EXTENDED REPORT

Strontium ranelate reduces the progression of experimental dog osteoarthritis by inhibiting the expression of key proteases in cartilage and of IL-1β in the synovium

Jean-Pierre Pelletier,1 Mohit Kapoor,1 Hassan Fahmi,1 Daniel Lajeunesse,1 Alexia Blesius,2 Juliette Mailet,2 Johanne Martel-Pelletier1

ABSTRACT
Objective To explore the disease-modifying effect, under therapeutic conditions, of strontium ranelate (SrRan) on the progression of joint structural changes and on the major pathophysiological pathways in an experimental osteoarthritis dog model.

Methods Dogs underwent sectioning of the anterior cruciate ligament, and 4 weeks after surgery received oral treatment of SrRan 25, 50 or 75 mg/kg per day, or placebo for 12 weeks. Methods included macroscopy, picrosirius red staining, histology, subchondral bone histomorphometry, quantitative PCR, and ELISA for CTX-II level in serum. Strontium plasma and synovial fluid levels were also measured.

Results At steady state, strontium blood exposures were within the clinical therapeutic range of osteoarthritis patients and correlated with strontium concentrations in synovial fluid. SrRan treatment significantly reduced the osteoarthritis cartilage lesions at all doses tested (p < 0.05). Significantly better preservation of the collagen network was also found in SrRan-treated dogs at 50 and 75 mg/kg per day (p = 0.03). The osteoarthritis subchondral bone thickening observed in osteoarthritis-placebo dogs was significantly reduced by SrRan at 50 mg/kg per day (p = 0.02). The increased gene expression levels of MMP-1, MMP-13 and cathepsin K in osteoarthritis cartilage were all significantly reduced by SrRan at 75 mg/kg per day (p ≤ 0.03) as were, in osteoarthritis synovium, IL-1β at 50 and 75 mg/kg per day (p = 0.05) and MMP-3 at all doses tested (p < 0.02). The serum level of CTX-II was reduced (p ≤ 0.04) by SrRan at 16 weeks in dogs treated with 50 and 75 mg/kg per day.

Conclusions This study is the first to demonstrate in vivo an animal model that SrRan reduced the progression of osteoarthritis structural changes. The inhibition of several key proteases as well as IL-1β may have contributed to the beneficial effect of SrRan.

INTRODUCTION

Osteoarthritis is the most frequent arthritic disease and is a crippling condition. Yet, its treatment remains primarily symptomatic in nature with a very limited number of therapeutic options available to reduce its progression.1,2

Significant advances have been made in understanding the pathophysiology of this disease. Moreover, a number of promising therapeutic targets are being identified, among which a consensus has emerged about the important role played by subchondral bone remodelling.3-5 By improving this tissue’s alterations, it might be possible to modify the progression of the disease’s structural changes.

Strontium ranelate (SrRan) is indicated for the treatment of osteoporosis.6-8 On human osteoarthritis subchondral bone osteoblasts, SrRan was found to inhibit these cells’ resorptive properties by reducing the synthesis of some matrix metalloproteinases (MMP) and modulating osteoprotegerin and receptor activator of nuclear factor κB ligand levels.9 SrRan was also reported to stimulate the cartilage matrix formation.10 Recent data from a clinical trial demonstrated that it can reduce the progression of the radiographic features of spinal osteoarthritis and back pain in women with osteoporosis.11 In a post-menopausal clinical trial, this drug was also found to reduce the urinary level of the cartilage biomarker collagen type II degradation (CTX-II).12

Anterior cruciate ligament (ACL) transection in dogs is a model of experimental osteoarthritis that has been used extensively and found to be reliable to study the disease pathophysiology including the cartilage, subchondral bone and synovial membrane structural changes.13,14 In contrast to smaller animal models, the size of the dog model provides a large amount of tissue that can be used for multiple analyses. Moreover, this animal model has been used successfully in testing the therapeutic effectiveness of disease-modifying osteoarthritis drugs (DMOAD), some of which were demonstrated to translate positively to findings from clinical trials in knee osteoarthritis patients.15,16

A number of drugs reducing subchondral bone remodelling have been found also to reduce the progression of cartilage lesions.15 These alterations have been demonstrated to be related to a combination of mechanical and biochemical abnormalities including an excess production of several proteases, nitric oxide and proinflammatory cytokines to which the subchondral bone is believed to contribute significantly.3 All together these findings provide strong support to test the hypothesis of the SrRan DMOAD potential.
We tested the effect of SrRan, at therapeutic doses, in the ACL dog model. The effects of the drug on osteoarthritis joint structural changes were evaluated on both the cartilage and subchondral bone. Moreover, analysis was also done on the collagen matrix network as well as the major pathophysiological pathways of the disease, namely the level of gene expression of some proteolytic enzymes and of interleukin (IL) 1, factors known to be involved in and most relevant to osteoarthritis pathophysiology.

