Efficacy and safety of oral strontium ranelate for the treatment of knee osteoarthritis: rationale and design of randomised, double-blind, placebo-controlled trial

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Objective: The osteoporosis drug strontium ranelate dissociates bone remodelling processes. It also inhibits subchondral bone resorption and stimulates cartilage matrix formation in vitro. Exploratory studies in the osteoporosis trials report that strontium ranelate reduces biomarkers of cartilage degradation, and attenuates the progression and clinical symptoms of spinal osteoarthritis, suggesting symptom- and structure-modifying activity in osteoarthritis. We describe the rationale and design of a randomised trial evaluating the efficacy and safety of strontium ranelate in knee osteoarthritis.

Research design, methods, and results: This double-blind, placebo-controlled trial (98 centres, 18 countries) includes ambulatory Caucasian men and women aged ⩾50 years with primary knee osteoarthritis of the medial tibiofemoral compartment (Kellgren and Lawrence grade 2 or 3), joint space width (JSW) 2.5 to 5 mm, and knee pain on most days in the previous month (intensity ⩾40 mm on a visual analogue scale). Patients are randomly allocated to three groups (strontium ranelate 1 or 2g/day, or placebo). Follow-up is expected to last 3 years. The primary endpoint is radiographic change in JSW from baseline in each group versus placebo. The main clinical secondary endpoint is WOMAC score at the knee. Safety is assessed at every visit. It is estimated that 1600 patients are required to establish statistical significance with power >90% (0.2 mm ±10% between-group difference in change in JSW over 3 years). Recruitment started in April 2006. The results are expected in spring 2012.

Clinical trial registration: The trial is registered on www.controlled-trials.com (number ISRCTN41323372).

Conclusions: This randomised, double blind, placebo-controlled study will establish the potential of strontium ranelate in improving structure and symptoms in patients with knee osteoarthritis.

Keywords: DMOAD, Joint space width, Knee osteoarthritis, Knee radiograph, Randomized clinical trial, Strontium ranelate, Structure-modifying treatment

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Introduction

Osteoarthritis leads to pain and joint stiffness, and is a major contributor to disability and social isolation. It affects roughly 10% of the population in the Western world1. Like all age-related diseases, osteoarthritis is more frequent in the elderly, and as many as 40% of the population aged over 65 years has knee or hip osteoarthritis[1, 2]. The absolute number of sufferers can be expected to rise in the future and the associated increasing burden of disease and disability is a priority for public health.

Current management options centre on reducing symptoms[3]. Non-pharmacological interventions such as physiotherapy, weight reduction, and exercise confer some pain relief. Pharmacological options include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids or hyaluronic acid, glucosamine sulphate, and chondroitin sulphate. Most are effective at modifying symptoms, but the therapeutic arsenal remains poor in treatments with an effect on disease progression. While there has been much research activity with promising agents, there is still a clear need for an effective disease- or structure-modifying drug (DMOAD)[3–9]. This is an important point, since the symptom-modifying drugs frequently prove to be insufficient as the disease progresses, and the only remaining option is surgical joint replacement, which is both costly and highly invasive.

There is clearly an urgent need for new therapies in osteoarthritis, particularly those with a structure-modifying activity. In this article, we describe the rationale and design of a large-scale, prospective, multicentre, international, double-blind placebo-controlled trial of strontium ranelate in patients with knee osteoarthritis.

Rationale

Osteoarthritis was long considered to be a disease involving the degeneration of cartilage. More recently, it has been recognised that it affects all of the structures in the joint, notably the subchondral bone[10]. However, it remains unknown whether the underlying trigger for the disease is an alteration in cartilage or subchondral bone metabolism, or both. Indeed, the subchondral bone plays a major role in osteoarthritis, both in the pathogenesis of the disease and in the expression of pain (e.g., painful microfractures of subchondral bone)[10, 11].

A treatment with an efficacy on bone remodelling, particularly one with an action on

the coupling of osteoblastic and osteoclastic activity and on the osteocyte, may therefore prove to be of value in the treatment of osteoarthritis. Strontium ranelate is an osteoporosis treatment with a mode of action that dissociates the bone remodelling process via both a bone-forming action and an antiresorptive effect[12]. Non-clinical studies indicate that strontium ranelate enhances preosteoblast replication and promotes osteoblastic differentiation, leading to a bone-forming activity. Strontium ranelatees effects on bone remodelling have been linked to activation of calcium-sensing receptors[13, 14], which are expressed by osteoclasts, osteoblasts, and osteocytes, as well as by chondro-cytes15. Its antiresorptive action appears to occur via modulation of the receptor activator of nuclear factor kappa B (RANK)/RANK ligand/osteoprotegerin system, which is essential for osteoclastogenesis[13, 16, 17].

