13.4 Unblinding Procedure

To ensure the overall blinding of the study, the treatment of patients included in the interim analysis will be unblinded by the Independent Data Monitoring Committee (IDMC, see 7.5.1).

The statistician of the IDMC will receive the sealed envelope containing the complete randomization list. Arrival has to be confirmed in writing (confirmation by e-mail will be acceptable). He will extract the medication numbers included in the interim analysis and perform the statistical analysis as described above.

The IDMC will not disclose any information regarding the contents of the randomization list to the sponsor.

10.13.5 Results

The results of the interim analysis will be sent to the Sponsor.

11 STUDY MANAGEMENT

11.1 Source Documents/Data

Each Investigation 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, certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source documents are printed, optical or electronic document containing source data. They may include, but are not limited to, patient's medical records, hospital charts if any, clinical and office 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 when applicable.

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

- 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 Process
- 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 relevant history and physical examination
- Results of blood pressure, heart rate, respiratory rate and body temperature
- Results of urine pregnancy test (only for female with childbearing potential)
- Results of radiographs when applicable

- Laboratory results notes/reports
- All concomitant medications and concurrent procedures
- Occurrence and status of any AE and SAE
- The date the patient exited the study, with a note as to whether the patient completed the study or the reason for discontinuation

The questionnaires are to be completed directly by the patient. The original pages, considered as source data, will be kept and filed on site (in the ISF).

All data captured for this study are to be recorded in the patient's notes first and then entered in the eCRF.

11.2 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 non-compliance in the future inclusions, if applicable.

During the course of the study, on-site monitoring visits and regular contacts with the Investigation Sites will be conducted by the Monitor 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 protocol, ICH-GCP, and all applicable regional and national regulatory requirements (see the reference documents in Section 12).

For instance, the following aspects will be closely verified:

- Procurement of signed and dated ICF
- Patient rights, including protection of privacy and confidentiality of personal data and medical records, wellbeing, and safety
- Patient recruitment, eligibility, selection, and inclusion
- Study procedures, including laboratory tests, investigation-related procedures and imaging procedures, if any
- Investigational medicinal product receipt, verification, and final delivery by the Pharmacist
- Investigational medicinal product receipt and verification by the Investigator
- Investigational medicinal product accountability and traceability
- SAE notification and reporting
- Emergency and pregnancy procedures
- Data generation and collection processes
- Accuracy of data collected and recorded in the eCRF
- Facilities and Site staff
- ISF (and other on-site source documentation)

Any detected non-compliance with the 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 and a Note to File, when applicable. This log will include the patient identification number, the date of deviation occurred and a summary of the deviation. All protocol deviations that have occurred during the study should be classified as minor or major. A patient with a major deviation is not included in the PP.

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 eCRF.

Following each monitoring visit, a follow-up letter will be sent to the Investigator detailing any action required by either the site staff or the Monitor. Any action 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.

The study site may also be patient to quality assurance audit by the Sponsor as well as inspection by appropriate Regulatory Agencies.

Investigators shall provide a curriculum vitae or equivalent. The curriculum vitae shall give name, date/place of birth, address, and place of work, and shall show the training, appointments, and any other information that will confirm the suitability of the clinical Investigator to be responsible for the clinical trial. All Investigators or other responsible people should be listed together on the "Site Signature and Delegation log". This log, kept up to date in the Investigator Site File, 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.

11.3 Source Documents/Data Verification

To ensure that data in the eCRF are accurate and complete, and in accordance with patient source documents and other source data (e.g., laboratory results reports), 100% of source data verification (SDV) will be performed by the Monitor on all data and eCRF including but not limited to SAE Forms and pregnancy-related documents, consisting in a comparison of the source documentation data with the eCRF and other records relevant to the study. This will require direct access to all original records for each patient.

For the patient questionnaires, 100% SDV will be performed by the Monitor on site. Following this SDV, any errors (discrepancies) greater than 3mm 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 informed consent and the presence on file of the signed and dated ICF will be verified for all patients screened, whether or not they were eligible.

