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REVIEW

Strontium Ranelate: the First Agent of a New Therapeutic Class in Osteoporosis

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ABSTRACT

Strontium ranelate is a new agent developed for the management of postmenopausal osteoporosis. It has a unique mode of action, based on an uncoupling between bone formation (increased) and bone resorption (decreased). To review its effectiveness we searched the MEDLINE database from 1985 to 2008, as well as databases such as the Cochrane controlled register, for citations or relevant articles. After this extensive search of the literature, a critical appraisal of the data was obtained through a consensus meeting (AN, MH, SS, OB, and J-YR). We found that strontium ranelate reduces vertebral, nonvertebral, major nonvertebral, and hip fractures over 1, 3, 4, and 5 years. Its spectrum of activity covers women with osteopenia, osteoporosis, and severe osteoporosis. Elderly subjects also show a reduction in vertebral and nonvertebral fractures. Bone mineral density may be used as a monitoring tool for strontium ranelate, since early changes are predictive of long-term fracture reduction. Biochemical markers of bone turnover reflect the uncoupling between resorption and formation. The safety profile of strontium ranelate compares favorably with the other currently marketed antiosteoporosis medications. Preliminary results suggest that strontium ranelate is able to reduce the progression of spine osteoarthritis. In conclusion, strontium ranelate has the potential to be a candidate for first-line treatment of osteopenia and osteoporosis. However, further research is needed before suggesting its widespread use in osteoarthritis.

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INTRODUCTION

Osteoporosis is characterized by a decrease in bone mass and deterioration in skeletal microarchitecture, which leads to increased fragility and susceptibility for fracture.[1] It is now widely accepted that one of the major determinants of skeletal weakness results from bone loss that occurs after menopause as a consequence of drastically increased osteoclastic resorption, which is only partially compensated for by a moderate rise in the rate of bone formation by osteoblasts.[2]

Strontium ranelate is composed of an organic moiety (ranelic acid) and two atoms of strontium.[3] Strontium ranelate was chosen among 26 strontium salts and was the compound that simultaneously presented the best physicochemical characteristics (eg, high percentage of strontium with two atoms of strontium linked to the molecule, solubility, no chelating properties, chirality, and stability), the best pharmacokinetic characteristics (eg, bioavailabilty and exposure to strontium), and good safety.[3] It has been shown to have specific action on bone cells.[4] Strontium ranelate, developed by Laboratoires Servier (Neuilly-sur-Seine, France), was recently demonstrated to significantly reduce vertebral and hip fracture risk in women with postmenopausal osteoporosis, and to have a good tolerability profile.[5]

REVIEW METHODS

We searched the MEDLINE database from 1985 to 2008 and databases such as the Cochrane controlled register, for citations or relevant articles. The search terms used were: "osteoporosis," "fracture," "strontium ranelate," and "treatment." The bibliographies of selected articles were searched for further relevant articles. Articles were rejected if they were not linked to original research. After this extensive search of the literature, a critical appraisal of the data was obtained through a consensus meeting of the authors (AN, MH, SS, OB, and J-YR).

MECHANISM OF ACTION

Strontium ranelate induces opposite effects on bone resorption and formation.[3] This dual original mode of action was demonstrated in experimental studies on bone cells and pharmacological studies in animals.[6] In vitro, it was shown to decrease bone resorption.[3] This effect resulted from a decreased differentiation and resorbing activity of osteoclasts and increased osteoclast apoptosis.[7] In contrast, strontium ranelate was shown to enhance preosteoblastic cell replication and collagen synthesis in culture without affecting bone mineralization.[8] In addition, it modulates the osteoprotegerin/receptor activator of nuclear factor kappa B ligand (OPG/RANKL) system in favor of OPG,

a molecule known as a strong regulator of osteoblast-induced osteoclastogenesis in human primary osteoblasts.[9] In vivo, strontium ranelate promoted bone formation and reduced bone resorption in intact mice, an effect that resulted in increased vertebral bone mass.[10] Additionally, it was found to reduce resorption and long bone loss induced by hind limb immobilization in rats.[10] Finally, strontium ranelate administration decreased bone resorption and maintained bone formation in adult ovariectomized rats, which resulted in prevention of bone loss, an increase in bone strength, and a positive effect on intrinsic bone properties.[11]

These pharmacological studies suggest that strontium ranelate acts by increasing bone formation and decreasing bone resorption and that these effects result in improved bone mass in vivo.[12,13]

PREVENTION OF POSTMENOPAUSAL BONE LOSS

Strontium ranelate was administered to 160 postmenopausal women in a 24-month, double-blind, placebo-controlled, prospective, randomized study.[14] Doses of 0.125, 0.5, and 1 g/day strontium ranelate taken orally were compared with placebo. All patients received 500 mg of elemental calcium daily. The main characteristics of the study population were: mean age 54 years; duration of menopause 3 years; lumbar bone mineral density (BMD) as measured by dual-energy x-ray (DXA) on Hologic densitometers: 0.931±0.135 g/cm^2 (mean±SD) corresponding to a mean lumbar T-score of −1.4±1.4. At the conclusion of the study, the lumbar BMD increased in a dose-dependent manner with strontium ranelate. The percentage variation of lumbar BMD from baseline was significantly different in the group receiving strontium ranelate 1 g/day as compared with placebo: +5.53% versus −0.75%, respectively (95% confidence interval [CI]: 3.90, 8.67, respectively; P<0.001). Increase in total hip and neck BMD averages were 3.2% and 2.5%, respectively. The percentage variation of total hip and femoral neck BMD were significantly different in the group receiving strontium ranelate 1 g/day as compared with placebo (+3.21% vs. −0.88%; 95% CI: 1.86, 6.31; +2.46% vs. −0.87%; 95% CI: 0.69, 5.96, respectively; both P<0.001). The overall percentage of study withdrawals due to adverse reactions was 15% in the placebo group and 11% in strontium ranelate-treated patients. In conclusion, compared with placebo, strontium ranelate 1 g/day significantly increased BMD of the spine and femur in early postmenopausal women over a 24-month period, while not causing any significant adverse reactions. The 1-g/day dose was therefore retained as the dose for preventive treatment of bone loss after menopause.

