EXTENDED REPORT

Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial

Jean-Yves Reginster,1 Janusz Badurski,2 Nicholas Bellamy,3 William Bensen,4 Roland Chapurlat,5 Xavier Chevalier,6 Claus Christiansen,7 Harry Genant,8 Federico Navarro,9 Evgeny Nasonov,10 Philip N Sambrook,11 Timothy D Spector,12 Cyrus Cooper13

ABSTRACT

Background Strontium ranelate is currently used for osteoporosis. The international, double-blind, randomised, placebo-controlled Strontium ranelate Efficacy in Knee Osteoarthritis triAl evaluated its effect on radiological progression of knee osteoarthritis.

Methods Patients with knee osteoarthritis (Kellgren and Lawrence grade 2 or 3, and joint space width (JSW) 2.5–5 mm) were randomly allocated to strontium ranelate 1 g/day (n = 558), 2 g/day (n = 566) or placebo (n = 559). The primary endpoint was radiographical change in JSW (medial tibiofemoral compartment) over 3 years versus placebo. Secondary endpoints included radiological progression, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and knee pain. The trial is registered (ISRCTN41323372).

Results The intention-to-treat population included 1371 patients. Treatment with strontium ranelate was associated with smaller degradations in JSW than placebo (1 g/day: −0.23 (SD 0.56) mm; 2 g/day: −0.27 (SD 0.63) mm; placebo: −0.37 (SD 0.59) mm); treatment-placebo differences were 0.14 (SE 0.04), 95% CI 0.05 to 0.23, p < 0.001 for 1 g/day and 0.10 (SE 0.04), 95% CI 0.02 to 0.19, p = 0.018 for 2 g/day. Fewer radiological progressors were observed with strontium ranelate (p < 0.001 and p = 0.012 for 1 and 2 g/day). There were greater reductions in total WOMAC score (p = 0.045), pain subscore (p = 0.028), physical function subscore (p = 0.099) and knee pain (p = 0.065) with strontium ranelate 2 g/day. Strontium ranelate was well tolerated.

Conclusions Treatment with strontium ranelate 1 and 2 g/day is associated with a significant effect on structure in patients with knee osteoarthritis, and a beneficial effect on symptoms for strontium ranelate 2 g/day.

INTRODUCTION

Osteoarthritis is characterised by degeneration of cartilage and other structures in the joint, including subchondral bone.1 It is the most prevalent joint disease, and up to 40% of those over 65 may suffer from knee or hip osteoarthritis.2 Current management strategies focus on relieving symptoms and improving function through non-pharmacological and pharmacological approaches, and surgical procedures, including osteotomy, subchondral bone stimulation and possibly joint distraction, with the final option of joint replacement if these efforts fail.1,3 Pharmacological approaches include analgesics, anti-inflammatory agents, intra-articular corticosteroids or hyaluronic acid, glucosamine sulphate, chondroitin sulphate or some experimental treatments, none of which are registered as structure-modifying.

Strontium ranelate is currently indicated for the management of postmenopausal osteoporosis, and may be hypothesised to act on both cartilage and subchondral bone. Preclinical in vitro studies indicate that it inhibits subchondral bone resorption4 and stimulates cartilage matrix formation in normal and osteoarthritic human chondrocytes.5,6 Exploratory analyses suggest that 3 years’ treatment with strontium ranelate attenuates radiological progression of spinal osteoarthritis and improves back pain.7 The aim of the 3-year international, double-blind, randomised, placebo-controlled trial—Strontium ranelate Efficacy in Knee Osteoarthritis triAl (SEKOIA)—described herein was to evaluate the effect of strontium ranelate on radiological and clinical progression of knee osteoarthritis.