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

As some data will be directly entered into the eCRF, the eCRF will be considered as source document for these data. The "Location of Source Data" 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 study and all results of evaluations will be recorded in the eCRF. The eCRF will be completed for each patient screened in the trial. For screening failure patients, only the demographic data, the inclusion and exclusion criteria and the reason of the screening failure must be kept. They will be completed as soon as possible after the patient visit.

Usually the Investigator enters all recordings in the eCRF, but the recording of data in the eCRF may be delegated by the Investigator to a designated representative (should be documented on the "Site Signature and Delegation Log"). The information recorded by the Investigator in the eCRF should preferably be in English. The eCRF must be signed and dated by the Investigator who takes responsibility for the punctuality, completeness, consistency, accuracy and legibility of the data reported to the Sponsor in the eCRF. The eCRF and related source data will be made available by the Investigator for data verification at each scheduled monitoring visit.

The completed original eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorised representatives of appropriate Agencies, without written permission from the Sponsor. Completed eCRF and SAE/Pregnancy-related documents will be collected by the Monitor during monitoring visits for analysis and filing. All original eCRF should be kept in the Sponsor's file. A copy of all these documents will be stored in the Investigator's archives after completion or discontinuation of the trial for duration of 20 years according to Sponsor's SOPs, and applicable laws.

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 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.

11.6 Audits and Inspections

Authorised representatives of the Sponsor, Monitor, Agencies, 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 investigation-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).

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

The presence of the Monitor on 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 Monitor 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, Agencies and/or ECs may wish to inspect their medical records.

Any results and information arising from the inspections by the Agencies and/or ECs will be immediately communicated by the Investigator to the Sponsor or its representative(s).

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 Sponsor, Agencies 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, legibility and accuracy of the data being reported.

11.8 Training of Staff

In addition, 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 efficacy of the study will be provided to the staff involved. The Investigator must inform the Monitor, in a timely manner, of any change in the study site staff.

11.9 Changes to the Protocol

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

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

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

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

- The safety, physical health, and mental integrity of the patients;
- The scientific value of the trial;
- The conduct or management of the trial;
- The quality and/or safety of any investigational medicinal product used in the trial.

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

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 well-being of human subjects
- Ethical principles for medical research involving human subjects
- Good Clinical Practice (GCP) regarding the conduct of clinical trials and investigational medicinal products for human use
- Clinical safety data management, notification, and reporting within the context of clinical trials
- 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 following reference documents:

- World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research involving Human Patients (with amendments)
- Charter of Fundamental Rights of the European Union (2012/C326/02)
- 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 (January 25, 2013, 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 - (September 1997, 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 1998, 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
- ICH Topic E2 A - Clinical Safety Data Management : Definitions and Standards for Expedited Reporting - (November 1994, 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 (June 2011, ENTR/CT3)
- Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance, Clinical Trial Module) - European Commission (April 2004, ENTR/CT4)
- 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)
- 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 Patient Information Sheet and Informed Consent Form (ICF), other written information to be provided to patients (such as the Patient Study Card), patient recruitment procedures, Investigator's Brochure, available safety information, information about payments and compensation available to patients, the Investigators current curriculum vitae and/or other documentation evidencing qualifications, a list of involved ECs and attendees, and any other documents that the ECs may need to fulfil its responsibilities, the suitability of the Investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subject.
- 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 Investigator and Investigating Site will not initiate nor apply any study procedure or deliver IMP or reference until approvals have been obtained from the CAs and ECs. Copies of any correspondence between the Investigator and the CAs and/or ECs will be given to the Monitor 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 8).

The Sponsor (with or without the support from the Monitor) is responsible for submitting to the CAs and ECs any amendment to the Study Protocol, and any changes to the Patient 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 Monitor) 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 Patient Data Protection and Confidentiality

The confidentiality of data and records that could identify patients will be protected in order to respect privacy and confidentiality rules, in accordance with all applicable 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 Agencies in any member state in which the study drug may ultimately be marketed, but the patient's name will

not be disclosed in these documents. The patient's name may be disclosed to the Sponsor (or any authorised representative, including the Monitor) or the Agencies, 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). The patients will be informed that the results will be kept and analysed in a computer but that nothing apart from what has been recorded in the eCRF will be registered. They will also be informed that their data will only be available to the above-mentioned entities.