**MATERIALS AND METHODS**

**Experimental groups**

Forty mature adult crossbred (mongrel) female dogs (1–3 years old), each weighing 25±3 kg, were used in this study. All aspects of the animal surgery and care were as previously described. The study protocol was approved by the institutional ethics committee and conducted according to the institutional animal protection committee and the Canadian Council on Animal Care regulations.

**Treatment groups**

The dogs were randomly assigned according to their body weight and divided into four experimental groups to which the animal care personnel were blinded. Group 1 (n=10) received placebo (empty gelatine capsules) and groups 2, 3 and 4 (n=10/group) received encapsulated SrRan at doses of 25, 50 and 75 mg/kg per day, respectively (expressed as an anhydrous compound; Servier, Suresnes, France), by mouth once daily between 07:30 and 08:30 hours, at least 2 h before feeding, starting 4 weeks after surgery and continuing until the dogs were sacrificed 12 weeks later. Dose levels were selected considering previous results from two repeated-dose studies performed on female beagles (unpublished data; Servier internal report) and strontium blood exposure in patients treated with 1 and 2 g/day of SrRan (unpublished data; Servier internal report). The low dose (25 mg/kg per day) was chosen to aim for the half-maximal response, the middle dose (50 mg/kg per day) to achieve the optimal response and the high dose (75 mg/kg per day) was a reasonable multiple of the middle dose.

**Circulating drug levels**

The plasma exposures to strontium (ie, area under the curve in 24 h) were calculated based on plasma concentrations of strontium measured in all SrRan-treated animals at steady state (ie, after 11 weeks of treatment) at eight time points (0 h, ie, just before dosing, and 1, 2, 3, 4, 6, 10 and 24 h post-dosing). The synovial fluid from osteoarthritis (operated) and contralateral (unoperated) knees of all SrRan-treated animals was extracted at the time of death. Strontium levels in plasma and synovial fluid were measured by a validated analytical method using inductively coupled plasma optical emission spectroscopy (Quality Assistance, Donstienes, Belgium) (unpublished data; Servier internal report).

**Macroscopic grading**

Following killing, the osteoarthritis and contralateral knees of each dog were dissected on ice and examined for gross morphological changes by two independent observers blinded to the treatment groups. Each macroscopic cartilage lesion was measured (surface, mm²) with an electronic digital calliper and graded (depth, score 0–4) as follows: 0=normal surface; 1=minimal fibrillation or a slight yellowish discoloration of the surface; 2=erosion extending into superficial or middle layers only; 3=erosion extending into deep layers; and 4=erosion extending to subchondral bone, as previously described. For the cartilage, histological evaluation was performed on sagittal full thickness of the tissue and included the subchondral bone from each femoral condyle and tibial plateau in line with the Osteoarthritis Research Society International recommendations. Two independent observers blinded to the treatment graded the severity (score 0–29) of the osteoarthritis lesions as follows: 0–10=structural changes; 0–12=cellular changes; 0–4=stainability with safranin-O; and 0–3=pannus formation. The cartilage was divided into three subregions as previously described, the final score corresponding to the sum of the scores for the three subregions (ie, score 0–27).

Each section of the articular cartilage was also processed to study the collagen infrastructure using the picrosirius red-polarisation staining method as previously described by our group. In brief, this evaluates the collagen disorganisation on a scale of 0–4 as follows: 0=normal architecture; or loss of integrity in 1=superficial zone; 2=superficial and middle layers; 3=down to the deep layer; and 4=throughout the entire thickness. The final score was the sum of the scores from the three subregions (ie, score 0–12).