Strontium ranelate has been tested in more than 6500 patients with postmenopausal osteoporosis in two major randomised phase 3 clinical trials, SOTI (Spinal Osteoporosis Therapeutic Intervention) and TROPOS (Treatment of Peripheral Osteoporosis), in which treatment reduced the relative risk for vertebral and non-vertebral fracture, including hip fracture in a post-hoc analysis of high-risk patients [18, 19].

The impact of strontium ranelate on human subchondral bone has been explored in an in vitro study comparing normal and osteoarthritic bone specimens. Strontium ranelate inhibited subchondral bone resorption by modulating the activity of matrix metalloproteinases, osteoprotegerin, and RANK ligand secreted by bone cells, notably osteoblasts[20]. These cells are key regulators of bone resorption, and the results support a positive impact of strontium ranelate on the pathophysiology of osteoarthritis. In addition to its action on subchondral bone remodelling, non-clinical studies suggest that strontium ranelate could act directly on cartilage by restoring the imbalance between anabolism and catabolism observed in osteoarthritis[21]. Strontium ranelate stimulates cartilage matrix formation in vitro in normal and osteoarthritic human chondrocytes[21]. This process was observed to occur via promotion of the synthesis of proteoglycans, which are decreased in osteoarthritis, without an effect on cartilage degradation. Together, these results support a positive impact of strontium ranelate on the pathophysiology of osteoarthritis.

The potential for an effect of strontium ranelate in patients with osteoarthritis has been explored in post hoc analyses of the phase 3 studies in osteoporosis. Thus, an analysis of 2617 participants in TROPOS was performed to assess its effect on cartilage[22, 23], selected on the basis of urinary sampling at every visit during the 3-year study. All of them had osteoporosis, and 22% (565 patients) had symptoms of osteoarthritis at baseline. Treatment with strontium ranelate was associated with 15% to 20% lower levels of a urinary biomarker of cartilage degradation (type II collagen C-telopeptide neoepitope [CTX-II]) ($P<0.0001$ versus placebo)[22]. This effect was apparent after 3 months, and was sustained over 3 years[23]; it was also independent of osteoarthritis status at baseline.

Another post hoc study aimed to determine the clinical effect of strontium ranelate in the progression of spinal osteoarthritis. This study pooled 1105 patients from SOTI or TROPOS with osteoporosis and concomitant radiological spinal osteoarthritis, and for whom lumbar X-rays were available at baseline and over the 3 years of treatment[24]. An overall osteoarthritis score, the Lane score[25], was calculated for each intervertebral space, encompassing scoring for the presence of osteophytes, disc space narrowing, and sclerosis in the lumbar intervertebral spaces. Treatment with strontium ranelate for 3 years was associated with a 42% lower overall osteoarthritis score ($P=0.0005$ versus placebo) and a 33% reduction in disc space narrowing score ($P=0.03$ versus placebo). There was also a 34% increase in the number of patients free of back pain ($P=0.03$ versus placebo)[24].

These promising clinical results were found in patients with postmenopausal osteoporosis, and cannot be applied directly to patients with osteoarthritis without osteoporosis.

However, they do suggest that strontium ranelate could improve the progression of osteoarthritis via a structure-modifying activity on cartilage degradation and subchondral bone, and provide symptom relief in painful joints. The aim of the randomised clinical trial described in this article is therefore to evaluate the superiority of strontium ranelate (1 g/day and 2 g/day) versus placebo in reducing the radiographic progression of articular cartilage damage over 3 years in men and women with knee osteoarthritis.