The written ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with all applicable 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 (or any authorised representative, including the Monitor), Agencies, 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 traceability of investigational medicinal products and reference, together with the requirements regarding protection of privacy and confidentiality of personal data and medical records, a unique identification code (Patient Identification Number) will be allocated during the 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 ISF at the Investigation 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. Details on the existing patients insurance are given in the Patient Information Sheet.

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, the participant, and the patient.

12.5 Financial Aspects

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

The Investigator at each site must comply with all the terms, conditions, and obligations of the "Investigational Site 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 20 years according to European directives, national laws and Sponsor's SOPs. Archiving responsibilities cannot be transferred to the Sponsor.

- Investigator's Trial Master Site File with the final Protocol and current Investigator Brochure
- Copy of completed eCRFs, SAE, and Pregnancy Forms
- Signed ICFs
- Patient screening and Enrolment Log and Patient Identification Code List
- Source documentation
- All 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 Agencies and/or ECs.

Before or at the end of the archiving period, the Sponsor can request an extension of the storage of all materials, or part of them, for a further period. An appropriate agreement will be drawn up accordingly. If an extension of the storage is not required, it is the responsibility of the Investigator to decide to destroy or keep these study-related materials after this archiving period. It is the responsibility of the Sponsor to inform the sites when archiving is no longer needed.

13 REPORTING AND PUBLICATIONS POLICY

13.1 Clinical Study Report

When all completed eCRFs and Data Clarification Forms (DCFs) have been collected, and data have been analysed, a draft of the Clinical Study Report will be produced and will be sent to the Coordinating Investigator and all Principal Investigators for review. If a reviewer does not agree with all or part of the Clinical Study Report, his/her comments shall be recorded and communicated to the other Principal Investigators. When agreement on the contents has been reached, the report will be signed by the Sponsor and Coordinating Investigator.

The Clinical Study Report 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.

In accordance with applicable requirements, the Sponsor will send the Clinical Study Report to both the Agencies and ECs within one year after the end of the trial.

13.2 Publications and Posters

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

Any and all study data, databases, results, materials, analysis, information, documents, and reports (including but not limited to eCRFs), collected, generated, created, written, and/or otherwise obtained during (or in connection with) the study under the Study Protocol (except

for study patient's medical records), whether in oral, written (including but not limited to documents, memorandum, minutes, reports, correspondence), graphic (including but not limited to drawings, figures, schema or other material) or computer-readable form, will become the property of the Sponsor.

The Investigator will retain any information or data of any kind pertaining to the study, including but not limited to study results from individual Study Sites, as well as any Sponsor Confidential Information for the purpose of the study, whether in any and all intangible and/or tangible expressions, in any media, in strict confidence, and shall not directly or indirectly publish, communicate, disseminate, display, deliver, distribute, reproduce, disclose, or otherwise make available such information and/or data to any third party prior written approval from the Sponsor.

Publication, communication (including but not limited to abstracts and posters), disclosure, release, or dissemination of any information or data of any kind pertaining to the Study, including study results from individual study sites, is however possible in mutual agreement between the Investigators 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, Investigation Sites, and the Sponsor' personnel; and
- The Sponsor shall be given thirty (30) days to review communications (abstracts and posters), and sixty (60) days to review publications; and
- In the event that the Sponsor does not object to the proposed communication or publication within thirty (30) days or sixty (60) days of its receipt, as the case may be, it will be deemed to have been approved; and
- In the event that the Sponsor objects to the proposed communication or publication for reasons relating to the patentability of an invention or the protection of any other forms of intellectual property rights that would be disclosed by such proposed communication or publication, then submission of the communication or publication will be delayed for a maximum of six (6) months to enable the Sponsor to protect its rights; and

- In the event that the Sponsor reasonably objects to the proposed communication or publication as conflicting with or compromising 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 with implemented due regards of the importance of scientific dissemination of the study results.

