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EXTENDED REPORT

Disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee osteoarthritis study SEKOIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss

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ABSTRACT

Objective To explore, using MRI, the disease-modifying effect of strontium ranelate (SrRan) treatment on cartilage volume loss (CVL) and bone marrow lesions (BMLs) in a subset of patients from a Phase III clinical trial in knee osteoarthritis (OA) (SrRan Efficacy in Knee OsteoarthrItis triAl (SEKOIA)).

Material and methods Patients with primary symptomatic knee OA were randomised to receive either SrRan 1 g/day or 2 g/day or placebo (SEKOIA study). A subset of these patients had MRIs at baseline, 12, 24 and 36 months to assess the knee cartilage volume and BMLs. Missing values were imputed and the analyses were adjusted according to Bonferroni.

Results In this MRI subset, the distribution of patients (modified intention-to-treat; n=330) was 113, 105 and 112 for SrRan 1 g/day, 2 g/day and placebo, respectively. The groups were fairly balanced at baseline regarding demographics, clinical symptoms or imaging characteristics. Treatment with SrRan 2 g/day significantly decreased CVL on the plateaus at 12 (p=0.002) and 36 (p=0.003) months compared with placebo. Of note, in the medial femur and plateau, SrRan 1 g/day, but not SrRan 2 g/day, had more CVL than placebo. In patients with BML in the medial compartment at baseline, the BML score at 36 months was decreased in both treatment groups compared with the placebo group (SrRan 1 g/day, p=0.002 and SrRan 2 g/day p=0.001, respectively), and CVL significantly decreased with SrRan 2 g/day (p=0.023) in the plateau compared with placebo.

Conclusions In knee OA patients, treatment with SrRan 2 g/day was found to have beneficial effects on structural changes by significantly reducing CVL in the plateau and BML progression in the medial compartment.

INTRODUCTION

Osteoarthritis (OA), the most common form of arthritis, is characterised mainly by degradation and loss of articular cartilage, subchondral bone remodelling and synovial membrane inflammation. The real therapeutic challenge for OA is the development of disease-modifying OA drugs (DMOADs) that can slow down the disease progression. Among the drugs that modify bone turnover, strontium ranelate (SrRan) is of particular interest as it has been demonstrated to have DMOAD properties.[1–3]

SrRan is a drug that inhibits in vitro bone resorption and induces a relative increase in bone formation[4 5] and is used in the treatment of osteoporosis.[6–8] A recent 3-year double-blind, randomised, placebo-controlled Phase III trial, the SrRan Efficacy in Knee OsteoarthrItis triAl (SEKOIA) (registration ISRCTN41323372), demonstrated that treatment with SrRan was associated with a significant protective effect on joint structure and clinically relevant improvement of symptoms in patients with knee OA.[1] In brief, the groups treated with SrRan at both 1 g/day and 2 g/day had less joint space narrowing (JSN) and fewer radiological progressors compared with placebo. In addition, patients treated with SrRan 2 g/day (intention-to-treat (ITT) population) had a greater reduction in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score and pain subscore than the placebo. Moreover, the drug was previously found to reduce the radiological progression of spinal OA and back pain in women with osteoporosis and OA after a 3-year treatment.[3]

In vitro, SrRan inhibited the production of key factors that lead to OA subchondral bone osteoblast bone resorption such as the matrix metalloproteinase (MMP)-2 and MMP-9.[9] In vivo in an experimental dog OA model, therapeutic dosages of SrRan significantly reduced the progression of knee OA structural changes and inhibited the expression of interleukin 1β (IL-1β) and key proteases involved in cartilage degradation.[2]

MRI allows the direct, precise and reliable evaluation of joint structural changes cross-sectionally and longitudinally. In recent years, quantitative MRI (qMRI)[10–12] has been instrumental in the successful evaluation of the joint structure modifying potential of a number of drugs and agents in clinical trials.[11 13–17]

The aim of this study was to explore, using qMRI, the effect of SrRan treatment on cartilage volume loss (CVL) and bone marrow lesions (BMLs) over time in a subset of patients from the SEKOIA trial.

PATIENTS AND METHODS

Study design, patient selection and treatment

The SEKOIA trial was a 3-year international multicentre, randomised, double-blind, placebo-controlled Phase III trial evaluating the structural (x-rays) and symptomatic effects of SrRan (1 or 2 g/day) in patients (n=1683) with knee OA.[1] The selection and exclusion criteria of the SEKOIA trial have been previously described.[1 18] The study design included a subset of patients from this cohort (about 30%) who would be selected to undergo MRI examinations and be included in the MRI substudy (figure 1). The sites were selected based on the availability of proper imaging facilities for MRI examinations. The number of sites was determined based on the total number of patients needed to be recruited for the MRI substudy with an original target of approximately 500 patients. Therefore, 541 patients from 23 MRI imaging centres were enrolled. From those, 103 patients were eliminated due to having no assessable MRI at baseline, resulting in 438 patients consecutively randomised (figure 1).

Knee MRI acquisition

MRI scans were performed at baseline and at 12, 24 and 36 months using 1.5 Tesla scanners (Siemens, Erlangen, Germany or General Electric, Milwaukee, Wisconsin, USA) with a dedicated knee coil[19] (see online supplementary methods).

CVL and change over time

The cartilage volume and change were measured using the proprietary software, Cartiscope (ArthroLab, Montreal, Quebec, Canada) as described[20] (see online supplementary methods). CVL over time was calculated for the entire (global) knee, the medial and lateral compartments, the femur, the plateau and their subregions, as described.[21]

Scoring of BMLs

Assessment of BMLs was performed in the same MRI sequences used for the cartilage assessment as described[22 23] (see online supplementary methods).

Symptoms

Disease symptoms were assessed at baseline as described[1] using the WOMAC Questionnaire[24] and the Visual Analogue Scale for global knee pain (0 mm=no pain, 100 mm=most severe pain).

Knee x-rays

The minimal joint space width (JSW) (mm) at the narrowest point in the medial tibiofemoral compartment was measured on a fixed flexion posteroanterior view (fixed angle 10°) at baseline and at 12, 24 and 36 months follow-up using a standardised semiautomated computerised method as previously described.[1 18]

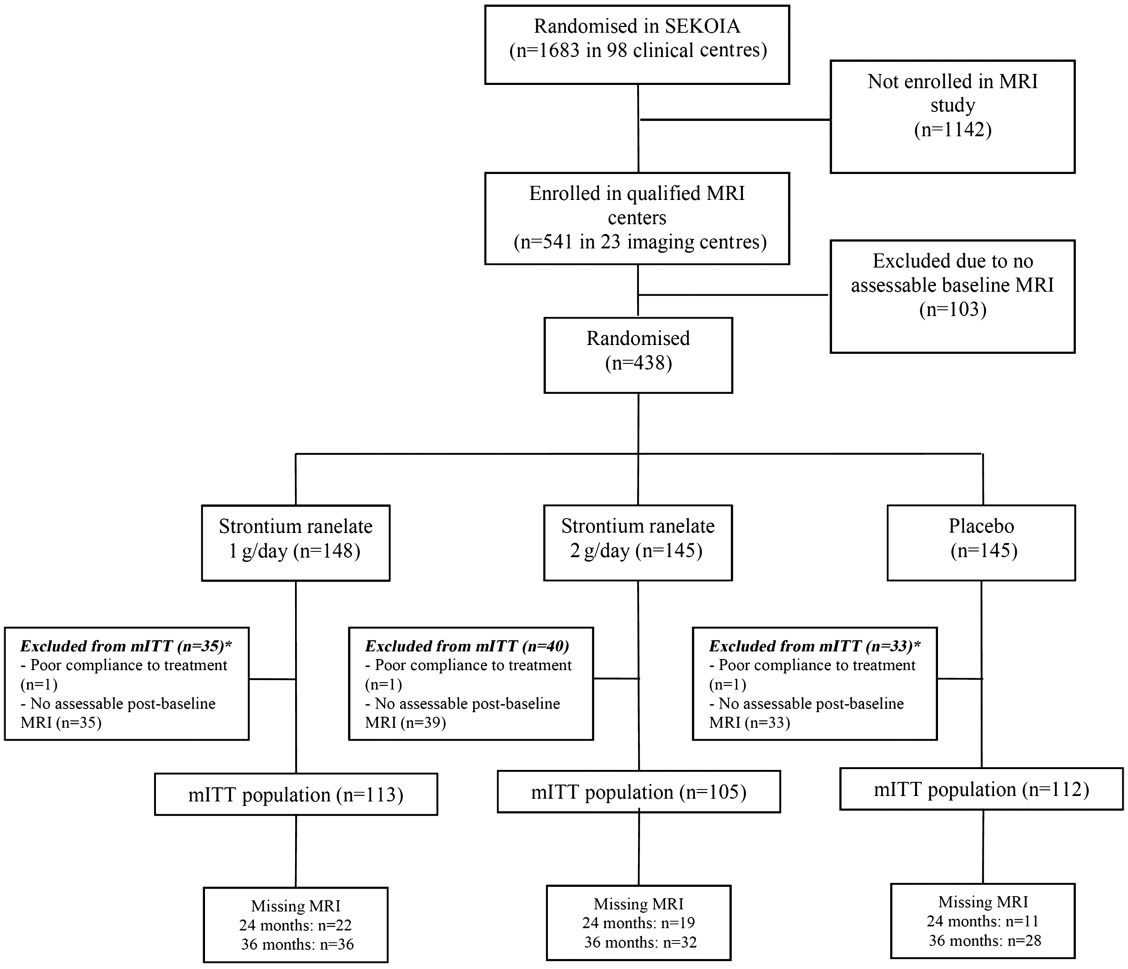

Figure 1 Trial profile. Modified intention-to-treat (mITT). Patients received at least one treatment and had at least two MRIs. *Patients may have had more than one reason for exclusion.

Outcomes

The primary endpoint of the study was the change in the cartilage volume in the global knee and in the medial and lateral compartments over 36 months in the treatment groups compared with placebo. The secondary endpoint was change in BML over 36 months.

Statistical analyses

Analyses were conducted on the modified intention-to-treat (mITT) population (n=330, 75% of the randomised patients), which included all randomised patients who received at least one dose of treatment and had at least two MRI examinations. The mITT analyses were carried out by imputing the missing data to the average change recorded (mean value imputed) among patients within their corresponding group at a specific time point (12, 24 and 36 months).

Comparison between the three groups was first performed using the Kruskal–Wallis test (non-normal distribution) or the χ^2 test for categorical variables. When the p values were <0.10, each treatment group was further analysed as two-by-two comparison using the Mann–Whitney test or the χ^2 test with Bonferroni adjustment. Finally, Spearman's correlation between % CVL and BML score change within each group and Pearson's correlation between % CVL in the medial tibiofemoral compartment and JSW loss within each group were performed.

RESULTS

Patient disposition

This study evaluated a subset (n=438) of the randomised patients from the original ITT population (n=1371) of the SEKOIA trial, who underwent MRI examinations (SrRan 1 g/day, n=148; SrRan 2 g/day, n=145; placebo, n=145) (figure 1). One hundred and eight patients (25%) were further eliminated because post-baseline MRI was not available or assessable, including three patients who also did not take the treatment. The mITT population included 330 patients (75% of randomised patients). No significant differences were found when comparing the original ITT population (n=1371) with the mITT population except for age in the SrRan 1 g/day group (60±7 years in the mITT population compared with 62±7 years in the original ITT population, p=0.001), which does not seem clinically relevant. Of note, the baseline demographics of the 330 included and the 108 excluded participants were found to be fairly similar except for gender, with more women in the 108 excluded participants, and baseline WOMAC physical score (p=0.017 and p=0.045, respectively). No significant differences were found with regard to the baseline cartilage volumes in the global knee and in the medial and lateral compartments (data not shown).

Table 1 mITT baseline demographics, clinical and imaging characteristics

	SrRan 1 g/day (n=113)	SrRan 2 g/day (n=105)	Placebo (n=112)	p Value*	Placebo versus SrRan 1 g/day p Value**	Placebo versus SrRan 2 g/day p Value**	SrRan 1 g/day versus SrRan 2 g/day p Value**
Demographics and clinical							
Age, years	60±7	63±7	62±8	0.062	0.307	>0.999	0.059
Women, n (%)	70 (62%)	70 (67%)	76 (68%)	0.616†			
BMI, kg/m²	30±5	30±5	30±5	0.684			
WOMAC							
Pain (0–100)	42.0±20.4	44.5±20.0	38.5±21.4	0.068	0.438	0.079	0.927
Function (0–100)	42.5±20.8	42.3±23.1	39.3±22.4	0.476			
Stiffness (0–100)	47.1±23.4	48.9±24.8	43.0±23.4	0.182			
Total (0–300)	132.9±59.0	135.1±62.1	122.1±62.9	0.284			
Pain VAS (0–100 mm)	51.1±21.5	54.9±23.2	49.8 ±23.9	0.211			
Imaging							
Kellgren–Lawrence, n (%)							
Grade 1	–	–	–				
Grade 2	77 (68%)	68 (65%)	75 (67%)	0.866†			
Grade 3	36 (32%)	37 (35%)	37 (33%)				
Joint space width (mm)	3.49±0.85	3.54 ±0.82	3.50 ±0.74	0.820			
MRI (mm³)							
Meniscal extrusion (yes)	19 (17%)	15 (14%)	26 (23%)	0.210†			
Presence of BML (yes)	44 (39%)	35 (33%)	46 (41%)	0.482†			
Global knee	11 439±3012	11 708±3313	11 076±2827	0.400			
Femur	7883 ±2141	8138 ±2276	7686 ±2003	0.374			
Plateau	3556 ±966	3570 ±1145	3390 ±895	0.430			
Medial compartment							
Femur	3833 ±1009	3965 ±1075	3730 ±955	0.286			
Plateau	1611 ±448	1624 ±523	1540 ±432	0.509			
Lateral compartment							
Femur	4050 ±1213	4173 ±1274	3956 ±1118	0.555			
Plateau	1945 ±580	1946 ±675	1849 ±534	0.524			

The results are shown as mean±SD unless otherwise indicated.
p Values were assessed using the *Kruskal–Wallis test, the †χ^2 test and the **Mann–Whitney test with Bonferroni adjustment.
BMI, body mass index; BML, bone marrow lesion; mITT, modified intention-to-treat; n, number of participants; SrRan, strontium ranelate; VAS, Visual Analogue Scale (0 mm=no pain, 100 mm=most severe pain); WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (each subscale, 100=worst score; total scale, 300=worst score).

Baseline characteristics

There were no statistically significant between-group differences at baseline with regard to demographics, clinical symptoms or imaging characteristics of the mITT patients (table 1).

Cartilage volume loss

A significant reduction in CVL was found in the global plateau in the SrRan 2 g/day group at 12 and 36 months compared with the placebo, with SrRan 2 g/day being superior to SrRan 1 g/day at all three time points (table 2).

In the medial compartment (table 2), there was a trend for SrRan 2 g/day to decrease the CVL in the plateau at 12 months compared with the placebo. Compared with SrRan 1 g/day, a significantly greater effect of SrRan 2 g/day was found at all time points in the plateau. In the medial femur, a decrease in CVL was found in the SrRan 2 g/day versus 1 g/day group at 36 months. Of note, in the medial femur and plateau, the differences found at 36 months between placebo and SrRan 1 g/day, although significant, were small and unlikely to be clinically relevant, as previously described.[25]

In the lateral compartment, there was a sustained and significant reduction in CVL in the plateau in patients treated with SrRan 2 g/day at all time points compared with placebo and at 24 and 36 months compared with SrRan 1 g/day (table 2). SrRan 1 g/day showed a significant reduction at 36 months compared with placebo (table 2). As age and WOMAC pain tended to differ between groups at baseline (table 1), we performed a multivariate regression adjusted for these factors, which still confirmed the beneficial effect of SrRan on the lateral plateau (data not shown).

Bone marrow lesions

The BMLs present at baseline were detected mainly in the medial compartment with very few patients having BML in the lateral compartment and those were of a small size (data not shown). Therefore, analyses were performed only on the medial compartment where BMLs were found at an increased prevalence in the femur compared with the plateau (table 3).

In the medial compartment, SrRan at both 1 g/day and 2 g/day significantly reduced the BML score change at 36 months compared with placebo. This is associated with a significant decrease in the medial femur and central condyle (table 3).

Additional analysis dividing the change in BML score into three categories (increase, decrease and stable) revealed a trend

Table 2 Cartilage volume loss (%)

	SrRan 1 g/day (n=113)	SrRan 2 g/day (n=105)	Placebo (n=112)	p Value*	Placebo versus SrRan 1 g/day p Value**	Placebo versus SrRan 2 g/day p Value**	SrRan 1 g/day versus SrRan 2 g/day p Value**
Global							
Knee (months)							
12	−3.53±3.23	−3.37±2.38	−3.59±2.79	0.871			
24	−5.51±2.92	−4.91±2.60	−4.93±3.00	0.059	0.159	>0.999	0.100
36	−7.22±2.90	−6.84±2.90	−6.94±2.90	0.122			
Femur (months)							
12	−3.28±4.14	−3.73±3.09	−3.38±3.34	0.604			
24	−5.31±3.70	−4.98±3.08	−4.59±3.35	0.136			
36	−6.93±3.57	−6.84±3.59	−6.35±3.19	0.051	0.159	0.181	0.347
Plateau (months)							
12	−3.99±3.70	−2.54±2.90	−3.98±3.34	0.002	>0.999	**0.002**	**0.017**
24	−5.79±3.34	−4.57±3.96	−5.59±4.21	0.009	0.827	0.155	**0.007**
36	−7.67±4.04	−6.72±3.92	−8.22±5.22	0.0003	0.188	**0.003**	**0.002**
Medial compartment							
Femur (months)							
12	−4.26±5.05	−4.80±4.17	−5.07±4.57	0.550			
24	−7.05±4.50	−6.73±4.36	−6.39±4.39	0.176			
36	−9.89±4.73	−8.91±4.53	−8.50±4.54	0.0005	0.001	0.266	**0.020**
Plateau (months)							
12	−4.16±5.71	−2.15±4.35	−3.40±5.01	0.013	>0.999	0.061	**0.021**
24	−5.75±5.33	−4.45±5.91	−4.67±6.18	0.036	0.115	>0.999	**0.054**
36	−8.02±5.62	−6.85±5.76	−7.19±7.74	0.001	0.010	0.685	**0.004**
Lateral compartment							
Femur (months)							
12	−2.29±4.79	−2.66±4.06	−1.73±3.93	0.214			
24	−3.62±4.09	−3.31±3.86	−2.83±4.52	0.049	0.071	0.277	0.895
36	−4.11±4.23	−4.86±4.49	−4.31±4.66	0.010	0.579	0.072	0.020
Plateau (months)							
12	−3.77±4.38	−2.85±3.79	−4.47±4.39	0.021	0.421	**0.016**	0.563
24	−5.75±3.58	−4.74±3.95	−6.46±5.21	0.017	0.784	**0.050**	**0.050**
36	−7.43±4.23	−6.63±4.46	−9.02±5.01	<0.0001	**0.011**	**<0.0003**	**0.007**

The results are percentage (%) of change expressed as mean±SD.
p Values were assessed using the *Kruskal–Wallis test and the **Mann–Whitney test with Bonferroni adjustment.
p Values in bold are significantly different.
n, number of participants; SrRan, strontium ranelate.

Table 3 Baseline BML score and changes in BML score at 36 months for patients with BML at baseline in the medial subregions

	SrRan 1 g/day		SrRan 2 g/day		Placebo					
	Mean±SD or %	n	Mean±SD or %	n	Mean±SD or %	n	p Value*	Placebo versus SrRan 1 g/day p Value**	Placebo versus SrRan 2 g/day p Value**	SrRan 1 g versus SrRan 2 g/day p Value**
Medial compartment										
Presence of BML at baseline: %, n	27%	31	22%	23	27%	30	0.596†			
Baseline BML score	1.52±0.68	–	1.22±0.52	–	1.77±0.97	–	0.054	>0.9999	0.061	0.190
36 months										
Difference from baseline	−0.39±0.76	–	−0.50±0.56	–	0.19±0.81	–	0.0002	**0.002**	**0.001**	>0.9999
Increase	13%	3	5%	1	38%	8				
Decrease	52%	12	55%	11	29%	6				
Stable	35%	8	40%	8	33%	7				
Total		23		20		21	0.069†	0.357	0.092	>0.9999
Medial femur										
Presence of BML at baseline: %, n	21%	24	17%	18	21%	24	0.675†			
Baseline BML score	1.25±0.61	–	1.00±0.00	–	1.54±0.83	–	0.011	0.385	0.013	0.229
36 months										
Difference from baseline	−0.47±0.60	24	−0.56±0.48	18	0.11±0.83	24	0.002	**0.014**	**0.006**	>0.9999
Increase	12%	2	0%	0	39%	7				
Decrease	59%	10	56%	9	33%	6				
Stable	29%	5	44%	7	28%	5				
Total		17		16		18	0.042†	0.460††	0.059††	0.923††
Medial central condyle										
Presence of BML at baseline: %, n	11%	12	10%	10	8%	9	0.801†			
Baseline BML score	1.08±0.29	–	1.00±0.00	–	1.22±0.44	–	0.269			
36 months										
Difference from baseline	−0.63±0.41	12	−0.50±0.47	10	0.20±0.59	9	0.003	**0.008**	**0.019**	>0.9999
Increase	0%	0	0%	0	40%	2				
Decrease	63%	5	50%	4	20%	1				
Stable	38%	3	50%	4	40%	2				
Total		8		8		5	0.101†			
Medial plateau										
Presence of BML at baseline: %, n	13%	15	9%	9	9%	10	0.438†			
Baseline BML score	1.13±0.35	–	1.11±0.33	–	1.60±0.84	–	0.154			
36 months										
Difference from baseline	−0.50±0.60	15	−0.25±0.43	9	0.0±0.47	10	0.069	0.089	0.560	0.974
Increase	0%	0	0%	0	17%	1				
Decrease	42%	5	25%	2	17%	1				
Stable	58%	7	75%	6	67%	4				
Total		12		8		6	0.345†			

p Values were assessed using the *Kruskal–Wallis test and the **Mann–Whitney test with Bonferroni adjustment for multiple comparisons, or if categorical variables, the †χ^2 test and the ††χ^2 test with Bonferroni adjustment for multiple comparisons.
p Values in bold are significantly different.
BML, bone marrow lesion; n, number of participants; SrRan, strontium ranelate.

towards a lower prevalence of increased score and a higher prevalence of decrease in the medial compartment and the medial femur in patients treated with SrRan 2 g/day compared with placebo. Of interest, there was no increase in the SrRan 2 g/day group in the medial femur, central condyle or plateau, or in the SrRan 1 g/day group in the medial central condyle or plateau (table 3).

Association between BML score and CVL

In patients with BML at baseline in the medial subregions (table 4), the greatest CVL in all groups was found in the central condyle with maximum loss at 36 months, at which time point SrRan 1 g/day and 2 g/day reduced it by 27% and 35%, respectively, compared with placebo. In this subregion, SrRan 1 g/day and 2 g/day were also shown to significantly reduce the BML score change at 36 months (table 3), suggesting an association between the decrease in BML score and the reduction of CVL.

As illustrated in table 4, there was a marked reduction in CVL in the medial plateau at all time points in the patients treated with SrRan, with the greatest effect found at 36 months for SrRan at 1 g/day (43%) and reaching statistical significance for SrRan 2 g/day (96%). In this subregion, the difference in effect between the two dosages of SrRan was also statistically significant in favour of 2 g/day at 36 months.

Interestingly, further analysis revealed a significant correlation between the change (increase) in BML score and the CVL in the medial tibiofemoral compartment in the placebo group (figure 2A). However, no such correlation was found in the two SrRan treatment groups (figure 2B, C), which is likely related to the reduction in the BML by SrRan (table 3).

Table 4 Cartilage volume loss (%) over time in patients with BML at baseline in medial subregions

	SrRan 1 g/day		SrRan 2 g/day		Placebo			Placebo versus SrRan 1 g/day	Placebo versus SrRan 2 g/day	SrRan 1 g/day versus SrRan 2 g/day
	n	Mean±SD	n	Mean±SD	n	Mean±SD	p Value*	p Value**	p Value**	p Value**
Medial compartment (months)										
12	31	−4.85±4.03	23	−3.80±3.26	30	−4.73±3.82	0.779			
24	31	−7.29±2.98	23	−5.58±5.60	30	−6.66±5.35	0.310			
36	31	−9.29±3.19	23	−7.84±5.67	30	−10.12±4.27	0.078	>0.999	0.180	0.116
Medial femur (months)										
12	24	−5.00±5.08	18	−5.71±3.85	24	−4.63±5.01	0.599			
24	24	−7.39±4.07	18	−6.50±5.71	24	−7.74±5.16	0.549			
36	24	−8.96±3.79	18	−10.49±5.89	24	−10.22±3.69	0.352			
Medial central condyle (months)										
12	12	−5.36±12.71	10	−5.82±5.68	9	−5.03±5.65	0.973			
24	12	−11.34±5.05	10	−6.63±7.05	9	−12.02±8.79	0.330			
36	12	−12.88±6.82	10	−11.45±4.72	9	−17.54±11.19	0.129			
Medial plateau (months)										
12	15	−3.50±6.36	9	0.29±6.84	10	−4.52±6.31	0.174			
24	15	−4.94±4.56	9	−1.85±6.68	10	−6.53±9.79	0.364			
36	15	−7.87±5.07	9	−0.55±3.30	10	−13.80±13.51	0.001	0.763	**0.023**	**0.002**

p Values were assessed using the *Kruskal–Wallis test and the **Mann–Whitney test with Bonferroni adjustment. BML, bone marrow lesion; n, number of participants; SrRan, strontium ranelate. p Values in bold are significantly different.

Correlation between radiographic and MRI changes

A significant positive correlation was found between the JSW loss, which measures the CVL in the medial tibiofemoral compartment, and the CVL in the same anatomical regions ($r=0.490$, $p<0.0001$). The correlations were also significant when analysed separately for the placebo ($r=0.545$, $p<0.0001$), the SrRan 1 g/day ($r=0.516$, $p<0.0001$) and SrRan 2 g/day ($r=0.434$, $p<0.0001$) groups.

DISCUSSION

The main aim of this study was to assess, using qMRI on a subset of patients from the SEKOIA study, the cartilage volume in the global knee and the medial and lateral compartments and BML changes over a period of 36 months in patients treated with SrRan compared with placebo. The therapeutic groups of the mITT patients subjected to MRI exams were fairly balanced from all baseline criteria. Based on both symptoms and imaging, these knee OA patients had a more moderate degree of disease compared with those in previous randomised controlled trials (RCTs) using MRI[13 20 22] and similar to a number of observational studies.[12 26 27]

Although the primary outcome, including the CVL in the global knee (table 2) and the medial and lateral compartments, was not met, the present study clearly shows a protective effect of SrRan 2 g/day on CVL in the global plateau in the mITT population, as early as 12 months and persisting up to 36 months, with SrRan 2 g/day being superior to 1 g/day at all time points. In addition, in the lateral plateau, both SrRan groups demonstrated a reduced CVL at 36 months and at all time points for SrRan 2 g/day. The finding of SrRan's preferential therapeutic reduction in CVL in the lateral plateau is an interesting and important addition to the original SEKOIA report,[1] which used a technique (x-ray) that only permits the exploration of the medial compartment. This is also consistent with the results of a number of RCTs, including those conducted with licofelone[13] and chondroitin sulfate,[16] and clinically relevant as a 4-year observation showed that the incidence of total knee replacement (TKR) was reduced in the patients from the latter study.[28] Although the exact reasons for SrRan's preferential protective effect on the lateral plateau remain unknown, one possible explanation could be that in the lateral compartment the cartilage lesions are less severe, thus the capacity of the tissue to repair may be greater. Moreover, the beneficial effect of SrRan on the lateral cartilage (plateau), where few or no BMLs were found, could be related to a direct protective effect on cartilage via catabolic and anabolic factors. Indeed, in a preclinical study using a dog model of OA,[2] a therapeutic concentration of SrRan significantly reduced the progression of cartilage lesions, which was associated with a decrease in the synthesis of catabolic factors such as MMPs by chondrocytes and IL-1β by the synovial membrane. Moreover, in addition to other recently reviewed potential modes of action,[29] SrRan was also shown to stimulate the cartilage matrix formation by increasing the proteoglycan production.[30]

Additional investigations were performed on the patient subpopulation with BML in the medial compartment, the main reason being that these patients usually have a more rapid disease progression,[12 21 23] which is of great interest in the context of a DMOAD study. Such stratification of patients specifically explores the effect of the drug treatment on BMLs per se and its potential impact on CVL. As expected, the BMLs were more prevalent in the medial compartment, although the prevalence was lower than reported in some of our previous RCTs,[13 16] but comparable with some observational studies.[26 27] This was likely due to the fact that, as mentioned above, the patient population in the present trial compared with previous ones had less severe knee OA. In the medial compartment, although no global effect of SrRan was evidenced in the mITT subset of patients, SrRan 2 g/day demonstrated, at 36 months in patients having BML at baseline, a marked reduction in CVL in the medial plateau, where it almost completely abolished the CVL. Interestingly, cartilage thickness loss in the central medial plateau was recently found to be the most predictive of TKR.[31] Both SrRan 1 g/day and 2 g/day were found to reduce the BML scores at 36 months in the medial compartment, and this reduction in score appeared to be due to a stabilisation in size or, more importantly, to a

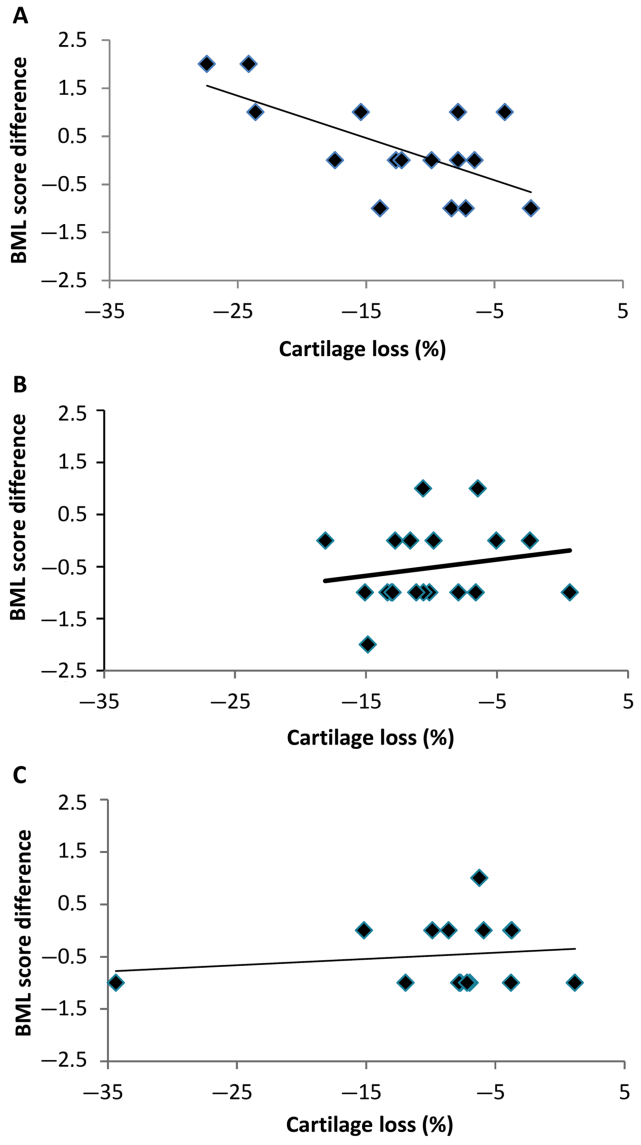

Figure 2 Correlation between cartilage volume loss (%) and bone marrow lesion (BML) score change in the medial tibiofemoral compartment at 36 months in (A) placebo, (B) strontium ranelate (SrRan) 1 g/day and (C) SrRan 2 g/day. A significant correlation was found between the change (increase) in BML score and the loss of cartilage volume in the (A) placebo group (n=16; r=−0.513; p=0.042), whereas no correlation was found in the (B) SrRan 1 g/day (n=19; r=0.275; p=0.254) and (C) SrRan 2 g/day (n=15; r=0.113; p=0.689). Of note, the number of patients is lower than in table 4 because imputation could not be applied for a correlation analysis.

decrease over time compared with placebo. The exact mechanisms by which SrRan exerts this effect on BML remain to be determined. However, in human OA subchondral bone osteoblasts, SrRan was shown to reduce the synthesis of several factors involved in bone remodelling such as MMPs and the receptor activator of nuclear factor κB ligand levels concomitant with the upregulation of osteoprotegerin.[9] In addition, the correlation found in the placebo group between % CVL and BML score was not found in the SrRan-treated groups. These findings again support a relationship between the presence of BML and CVL.[16 21 23] All together, these structural effects may argue for a combined action of SrRan; directly, by acting on the cartilage by the regulation of local biochemical mediators/macromolecules that are responsible for increasing the cartilage degradation[2 9 29] and indirectly, by targeting the BML, thus interacting with the degradative cross-talk pathways between the subchondral bone and the cartilage.

Further analysis showed a positive and significant correlation between the CVL determined by MRI and JSW loss, a finding consistent with previous reports.[32 33] One could therefore be tempted to speculate that patients with BML experience greater JSW loss. In this line of thought, it is interesting to note that the percentage of patients with BML in the medial compartment at baseline (about 25%) was similar to the percentage (about 27%) of radiological progressors (patients with JSW loss >0.5 mm/36 months) reported in the SEKOIA study.[1]

We believe these findings in patients with BML to be most relevant from a clinical perspective for many reasons, a main one being that the presence of BML in the medial compartment is a known strong risk factor for TKR.[34 35] In the context of a DMOAD study and as previously reported, a reduction in the absolute loss of cartilage of ≥8% in the medial compartment is known to reduce the risk for TKR.[34] The findings from the present study with regard to the reduction in CVL particularly with the SrRan dosage of 2 g/day are within that threshold and, therefore, it is conceivable that SrRan may reduce the need for joint surgery. This conclusion is also in line with those drawn from the original SEKOIA study using JSN as a surrogate for CVL.[1]

As for limitations, first, one could argue that the best sequence to evaluate BMLs is the fluid-sensitive fast spin echo with fat suppression (FS), while in this study, the BMLs were assessed using the T1-weighted gradient echo FS. However, this is to no avail as a recent study demonstrated in knee OA patients that the sensitivity to change of both sequences in the assessment of BML prevalence and size change over time was similar.[26] Second, although both the results from x-ray and those from the present MRI study support a structural effect of SrRan, the major difference is that in the original SEKOIA RCT, both SrRan dosages effectively reduced the loss of JSW[1] while in the MRI study more effects are seen with SrRan 2 g/day. Although no relevant differences were found between baseline characteristics of the original cohort and of this MRI subset of patients, the smaller sample size of the MRI subset (25% of the SEKOIA population) may have created an imbalance with regard to the incidence of risk factors, other than demographic and clinical, known to be associated with disease progression, such as BMLs and meniscal lesions, which could explain some of the differences between the two analyses and may also be a statistically limiting factor.

In summary, the present study shows that treatment with SrRan 2 g/day can reduce knee OA CVL predominantly in the plateau and that in patients with BML, a protective effect of SrRan was found to substantially reduce the CVL in the medial plateau. Taken together, these findings are supportive of the x-ray data from the original SEKOIA study[1] showing that SrRan has a DMOAD effect in knee OA patients.

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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 manuscript. A data review committee (J-PP, JM-P, PD) analysed the data and was responsible for their accuracy.

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Competing interests ArthroLab Inc. received a grant from Servier (Suresnes, France). JM-P and J-PP are shareholders of ArthroLab Inc. and have both received consulting fees from Servier. J-PR is a consultant for ArthroLab Inc. FA is an employee of ArthroLab Inc.

Patient consent Obtained.

Ethics approval This is a substudy. The original study was approved by various ethics committees.

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Disease-modifying effect of strontium ranelate in a subset of patients from the Phase III knee osteoarthritis study SEKOIA using quantitative MRI: reduction in bone marrow lesions protects against cartilage loss

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