Study design

This international, multicentre, randomised, double-blind, placebo-controlled phase 3 trial was set up with three parallel groups (strontium ranelate 1 g/day and 2 g/day, and placebo). The study is being performed in 98 centres in 18 countries (Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, France, Germany, Italy, The Netherlands, Lithuania, Poland, Portugal, Romania, Russia, Spain, and UK). The study design is presented in Figure 1 and the main selection/non-selection criteria and inclusion/exclusion criteria in Table 1. In brief, male and female Caucasian ambulatory patients aged ⩾50 years are eligible for selection if they have primary knee osteoarthritis according to American College of Rheumatology criteria , including pain on most of the days of the previous month (at least half) with intensity assessed as ⩾40 mm on a visual analogue scale (VAS) ranging from 0 to 100 mm. They are eligible for inclusion at M0 provided radiography indicates the presence of Kellgren and Lawrence grade 2 or 3 , and a joint space width (JSW) of between 2.5 and 5 mm with predominant osteoarthritis of the medial compartment of the knee. The target knee is determined by the investigator at selection. If both knees fulfil the selection criteria, then the target knee is defined as the most clinically painful (i.e. the one with the

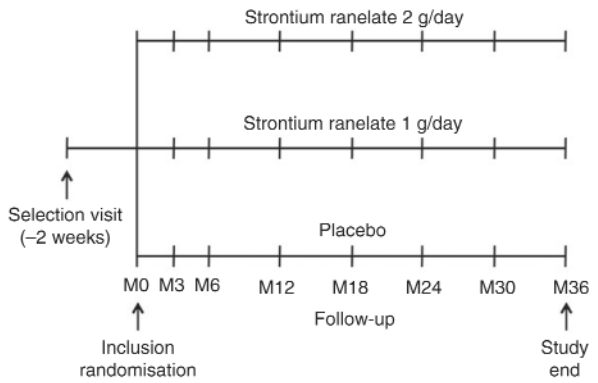

Figure 1. Study design.

highest score for knee pain on the VAS). If both knees are equally painful at selection, then the target knee is defined at inclusion as the one with the highest Kellgren and Lawrence grade and/or the lowest JSW. If both knees are equally painful at selection and have the same radiological score at inclusion, then the target knee is defined according to the investigatores judgement.

The study protocol and other documents related to informed consent and investigator information have been reviewed by independent ethics committees in the countries concerned, and by the investigators, the coordinators, or the sponsor in accordance with local regulatory requirements. Written informed consent is obtained from all participants. The study is being performed in accordance with the ethical principles laid out in the Declaration of Helsinki (1964 and its text revisions) and is registered in the Current Controlled Trials database (www.controlled-trials.com; number ISRCTN41323372).

Table 1. Main criteria for selection, non-selection, inclusion, and non-inclusion, VAS, visual analogue scale.

Selection criteria
• Caucasian males or females
• Aged ≥50 years
• Ambulatory (able to walk unassisted)
• Primary knee osteoarthritis according to American College of Rheumatology criteria (knee pain on more than half of the days in the previous month with intensity ≥40 on a 0–100 VAS), and at least three of the following six criteria: age >50 years; stiffness <30 min; crepitus; bony tenderness; bony enlargement; no palpable warmth
• Written informed consent
Non-selection criteria
• Knee prosthesis or one planned within a year
• Recent hip prosthesis (<1 year), or poorly tolerated hip prosthesis, or one planned within the next year)
• Previous osteotomy on a lower limb
• Previous surgical operation on target knee (involving arthroscopy) <1 year prior to selection
• Clinically significant hip osteoarthritis
• Any knee intra-articular injection during the previous 3 months (6 months for hyaluronic acid)
• Secondary osteoarthritis of the knee: post-traumatic (severe traumatism, clinically significant and documented), articular fracture, clinically significant deformities of the lower limbs (varus or valgus), septic arthritis, inflammatory joint disease, gout, major chondrocalcinosis (pseudogout), Paget's disease of the bone, ochronosis, acromegaly, haemochromatosis, Wilson's disease, primary osteochondromatosis, osteonecrosis, haemophilia
• Medical history of venous thromboembolism (including pulmonary embolism) or at high risk for venous thromboembolism
• Progressive major illnesses (life-threatening cardiovascular disease, haematopoietic cancers including myeloma, cancers with a risk of bone metastases, other cancers within the previous 5 years except for basalioma and completely excised squamous cell carcinoma)
• History of severe alcohol abuse (≥160 g/day)
• Severe renal insufficiency (creatinine clearance <30 mL/min with the Cockroft formula)
• Known carriers of human immunodeficiency virus or hepatitis B or C
• Unexplained significant weight loss (>10% of body weight within the previous year)
• Previous treatment likely to have an action on cartilage or bone metabolism: oral or intravenous bisphosphonates <1 year prior to selection; teriparatide or raloxifene <7 days prior to selection; diacerein, glucosamine (sulphate or other forms, ≥1500 mg/day), chondroitin sulphate, or avocado/soybean unsaponifiables <3 months prior to selection; intra-articular hyaluronic acid injections <6 months prior to selection; medications with matrix metalloprotease inhibitory properties (e.g., tetracycline or structurally related compounds) <3 months prior to selection
• Glucocorticoids (oral, inhaled >1500 μg/day, or intra-articular <3 months prior to selection)
Inclusion criteria
• Presence of Kellgren and Lawrence grade 2 or 3 osteoarthritis on knee X-ray
• Joint space width between 2.5 and 5 mm
Non-inclusion criterion
• Presence of predominant osteoarthritis of the lateral compartment of the knee