**Histological grading**

The cartilage of each knee of all animals was removed from the weight-bearing lesional areas of the femoral condyles and tibial plateaus, and the synovial membrane was dissected away. Tissues were prepared and stained for histological evaluation as previously described. For the cartilage, histological evaluation was performed on sagittal full thickness of the tissue and included the subchondral bone from each femoral condyle and tibial plateau in line with the Osteoarthritis Research Society International recommendations. Two independent observers blinded to the treatment graded the severity (score 0–29) of the osteoarthritis lesions as follows: 0–10=structural changes; 0–12=cellular changes; 0–4=stainability with safranin-O; and 0–3=pannus formation. The cartilage was divided into three subregions as previously described, the final score corresponding to the sum of the scores for the three subregions (ie, score 0–27).

**Synovial membrane**

Samples including the subchondral and trabecular bones were dissected from the weight-bearing surfaces of the tibial plateaus of the osteoarthritis and contralateral knees of all dogs. Specimens were processed as previously described.

**Bone histomorphometry**

Bone histomorphometry performed on three non-consecutive sections of each specimen using a method modified from Matsui et al. From each section, three representative fields (2000 × 1000 μm) were identified (original magnification ×60). The calcified cartilage/subchondral bone junction was used as the upper limit of each field. All measurements were made by a single experienced observer who was blinded to the experiment.

The histomorphometric data were collected using the standard convention of Parfitt et al and included the bone volume to tissue volume ratio (BV/TV%), trabecular thickness (Tb Th, μm), and subchondral bone plate thickness (μm). The measurements taken for the three fields were then averaged for each section as previously described and were used for the statistical analysis.

**Real-time PCR**

Total RNA was extracted from cartilage and synovial membrane samples collected from osteoarthritis and contralateral knees of all animals using Trizol reagent (Invitrogen, Carlsbad, California, USA) followed by RNeasy Plant Mini Kit purification (Qiagen, Valencia, California, USA). The RNA was then processed as described and PCR performed with the...
Rotor-Gene RG-3000 (Qiagen) using the QuantiTect SYBR Green PCR kit (Qiagen) following the manufacturer’s specifications. Gene quantification in cartilage was performed using primers for MMP-1 (5′-AAGCAGGTCTACAGGCCC-3′ (sense) and 5′-AGTCAGTGTCATCTGCG-3′ (antisense)), MMP-13 (5′-TTGGTAGATGTGACACTC-3′ (sense) and 5′-ATCTGGCAAGATAAAATGTCC-3′ (antisense)), ADAMTS5 (5′-GTCGGCAGCATATCTC-3′ (sense) and 5′-TGATGGTGGCTGAAGTACAC-3′ (antisense)), cathepsin K (5′-TGTGAAAGAGTGGGTGCT-3′ (sense) and TCGGCGACCTGGCC-3′ (antisense)), and in the synovial membrane for MMP-2 (5′-GACCAGGACTGGCTCATTTG-3′ (sense) and 5′-GTGTAATGTTGGCTTCAACAG-3′ (antisense)), MMP-3 (5′-CAATTCGACAGATGCCATG-3′ (sense) and 5′-GTAAGCTCTGGATCATCAG-3′ (antisense)), MMP-9 (5′-AACAGACTCCGACGTCGAC-3′ (sense) and 5′-AGGCCTGTGCGCCAGGATCGACGACCAGG-3′ (antisense)), and GAPDH (5′-AGGCTGTGGCTCAGGTTCAG-3′ (sense), 5′-CTCGCCAGTGAAATGATG-3′ (antisense)) as the housekeeping gene. The primer efficiency for the target gene was the same as the housekeeping gene GAPDH. Plasmid DNA containing the CATCAGAGGTGGAAGAGTGGGTGTC-0 gene of interest was used to generate a standard curve. The data for the housekeeping gene GAPDH.

RESULTS

Safety

All dogs completed the study and was well tolerated throughout the dosing period. There was no significant change in the weight of the dogs or evidence of any meaningful side effects during the conduct of the study.

Circulating drug levels

The serum concentrations of Sr (ie, area under the curve in 24 h) measured at steady state in animals treated with SrRan at dose levels of 25, 50 and 75 mg/kg per day were, respectively, 98 ±22, 196±42 and 237±46 mg/l, which were included in the range of strontium serum exposures observed in the pivotal clinical study with osteoarthritis patients treated at doses of 1 g and 2 g/day of SrRan (unpublished data; Servier internal report). The synovial fluid strontium concentrations in the osteoarthritic knee of 3.05±0.72, 3.29±1.93 and 7.74±2.50 mg/l at dose levels of 25, 50 and 75 mg/kg per day, respectively, were similar to those in the contralateral knee (control placebo) (ratios range from 1.0 to 1.2) and correlated to strontium plasma exposures (r²=0.92 and r²=0.95, respectively) for osteoarthritis knees and the control placebo.