METHODS

Study design and patients

SEKOIA was an international, multicentre, randomised, double-blind, placebo-controlled phase 3 trial in outpatients with knee osteoarthritis mainly in secondary care. This 3-year study was performed in 98 centres in 18 countries. The selection criteria defined eligible patients as Caucasian ambulatory men and women aged ≥50 years with knee osteoarthritis according to American College of Rheumatology criteria,8 with pain on at least half of the days of the previous month (intensity ≥40 mm on a 100-mm visual analogue scale). On radiography, included patients were Kellgren and Lawrence grade 2 (ie, definite osteophytes and possible narrowing of joint space) or grade 3 (ie, moderate multiple osteophytes, definite narrowing of joint space and some sclerosis, and possible deformity of bone ends), and had joint space width (JSW) of 2.5 to 5 mm with predominant knee osteoarthritis of the medial tibiofemoral compartment. The investigator defined the target knee at selection. If both knees fulfilled the
Glucocorticoids (oral, inhaled >1500 mg/day) were not allowed. The quality control of radiographs was performed on both knees at selection and collection (eg, depiction, positioning and beam angle); and onsite and centralised digitisation and measurement (joint space narrowing (JSN) ≥0.5 mm, and lack of improvement in WOMAC pain (<20%) over 3 years; WOMAC scores; global knee pain; and urinary CTX-II levels).

The primary endpoint was radiographical change in JSW from baseline to last evaluation over 5 years in treatment groups versus placebo. Secondary endpoints included radiological progression (joint space narrowing (JSN) ≥0.5 mm over 5 years); radioclinical progression (JSN ≥0.5 mm, and lack of improvement in WOMAC pain (≤20%) over 3 years; WOMAC scores; global knee pain; and urinary CTX-II levels.

Statistical methods
At the time of the study design, the literature data on JSN progression were unclear, and a possible extension of the follow-up time to 3 years was planned if radiological progression was lower than expected. The initial sample size calculation estimated that 960 patients would be necessary for >90% power, assuming an SD of 0.7 and a 40% dropout rate to detect a significant between-group difference in JSN of 0.3 mm at 2 years (two-sided Dunnett test, 5% type I error). This was amended to 0.2 mm (±10%, ie, between 0.18 and 0.22 mm) in May 2007, following new findings of a lower progression in JSN in the placebo group than previously published, leading to an estimated sample size of 2127 patients. In March 2008, the Executive Committee decided to prolong the study to 3 years, in view of results of a blinded re-estimation of radiological progression (212 patients) indicating JSN of 0.06±0.42 mm after 1 year. The final estimated sample size was therefore 1800 patients allowing a treatment-placebo difference in JSN of 0.2 mm (±10%) at 3 years with an SD of 0.5 mm.

All efficacy analyses were conducted according to the intention-to-treat (ITT) principle. The ITT population included all randomised patients who had taken at least one dose of treatment and who had an assessable baseline and one post-baseline evaluation of JSW.
Baseline characteristics are presented as numbers (%) or mean ±SD. Treatment-placebo difference in primary endpoint from baseline to last value was analysed using a general linear model with baseline, centre and gender as covariates, producing estimates and SEs of the adjusted differences, 95% CIs (Dunnett-Hsu 18). A range of sensitivity analyses (described in online supplementary table S1) were conducted to investigate the impact of missing data on treatment effect. For secondary outcomes, treatment-placebo differences in radiological and radioclinical progression from baseline to last value were analysed as estimates of the between-group difference (SE) with associated 95% CI and p value (χ² test). Treatment-placebo differences in WOMAC scores and global knee pain were analysed using mixed model for repeated measurements and the adjusted general linear model. Treatment effect was studied using a Mann-Whitney-Wilcoxon test for CTX-II (non-Gaussian distribution). Safety data are presented as number (%) of events.

The two-sided type I error rate was set at 5%. The results were analysed by the Biostatistics Division of the Institut de Recherches Internationales Servier, using SAS (V.9.1). The main analysis was confirmed by the Department of Public Health Epidemiology and Health Economics, University of Liege, Belgium.

Role of the funding source
The Executive Committee was responsible for the study design, interpretation of the results, and manuscript preparation; they had full access to study data. The sponsor was responsible for data management and statistical analyses. The sponsor supported the work of the Executive Committee, but made no scientific or research decisions independent of this committee.

RESULTS
Three thousand four hundred and thirty-eight patients were selected, 1683 were included and allocated to treatment (558 strontium ranelate 1 g/day; 566 strontium ranelate 2 g/day; and 559 placebo) and 974 (58%) patients completed the study (figure 1).