Treatment, follow-up, and investigations

At inclusion, patients are instructed to take one sachet daily at bedtime of the study treatment (strontium ranelate 1 g/day or 2 g/day or placebo) in about 50 mL of water, preferably at least 2 hours after eating, and for the duration of the study. Treatment allocation is performed through a centralised interaction voice response system, with balanced randomisation between the three groups and stratification by centre and gender. Patients and investigators are blinded to treatment allocation and the study treatments have identical appearance (packaging, labelling, and appearance of granules). Treatments likely to have an action on cartilage or bone metabolism (Table 1) and glucocorticoids are prohibited throughout the study. Physiotherapy, rehabilitation, and alternative medicines are permitted, as is pain relief with analgesics or NSAIDs, as necessary. However, any pain medication is stopped within at least five half-lives before the visit to allow proper symptom assessment.

Selection and inclusion criteria, medical history, informed consent, concomitant treatments or procedures, and vital signs are evaluated at selection and/or inclusion (M0). The participants return for visits at 3 and 6 months (M3 and M6), and then every 6 months up to 3 years (Figure 1). The study investigation schedule is shown in Table 2.

Knee radiographs

Radiography of the knee is performed by a standardised technique[28] at inclusion (both knees) and at the yearly visits (M12, M24, and M36) for the target knee, or upon withdrawal from the study. A fixed flexion posteroanterior view is recorded, in which both knees are in contact with the cassette and coplanar with the hips, patellae, and tips of the great toe.

A reproducible position of the knee is achieved using a SynaFlexer™ Plexiglass positioning frame (Synarc Inc., San Francisco, CA, USA), which is designed for serial examinations within and across subjects[28]. The X-ray beam is tilted at a fixed angle of 10° to optimise alignment of the medial tibial plateau.

A number of procedures have been set up for quality control of knee radiographs at inclusion and on follow-up (depiction, positioning, presence of side marker and 10-mm radiopaque ruler for magnification, beam angle, and posteroanterior projection). In the case of poor quality, the investigator is requested to repeat the examination. All radiology technicians receive 2 dayse training at the start of the study by experienced radiologists (Synarc, Hamburg, Germany); they are also provided with a technical reference manual and a quick reference guide. Over the course of the study, they receive further training on a yearly basis for 3 years. The sites are instructed to check that the flatness of the medial tibial plateau is similar between screening and follow-up, and a dedicated quality control procedure is implemented to verify consistency of joint space identification, the medial tibial plateau, and X-ray beam

Table 2. Study investigation schedule for the main endpoints.

	Selection	M0	M3	M6	M12	M18	M24	M30	M36
Informed consent	X								
Selection/inclusion criteria	X	X							
Medical history	X								
Vital signs	X	X	X	X	X	X	X	X	X
Compliance			X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X	X
Efficacy measurements									
Primary endpoint									
• Radiography of the knee (X-ray)	X				X		X		X
Main secondary endpoints									
• Algofunctional evaluation of the knee (WOMAC)		X		X	X	X	X	X	X
• Pain intensity in the knee (VAS)	X	X		X	X	X	X	X	X
• Knee flare-up frequency (patient diary)			X	X	X	X	X	X	X
• Pain medication and NSAID consumption (patient diary)			X	X	X	X	X	X	X
• Physical assessment of knee	X	X	X	X	X	X	X	X	X
• Biochemical bone and cartilage markers		X	X	X	X	X	X	X	X
• MRI		X			X		X		**X**
• Quality of Life (SF-36)		X		X	X	X	X	X	X
Safety measurements									
• Adverse events	X	X	X	X	X	X	X	X	X
• Laboratory examinations (biological acceptability)	X		X	X	X	X	X	X	X
• Blood sample for pharmacokinetics		X	X	X	X	X	X	X	X

NSAID, non-steroid anti-inflammatory drug; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

orientation, insofar as these parameters are the primary determinants of JSW measurements. All inclusion radiographs are evaluated for eligibility according to Kellgren and Lawrence score, JSW, and predominance of osteoarthritis in the medial compartment.