Evaluation of cartilage and synovial membrane lesions

Only minimal macroscopic cartilage lesions were found in the control placebo group (table 1). In the osteoarthritis knee, the macroscopic lesions in the SrRan treatment groups compared to those in the osteoarthritis placebo group were decreased in size and depth on both the femoral condyles and the tibial plateaus (figure 1, table 1). A significant reduction in lesion surface was found at all SrRan doses tested on the tibial plateaus (p=0.02) and at 50 mg/kg per day of SrRan on the femoral condyles (p=0.04). A significant reduction in lesion depth by SrRan treatment was found on the femoral condyles at 50 and 75 mg/kg per day (p=0.05, p=0.01, respectively). The trend test was significant for cartilage lesion surface on both tibial plateaus (p=0.02) and femoral condyles (p=0.05), and for lesion depth on femoral condyles (p=0.03) (table 1). The severity of osteoarthritis histological lesions in cartilage and synovium was found to be similar in all therapeutic groups compared to osteoarthritis placebo for the total histological score as well as for all subscores (data not shown).

Table 1 Macroscopic osteoarthritis cartilage lesions on femoral condyles and tibial plateaus

<table>
<thead>
<tr>
<th>Groups</th>
<th>Dogs (n)</th>
<th>Surface Femoral condyles (mm²)</th>
<th>Tibial plateaus (mm²)</th>
<th>Depth Femoral condyles (score 0–4)</th>
<th>Tibial plateaus (score 0–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control placebo</td>
<td>10</td>
<td>1.7±5.4 (p=0.0001)</td>
<td>68.4±43.7 (p=0.0001)</td>
<td>0.2±0.6 (p=0.0001)</td>
<td>0.9±0.6 (p=0.0001)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>10</td>
<td>129.6±63.4</td>
<td>180.7±49.5</td>
<td>2.7±0.9</td>
<td>2.9±0.6</td>
</tr>
<tr>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SrRan (25 mg/kg per day)</td>
<td>10</td>
<td>126.0±63.7</td>
<td>151.1±60.5 (p=0.03)</td>
<td>2.6±1.1</td>
<td>2.6±0.7</td>
</tr>
<tr>
<td>SrRan (50 mg/kg per day)</td>
<td>10</td>
<td>84.5±62.1 (p=0.04)</td>
<td>139.1±49.4 (p=0.02)</td>
<td>2.0±1.2 (p=0.05)</td>
<td>2.7±0.7</td>
</tr>
<tr>
<td>SrRan (75 mg/kg per day)</td>
<td>10</td>
<td>107.3±64.8</td>
<td>146.4±58.0 (p=0.02)</td>
<td>2.2±1.0 (p=0.01)</td>
<td>2.7±0.8</td>
</tr>
</tbody>
</table>

Values are mean±SD of the lesion scores on the medial and lateral femoral condyles or tibial plateaus. Statistical analyses were performed by Mann–Whitney U test versus the osteoarthritis placebo group and p≤0.05 was considered significant. Dose effect of the drug treatment was tested using the Jonckheere–Terpstra trend test: surface femoral condyles (p=0.05); surface tibial plateaus (p=0.02); depth femoral condyles (p=0.03); depth tibial plateaus (NS). SrRan, strontium ranelate.
Figure 1  Macroscopic appearance of cartilage from the femoral condyles (left) and the tibial plateaus (right) of control placebo, osteoarthritis (OA) placebo and strontium ranelate (SrRan)-treated dogs at 16 weeks post-surgery. Erosion and pitting (areas indicated by circles) of the condyles and plateaus were evident in the osteoarthritis placebo-treated dogs. In SrRan-treated dogs, a decrease in the severity of lesions on the condyles and plateaus was seen. A, anterior; P, posterior.
The cartilage collagen network disorganisation score in the osteoarthritis cartilage measured in the osteoarthritis placebo dogs (5.4±1.3) was significantly greater than the control placebo (2.3±1.5; p=0.001) and was significantly decreased at 50 (p=0.03) and 75 (p=0.03) mg/kg per day of SrRan: 3.9±1.5 and 4.3±0.7, respectively (figure 2). The trend test was found to be significant (p=0.02).

**Bone histomorphometry**

Histomorphometric analysis demonstrated no difference for the BV/TV or the Tb.Th of the osteoarthritis and contralateral knees in the SrRan-treated dogs at any of the doses tested compared to the osteoarthritis placebo group, respectively (data not shown). However, the subchondral bone plate thickness in the placebo-treated dogs was significantly higher in the osteoarthritis placebo versus control placebo knee (824.5±106.7 μm vs 740.2±62.9 μm; p=0.04). Treatment with SrRan reduced the subchondral bone plate thickness of the osteoarthritis knee (25 mg/kg per day, 758.4±120.9 μm; 50 mg/kg per day, 686.9±109.9 μm; 75 mg/kg per day, 766.5±103.1 μm) and compared to osteoarthritis placebo, statistical significance was reached only at 50 mg/kg per day of SrRan (p=0.02) (figure 3).

**Expression of factors**

The expression levels of all factors measured were found to be significantly increased in osteoarthritis placebo versus control placebo (table 2) in cartilage (MMP-1, MMP-13, ADAMTS5,
Table 2 Gene expression levels in cartilage and synovial membrane

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cartilage</th>
<th>Synovial membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMP-1 (10^−3)</td>
<td>MMP-13</td>
</tr>
<tr>
<td>Control placebo</td>
<td>0.8±0.2 (p=0.0001)</td>
<td>5.6±5.3 (p=0.002)</td>
</tr>
<tr>
<td>Osteoarthritis placebo</td>
<td>17.5±20.9</td>
<td>28.2±19.2</td>
</tr>
<tr>
<td>SrRan (25 mg/kg per day)</td>
<td>18.8±13.7</td>
<td>27.5±30.3</td>
</tr>
<tr>
<td>SrRan (50 mg/kg per day)</td>
<td>12.7±20.4</td>
<td>19.5±24.3</td>
</tr>
<tr>
<td>SrRan (75 mg/kg per day)</td>
<td>4.2±5.3 (p=0.02)</td>
<td>12.3±8.2 (p=0.03)</td>
</tr>
</tbody>
</table>

Values are mean±SD. Statistical analyses were performed by Mann–Whitney U test versus the osteoarthritis placebo group and p≤0.05 was considered significant. Dose effect of drug treatment was tested using the Jonckheere–Terpstra trend test: cartilage, MMP-1 (p=0.002); MMP-13 (p=0.02); ADAMTS5 (p=0.03); cathepsin K (p=0.001); synovial membrane, IL-1β (p=0.02); MMP-3 (p=0.0001). For MMP-3 in the synovial membrane, n=5.

IL, interleukin; MMP, matrix metalloproteinases; SrRan, strontium ranelate.

cathepsin (MMP-3), except for IL-1β in synovium for which a trend was observed (p=0.09).

In cartilage, a reduction in messenger RNA levels, which reached statistical significance compared to osteoarthritis placebo was found for MMP-1 (p=0.02), MMP-13 (p=0.05) and cathepsin K (p=0.0001) at 75 mg/kg per day of SrRan, with a trend towards significance for ADAMTS5 at 75 mg/kg per day of SrRan (p=0.06) (table 2). In the synovial membrane, the gene expression level of IL-1β was significantly reduced by SrRan treatment at both 50 and 75 mg/kg per day (p=0.05) as were the MMP-3 mRNA levels at all concentrations tested (25 mg/kg per day, p=0.02; 50 mg/kg per day, p=0.008; 75 mg/kg per day, p=0.008) (table 2). Drug treatment had no effect on the level of expression of MMP-1, MMP-2 and MMP-9 in the synovial membrane (data not shown). The trend test was found to be significant for all factors studied with SrRan treatment (table 2).

Levels of CTX-II in serum

The levels of CTX-II in serum were reduced by SrRan treatment at 8 weeks at the dosage of 50 mg/kg per day (p=0.01) and at 16 weeks at both 50 and 75 mg/kg per day (p=0.03, p=0.04, respectively), with the trend test significant (p=0.005) at the latter time (table 3).

DISCUSSION

This study demonstrated that SrRan can reduce the progression of osteoarthritis structural changes in the ACL dog model, namely the erosion of articular cartilage and thickening of the subchondral plate. The effect of the drug treatment was shown to be associated with a reduction in the expression levels of key catabolic factors involved in osteoarthritis structural changes.

The experiments were conducted under therapeutic conditions to reproduce conditions that are as close as possible to the natural disease. The findings of structural and metabolic changes observed in the osteoarthritis placebo-treated dogs are in line with previous findings in this osteoarthritis model.

In cartilage, the significant reduction by SrRan of the osteoarthritis lesions and the collagen disorganisation was found to be dose related, being generally more pronounced with the two highest doses tested. A similar trend was found for the reduction in the expression levels of the proteases in cartilage and CTX-II in serum. These findings bring additional support to the relationship between the breakdown of the matrix and the level of proteases. In turn, these results are in line with a number of previous studies in this osteoarthritis model that have demonstrated that drugs and agents that decrease the level of key proteases in osteoarthritis cartilage also reduce the progression of lesions.

Although the exact mechanism of action of SrRan on these proteases’ production remains to be determined, recent data on the Wnt system could provide an interesting explanation. The Wnt-induced signalling protein 1 (WISP-1) was found to be markedly increased in articular tissues in two experimental osteoarthritis mouse models and in humans, and to induce in an IL-1β-independent manner the expression level of several MMP as well as ADAMTS. In addition, although SrRan treatment had no particular effect of reducing the histological severity of synovitis, it effectively reduced the expression of IL-1β, a most relevant pro-inflammatory cytokine produced by the osteoarthritis synovium. This effect probably adds to that of SrRan on the protease expression and is relevant to a DMOAD effect of the drug. Although the mechanism by which SrRan reduces IL-1β remains unknown, the recent report that SrRan can antagonise nuclear factor κB activation in osteoblasts and osteoclasts may provide an explanation for this effect, as IL-1β is a well known activator of that pathway.

In osteoarthritis animal models, a remodelling of the subchondral bone is believed to be biphasic in nature, with a predominance of bone resorption in the early phase followed by a deposition phase in which there is an increase in bone formation. An increase in subchondral bone resorption has previously been reported in the dog ACL model in the early phase of the disease, such as 8–10 weeks post-surgery. In the present study, which lasted 16 weeks, a thickening of the...
subchondral bone in the osteoarthritis placebo group indicates that the remodelling process of this tissue had entered into a deposition phase. Previous studies have reported that under these conditions, the subchondral bone matrix becomes under-mineralised due to an abnormal phenotype in the newly synthesised type I collagen. These changes induced an abnormal biophysical property of the tissue as well as an abnormal homeostasis between the subchondral bone and the cartilage that can promote the development of cartilage lesions. Treatment with SrRan was found to reduce the thickening of the subchondral bone plate to a value similar to that found in the contralateral knee, indicating that the drug treatment had a positive effect on the metabolism of osteoarthritis subchondral bone remodelling of ‘normalising’ the structure of the tissue. This protective effect on subchondral bone may in fact be a determining factor of the DMOAD effect of SrRan, in addition to the reduction in catabolic pathways, which may be partly reflected by the reduction in cartilage changes. An inhibition of the excessive remodelling (resorption) in the early phase of the disease would be an interesting hypothesis that would be in line with the known mode of action of the drug and in accordance with the in-vitro data showing the reduced resorptive properties of SrRan on osteoarthritis subchondral bone osteoblasts. Additional in-vivo studies of SrRan on the subchondral bone remodelling such as on the bone marrow lesions should be explored, as these lesions have been associated with cartilage lesions in this animal model as well as in humans. Moreover, a study of longer duration should also be performed that would allow better knowledge of the long-term effect of the drug, which is most relevant in the context of a chronic disease process.

In summary, this study provides novel information about the mode of action through which SrRan exerts a beneficial effect on osteoarthritis joint structures, which is a strong rationale supporting the positive finding of the SrRan phase III clinical trial in knee osteoarthritis patients.

Acknowledgements The authors would like to thank Christelle Boileau, Frédéric Parié, Stéphane Tremblay and Changshun Geng for their expert technical assistance and Virginia Wallis for assistance with the manuscript preparation.

Contributors All the authors have read and approved the manuscript and contributed to the study design, data analysis and interpretation of data, and writing the paper. A data review committee (JPP, JMP) analysed the data and was responsible for their accuracy.

Funding This study was supported in part by a grant from Servier (Suènnes, France).

Competing interests JMP and JPP received a grant and consulting fees from Servier, (Suènnes, France). AB and JM are employees of Institut de Recherches Internationales Servier. MK, HF, DL declare no competing interests.

Provenance and peer review Not commissioned; externally peer reviewed.

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Ann Rheum Dis 2013 72: 250-257 originally published online October 13, 2012
doi: 10.1136/annrheumdis-2012-201710

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