14 REFERENCES

- Attur M, Krasnokutsky-Samuels S, Samuels J, Abramson SB. Prognostic biomarkers in osteoarthritis. Curr Opin Rheumatol. 2013; 25: 136-44.
- Axelrad T.W, Einhorn T.A. Use of Clinical Assessment Tools in the Evaluation of Fracture Healing. Injury. Int. J. Care Injured 42 (2011) 301-305.
- Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. Curr Opin Rheumatol. 2002 Mar;14(2):109-14. Review.
- Bellamy N. WOMAC: a 20-year experimental review of a patient-centered self-reported health status questionnaire. J Rheumatol. 2002; 29: 2473-2476.
- Bellamy N. The WOMAC Knee and Hip Osteoarthritis Indices: development, validation, globalization and influence on the development of the AUSCAN Hand Osteoarthritis Indices. Clin Exp Rheumatol. 2005; 23: S148-153.
- Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988; 15: 1833-1840.
- Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. Viscosupplements for the treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews. 2009, Issue 1.
- Bellamy N, Carr A, Dougados M, Shea B, Wells G. Towards a definition of "difference" in osteoarthritis. J Rheumatol. 2001 Feb;28(2):427-30. Review
- Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J, Clavel-Sainz C. Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee osteoarthritis over a 6-month period. Rev Esp Cir Ortop Traumatol. 2012; 56:274-80.
- Breivik H, Borchgrevink PC, Allen SM, Rosseland L, Breivik Hals EK, Kvarstein G, Stubhaug A. Assessment of pain. Br. J. Anaesth. 2008; 101:17-24.
- Bryant D, Fernandes N. Measuring patient outcomes: a primer. Injury. 2011; 42: 232-235.
- Chevalier X, Jerosch J, Goupille P, van Dijk N, Luyten FP, Scott DL, Bailleul F, Pavelka K. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis. 2010 Jan;69(1):113-9

- Drieser R.L., Avouac B., Bardin T. Efficacy of one intra-articular injection of 2% natural sodium hyaluronate is non inferior to chemically crosslinked hylan G-F 20 in the treatment of painfull tibiofemoral osteoarthritis. Poster at the World Congress on Osteoporosis, 2015.
- Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. J Rheumatol. 2000 Nov;27(11):2635-41.
- Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: New insights. Part 1: The disease and its risk factors. Ann Intern Med. 2000; 133: 635-646.
- Gerich J. Visual analogue scales for mode-independent measurement in self-administered questionnaires. Behav Res Methods. 2007; 39: 985-92.
- Godwin M, Dawes M. Intra-articular steroid injections for painful knees. Systematic review with meta-analysis. Can Fam Physician. 2004; 50: 241–248.
- Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med 2001; 33(5): 350-7
- Hochber,Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrica 1988; 75: 800-2
- Huang TL, Hsu HC, Yang KC, Yao CH, Lin FH. Effect of different molecular weight hyaluronans on osteoarthritis-related protein production in fibroblast-like synoviocytes from patients with tibia plateau fracture. J Trauma. 2010; 68:146-52.
- Iannone F, Lapadula G. The pathophysiology of osteoarthritis. Aging Clin Exp Res. 2003; 15: 364-72.
- Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. J Bone Joint Surg Am. 2002 ;84-A :1522-7
- Koenig F, Brannath W, Bretz F, Posch M. Adaptive Dunnett tests for treatment selection. Statist. Med. 2008; 27:1612-1625
- Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006 Feb;26(4):325–30.
- Lajeunesse D, Reboul P. Subchondral bone in osteoarthritis: A biologic link with articular cartilage leading to abnormal remodeling. Curr Opin Rheumatol. 2003; 15: 628-633.
- Lequesne MG, Maheu E. Clinical and radiological evaluation of hip, knee and hand osteoarthritis. Aging Clin Exp Res. 2003; 15: 380-390.
- Lewis RW, Billington R, Debryune E, Gamer A, Lang B, Carpanini F. Recognition of adverse and nonadverse effects in toxicity studies. Toxicol Pathol. 2002; 30:66-74.