All radiographs are centralised and digitised using an Array Dicom Scanner, stored in uncompressed DICOM 3 format by Synarc (Hamburg, Germany), and sent to the Central Reading Centre team (Association Prevention des Maladies Osseuses, Lyon, France) for reading (D. Gensburger). A second independent reading was performed in a second Central Reading Centre (Liege, Belgium) by a reader trained using the same method (R. Deroisy). The minimal JSW (mm) at the medial tibiofemoral compartment is measured using a standardised semi-automated computerised method, described in detail elsewhere[29]. The magnification factor is determined using a 10-mm radio-opaque ruler. The reader then crops the image by selecting a centred rectangular region of interest that includes a horizontal tangent to the inferior edges of femoral condyles and places two perpendiculars in contact with the convexity of the condyle margins. The software automatically generates two parallel lines, 15 mm apart, with one at 10 mm from the condyle line. In the area defined by these two lines, the observer delineates the tibial and femoral bone margins, to depict a polygon. The JSW corresponds to the diameter of the smallest circle included in this polygon. The X-rays are read in pairs, in chronological order. The reader is blinded to treatment allocation and patient identity. Time sequence is unblinded and each follow-up image is measured in comparison with the image at inclusion; this is known to improve the sensitivity and reproducibility of the reading[30–32].

Prior to the study, and at yearly intervals during the study, intra-reader reproducibility was evaluated for each reading centre on 70 pairs of knee radiographs unlinked to the study itself, indicating good reproducibility[30].

Other knee X-ray parameters include radiological progression (joint space narrowing [JSN] ⩾0.5 mm over 3 years) and radioclinical progression (JSN ⩾0.5 mm without a clinically relevant improvement, i.e. 20% or less improvement on the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain sub-scale versus baseline over 3 years)[33].

Other main investigations

WOMAC is assessed at inclusion and at 6-month intervals thereafter. WOMAC is a self-administered questionnaire designed to assess health status and health outcomes in osteoarthritis via 24 questions targeting areas of pain, stiffness, and physical function[34], expressed on a VAS. WOMAC is available in all the languages necessary for the countries in the study.

Knee pain is assessed at selection, inclusion, and at 6-month intervals thereafter using a VAS. To ensure that pain is evaluated under identical clinical conditions at every time-point throughout the study, patients are instructed to stop any pain medication within an appropriate washout period of at least five half-lives (i.e. 48 h for most analgesics and NSAIDs, 72 h for celecoxib) before the visits. A physical assessment of the knee is performed at all visits for swelling and warmth, as well as the presence of effusion. Participants are also asked to telephone an electronic patient diary once weekly to record parameters associated with pain in an electronic database. These include the frequency of knee flares and their intensity (graded as 1 = low pain, 2 = moderate pain, or 3 = intense pain), and the consumption of pain medication and NSAIDs (number of days and number of tablets per day).

Blood and urine samples (10 mL each) are collected after an overnight fast, at inclusion and all visits thereafter. The samples are assessed for biomarkers for cartilage (serum C propeptide of type II procollagen, serum hyaluronic acid, and urinary CTX-II) and bone (serum bone specific alkaline phosphatase and type I collagen C-telepeptide cross-links)[35, 36], as well as biological acceptability (haematology, blood and urine biochemistry, and haemostasis) and pharmacokinetics (serum strontium).

Magnetic resonance imaging (MRI) of the target knee is performed at inclusion, and yearly thereafter in selected and validated centres in a subset of patients. The MRI scans are read centrally (two Central Reading Centres, Arthrolab, Montreal, Canada, and Synarc, San Francisco, USA) and endpoints include joint cartilage volume[37], assessment of bone marrow lesions and meniscal alterations, characteristics of other non-cartilagenous components of the knee joint, using the whole organ magnetic resonance imaging score (WORMS)[38].

The SF-36 questionnaire is used at inclusion and every 6-monthly visit for assessment of global quality of life. Compliance is measured at every visit from M3 onwards by counting the number of sachets the patient returns to the investigator. Safety is assessed at every visit, including recording of adverse events, bodyweight, height, blood pressure, and heart rate.