The ITT population included 1371 patients (82% of randomised patients) followed for 29.8±10.5 months (mean±SD).

There were no relevant between-group differences at baseline (table 1). Mean age of the randomised patients was 62.9 ±7.5 years with a majority of women (70%). Body mass index was 29.9±5.0 kg/m². The target knee JSW was 3.50±0.84 mm at baseline, patients were Kellgren and Lawrence grade 2 (62%) or 3 (38%) and total WOMAC score was 132.4±62.4 mm. The mean duration of knee osteoarthritis was 76.7 ±77.7 months (about 6.4 years). One thousand three hundred and four (76%) patients reported a medical history of musculoskeletal or connective tissue disorders, mainly back pain (9%), arthralgia (8%), osteopenia (5%) and osteoporosis (5%). At inclusion, 1148 (68%) patients were taking treatment for osteoarthritis, mainly propionic acid-related treatments (18%), acetic acid derivatives (12%) or anilides (32%). Only seven patients were taking glucosamine and one chondroitin sulphate. In general, 59% of the patients were receiving analgesics, and three patients systemic corticosteroids for their osteoarthritis. There were no relevant differences in baseline characteristics between completed and withdrawn patients, between randomised and ITT populations or between ITT groups at baseline (table 1).

Mean compliance was 98.3±9.3% (ITT population). During the study, 1278 patients (76% of the randomised set) received at least one concomitant treatment for osteoarthritis, mainly propionic acid derivatives (25%), acetic acid derivatives (18%) and anilides (39%). Forty-six per cent of the patients took analgesics with an indication for osteoarthritis, 13 patients received glucosamine, three chondroitin sulphate, and two a combination of the two agents; 5% of the patients received systemic corticosteroids for their osteoarthritis. There was no relevant between-group difference (see online supplementary table S2).

JSN in the placebo group was −0.37±0.59 mm over the study. Treatment with strontium ranelate was associated with significantly attenuated JSN versus placebo, with −0.23±0.56 mm for 1 g/day and −0.27±0.63 mm for 2 g/day from baseline to end (table 2). The estimate of the treatment-placebo difference was significant for both dosages (p<0.001 for 1 g/day...
Clinical and epidemiological research

Table 1 Demographical and clinical characteristics at baseline in randomised patients and in the ITT population

<table>
<thead>
<tr>
<th></th>
<th>Randomised patients (N=1683)</th>
<th>ITT population (N=1371)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strontium ranelate 1 g/day (n=558)</td>
<td>Strontium ranelate 2 g/day (n=566)</td>
</tr>
<tr>
<td>Demographical parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.4 (7.4)</td>
<td>63.5 (7.5)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>394 (71%)</td>
<td>399 (71%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.1 (5.1)</td>
<td>29.8 (4.8)</td>
</tr>
<tr>
<td>Disease characteristics (target knee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint space width (mm)</td>
<td>3.45 (0.87)</td>
<td>3.54 (0.80)</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or means (SD).

*No significant difference for any variable between the corresponding groups for randomised or ITT patients.

†WOMAC score is measured on a 300-mm scale; WOMAC subscores are normalised to 100 mm.

‡WOMAC scale is evaluated on a 300-mm scale; WOMAC subscores are normalised to 100 mm, and global knee pain is reported on a 100-mm scale.

and p=0.018 for 2 g/day) (figure 2). Similar results were found in the second reading and a range of sensitivity analyses to assess the impact of missing data (see online supplementary table S1).

There were significantly fewer radiological and radioclinical progressors with strontium ranelate 1 and 2 g/day (table 2). Treatment with strontium ranelate 2 g/day was associated with significantly lower WOMAC total score (p=0.045) and pain

Table 2 Outcomes in the intention-to-treat population (n=1371)

<table>
<thead>
<tr>
<th></th>
<th>Strontium ranelate 1 g/day (n=445)</th>
<th>Strontium ranelate 2 g/day (n=454)</th>
<th>Placebo (n=472)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>Difference versus placebo (SE, (95% CI)) p Value</td>
<td>Value</td>
</tr>
<tr>
<td>Primary endpoint, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint space width (mm)</td>
<td>-0.23 (0.56)</td>
<td>0.14 (0.04) (0.05 to 0.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression of disease, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiological progression*</td>
<td>99 (22%)</td>
<td>-10.80 (2.9) (16.54 to -5.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radioclinical progression†</td>
<td>32 (8%)</td>
<td>-3.94 (1.98) (-7.83 to 0.05)</td>
<td>0.049</td>
</tr>
<tr>
<td>Symptoms of disease, mean (SD)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC total score (/300 mm)</td>
<td>-41.8 (62.3)</td>
<td>-1.3 (4.0) (9.0 to 6.5)</td>
<td>0.749</td>
</tr>
<tr>
<td>WOMAC pain subscore (/100 mm)</td>
<td>-14.6 (22.6)</td>
<td>0.1 (1.3) (2.8 to 2.7)</td>
<td>0.969</td>
</tr>
<tr>
<td>WOMAC stiffness subscore (/100 mm)</td>
<td>-15.6 (26.9)</td>
<td>-1.0 (1.6) (-4.1 to 2.1)</td>
<td>0.523</td>
</tr>
<tr>
<td>WOMAC physical function subscore (/100 mm)</td>
<td>-12.2 (21.1)</td>
<td>-0.4 (1.3) (3.0 to 2.2)</td>
<td>0.772</td>
</tr>
<tr>
<td>Global knee pain (VAS), (/100 mm)</td>
<td>-22.9 (29.0)</td>
<td>-0.24 (1.64) (-3.45 to 2.97)</td>
<td>0.884</td>
</tr>
</tbody>
</table>

Values are number (%) at end for progressors, mean (SD) change from baseline to end for symptoms.

*Joint space narrowing (JSN) ≥0.5 mm over 3 years.

†JSN ≥0.5 mm and lack of improvement in WOMAC pain ≤20% pain over 3 years.

‡WOMAC score is evaluated on a 300-mm scale; WOMAC subscores are normalised to 100 mm, and global knee pain is reported on a 100-mm scale.

VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
subscore \( (p=0.028) \), and a trend toward lower physical function subscore \( (p=0.099) \) and global knee pain \( (p=0.065) \) (table 2, figure 2). None of these reductions was significant at 1 g/day. Urinary CTX-II decreased in all groups, and the between-group difference in the relative change was significant for both dosages versus placebo \( (p=0.003 \) for 1 g/day and \( p=0.021 \) for 2 g/day).

The change in JSW from baseline was significantly different from placebo in both treatment groups at 12, 24 and 36 months, with no difference between the dosages at any time \((p=0.601 \) at 12 months, \( p=0.149 \) at 24 months and \( p=0.311 \) at 36 months). The reduction in total WOMAC score and pain subscore was numerically greater with treatment than placebo at every visit, with a significant between-group difference for pain subscore at 36 months \( (p=0.029 \) for 2 g/day). The treatment-placebo difference in radiological and radioclinical progressors was significant in both treatment groups at every visit (figure 5).

Strontium ranelate was well tolerated (table 3).\(^1\) The rate of venous thromboembolic events was <1% in all groups, and there were no cases of drug reaction with eosinophilia and systemic symptoms. There were no relevant differences in clinical or laboratory parameters, with the possible exception of creatine phosphokinase, which increased from baseline with treatment \((11.7±85.6 \text{ and } 20.7±104.4 \text{ IU/l with 1 and 2 g/day, respectively})\), but not placebo \((−0.4±68.1 \text{ IU/l})\); eight patients (three, one and four patients in the 1 g/day, 2 g/day, and placebo groups, respectively) had values greater than five times the upper limit of normal.

### DISCUSSION

Our results demonstrate that strontium ranelate has structure-modifying activity in patients with knee osteoarthritis, with significantly smaller degradations in JSW over the study \((p<0.001 \) for 1 g/day and \( p=0.018 \) for 2 g/day vs placebo). There were fewer patients with radiographical and radioclinical progression of osteoarthritis in the treatment groups. Additionally to this structural effect, symptomatic improvement was observed, with a significant impact on WOMAC total score and pain subscore \( (p=0.045 \) and \( p=0.028 \), respectively), and a trend towards improvement in global knee pain \( (p=0.065) \) at 2 g/day, but not 1 g/day. The safety profile of strontium ranelate was satisfactory, in line with knowledge of this agent.\(^{20} \) \(^{21} \) There was a slight mean increase in creatine phosphokinase in the treated groups as previously described for strontium ranelate.\(^{20} \) Pooled analysis in osteoporotic patients treated with strontium ranelate showed that increases were mainly mild, transient and reversible\(^{22} \); they were not associated with any clinical muscular symptoms.

These results come from a single study with a large sample size. The robustness of our observation of a structure-modifying effect for strontium ranelate is demonstrated by a range of sensitivity analyses and the rigorous methodology used for radiography acquisition and reading.\(^{19} \) In this context, the trial was carried out in accordance with current European and US regulatory guidelines,\(^{23} \) \(^{24} \) in terms of design and efficacy evaluation.

Osteoarthritis is not a uniform disease entity, and different phenotypes clearly exist, driven by variable changes in bone, cartilage and synovium; the links between these phenotypes are unclear.\(^1 \) Strontium ranelate may exert structure-modifying effects through influences on chondrocyte and bone cell function. Evidence to support an action on cartilage via chondrocytes includes: the treatment-placebo difference in urinary CTX-II in our study, which suggests lower cartilage metabolism and possibly reduced osteophyte formation; a report that strontium ranelate stimulates cartilage matrix formation in vitro,\(^5 \) implying restoration of the balance between chondrocyte formation and resorption; a direct effect of strontium ranelate on proteoglycan synthesis,\(^5 \) and an indirect effect on insulin growth factor-1 (IGF-1).\(^6 \)\(^2 \)\(^5 \)

Strontium ranelate is known to influence bone; however, it is unclear whether its effect on cartilage is direct or secondary to an effect on subchondral bone. Defective subchondral bone metabolism in osteoarthritis could modify chondrocytes in cartilage via local factors released during subchondral bone remodelling.\(^2 \) Strontium ranelate may decrease in vitro subchondral bone resorption via the osteoprotegerin/RANK ligand pathway...
in subchondral osteoblasts and by downregulating metalloproteases 2 and 9.4 Similar findings have been reported for strontium ranelate in osteoporotic bone.27 28 These effects on subchondral bone may directly alter the progression of osteoarthritis, or modify cartilage response to mechanical loading.

We observed differential effects of the two doses of strontium ranelate: structure appeared to be modified at both 1 and 2 g/day, while symptoms required 2 g/day for significant amelioration.

This supports published evidence for different aetiological pathways in structural and symptomatic osteoarthritis.29 Osteoarthritic pain may have several causes (synovitis, osteophytes and bone marrow oedema), which are all related to inflammation or bone, rather than cartilage, which is considered to be aneural. We could hypothesise that both dosages affect the aetiological pathways leading to structure modification, but only 2 g/day has an additional effect on pain, possibly through its action on bone though further clinical and preclinical studies are required to explore this in more depth. In line with this, strontium ranelate has strong dose-dependent effects on bone mineral density in osteoporosis with a clinical effect at 2 g/day.30 Further evidence to support heterogeneity between structure and symptoms is the inconsistency noted between radiological grade and knee pain or function.31 32 Alternative interpretations include floor and ceiling effects in pain outcome measures; and the fluctuating symptomatic natural history of osteoarthritis.33 These results raise the interesting question of whether structure modification and pain relief can both be gained by a single drug or whether a combination of drugs would be necessary in osteoarthritis.

Strontium ranelate 2 g/day would therefore be the most appropriate dosage for clinical practice since it was associated with a 27% reduction in radiological JSN (a surrogate of cartilage loss) versus placebo. This translates into nearly a year of average radiological osteoarthritis progression saved over 3 years. Moreover, our results imply that 14 patients (95% CI 9 to 57) would need to be treated with 2 g/day strontium ranelate over the study duration to prevent one case of radiological progression ≥0.5 mm, a threshold known to predict osteoarthritiserelated surgery.34 Moreover, the modification of structure observed in patients with knee osteoarthritis with strontium ranelate in our study is clinically relevant, since it is accompanied by a beneficial effect on symptoms.

There are several limitations to our study. One is the difficulty of evaluating the magnitude of pain changes due to both a relatively high placebo response, which is common to all other osteoarthritis trials,35 and the difficult interpretation of changes evaluated as means as opposed to individual improvements. The dropout rate (14% annualised; mostly for non-medical reasons (consent withdrawal)) could be regarded as a limitation; however, the annualised rate is similar to those reported for other osteoarthritis trials (11% to 16%).33 36–40 Aside from a possible role of the disease itself, the rate of withdrawals may be affected by study duration and the number of assessments in a relatively

### Table 3 Emergent adverse events according to the summary of product characteristics19 and those leading to drug withdrawal

<table>
<thead>
<tr>
<th>Patients with an event (%)</th>
<th>Patients with an event leading to treatment withdrawal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strontium ranelate 1 g/day (n=548)</td>
<td>Strontium ranelate 2 g/day (n=564)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>32 (6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Venous thromboembolism events</td>
<td></td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Allergic dermatitis</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Eczema</td>
<td>5 (0.9%)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (0.7%)</td>
</tr>
</tbody>
</table>

Data are number of events or number of patients (%) in patients included in the study who had taken at least one dose of study drug.
young population. This was anticipated in the sample size calculations, and sensitivity analyses demonstrated minimal impact of missing data. Moreover, the baseline characteristics of dropouts were similar to those of the ITT population and completers, implying that premature withdrawal did not lead to the selection of a particular subgroup. Another limitation is the possibility of different phenotypes in osteoarthritis, suggesting that strontium ranelate might be more effective in certain subgroups of osteoarthritis patients, for example, those with dominant subchondral bone changes. Finally, like all studies of this type, potential causes of radiographical JSN other than cartilage thinning, such as meniscal extrusion, cannot be excluded.

In conclusion, treatment with strontium ranelate 1 and 2 g/day was associated with a significant effect on structure in patients with knee osteoarthritis. Additionally to this structure-modifying activity, there was a beneficial effect on symptoms at 2 g/day.

Author affiliations
1 Department of Public Health Epidemiology and Health Economics, University of Liege, Liege, Belgium
2 Centre of Osteoporosis and Osteoarticular Diseases, Białystok, Poland
3 Centre of National Research on Disability (CONROD), University of Queensland, Herston, Queensland, Australia
4 DeGroot School of Medicine, McMaster University Hamilton, Hamilton, Ontario, Canada
5 INSERM UMR 1033, Service de Rhumatologie et Pathologie Osseuse, Hôpital Edouard Herriot, Université de Lyon, Lyon, France
6 Service de Rhumatologie, Hôpital Henri Mondor, Créteil, France
7 Synarc, Centre for Clinical and Basic Research (CCBR), Ballerup, Denmark
8 Radiology, Medicine, Epidemiology and Orthopedic Surgery, University of California, San Francisco and Synarc, San Francisco, California, USA
9 Rheumatology Department, Hospital Universitario Virgen Macarena, Sevilla, Spain
10 State Institute of Rheumatology, Russian Academy of Medical Sciences, Moscow, Russian Federation
11 Institute of Bone and Joint Research, Royal North Shore Hospital, St Leonards, NSW, Australia
12 Department of Twin Research and Genetic Epidemiology, Kings College London, St Thomas’ Hospital, London, UK
13 MRC Lifecourse Epidemiology Unit, NIHR Musculoskeletal Biomedical Research Unit, University of Southampton, University of Oxford, Oxford, UK

Contributors All authors participated in the design of the study, the interpretation of the data, and the writing of the article. The statistical analysis was done by the sponsor and the main analysis was independently confirmed by the Department of Public Health Epidemiology and Health Economics, University of Liege, Belgium. All authors have read and approved the final version. Study committees, coordinators and investigators are listed in an online appendix.

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