- Manek NJ, Lane NE. Osteoarthritis: Current concepts in diagnosis and management. *Am Fam Physician*. 2000; 15: 1795-1804.
- McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA. 2006; 296:1633-44.
- Mobasheri A and Henrotin Y. Biomarkers of Osteoarthritis: A Review of Recent Research Progress on Soluble Biochemical Markers, Published Patents and Areas for Future Development. Recent Patents on Biomarkers. 2011; 1:25-43.
- Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002; 347:81–88.
- Pagnano M, Westrich G. Successful nonoperative management of chronic osteoarthritis pain of the knee: safety and efficacy of retreatment with intra-articular hyaluronans. Osteoarthritis Cartilage. 2005; 13:751-61.
- Pavelka K, Uebelhart D., Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial®) vs hylan G-F20 (Synvisc®) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel-group non-inferiority study. Osteoarthritis Cartilage. 2011 Nov;19(11):1294-300.
- Pelletier JP, DiBattista JA, Roughley P, McCollum R, Martel-Pelletier J. Cytokines and inflammation in cartilage degradation. Rheum Dis Clin North Am. 1993; 19:545–68.
- Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis: Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials. Ann Rheum Dis. 2000; 59: 936–944.
- Petersson IF, Jacobsson LT. Osteoarthritis of the peripheral joints. Best Pract Res Clin Rheumatol. 2002; 16:741-760.
- Raman R, Dutta A, Day N, Sharma HK, Shaw CJ, Johnson GV. Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee—a prospective randomized clinical trial. Knee. 2008 Aug;15(4):318–24.
- Roth SH. Nonsteroidal anti-inflammatory drug gastropathy: new avenues for safety. Clin Interv Aging. 2011; 6: 125–131.
- Romero-Sandoval A, Eisenach JC. Clonidine reduces hypersensitivity and alters the balance of pro- and anti-inflammatory leukocytes after local injection at the site of inflammatory neuritis. Brain Behav Immun. 2007 Jul;21(5):569-80.

- Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. Pharmacoeconomics, 1999; 15: 141-55.
- Schepers T, Kieboom BC, Bessems GH, Vogels LM, van Lieshout EM, Patka P. Subtalar versus triple arthrodesis after intra-articular calcaneal fractures. Strategies Trauma Limb Reconstr. 2010 Aug;5 (2):97-103. Epub 2010 Mar 23.
- Shearer D, Morshed S. Common generic measures of health related quality of life in injured patients. Injury, Int. J. Care Injured 42. 2011:241–247
- Stucki G, Sangha O, Stucki S, Michel BA, Tyndall A, Dick W, Theiler R. Comparison of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and a self-report format of the self-administered Lequesne-Algofunctional index in patients with knee and hip osteoarthritis. Osteoarthritis Cartilage. 1998; 6: 79-86.
- Sun R, Zhao W, Hao Q, Tian H, Tian J, Li L, Jia W, Yang K. Intra-articular clonidine for post-operative analgesia following arthroscopic knee surgery: a systematic review and meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2014 Sep;22(9):2076-84.
- Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010; 26: 355-369.