Endpoints

The primary endpoint is radiographic change in JSW (mm) of the medial tibiofemoral compartment from baseline versus placebo. The main secondary endpoints are listed in Table 3.

Statistical methods

The sample size was estimated according to a treatment-placebo difference in change in JSW between baseline and last value for over 3 years, using the two-sided Dunnett test with a 5% type I error. We estimated that 1600 patients would have to be included to establish statistical significance with a power of >90% for a between-group difference in change in JSW over 3 years of 0.2 mm (range, 0.18 to 0.22 mm), assuming a 40% drop-out rate and an SD of 0.5 mm. This estimation is in line with the mean rate of JSN of 0.10 mm/year reported elsewhere[39–41].

For the primary endpoint, the strontium ranelate treatment groups will be compared with placebo using a general linear model (with Dunnett's multiple comparison procedure) with baseline, centre and gender as covariates, producing adjusted mean differences, their 95% confidence intervals and the associated P value. Descriptive statistics will be provided for secondary endpoints, with comparisons using a χ^2 test for radiological and radioclinical progression; a general linear model for WOMAC and SF-36 scores; and descriptive statistics for the data retrieved from patient diaries. The safety analysis will involve a description of adverse events and laboratory parameters.

The two-sided type I error rate will be set at 5%. The results of the study will be analysed by the Biostatistics Division of the Institute de Recherche Internationales Servier.

Table 3. Primary and main secondary endpoints.

Primary endpoint	Radiographic change in JSW (mm) of the medial tibiofemoral compartment from baseline versus placebo
Main secondary endpoints	• Radiological progression (JSN $\geq$ 0.5 mm over 3 years) • Radioclinical progression (JSN $\geq$ 0.5 mm without a clinically relevant improvement, i.e. 20% or less improvement on the WOMAC pain subscale versus baseline over 3 years) • Algofunctional assessment (WOMAC score) at the knee • Global knee pain (VAS) • Physical assessment of knee for inflammation, warmth, or presence of effusion • Frequency of knee pain flare-ups and consumption of analgesics or NSAIDs (patient diary) • Biochemical cartilage and bone markers • MRI parameters • SF-36 score

JSN, joint space narrowing; JSW, joint space width; NSAID, non-steroid anti-inflammatory drug; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Study organisation

Three supervisory committees were set up for study. The Executive Committee guarantees the overall scientific quality of the study, oversees its conduct, and will review and validate the results. It is also responsible for the development of the study protocol and its amendments, in collaboration with the Steering Committee, which includes the National Coordinators and representatives of the Central Reading Centres. The Safety Committee comprises three members. The members of these committees are listed in the Appendix to this paper. The study is funded by Servier, France.

Conclusion

This large randomised double-blind, placebo-controlled study will establish the potential of strontium ranelate in improving joint structure and symptoms in patients with knee osteoarthritis. The first patient was randomised in the study on 28 April 2006. A total of 1683 patients have been included. The mean age of the randomised population at baseline was 62.9±7.5 years, with 29.6% males and 70.4% females; their body mass index was 29.9±5.0 kg/m^2. As regards evaluation of osteoarthritis, the mean JSW was 3.50±0.84 mm and 61.7% of randomised patients were Kellgren and Lawrence grade 2. Mean knee pain score on the VAS was 54.0±22.3 mm, and mean WOMAC global score was 132.1±62.4. The results are expected in the spring of 2012.

Transparency

Declaration of funding

The study is funded by Servier, France. The sponsor supports the work of the Executive Committee, but does not make any scientific or research decisions independent of this Committee, which was responsible for the decision to submit the final version of the manuscript for publication.

Declaration of financial/other relationships

All authors were involved in the conception and design of the study and the preparation of the manuscript. The final version was approved by all authors.

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Appendix

Executive Committee

J.-Y. Reginster (Chairman), C. Cooper (International Coordinator), C. Christiansen, P. Delmas (deceased July 2008), R. Chapurlat (from 2008 onward), H. Genant, J. Zacher, N. Bellamy.

Steering Committee

C. Cooper (International Coordination, Chair), National Coordinators (see below), and representatives from the Central Reading Centres for knee X-rays centre (M. Arlot), knee X-rays and MRI scans (H. Genant, Synarc), MRI scans (J.-P. Pelletier, J. Martel-Pelletier), and the biochemical marker central laboratory (J. Collette).

Safety Committee

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