TREATMENT OF POST-MENOPAUSAL OSTEOPOROSIS

The effects of strontium ranelate in postmenopausal women with vertebral osteoporotic fractures were assessed during a double-blind, placebo-controlled trial.[15] Either strontium ranelate (0.5, 1, or

2 g/day) or placebo was given to 353 white women (mean age 66 years; lumbar BMD by DXA 0.699±0.098 g/cm^2 corresponding to mean lumbar T-score of –3.9±1.0; mean number of prevalent vertebral fracture per patient 2.7±2.5; mean menopausal duration 18±8 years; and mean body mass index [BMI] 25±3 kg/m^2). All patients were also given a daily supplement of calcium (0.5 g) and vitamin D3 (800 IU). At the conclusion of this 2-year study, strontium ranelate dose-dependently increased the lumbar BMD values by comparison with baseline (+5.9% for 0.5 g, +8.3% for 1 g, and +13.6% for 2 g). The annual increase in lumbar BMD in the group receiving strontium ranelate 2 g/day was +7.3% and significantly different (P<0.001) when compared with placebo. A significant increase in bone alkaline phosphatase was associated with a simultaneous and significant decrease in N-telopeptide crosslinks throughout the 2-year period in the group receiving strontium ranelate 2 g/day. During the second year of treatment, the 2-g/day dose was associated with a 44% reduction in the number of patients experiencing a new vertebral deformity. Bone histomorphometry showed no mineralization defects. The same percentage of withdrawals following an adverse effect (10%) was observed for patients receiving placebo and for those receiving strontium ranelate 2 g/day.[15]

Further analysis of this trial investigated strontium ranelate interactions with bone mineral.[16] Transiliac bone biopsies were quantified by x-ray microanalysis for strontium ranelate uptake and the distribution in bone mineral. Changes in the mean and distribution of the degrees of mineralization of bone (MDMB) were measured by quantitative microradiography. In strontium ranelate-treated women, strontium ranelate was dose-dependently deposited into compact and cancellous bone, with significantly higher contents in new bone than in old bone. Measurement of strontium concentration in iliac crest bone biopsies from patients treated up to 60 months in the phase 3 studies with strontium ranelate 2 g/day indicated that the strontium content in total bone (expressed as the ratio Sr/[Sr+Ca])mmol%) reached a plateau at month 36. Strontium ranelate was mainly deposited on new bone. MDMB was not significantly different in strontium ranelate and placebo groups at either compact or cancellous bone levels.

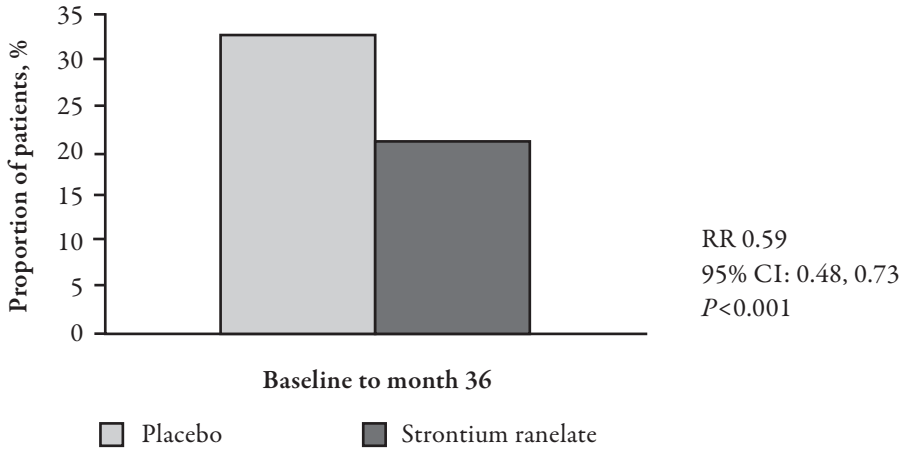
Strontium ranelate has been investigated in a large phase 3 program, initiated in 1996, which includes two extensive clinical trials for the treatment of established osteoporosis (Table 1).[17-19] The SOTI (Spinal Osteoporosis Therapeutic Intervention) study was aimed at assessing the effect of strontium ranelate on the risk of vertebral fractures.[17] The TROPOS (Treatment Of Peripheral Osteoporosis) trial aimed to evaluate the effect of strontium ranelate on peripheral (nonspinal) fractures.[18] All patients included in these two studies had previously participated in a run-in study: the FIRST (Fracture International Run-In Strontium Ranelate Trials) trial, aimed at starting the normalization of calcium and vitamin D.[20] The patients received a calcium/vitamin D supplement through-

Table 1. Relative risk reduction of osteoporotic vertebral and nonvertebral fractures during the SOTI and TROPOS studies.

	Placebo	Strontium ranelate	RR reduction vs. placebo	RR	95% CI	*P* value
SOTI	***n*=723**	***n*=719**				
New vertebral fractures over 3 years[17]			41%	0.59	0.48, 0.73	<0.001
New vertebral fractures over the first year[17]			49%	0.51	0.36, 0.74	<0.001
TROPOS	***n*=2453**	***n*=2479**				
New nonvertebral fractures over 3 years[18]			16%	0.84	0.702, 0.995	0.04
New major nonvertebral fractures over 3 years[18]			19%	0.81	0.66, 0.98	0.031
New nonvertebral fractures over 5 years[19]			15%	0.85	0.73, 0.99	0.032
TROPOS subgroup*	***n*=995**	***n*=982**				
New hip fractures over 3 years[18]			36%	0.64	0.412, 0.997	0.046
New hip fractures over 5 years[19]			43%	0.57	0.33, 0.97	0.036

*TROPOS subgroup: women age ≥74 years and with femoral-neck BMD T-score ≤–2.4 according to NHANES normative value.
BMD=bone mineral density; CI=confidence interval; NHANES=National Health and Nutrition Examination Survey; RR=relative risk; SOTI=Spinal Osteoporosis Therapeutic Intervention; TROPOS=Treatment Of Peripheral Osteoporosis.

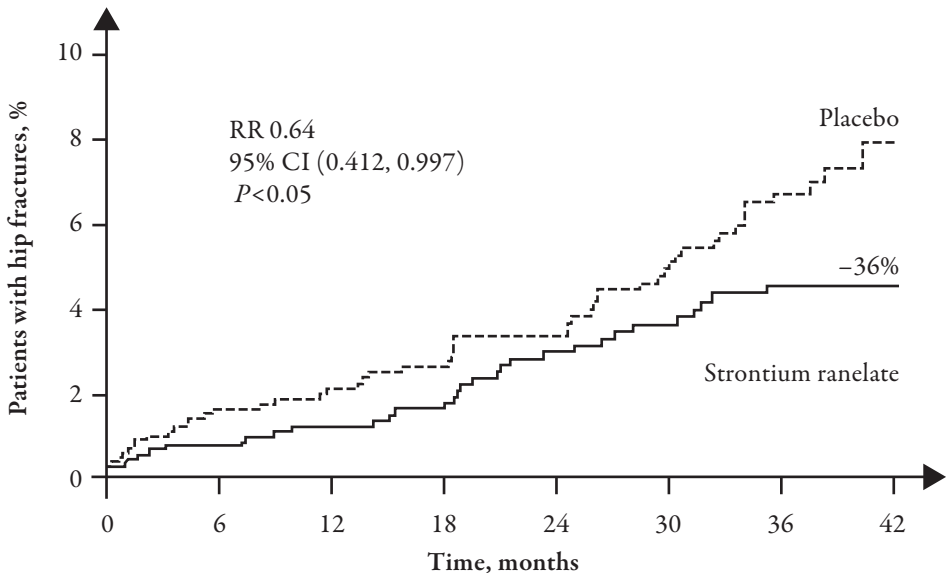
Figure 1. Proportion of patients who had one or more incidence of vertebral fractures over 3 years in the SOTI (Spinal Osteoporosis Therapeutic Intervention) study intention-to-treat population.[17] *Analysis over 3 years restricted to patients with assessable x-rays on the first day of the trial and postbaseline (n=719 patients in the strontium ranelate group and n=723 in the placebo group).



out the studies, which were individually adapted according to their deficiencies (500 or 1000 mg calcium, and 400 or 800 IU vitamin D3).[20] Both studies were multinational, randomized, double-blind, and placebo-controlled, with two parallel groups (strontium ranelate 2 g/day vs. placebo) involving 75 clinical centers in 12 countries in Europe and Australia.[17,18] The study duration was 5 years, with main statistical analysis planned after 3 years of follow-up.

From more than 9000 osteoporotic postmenopausal women who took part in FIRST, 1649 patients were included in SOTI (mean age 70 years), and 5091 patients were included in TROPOS (mean age 77 years).[21] In these two studies, the main statistical analysis was performed in the intent-to-treat population (ITT), defined as patients who took at least one sachet of study treatment and with baseline and post-baseline evaluation of the main criteria. The primary analysis of SOTI[17] (ITT, n=1442) (Table 1), evaluating the effect of strontium ranelate 2 g/day on vertebral fracture rates, revealed a 41% reduction in relative risk (RR) of experiencing a new vertebral fracture (semiquantitative assessment) with strontium ranelate throughout the 3-year study compared with placebo (139 patients with vertebral fracture vs. 222, respectively [RR 0.59; 95% CI: 0.48, 0.73; P<0.001]) (Figure 1). The RR of experiencing a new vertebral fracture was significantly reduced in the strontium ranelate group as compared with the placebo group for the first year. Over the first 12 months, RR reduction was 49% (RR 0.51; 95% CI: 0.36, 0.74, respectively; Cox model P<0.001) (Table 1). These results have also been confirmed when combining both diagnostic meth-

Figure 2. Proportion of patients (osteoporotic patients aged 74 years and over) who had one or more hip fractures over 3 years in the TROPOS (Treatment Of Peripheral Osteoporosis) study intention-to-treat population.[12]



ods (semiquantitative plus quantitative) for incident vertebral fracture.

Semiquantitative assessment was performed according to the semiquantitative visual grading of vertebral deformities recommended by Genant et al.[22] Bone-specific alkaline phosphatase increased in the strontium ranelate group, while serum type I collagen C telopeptide crosslinks decreased. The lumbar BMD increased in the treated group when compared with the placebo group (+11.4% vs. –1.3%, respectively; $P<0.001$). Strontium ranelate was well tolerated without any specific adverse events.[17,18,23]

The primary analysis of TROPOS (ITT, $n=4932$), evaluating the effect of strontium ranelate 2 g/day on nonvertebral fracture, showed a 16% RR reduction in all vertebral fractures over a 3-year follow-up period (RR 0.84; 95% CI: 0.702, 0.995; $P=0.04$).[18] Strontium ranelate treatment was associated with a 19% reduction in risk of major nonvertebral osteoporotic fractures (RR 0.81; 95% CI: 0.66, 0.98; $P=0.031$). In the high-risk fracture subgroup ($n=1977$; women; mean age ≥74 years; femoral-neck BMD T-score of less than or equal to –2.4 according to National Health and Nutrition Examination Survey [NHANES] normative value), treatment was associated with a 36% reduction in risk of hip fracture (RR 0.64; 95% CI: 0.412, 0.997; $P=0.046$) (Figure 2).

Of the 5091 patients, 2714 (53%) completed the study up to 5 years.[19] The

risk of nonvertebral fracture was reduced by 15% in the strontium ranelate group compared with the placebo group (RR 0.85 [95% CI: 0.73, 0.99]). The risk of hip fracture was decreased by 43% (RR 0.57 [95% CI: 0.33, 0.97]), and the risk of vertebral fracture was decreased by 24% (RR 0.76 [95% CI: 0.65, 0.88]) in the strontium ranelate group. After 5 years, the safety profile of strontium ranelate remained unchanged compared with the 3-year findings.[19]

In order to assess the efficacy of strontium ranelate according to the main determinants of vertebral fracture risk (age, baseline BMD, prevalent fractures, family history of osteoporosis, baseline BMI, and addiction to smoking), data from SOTI and TROPOS (n=5082) were pooled (strontium ranelate 2 g/day group [n=2536]; placebo group [n=2546]; average age 74 years; 3-year follow-up).[24] Strontium ranelate decreased the risk of both vertebral (RR 0.60; 95% CI: 0.53, 0.69; P<0.001) and nonvertebral (RR 0.85; 95% CI: 0.74, 0.99; P=0.03) fractures. The decrease in risk of vertebral fractures was 37% (P=0.003) in women aged <70 years, 42% (P<0.001) for those aged 70 to 80 years, and 32% (P=0.013) for those aged ≥80 years (Table 2). The RR of vertebral fracture was 0.28 (95% CI: 0.07, 0.99) in osteopenic and 0.61 (95% CI: 0.53, 0.70) in osteoporotic women, and baseline BMD was not a determinant of efficacy. The incidence of vertebral fractures in the placebo group increased with the number of prevalent vertebral fractures, but this was not a determinant of the effect of strontium ranelate. In 2605 patients, the risk of experiencing a first vertebral fracture was reduced by 48% (P<0.001). The risk of experiencing a second vertebral fracture was reduced by 45% (P<0.001; 1110 patients). Moreover, the risk of experiencing more than two vertebral fractures was reduced by 33% (P<0.001; 1365 patients). Family history of osteoporosis, baseline BMI, and addiction to smoking were not determinants of efficacy. This study showed that a 3-year treatment with strontium ranelate leads to antivertebral fracture efficacy in postmenopausal women independently of baseline osteoporotic risk factors (Table 2).[24]

Prevalent vertebral fractures increased the risk of subsequent vertebral and nonvertebral fractures,[25,26] as well as the risk of hip fracture with at least twofold excess. The risk of further fracturing has been shown to be higher among younger people compared with the elderly.[26] However, few data are available in clinical trials in patients <65 years. The efficacy of strontium ranelate was assessed in osteoporotic patients aged 50-65 years, most of whom had a prevalent vertebral fracture, presenting a subgroup of patients having a very high lifetime risk of fractures.[27] Among the patients included in the SOTI study, 385 were aged 50-65 years, of which 353 were eligible for assessment of the efficacy of strontium ranelate on vertebral fractures according to the ITT principle.[27] Over 3 years, treatment with strontium ranelate significantly reduced the risk of vertebral fracture by 43% (RR 0.57; 95% CI: 0.36, 0.92; P=0.019), with a 16.9% incidence of vertebral fractures in the strontium ranelate group

Table 2. Relative risk (95% CI) of vertebral fractures in patients treated with strontium ranelate (2 g/day) for 3 years, compared with placebo, according to baseline characteristics: age, BMD, and prevalent fractures.[24]

	Placebo (*n*=2546)	Strontium ranelate (*n*=2536)	RR reduction vs. placebo	RR (95% CI)	*P* value
Age					
<70 years	379	371	37%	0.63	0.003
*N**	102 (28.2%)	66 (18.7%)		(0.46, 0.85)	
70-80 years	1715	1722	42%	0.58	<0.001
*N**	341 (22.0%)	208 (13.2%)		(0.48, 0.68)	
≥80 years	443	452	32%	0.68	0.013
*N**	100 (26.5%)	67 (19.1%)		(0.50, 0.92)	
BMD			**100%**		
T-score (hip and spine) >−2.5	84	92	72%	0.28 (0.07, 0.99)	0.045
*N**	9 (12%)	3 (3.6%)			
T-score (hip and spine) ≤−2.5	2462	2444	39%	0.61 (0.53, 0.70)	<0.001
*N**	534 (24.1%)	338 (15.4%)			
Prevalent vertebral fracture			**100%**		
0	1285	1320	48%	0.52	<0.001
*N**	161 (14.4%)	87 (7.5%)		(0.40, 0.67)	
1	577	533	45%	0.55	<0.001
*N**	130 (25.2%)	70 (14.5%)		(0.41, 0.74)	
≥2	683	682	33%	0.67	<0.001
*N**	252 (40.3%)	184 (29.8%)		(0.55, 0.81)	

**N*=total number of patients having at least one new vertebral fracture (percentage).
BMD=bone mineral density; CI=confidence interval; RR=relative risk.

versus 29.6% in the placebo group. This efficacy in reducing the risk of vertebral fractures was sustained over 4 years of treatment with strontium ranelate, with a reduction of 35% (RR 0.65; 95% CI: 0.42, 0.99; *P*=0.049) and an incidence of vertebral fractures of 21.6% in the strontium ranelate group versus 32.8% in the placebo group. There was a trend for a reduction in the risk of vertebral fracture over the first year, which was not statistically significant. A significant effect of strontium ranelate compared with placebo was also observed on symptomatic vertebral fractures (defined as radiological fractures plus concomitant back pain or a decrease in body height by at least 1 cm) with a 54% reduction in the risk of symptomatic

vertebral fracture over 3 years (RR 0.46; 95% CI: 0.22, 0.97; *P*=0.033), sustained over 4 years with a 52% reduction (RR 0.48; 95% CI: 0.24, 0.95; *P*=0.030).

Over the 4-year follow-up, clinical, serious, and drug-related adverse effects were similar in placebo and treated groups (no clinically significant difference between groups regarding incidence of nausea, diarrhea, headache, dermatitis, eczema, venous thromboembolism [VTE] events) and the overall safety profile was very similar to that already described for the whole SOTI study population over 3 and 4 years. No case of pulmonary embolism or hypersensitivity reaction was observed in this study population.[27]

Women aged ≥80 years comprise about 8% of the postmenopausal population but contribute >30% of all fragility fractures and 60% of hip fractures because of the high prevalence of osteoporosis and high incidence of falls in this group.[28] As this group of women constitutes the fastest growing segment of the general population, the number of elderly individuals with osteoporosis will increase markedly in the coming years.[29] Despite the important contribution to the public health burden of fractures made by this group, few studies of fracture prevention have focused on the elderly population.[30]

To determine whether strontium ranelate also reduces fractures in elderly patients, an analysis based on preplanned pooling of data from the SOTI and TROPOS trials included 1488 women between 80 and 100 years of age followed for 3 years.[31] Yearly spinal x-rays were performed in 895 patients. Only radiographically confirmed nonvertebral fractures were included. Baseline characteristics did not differ in placebo and treatment arms. In the ITT analysis, the risk of vertebral, nonvertebral, and clinical (symptomatic vertebral and nonvertebral) fractures was reduced within 1 year by 59% (*P*=0.002), 41% (*P*=0.027), and 37% (*P*=0.012), respectively. At the end of 3 years, vertebral, nonvertebral, and clinical fracture risks were reduced by 32% (*P*=0.013), 31% (*P*=0.011), and 22% (*P*=0.040), respectively. The medication was well tolerated, and the safety profile was similar to that in younger patients. The investigators concluded that treatment with strontium ranelate safely reduced the risk of vertebral and nonvertebral fractures in women with osteoporosis aged ≥80 years.

Many fractures that occur in women with moderate fracture risk are due to osteopenia. Strontium ranelate was studied in 1431 postmenopausal women with osteopenia.[32] In women with lumbar spine osteopenia, strontium ranelate decreased the risk of vertebral fracture by 41% (RR 0.59; 95% CI: 0.43, 0.82; *P*=0.002), by 59% in women with no prevalent fractures (RR 0.41; 95% CI: 0.17, 0.99; *P*=0.039), and by 38% in women with prevalent fractures (RR 0.62; 95% CI: 0.44, 0.88; *P*=0.008). In women with osteopenia both at the lumbar spine and the femoral neck, strontium ranelate reduced the risk of fracture by 52% (RR 0.48; 95% CI: 0.24, 0.96; *P*=0.034).

To assess the capacity of strontium ranelate to restore normal BMD (T-score more than or equal to –1) in postmeno-

pausal osteopenic women (T-score –1 to –2.5) at baseline, a post-hoc analysis from SOTI and TROPOS studies of 1428 patients randomly assigned to receive either strontium ranelate 2 g/day or placebo for 3 years was performed.[33] BMD was measured at baseline and each year for 3 years. Results were analyzed on an ITT basis. At lumbar spine, after 1, 2, and 3 years' treatment with strontium ranelate, 26.4%, 42.1%, and 58.2%, respectively, of osteopenic patients normalized their BMD, compared with 6.6%, 8.9%, and 11.9% in the placebo group (all $P<0.001$). At total hip, the percentage of patients normalizing their BMD was 5.4%, 10.0%, and 19.6% in the strontium ranelate group and 1.8%, 1.4%, and 1.6% in the placebo group (all $P<0.001$). Strontium ranelate was able to normalize BMD in a significant proportion of osteopenic patients after 1, 2, and 3 years of treatment.

Significant increases in lumbar spine, femoral neck, and total hip BMD have been consistently reported in all populations exposed to strontium ranelate.[15,17,18,34] To analyze the relationship between BMD changes and fracture incidence during 3-year treatment with strontium ranelate, patients from the strontium ranelate arm of the SOTI and TROPOS trials were evaluated.[35] The outcome measures included BMD at the lumbar spine, femoral neck, total proximal femur assessed at baseline and after a follow-up of 1 and 3 years, semiquantitative visual assessment of vertebral fractures, and nonvertebral fractures based on written documentation. After 3 years of strontium ranelate 2 g/day, each percentage point increase in femoral neck and total proximal femur BMD was associated with a 3% (95% adjusted CI: 1%, 5%) and 2% (1%, 4%) reduction in risk of new vertebral fracture, respectively. The 3-year changes in femoral neck and total proximal femur BMD explained 76% and 74% of the reduction in vertebral fractures observed during the treatment, respectively. Changes at 3 years in spine BMD were not statistically associated with the incidence of new vertebral fracture ($P=0.10$). No significant associations were found between 3-year changes in BMD and incidence of new nonvertebral fractures, but a trend was found for femoral neck BMD ($P=0.09$) and total proximal femur BMD ($P=0.07$). An increase in femoral neck BMD after 1 year was significantly associated with the reduction in incidence of new vertebral fractures observed after 3 years ($P=0.04$). The investigators concluded that, during 3-year strontium ranelate treatment, an increase in femoral neck BMD was associated with a proportional reduction in vertebral fracture incidence.

In a post-hoc analysis of 465 women aged >74 years with low BMD at the femoral neck (T-score less than or equal to –2.4) selected from the population of the TROPOS trial, BMD was assessed at the femoral neck at baseline and after a follow-up of 3 years.[36] Hip fractures were reported from the hospital database. After adjusting for age, BMI, femoral neck BMD at baseline, and number of prevalent vertebral fractures, for each 1% increase in femoral neck BMD observed after 3 years, the risk to experi-

ence a hip fracture after 3 years decreased by 7% (95% CI: 1%, 14%; P=0.04). In patients experiencing a hip fracture over 3 years of treatment with strontium ranelate, femoral neck BMD increased by 3.41% (standard error [SE] 1.02%) compared with 7.235% (SE 0.81%) in patients without hip fracture (P=0.02).

The safety of strontium ranelate on bone was investigated through analysis of 141 transiliac bone biopsies performed in a subset of women enrolled in the STRATOS (Strontium, Administration for Treatment of Osteoporosis), SOTI, or TROPOS trials.[37] Histomorphometry provided a two-dimensional (2D) demonstration of the bone safety of strontium ranelate, with significantly higher mineral apposition rate in cancellous bone (+9% vs. control, P=0.019). Osteoblast surfaces were significantly higher (+38% vs. control, P=0.047). Three-dimensional (3D) analysis of 3-year biopsies with strontium ranelate (20 biopsies) and placebo (21 biopsies) using microcomputed tomography showed significant changes in microarchitecture within the strontium ranelate group, higher cortical thickness (+18%, P=0.008) and trabecular number (+14%, P=0.05), and lower structure model index (–22%, P=0.01) and trabecular separation (–16%, P=0.04), with no change in cortical porosity. These analyses have provided evidence of the good bone safety of strontium ranelate in the treatment of postmenopausal osteoporosis and are fully consistent with the mode of action of strontium ranelate involving dissociation between bone formation and bone resorption. The change in 3D trabecular and cortical microarchitecture may improve bone biomechanical competence and explain the decreased fracture rate after strontium ranelate treatment.

Quality of life was a secondary endpoint in the strontium ranelate phase 3 studies using QUALIOST (Quality of Life Questionnaire In Osteoporosis), a dedicated Questionnaire for vertebral osteoporosis.[38] QUALIOST was used to assess quality of life in 1240 patients from the SOTI trial who completed the questionnaire at baseline and every 6 months.[39] After 3 years of treatment, strontium ranelate had a beneficial effect on quality of life compared with placebo (P=0.016 for global score; P=0.019 and P=0.032 for emotional and physical scores, respectively).[39] The improvement in the emotional score was related to fewer negative feelings and concerns regarding the disease, and the improvement in the physical score was associated with reduced pain and increased mobility.

STRONTIUM RANELATE AND OSTEOARTHRITIS

Osteoarthritis (OA) is a major cause of disability and is one of the most frequent musculoskeletal disorders.[40] For decades, the traditional pharmacological management of OA has been mainly symptomatic, without the support of any well-documented findings on the influence of treatment on disease duration and progression. Drugs with a favorable action on joint structure, which are therefore able to delay the progression of the disease, are termed structure-modify-

ing drugs.[41,42] During the last few years, several randomized controlled trials have been performed to assess the structure-modifying effect of various compounds, such as diacerein,[43] glucosamine sulfate,[44,45] chondroitin sulfate,[46,47] and doxycycline.[48] However, all these trials specifically addressed lower-limb OA (ie, OA of the knee and/or hip), whereas very few data are currently available concerning spinal OA.[49] Moreover, the pathophysiology of hip or knee OA differs from that of spinal OA.[50]

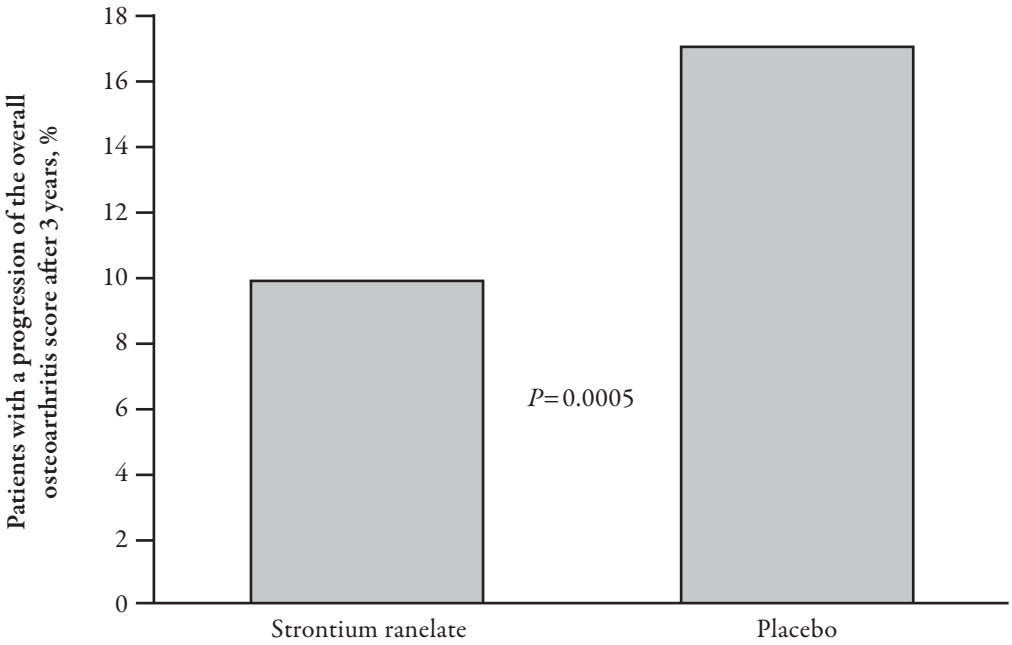
Previous studies have provided the preclinical basis for the in-vivo testing of strontium ranelate in OA. In human normal and OA chondrocytes that are treated with or without interleukin 1b (IL-1b), strontium ranelate has been shown to stimulate the synthesis of type II collagen and proteoglycan.[51] Moreover, 1 mM strontium ranelate increased the stimulatory effect of insulin-like growth factor (IGF) on proteoglycan synthesis, but did not reverse the inhibitory effect of IL-1b.[51]

In a 3-year post-hoc analysis of the pool of SOTI and TROPOS studies, strontium ranelate was also shown to significantly decrease, at all time points, the levels of urinary C-terminal telopeptides of type II collagen (u-CTX-II), a cartilage degradation biomarker with high tissue specificity, compared with placebo.[52]

Lumbar spine vertebral radiographs from the SOTI and TROPOS trials were evaluated at baseline (month 0 [M0]) and after 3 years (month 36 [M36]; or M24 in 579 patients for whom M36 radiographs were unavailable or not assessable). In SOTI and TROPOS, only lateral spine radiographs were available. A total of 4224 patients had both a baseline and postbaseline x-ray.[53] Four intervertebral spaces (L1-L2, L2-L3, L3-L4, and L4-L5) were examined for the presence and severity of anterior osteophytes (score 0-3), posterior osteophytes (score 0-3), joint space narrowing (score 0-3), and sclerosis (score 0-1). They were graded using an atlas according to the method of Lane et al.[54] This enabled calculation of an overall OA score for each intervertebral space (graded from 0 to 2) as suggested in the original publication.[54] Of the 4224 patients, 2395 had all lumbar intervertebral spaces assessable. At the end of the 3-year follow-up, 13.4% of patients experienced an increase in overall spinal OA score involving at least one intervertebral space. The proportion of patients with an overall OA score progression was 3.9%, 3.7%, 4.8%, and 3.6% for the L1-L2, L2-L3, L3-L4, and L4-L5 intervertebral spaces, respectively.[53]

After 3 years of study, only 9.9% in the strontium ranelate group experienced an increase in the overall OA score, versus 17.1% in the placebo group (Figure 3).[53] The proportion of patients with an increase in the overall OA score was reduced by 42% in the strontium ranelate group, compared with placebo (RR 0.58; 95% CI: 0.42, 0.79; P=0.0005). After 3 years of treatment the number of patients in whom the disc space narrowing score worsened was significantly reduced by 33% in the strontium ranelate group, compared with placebo (RR 0.67; 95% CI: 0.47, 0.97; P=0.03). There was also

Figure 3. Percentage of patients with an increase in the overall osteoarthritis score after 3 years of follow-up among the whole study population.[43]



an absolute reduction in the proportion of patients with an increased severity of the osteophyte score in the strontium ranelate group, compared with placebo, but this finding did not reach statistical significance.

After 3 years of treatment, more patients from the strontium ranelate group (84 of 201; 41.8%) experienced an improvement in back pain (decrease by at least one point on the Likert scale) compared with placebo (62 of 198; 31.3%; P=0.03). This study suggests that strontium ranelate reduces the progression of radiographic spinal OA and back pain in women with osteoporosis and spinal OA. Furthermore, it has implications not only in the potential treatment of chronic back pain, but also for progression of OA at other sites.

Strontium Ranelate Tolerability Profile

A recently published study used the UK General Practice Research Database to assess the risk of several recently reported adverse events linked to the use of strontium ranelate for osteoporosis in postmenopausal women.[55] The self-controlled case-series method was used to minimize the potential for biases in the quantification of risk estimates.

Age-adjusted rate ratios for VTE, gastrointestinal disturbance, minor

skin complaint and memory loss were 1.1 (95% CI: 0.2, 5.0), 3.0 (95% CI: 2.3, 3.8), 2.0 (95% CI: 1.3, 3.1), and 1.8 (95% CI: 0.2, 14.1), respectively. No cases of osteonecrosis of the jaw, Stevens-Johnson syndrome or drug rash with eosinophilia and systemic symptoms were found. Although this study confirmed the association between strontium ranelate and adverse events identified in the phase 3 publications, there was no evidence of an association between strontium ranelate and the aforementioned potentially life-threatening adverse events.

In the SOTI and TROPOS trials, the incidence of adverse events, serious adverse events, and withdrawals due to adverse events was similar in the strontium ranelate and placebo groups.[56,57] During the first 3 months of treatment, nausea, diarrhea, headache, dermatitis, and eczema were more frequently associated with strontium ranelate compared to placebo; but, thereafter, there was no difference in incidence between strontium ranelate and placebo groups concerning nausea and diarrhea. Importantly, there were no age-associated increases in adverse events when the safety of strontium ranelate was assessed in a prespecified analysis in individuals aged ≥80 years.[31]

In the SOTI and TROPOS trials, small changes in homeostasis parameters were observed (decrease in calcium and parathyroid hormone serum levels, increase in blood phosphorus).[17,18] The levels were transient and not associated with any clinical sequelae. It has been suggested that these observations may be linked to the activation of the calcium-sensing receptors by strontium. A slight transient increase in serum creatine phosphokinase concentrations was observed in strontium ranelate-treated patients.[17,18] This was not associated with an increase in muscular symptoms and, in the majority of patients, values returned to normal during the trial without any change in treatment.

In pooled data from the SOTI and TROPOS trials, there was an apparent increased risk of VTE in the strontium ranelate group (0.6% vs. 0.9% per year), although the annual incidence was similar in the strontium ranelate and placebo groups in the individual trials.[17,18] It has been suggested that the reason for the initial finding may have been an imbalance in the number of people with previous VTE in the active treatments arms. When treatment arms were corrected for this, there was no significant increase in VTE risk in the strontium ranelate arm.

Recently, the postmarketing experience of patients treated with strontium ranelate reported cases of DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome (<20 for 570,000 patient-years of exposure).[57] This incidence is in the vicinity of what has been previously reported as severe skin reactions, with most of the other currently marketed antiosteoporosis medications. A causative link has not been firmly established, as strontium is a trace element naturally present in the human body, and ranelic acid is poorly absorbed.[6] However, as possible fatalities have been linked to this syndrome, it seems reasonable to immediately discontinue strontium ranelate

and other concomitant treatments known to induce such a syndrome when major suspicious skin disorders occur within 2 months of treatment initiation[58] and to introduce adapted treatment and follow-up to avoid systemic symptoms.

Treatment Adherence

It is acknowledged that adherence rates observed in controlled clinical trials are higher than those observed in "real world" situations; nevertheless, adherence to strontium ranelate treatment in the phase 3 clinical trials was good. In the SOTI trial, 83% of patients adhered to therapy in the strontium ranelate group compared with 85% in the placebo group at 3 years.[17] In the TROPOS trial, mean adherence was 82% overall in both the strontium ranelate and placebo treatment groups.[18]

CONCLUSIONS

Strontium ranelate is a treatment of postmenopausal osteoporosis with a new mechanism of action, which both increases bone formation and decreases bone resorption. Through a wide phase 3 program, the efficacy of strontium ranelate has been investigated in various patient profiles. Strontium ranelate decreases vertebral, nonvertebral, and hip fractures in osteoporotic postmenopausal women. The efficacy of strontium ranelate was sustained over 5 years and was demonstrated in a large scatter of patients, including elderly patients, women with severe osteoporosis, and women with osteopenia. The efficacy of strontium ranelate, in the management of fracture reduction, in all these subgroups of patients, compares favorably with other medications currently licensed and/or marketed in osteoporosis (Tables 3 and 4). Strontium ranelate might

Table 3. Effect on vertebral fracture rates (from randomized controlled trials).

	Osteopenia	Osteoporosis without prevalent vertebral fractures	Established osteoporosis with prevalent vertebral fractures
Raloxifene	●	■	■
Alendronate	NA	■	■
Risedronate	NA	●	■
Teriparatide	NA	NA	■
Strontium ranelate	●	■	■
Calcitonin	NA	NA	■
Ibandronate	NA	NA	■
Zoledronic acid	NA	■	■

■=preplanned analysis in the entire study population; ●=post-hoc analysis; NA=no evidence available.

Table 4. Effect on nonvertebral/hip fracture rates (from randomized controlled trials).

	Nonvertebral		Hip fractures	
	Osteoporosis without prevalent vertebral fractures	Established osteoporosis with prevalent vertebral fractures vertebral	Osteoporosis without prevalent fractures	Established osteoporosis with prevalent vertebral fractures
Raloxifene	NA	●	NA	NA
Alendronate	■	■	NA	■
Risedronate	NA	■	NA	■
Teriparatide	NA	■	NA	NA
Strontium ranelate	●	■	●	▲
Calcitonin	NA	■	NA	●
Ibandronate	NA	●	NA	NA
Zoledronic acid	■	■	■	■

■ =preplanned analysis in the entire study population; ▲ =preplanned analysis on a subset of the study population; ● =post-hoc analysis; NA=no evidence available.

also have a potential as a structure-modifying disease in OA. Coupled with a high compliance rate in clinical trials and a good safety profile, these results support the use of strontium ranelate as a first-line treatment of postmenopausal osteoporosis.

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REFERENCES

1. Cooper C, Westlake S, Harvey N, et al. Review: developmental origins of osteoporotic fracture. *Osteoporos Int*. 2006;17:337-347.

2. Russell RGG. Pathogenesis of osteoporosis. In: Hochberg MC, Siman AJ, Smolen SJ, Weinblatt ME, Weisman MH, eds. *Rheumatology*. 3rd edition. New York: Mosby; 2003:2075-2147.

3. Marie PJ, Hott M, Modrowski D, DePollak, et al. An uncoupling agent containing strontium prevents bone loss by depressing bone resorption and maintaining bone formation in estrogen-deficient rats. *J Bone Miner Res*.1993;8:607-615.

4. Canalis E, Hott M, Deloffre P, Tsouderos Y, Marie PJ. The divalent strontium salt S12911 enhances bone cell replication and bone formation in vitro. *Bone*. 1996;18:517-523.

5. Reginster JY, Sarlet N, Lejeune E, Leonori L. Strontium ranelate: a new treatment for postmenopausal osteoporosis with a dual mode of action. *Curr Osteoporos Rep*. 2005;3:30-34.

6. Reginster JY. Strontium ranelate in osteoporosis. *Curr Pharm Des*. 2002;8: 1907-1916.

7. Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. *Calcif Tissue Int*. 2001;69:121-129.

8. Boivin G, Deloffre P, Perrat B, et al. Strontium distribution and interactions with bone mineral in monkey iliarc bone after strontium salt (S12911) administration. *J Bone Miner Res*. 1996;11:1302-1311.

9. Atkins GJ, Welldon KJ, Halbout P, Findlay DM. Strontium ranelate treatment of

human primary osteoblasts promotes an osteocyte-like phenotype while eliciting and osteoprotegerin response. *Osteoporos Int*. 2008. In press.

10. Kendler D. Strontium ranelate - data on vertebral and nonvertebral fracture efficacy and safety: mechanism of action. *Curr Osteoporos Rep*. 2006;4:34-39.

11. Morohashi T, Sano T, Harai K, Yamada S. Effects of strontium on calcium metabolism in rats - II. Strontium prevents the increased rate of bone turnover in ovariectomized rats. *Jpn J Pharmacol*. 1995;68:153-159.

12. Marie P. Strontium ranelate: a physiological approach for optimizing bone formation and resorption. *Bone*. 2006;38 (suppl. 1):S10-S14.

13. Ammann P. Strontium ranelate: a physiological approach for an improved bone quality. *Bone*. 2006;38 (suppl. 1):S15-S18.

14. Reginster JY, Deroisy R, Dougados M, Jupsin I, Colette J, Roux C. Prevention of early postmenopausal bone loss by strontium ranelate: a randomized, two-year, double-blind, dose-ranging, placebo-controlled trial. *Osteoporos Int*. 2002;13:925-931.

15. Meunier PJ, Slosman DO, Delmas PD, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis: a 2-year randomized placebo controlled trial. *J Clin Endocrinol Metab*. 2002;87:2060-2066.

16. Boivin G, Foos E, Tupinon-Mathieu I, Meunier PJ. Strontium deposition in bone is dose dependent and does not alter the degree of mineralization of bone in osteoporotic patients treated with strontium ranelate. *J Bone Miner Res*. 2000;15(suppl. 1):305.

17. Meunier PJ, Roux C, Seeman E, et al. The effect of strontium ranelate on the risk of vertebral fracture in women with post menopausal osteoporosis. *N Engl J Med*. 2004;350:459-468.

18. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. *J Clin Endocrinol Metab*. 2005;90: 2816-2822.

19. Reginster JY, Felsenberg D, Boonen S, et al. Effects of long-term strontium ranelate on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis. *Arthritis Rheum*. 2008;58:1687-1695.

20. Meunier PJ, Reginster JY. Design and methodology of the phase 3 trials for the clinical development of strontium ranelate in the treatment of women with postmenopausal osteoporosis. *Osteoporos Int*. 2003;14 (suppl. 3): 66-76.

21. Reginster JY, Spector T, Badurski J, et al. A short-term run-in study can significantly contribute to increasing the quality of long-term osteoporosis trials. The strontium ranelate phase III program. *Osteoporos Int*. 2002;13(suppl. 1):S30.

22. Genant HK, Wu CY, Van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8:1137-1148.

23. Meunier PJ, Roux C, Ortolani S, et al. Strontium ranelate reduces the vertebral fracture risk in women with postmenopausal osteoporosis. *Osteoporos Int*. 2002;13 (suppl. 1):O45.

24. Roux C, Reginster JY, Fechtenbaum J, et al. Vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis is independent of baseline risk factors. *J Bone Miner Res*. 2006;21:536-542.

25. Naves M, Diaz Lopez JB, Gomez C, Rodriguez Rebollar A, Rodriguez Garcia M, Cannata Andia JB. The effect of vertebral fracture as a risk factor for osteoporotic fracture and mortality in a Spanish population. *Osteoporos Int*. 2003;14:520-524.

26. van Staa TP, Leufkens HGM, Cooper C. Does a fracture at one site predict later fractures at other sites? A British cohort study. *Osteoporos Int*. 2002;13:624-629.

27. Roux C, Fechtenbaum J, Kolta S, Isaia G, Cannata Andia JB, Devogelaer JP. Strontium ranelate reduces the risk of vertebral fracture in young postmenopausal women with severe osteoporosis. *Ann Rheum Dis*. 2008;67:1736-1738.

28. Population Division of the Department of Economic and Social Affairs of the Nations Secretariat 2002. World population prospects: the 2002 revision and world urban prospects. Available at: www.esa.un.org. Accessed October 1, 2008.

29. Ettinger MP. Aging bone and osteoporosis: strategies for preventing fractures in the elderly. *Arch Intern Med*. 2003;163:2237-2246.

30. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip intervention program study group. *N Engl J Med*. 2001;344:333-340.

31. Seeman E, Vellas B, Benhamou C, et al. Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. *J Bone Miner Res*. 2006;21:1113-1120.

32. Seeman E, Devogelaer J, Lorenc R, et al. Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. *J Bone Miner Res*. 2008;23:433-438.

33. Malaise O, Bruyere O, Reginster JY. Strontium ranelate normalizes bone mineral density in osteopenic patients. *Aging Clin Exp Res*. 2007;19:330-333.

34. Reginster JY, Meunier PJ. Strontium ranelate phase 2 dose-ranging studies: PREVOS and STRATOS studies. *Osteoporos Int*. 2003;14:S56-S65.

35. Bruyere O, Roux C, Detilleux J, et al. Relationship between bone mineral density changes and fracture risk reduction in patients treated with strontium ranelate. *J Clin Endocrinol Metab*. 2007;92:3076-3081.

36. Bruyere O, Roux C, Badurski J, et al. Relationship between change in femoral neck bone mineral density and hip fracture incidence during treatment with strontium ranelate. *Curr Med Res Opin*. 2007;23:3041-3045.

37. Arlot ME, Jiang Y, Genant HK, et al. Histomorphometric and μ-CT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate. *J Bone Miner Res*. 2008;23:215-222.

38. de la Loge C, Sullivan K, Pinkney R, Marquis P, Roux C, Meunier PJ. Cross-cultural validation and analysis of responsiveness of the QUALIOST®: QUAlity of Life questionnaire In OSTeoporosis. *Health Qual Life Outcomes*. 2005;3:69.

39. Marquis P, de la Loge C, Diaz-Curiel M, Spector T, Meunier PJ. Beneficial effects of strontium ranelate on the quality of life in patients with vertebral osteoporosis (SOTI study). *Osteoporos Int*. 2005;16:S54

40. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum*. 1998;41:778-799.

41. Recommendations for the registration of drugs used in the treatment of osteoarthritis. Group for the Respect of Ethics and Excellence in Science (GREES): osteoarthritis section. *Ann Rheum Dis*. 1996;55:552-557.

42. Altman R, Brandt K, Hochberg M, et al. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. *Osteoarthritis Cartilage*. 1996;4:217-243.

43. Dougados M, Nguyen M, Berdah L, Mazieres B, Vignon E, Lequesne M. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Evaluation of the chondromodulating effect of diacerein in OA of the hip. *Arthritis Rheum*. 2001;44:2539-2547.

44. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet*. 2001;357:251-256.

45. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med*. 2002;162:2113-2123.

46. Michel BA, Stucki G, Frey D, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis Rheum*. 2005;52:779-786.

47. Uebelhart D, Malaise M, Marcolongo R, et al. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. *Osteoarthritis Cartilage*. 2004;12:269-276.

48. Brandt KD, Mazzuca SA, Katz BP, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo controlled, double-blind trial. *Arthritis Rheum*. 2005;52:2015-2025.

49. Neogi T, Nevitt MC, Ensrud KE, Bauer D, Felson DT. The effect of alendronate on progression of spinal osteophytes. *Arthritis Rheum*. 2006;54(suppl.):S822.

50. Martel-Pelletier J, Lajeunesse D, Fahmi H, Tardif G, Pelletier JP. New thoughts on the pathophysiology of osteoarthritis: one more step toward new therapeutic targets. *Curr Rheumatol Rep*. 2006;8:30-36.

51. Henrotin Y, Labasse A, Zheng SX, et al. Strontium ranelate increases cartilage matrix formation. *J Bone Miner Res*. 2001;16: 299-308.

52. Alexanderson P, Karsdal M, Qvist P, Reginster JY, Christiansen C. Strontium ranelate reduces the urinary level of cartilage degradation biomarker CTX-II in postmenopausal women. *Bone*. 2007;40: 218-222.

53. Bruyere O, Delferriere D, Roux C, et al. Effects of strontium ranelate on spinal osteoarthritis progression. *Ann Rheum Dis*. 2008;67;335-339.

54. Lane NE, Nevitt MC, Genant HK, Hochberg MC. Reliability of new indices of radiographic osteoarthritis of the hand and hip and lumbar disc degeneration. *J Rheumatol*. 1993;20:1911-1918.

55. Grosso A, Douglas I, Hingorani A, MacAllister R, Smeeth L. Post-marketing assessment of the safety of strontium ranelate; a novel case-only approach to the early detection of adverse drug reactions. *Br J Clin Pharmacol*. 2008;66:689-694.

56. Shea B, Wells G, Cranney A, et al. Osteoporosis Methodology Group; Osteoporosis Research Advisory Group. Calcium supplementation on bone loss in postmenopausal women. *Cochrane Database Syst Rev*. 2004;(1):CD004526.

57. Question and answers on the safety of Protelos/Osseor (strontium ranelate). London: European Medicines Agency; 2007. Ref. EMEA/534613/2007. Available at: www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/Protelos_Q&A_53461307en.pdf. Accessed October 1, 2008.

58. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology*. 2003;206:353-356.