15 ANNEXES

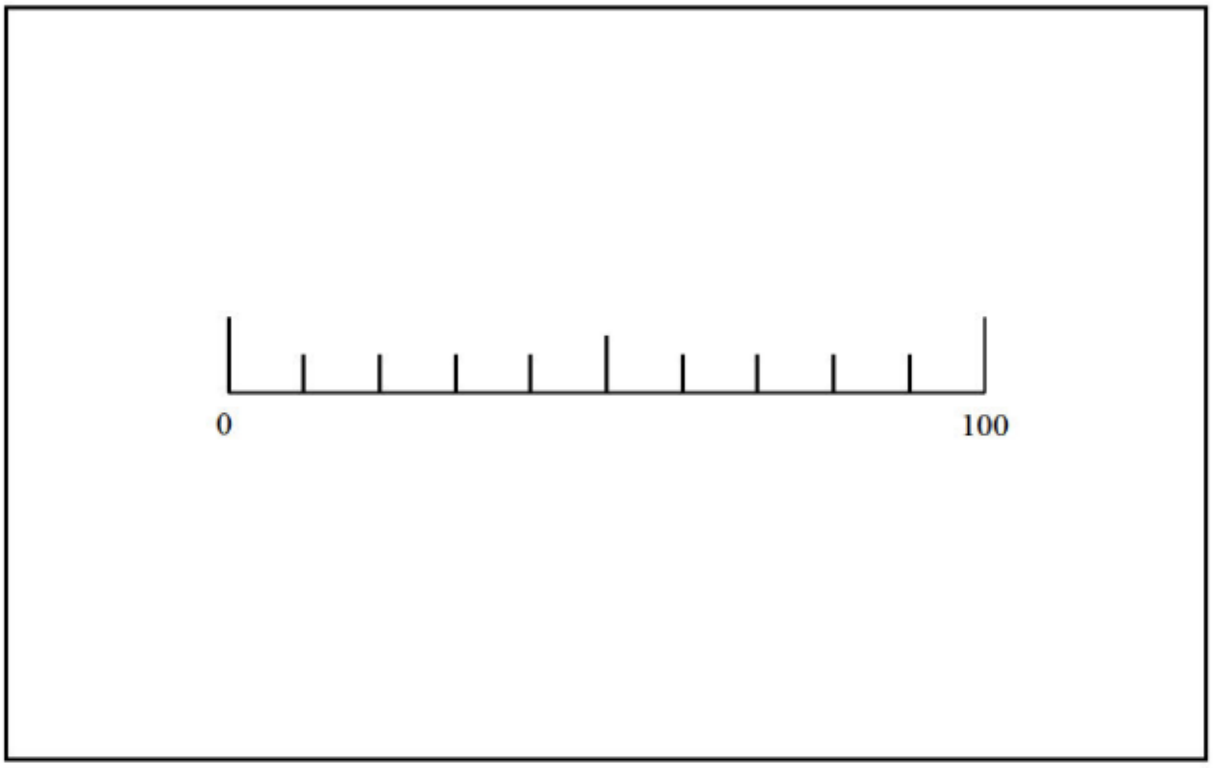
15.1 ANNEX 1 : WOMAC® VA3.1 QUESTIONNAIRE

See the documents attached.

15.2 ANNEX 2: PAIN VISUAL ANALOGUE SCALE

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

Please indicate by an "X" on the horizontal line below the position qualifying the best the intensity of the pain you felt and still feel at the knee over the last three days, considering that 0 represents no knee pain and 100 extreme knee pain.



Study coordinator use only: _____ mm

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

15.5 ANNEX 5: RADIOLOGICAL EVALUATION

[redacted]

The Kellgren-Lawrence Grading System consists of Grade 0, Grade I, Grade II, Grade III and Grade IV. This categorical scale incorporates important radiographic features of OA:

- Joint space narrowing: bone is visible on X-rays but the articular cartilage that covers it is not. A normal joint therefore appears to have a space between the bones. Any decrease in space implies a reduction in cartilage cover.
- Osteophytes: small bony projections that form around joint margins. They are responsible for limiting range of motion and can cause pain.
- Sclerosis: this means 'hardening' and is a sign of osteoarthritis, seen as increased white areas in the bone at the joint margins.

The Kellgren-Lawrence Grading System of OA is summarised in Table 9 below.

Table 9: *The Kellgren-Lawrence Grading System of Osteoarthritis*

Radiographic Criteria for Assessment of OA		
Grade 0	None	No features of OA
Grade I	Doubtful	Doubtful narrowing of joint space and possible osteophytic lipping
Grade II	Minimal	Definite osteophytes, definite narrowing of joint space
Grade III	Moderate	Moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour
Grade IV	Severe	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour