

# Effects of Long-Term Strontium Ranelate Treatment on the Risk of Nonvertebral and Vertebral Fractures in Postmenopausal Osteoporosis

## Results of a Five-Year, Randomized, Placebo-Controlled Trial

Jean-Yves Reginster,<sup>1</sup> Dieter Felsenberg,<sup>2</sup> Steven Boonen,<sup>3</sup> Adolfo Diez-Perez,<sup>4</sup> Rene Rizzoli,<sup>5</sup> Maria-Luisa Brandi,<sup>6</sup> Tim D. Spector,<sup>7</sup> Kim Brixen,<sup>8</sup> Stefan Goemaere,<sup>9</sup> Catherine Cormier,<sup>10</sup> Adam Balogh,<sup>11</sup> Pierre D. Delmas,<sup>12</sup> and Pierre J. Meunier<sup>13</sup>

**Objective.** This study was undertaken to assess the effect of strontium ranelate on nonvertebral and vertebral fractures in postmenopausal women with osteoporosis in a 5-year, double-blind, placebo-controlled trial.

Supported by Servier.

<sup>1</sup>Jean-Yves Reginster, MD, PhD: University of Liège, Liège, Belgium; <sup>2</sup>Dieter Felsenberg, MD, PhD: Free & Humboldt University, Berlin, Germany; <sup>3</sup>Steven Boonen, MD, PhD: Leuven University, Leuven, Belgium; <sup>4</sup>Adolfo Diez-Perez, MD, PhD: Hospital del Mar, Barcelona, Spain; <sup>5</sup>Rene Rizzoli, MD: Hôpital Cantonal, Geneva, Switzerland; <sup>6</sup>Maria-Luisa Brandi, MD, PhD: Policlinico Careggi, Florence, Italy; <sup>7</sup>Tim D. Spector, MD, FRCP: St Thomas' Hospital, London, UK; <sup>8</sup>Kim Brixen, MD, PhD: Odense University Hospital, Odense, Denmark; <sup>9</sup>Stefan Goemaere, MD: Universitair Ziekenhuis Ghent, Ghent, Belgium; <sup>10</sup>Catherine Cormier, MD: Hôpital Cochin, Paris, France; <sup>11</sup>Adam Balogh, MD, PhD: University of Debrecen, Debrecen, Hungary; <sup>12</sup>Pierre D. Delmas, MD: INSERM Lyon, Lyon, France; <sup>13</sup>Pierre J. Meunier, MD: Faculty Laennec, Lyon, France.

Dr. Reginster has received consulting fees and/or payment for advisory board service (less than \$10,000 each) from Servier, Novartis, Negma, Eli Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merck, Nycomed, NPS, and Theramex; he has received speaking fees from Merck Sharp and Dohme, Eli Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, and Novo Nordisk. Dr. Reginster also has received grant support from Bristol-Myers Squibb, Merck Sharp and Dohme, Rottapharm, Teva, Eli Lilly, Novartis, Roche, GlaxoSmithKline, and Amgen. Dr. Felsenberg has received consulting fees, speaking fees, and/or study support (less than \$10,000 each) from Servier, Roche, GlaxoSmithKline, Eli Lilly, Merck Sharp and Dohme, Teva, Chugai, Novartis, General Electric, Procter & Gamble, and Nycomed. Dr. Boonen has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Amgen, Merck, Procter & Gamble, Sanofi-Aventis, Servier, and Novartis. Dr. Diez-Perez has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Novartis, Eli Lilly, Procter & Gamble, Roche, and Amgen. Dr. Rizzoli has received consulting fees and/or speaking fees (more than \$10,000 each) from Servier, Roche, and Novartis. Dr. Brandi has received consulting fees, speaking

**Methods.** A total of 5,091 postmenopausal women with osteoporosis were randomized to receive either strontium ranelate at 2 gm/day or placebo for 5 years. The main efficacy criterion was the incidence of nonvertebral fractures. In addition, incidence of hip fractures was assessed, by post hoc analysis, in the subset of 1,128 patients who were at high risk of fractures (age 74 years or older with lumbar spine and femoral neck bone mineral density T scores  $-2.4$  or less). The incidence of new vertebral fractures was assessed, using the semi-quantitative method described by Genant, in the 3,646 patients in whom spinal radiography (a nonmandatory procedure) was performed during the course of the study. Fracture data were analyzed using the Kaplan-Meier survival method.

**Results.** Of the 5,091 patients, 2,714 (53%) completed the study up to 5 years. The risk of nonvertebral

fees, and/or honoraria (less than \$10,000 each) from Merck Sharp and Dohme, Servier, Nycomed, Procter & Gamble, Eli Lilly, GlaxoSmithKline, and Roche. Dr. Spector has received consulting fees and/or speaking fees (more than \$10,000) from Servier. Dr. Brixen has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Servier, Eli Lilly, Nycomed, Novartis, and Osteologix. Dr. Goemaere has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Nycomed, Roche, Sanofi-Aventis, and Servier. Dr. Delmas has received consulting fees, speaking fees, and/or honoraria (less than \$10,000) from Servier. Dr. Meunier has received consulting fees (more than \$10,000) from Servier.

Address correspondence and reprint requests to Jean-Yves Reginster, MD, PhD, Department of Epidemiology, Public Health and Health Economics, University of Liège—CHU Centreville, 45 Quai Godefroid Kurth, 4020 Liège, Belgium. E-mail: jyreginster@ulg.ac.be.

Submitted for publication August 2, 2007; accepted in revised form February 20, 2008.

fracture was reduced by 15% in the strontium ranelate group compared with the placebo group (relative risk 0.85 [95% confidence interval 0.73–0.99]). The risk of hip fracture was decreased by 43% (relative risk 0.57 [95% confidence interval 0.33–0.97]), and the risk of vertebral fracture was decreased by 24% (relative risk 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.

**Conclusion.** Our findings indicate that treatment of postmenopausal osteoporosis with strontium ranelate results in a sustained reduction in the incidence of osteoporotic nonvertebral fractures, including hip fractures, and vertebral fractures over 5 years.

Osteoporotic fractures are one of the most common causes of disability (1) and their incidence is predicted to increase sharply during coming decades due to an aging population and an increase in age-adjusted incidence in many countries (1–3). Such fractures account for a significant and increasing fraction of overall health care expenditures (3,4).

Bone material is continually replaced through resorption and formation processes at specific sites of remodeling. In postmenopausal women there is an increase in the overall bone turnover rate, and an imbalance in the rates of bone resorption and formation at individual remodeling sites, leading to net bone loss and the bone fragility that underlies osteoporotic fractures (5). Strontium ranelate is a new oral antiosteoporotic agent. Experimental studies have shown that it affects both sides of the bone remodeling imbalance, stimulating bone formation and reducing resorption at remodeling sites (6–9).

In the Spinal Osteoporosis Therapeutic Intervention study of women with  $\geq 1$  prevalent vertebral fracture, strontium ranelate reduced the risk of new vertebral fracture by 41% over 3 years (10). The present study, the Treatment of Peripheral Osteoporosis Study, was designed to evaluate the efficacy of strontium ranelate in reducing nonvertebral (peripheral) fractures (main criterion of efficacy) and vertebral fractures (1 secondary criterion of efficacy) over 5 years in postmenopausal women with osteoporosis. Statistical analysis of 3-year results, showing a significant reduction in nonvertebral fracture risk of 16% relative to placebo, have been published previously (11). Here we present the results of the full 5-year period of the Treatment of Peripheral Osteoporosis Study.

## PATIENTS AND METHODS

**Study protocol.** The Treatment of Peripheral Osteoporosis Study was a randomized, double-blind, placebo-controlled trial performed in postmenopausal women in 75 centers in Australia and 11 European countries. Patients were treated on an outpatient basis, and the investigators were specialists in rheumatology and/or endocrinology. All patients were initially enrolled in an open-label phase-in portion of the study, during which their vitamin D and calcium status was assessed and supplemented if required. Calcium was supplemented using doses of 500 mg or 1,000 mg to reach a total daily intake of  $>1,000$  mg. Vitamin D was supplemented daily according to baseline serum 25-hydroxyvitamin D (25[OH]D) levels. Patients received 800 IU/day when serum 25(OH)D was  $<45$  nmoles/liter and 400 IU/day when it was  $>45$  nmoles/liter. Details of vitamin D and calcium supplementation and dose adaptation have been published previously (12). The final supplementation doses established during the phase-in portion of the study were maintained during the subsequent randomized study.

Methodologic details have been described previously (11,12). Briefly, patients were randomized to receive strontium ranelate at 2 gm/day or placebo for 5 years; this design was preplanned at the beginning of the study. Study visits were scheduled at baseline, month 3, month 6, and every 6 months thereafter. For patients who dropped out over the study period, no final 5-year assessment was performed. Strontium ranelate and placebo were administered as powder, supplied in sachets, to be taken with water, and were of identical appearance, weight, and taste. At baseline, patients were given sachets for a 6-month period. The investigator asked the patient to return the therapeutic units at each visit, in order to calculate compliance. Compliance was therefore calculated as the percentage of sachets given to the patient that were actually taken.

The trial protocol was approved by independent ethics committees in each country and/or center, and the study was conducted in accordance with the ethics principles of the Declaration of Helsinki, 1964, as revised in Hong Kong in 1989. All patients provided written informed consent.

Patients had to be  $\geq 74$  years old, or 70–73 years old with an additional risk factor for osteoporotic fracture, such as personal or maternal history of osteoporosis-related fracture after menopause, residence in a retirement home, or frequent falls ( $>4$  per year). Additionally, femoral neck bone mineral density (BMD) had to be  $\leq 0.600$  gm/cm<sup>2</sup>, corresponding to a T score of less than  $-2.5$  (relative to the reference population determined by Hologic [Waltham, MA]). Patients were excluded from the study if they had had thoracic, abdominal, or pelvic irradiation within the preceding 5 years; had severe malabsorption or other severe gastrointestinal disease; severe liver or renal insufficiency; documented hypercalciuria without calcium supplementation; significant hyperthyroidism; or skeletal disease, including secondary osteoporosis, hyper- or hypoparathyroidism, Paget's disease of the spine, pelvis, or femur, and vertebral fracture related to premenopausal bone fragility. Patients were also excluded if they were receiving or had recently received treatment with agents likely to interfere with bone metabolism (except vitamin D or calcium), including bisphosphonates, ipriflavone, estrogens, anti-estrogens, pro-

gestogens, anabolic steroids, calcitonin, calcitriol, 1 $\alpha$  vitamin D, fluoride salts, and any other drugs currently in development for bone disease.

The main efficacy criterion was the incidence of osteoporosis-related nonvertebral fractures, determined by investigators on the basis of patient records (radiograph, radiologic report, and copy of the hospital report). Fractures of the coccyx, skull, jaw, face, phalanges (fingers and toes), and ankle were not regarded as osteoporosis related (13) and were not considered. Major nonvertebral osteoporotic fractures were defined as those of the hip, wrist, pelvis/sacrum, ribs/sternum, clavicle, and humerus, and were analyzed as a secondary criterion. Hip fractures were analyzed post hoc in a subgroup of patients at high risk of hip fractures, that is, age 74 years or older with lumbar spine and femoral neck BMD T scores of  $-2.4$  or less (relative to a Third National Health and Nutrition Examination Survey reference population).

Vertebral fractures were determined from standardized radiographs taken at baseline and annually thereafter. Since vertebral fractures were a secondary criterion, vertebral radiographs were not mandatory but were obtained for the largest possible number of patients. Reasons for not obtaining vertebral radiographs were technical or logistical problems or an investigator's decision regarding the individual patient's status. The vertebral radiographs were analyzed by the semi-quantitative method described by Genant (14), using a 4-point grading scale. A new vertebral fracture was defined as a change from grade 0 to grade  $\geq 1$ . Radiographs were assessed at a central reading facility (Centre d'Evaluation des Maladies Osseuses, France), by an investigator (Professor C. Roux) who was blinded with regard to treatment assignment.

Standing body height was measured at each study visit by a standardized procedure using a Harpenden stadiometer. Total hip, femoral neck, and lumbar spine BMD were measured at baseline and every 6 months thereafter by dual x-ray absorptiometry using Hologic devices. All scans were analyzed at a central location, and a cross-calibration program was applied (15). The distribution of strontium in bone and its greater absorption of x-rays compared with calcium may account for  $\sim 50\%$  of observed increases in BMD with strontium ranelate treatment (16).

Adverse events (AEs) reported spontaneously by patients or elicited during the interview were recorded at each study visit. Vital signs (weight, systolic and diastolic blood pressure, and heart rate) and blood and urinary parameters were assessed over the course of the study, as previously described (11,12).

**Statistical analysis.** Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients who took  $\geq 1$  sachet of study drug and for whom there was  $\geq 1$  item of data on the incidence of new nonvertebral fractures. To be included in the analysis of vertebral fractures, patients were required to have an assessable vertebral radiograph at baseline and  $\geq 1$  assessable vertebral radiograph postbaseline.

Statistical methods used were similar to those previously described for the 3-year results (11). Briefly, the proportions of patients who experienced first new incident osteoporotic nonvertebral fracture and  $\geq 1$  first new incident osteoporotic vertebral fracture over a period of time were determined by the Kaplan-Meier survival method, as pre-

planned in the protocol. Analysis of osteoporosis-related peripheral fractures was therefore carried out on all available data on the first new peripheral or vertebral fracture up to the cutoff date, regardless of the date of the last study visit or whether the patient was still receiving treatment.

Consequently, since the population selection bias increases year after year, any isolated yearly statistical comparison regarding the occurrence of fractures would provide biased (as well as inaccurate) estimates and would result in misleading clinical interpretation. Therefore, treatment groups were compared using the Cox proportional hazards model over 5 years. The incidence of nonvertebral fractures was adjusted for age, country of residence, body mass index, and femoral neck BMD, and the incidence of vertebral fractures was adjusted for age, country of residence, prevalent vertebral fractures, and lumbar spine BMD, as recommended by European Medicines Evaluation Agency (EMA) Guidelines (CPMP/EWP/2863/99, 05/22/2003). The nonparametric log rank test was used to confirm the results of the Cox models. The Type I error rate (2-sided) was set at 5%. Between-group comparisons of BMD were performed using analysis of covariance, with baseline value as the covariate, and Student's 2-tailed *t*-test. The numbers of patients with a body height loss of  $\geq 1$  cm were compared using the chi-square test.

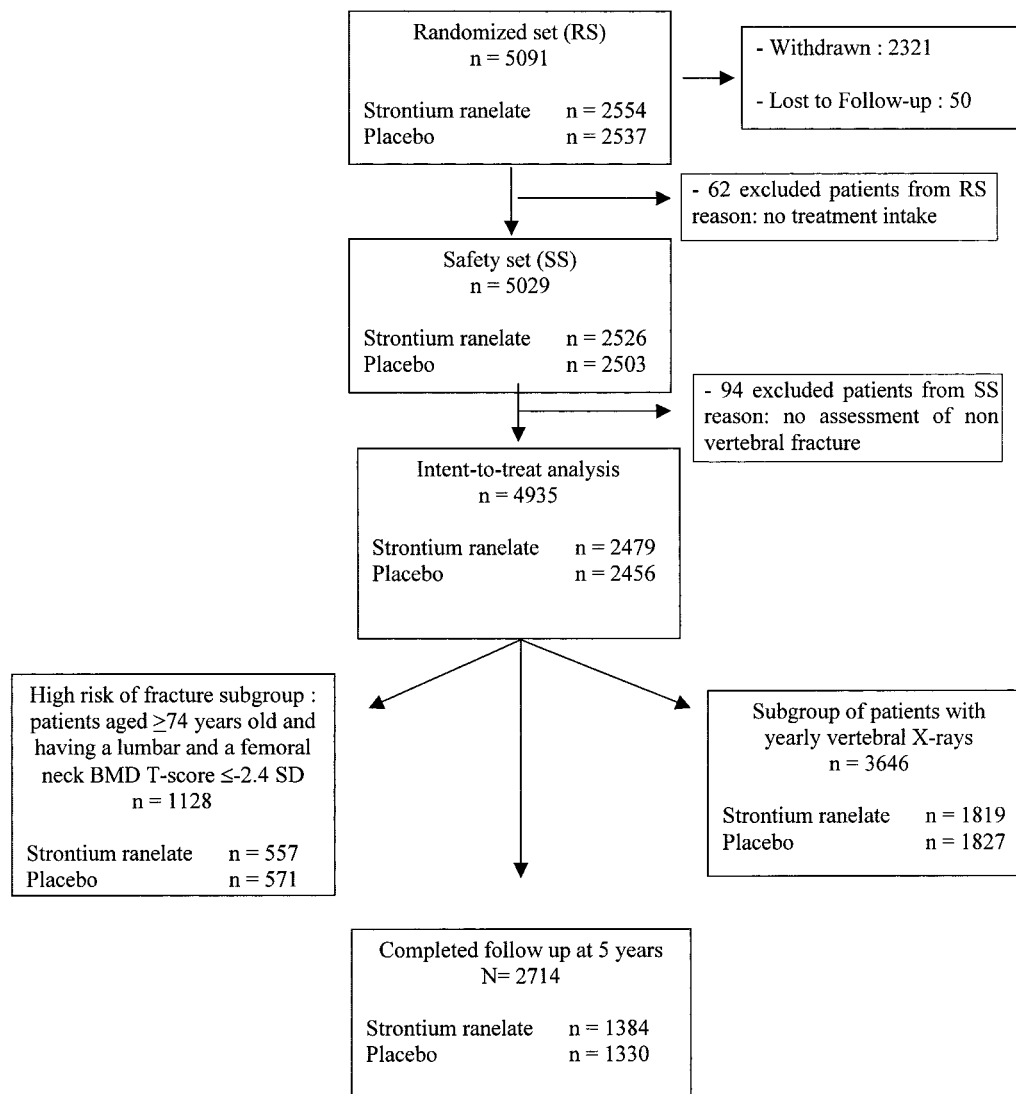
## RESULTS

A total of 5,091 patients were randomized for this study. Of those, 4,935 patients (97%) were included in the ITT analysis. Similar proportions of randomized patients were included in the ITT populations in the strontium ranelate group (2,479 patients [97% of randomized patients]) and the placebo group (2,456 patients [97% of randomized patients]). The 156 patients excluded from the ITT analysis had either no exposure to the study drug or no postbaseline assessment of peripheral fractures. Baseline demographic and clinical characteristics of patients included in the ITT population are shown in Table 1; there were no relevant

**Table 1.** Baseline characteristics of the ITT population, by treatment group\*

	Strontium ranelate group (n = 2,479)	Placebo group (n = 2,456)
Age, years	76.7 $\pm$ 5.0	76.8 $\pm$ 5.0
Time since menopause, years	28.4 $\pm$ 7.3	28.5 $\pm$ 7.5
No. (%) of patients with $\geq 1$ prevalent nonvertebral fracture	975 (39.3)	929 (37.8)
No. (%) of patients with $\geq 1$ prevalent vertebral fracture	716 (32.6)	750 (34.5)
Lumbar spine BMD		
Measurement, gm/cm <sup>2</sup>	0.797 $\pm$ 0.156	0.797 $\pm$ 0.155
T score	-2.83 $\pm$ 1.63	-2.84 $\pm$ 1.62
Femoral neck BMD		
Measurement, gm/cm <sup>2</sup>	0.552 $\pm$ 0.066	0.553 $\pm$ 0.067
T score	-3.13 $\pm$ 0.59	-3.13 $\pm$ 0.60

\* Except where indicated otherwise, values are the mean  $\pm$  SD. ITT = intent-to-treat; BMD = bone mineral density.



**Figure 1.** Overall disposition of the patients. BMD = bone mineral density.

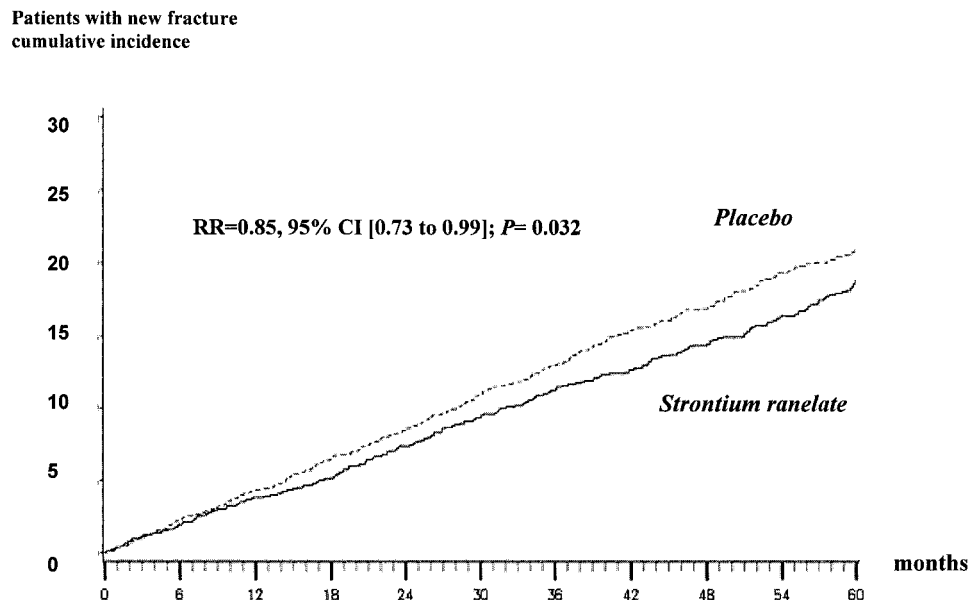
differences between treatment groups at baseline. The baseline demographic and clinical characteristics of the dropout population were similar to those of the entire population (data not shown).

Although spinal radiographs were not mandatory, 3,646 (74%) of the patients in the ITT population (1,819 patients in the strontium ranelate group and 1,827 patients in the placebo group) had such radiographs and were assessed for vertebral fractures. The proportion of patients in this subset with  $\geq 1$  prevalent vertebral fracture was 33.6%. Of the 3,646 patients who had spinal radiographs over the study period, 2,183 (60%) had a spinal radiograph at 5 years.

The subset of patients analyzed for hip fractures

included 1,128 patients, with a mean  $\pm$  SD age of  $79.2 \pm 4.4$  years. Their mean lumbar spine T score was  $-4.2$ , and mean femoral neck T score was  $-3.6$ . The proportion of patients in this subset with  $\geq 1$  prevalent nonvertebral fracture was 40.1%. Of the 939 patients in this subset who had an assessable vertebral radiograph at baseline, the proportion of patients with  $\geq 1$  prevalent vertebral fracture was 46.8%.

Of the 5,091 patients randomized, 2,714 patients (53%) completed the study (attended the 5-year visit), with similar proportions in the 2 treatment groups (Figure 1). The mean  $\pm$  SD duration of exposure to randomized treatment was  $1,126 \pm 668$  days. Global compliance was 81.6%. Altogether 2,321 patients pre-



**Figure 2.** Proportion of patients experiencing  $\geq 1$  incident osteoporosis-related nonvertebral fracture over a period of 60 months in the 2 treatment groups. RR = relative risk; 95% CI = 95% confidence interval.

maturely withdrew from the study. The reasons for first-time study drug discontinuation and withdrawal were AEs (19.1%), protocol deviation (0.2%), aggravated osteoporosis (0.3%), and nonmedical reasons (20.7%). In addition, 0.9% of the patients were lost to followup.

Over 5 years, the risk of new nonvertebral osteoporotic fractures (the primary efficacy criterion) was reduced significantly, by 15%, in the strontium ranelate group compared with the placebo group (incidence 18.6% versus 20.9%; relative risk 0.85 [95% confidence interval 0.73–0.99],  $P = 0.032$ ) (Figure 2). The number of patients in whom treatment was needed in order to

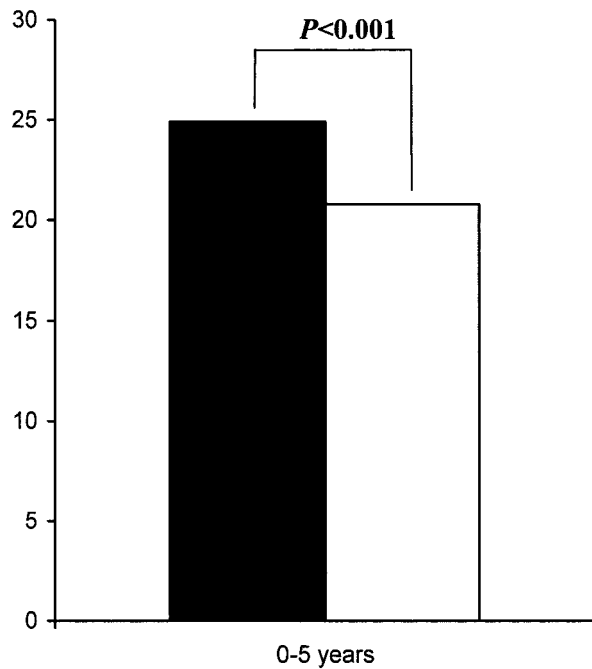
prevent 1 new nonvertebral fracture over 5 years was 44 (95% confidence interval 20–191). The risk of new major nonvertebral osteoporotic fracture (including wrist, pelvic/sacrum, ribs/sternum, clavicle, humerus, and hip fractures) was reduced by 18% with strontium ranelate (incidence 14.8% versus 16.9%; relative risk 0.82 [95% confidence interval 0.69–0.98],  $P = 0.025$ ). The results for each fracture site are presented in Table 2. The number of patients in whom treatment was needed in order to prevent 1 new major nonvertebral fracture over 5 years was 46 (95% confidence interval 21–232). In the subset of patients analyzed for hip fractures, the risk of hip fracture was reduced signifi-

**Table 2.** Proportion of patients with  $\geq 1$  incident nonvertebral osteoporotic fracture and total number of nonvertebral osteoporotic fractures over a period of 5 years, by treatment group\*

	No. (%) of patients with $\geq 1$ incident nonvertebral fracture		Total no. of fractures	
	Strontium ranelate group (n = 2,479)	Placebo group (n = 2,456)	Strontium ranelate group (n = 2,479)	Placebo group (n = 2,456)
All nonvertebral fractures	312 (18.6)	359 (20.9)	433	554
Major nonvertebral osteoporotic fractures	246 (14.8)	291 (16.9)	326	442
Wrist	86 (5.1)	87 (5.1)	97	97
Pelvic/sacrum	27 (1.5)	42 (2.4)	37	67
Ribs/sternum	37 (2.3)	61 (3.6)	66	123
Clavicle	6 (0.4)	8 (0.4)	6	8
Humerus	26 (1.7)	43 (2.7)	27	44
Hip (proximal femur)	88 (5.5)	98 (5.9)	93	103

\* Percentages are the incidence obtained using the Kaplan-Meier method.

**Proportion of patients with new vertebral fracture (%)**



**Figure 3.** Proportion of patients in whom  $\geq 1$  incident osteoporosis-related vertebral fracture occurred during the 5 years of study, determined by the Kaplan-Meier method. A total of 3,646 patients were evaluated for vertebral fractures. The numbers of patients experiencing  $\geq 1$  new vertebral fracture were 307 in the strontium ranelate group (open bar) and 384 in the placebo group (solid bar). The total numbers of new vertebral fractures detected over the study period were 452 in the strontium ranelate group and 583 in the placebo group.

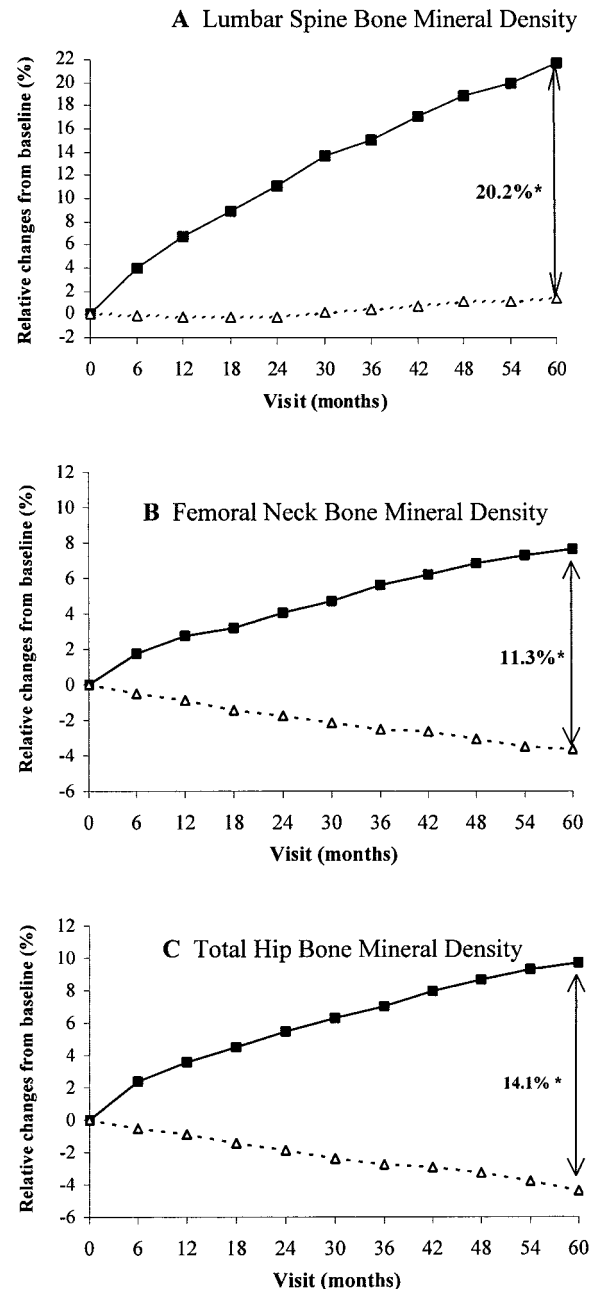
cantly in the strontium ranelate group, by 43% compared with the placebo group (incidence 7.2% versus 10.2%; relative risk 0.57 [95% confidence interval 0.33–0.97],  $P = 0.036$ ).

The risk of new vertebral fracture over the 5-year period was reduced by 24% with strontium ranelate compared with placebo (incidence 20.8% versus 24.9%; relative risk 0.76 [95% confidence interval 0.65–0.88],  $P < 0.001$ ) (Figure 3). The number of patients in whom treatment was needed in order to prevent 1 new vertebral fracture over 5 years was 25 (95% confidence interval 14–97).

The risk of any new osteoporotic fracture (vertebral or nonvertebral) was significantly reduced, by 20%, in the strontium ranelate group compared with the placebo group (incidence 29.1% versus 33.9%; relative risk 0.20 [95% confidence interval 0.71–0.90],  $P < 0.001$ ). The number of patients in whom treatment was

needed in order to prevent 1 new osteoporotic fracture (either vertebral or nonvertebral) over 5 years was 21 (95% confidence interval 13–55).

Significantly fewer patients in the strontium ranelate group than in the placebo group experienced a



**Figure 4.** Changes in A, lumbar spine, B, femoral neck, and C, total hip bone mineral density over a period of 60 months in patients treated with strontium ranelate (squares) and patients treated with placebo (triangles). All between-group differences were significant. \* =  $P < 0.001$ .

reduction in body height of  $\geq 1$  cm than in the placebo group (39% versus 43%;  $P = 0.003$ ). Lumbar spine, femoral neck, and total hip BMD increased progressively in the strontium ranelate group, but remained unchanged or decreased slightly in the placebo group (Figure 4). Differences between groups were significant for each site ( $P < 0.001$  in each case). Increases in relative mean BMD in the strontium ranelate group compared with the placebo group during the last 2 years of the study (from the 3-year visit to the 5-year visit) were 4.9% for lumbar spine, 1.8% for femoral neck, and 2.0% for total hip BMD.

The safety profile of strontium ranelate over 5 years of treatment was similar to that observed over 3 years (11). Treatment was well tolerated. The incidence of AEs was well balanced between the 2 groups (95.3% in the strontium ranelate group versus 94.9% in the placebo group), as was the incidence of serious AEs (30.9% in the strontium ranelate group versus 30.0% in the placebo group). More patients in the strontium ranelate group than in the placebo group reported nausea (7.8% versus 4.8%), diarrhea (7.2% versus 5.45%), headache (3.6% versus 2.7%), dermatitis (2.3% versus 2.0%), and eczema (2.0% versus 1.5%). The incidence of venous thromboembolic events was 2.7% in the strontium ranelate group versus 2.1% in the placebo group (odds ratio 1.30, 95% confidence interval 0.90–1.88), and the difference between groups was not statistically significant. The new cases of each symptom reported during the final 2 years of followup were well balanced between the strontium ranelate and placebo groups.

## DISCUSSION

Both nonvertebral and vertebral osteoporotic fractures are associated with increased mortality and morbidity (1,17). Our findings showed that 5 years of treatment with strontium ranelate at 2 gm/day produced significant reductions, relative to placebo and analyzed on an ITT basis, in nonvertebral fractures, with risk reductions of 15% for all nonvertebral osteoporotic fractures and 18% for major nonvertebral osteoporotic fractures. The risk of any new osteoporotic fracture was reduced by 20%. In the subgroup of patients included in the analysis of hip fractures, the risk of hip fracture was reduced significantly, by 43%.

The reduction in risk of nonvertebral fracture of 15% over 5 years in the Treatment of Peripheral Osteoporosis Study is similar to the 16% reduction obtained over 3 years (11). The Treatment of Peripheral Osteoporosis Study differed from published randomized stud-

ies of currently approved antiosteoporotic drugs in that patients committed at the outset to 5 years of randomized treatment. In contrast, most published studies of more than 3 years' duration have involved extension periods, although there have been studies of alendronate (18) and raloxifene (19) that involved 4-year randomized initial treatment periods. However, no significant reduction in nonvertebral fracture risk was found in either of those studies.

In a 2-year extension of an initial 3-year study of risedronate (20), the risk of new vertebral fractures was reduced by 59% relative to placebo, but there was no significant reduction in the risk of nonvertebral fractures. Some patients continued in a further 2-year extension, but fracture rates could not be compared over this period because all patients received risedronate (21). Another study monitored the long-term effects of alendronate in 1,099 women previously treated with alendronate for 3–6 years, who were randomized to continue alendronate or receive placebo for a further 5 years (22,23). Over this new 5-year period, clinical spine fracture risk was reduced by 55%, but the risks of morphometric spine fractures and nonvertebral fractures were not reduced significantly. Alendronate was also evaluated over a 10-year period in a series of 3 extensions to a 3-year study. Increases in BMD were maintained throughout, but fracture rates could not be compared, because all treatment groups received alendronate at some stage (24,25).

Nonvertebral fractures were assessed during a 4-year extension of a 4-year study of raloxifene, but the incidence of nonvertebral fractures was the same in the raloxifene and placebo groups (22.9%) over the 8-year period (26). In the recent Raloxifene Use for The Heart trial (27), which had a median followup of 5.6 years, the clinical vertebral fracture risk (secondary end point) was decreased by 35% in the treated group compared with the placebo group. In the same study, the incidence of clinical nonvertebral fractures was similar in the raloxifene and placebo groups (hazard ratio 0.96,  $P = 0.59$ ). Significant long-term reduction of fracture risk has been demonstrated with estrogen therapy during the Women's Health Initiative trial (28), but due to the increased incidence of strokes, estrogen therapy for osteoporosis has been reconsidered.

The reduction in vertebral fracture risk of 24% over 5 years in the present study was smaller than that reported for the 3-year period (39%) (11). A similar phenomenon has been reported for vertebral fractures over a shorter time period, in 2 studies of risedronate, in which risk reductions of 65% and 61% over 1 year

decreased to 41% and 49%, respectively, over 3 years (29,30). Comparisons of cumulative end points at different times during a long-term study must be interpreted with caution. The patients at risk of a given end point, although well balanced between treatment groups in terms of disease characteristics and level of risk at randomization, become progressively unbalanced between groups over time if the treatments differ in efficacy. Attrition of high-risk patients will be more rapid in the low efficacy (generally, placebo) group. In the later parts of the study, therefore, the placebo group will effectively contain fewer high-risk patients than the active treatment group, and the effects of active treatment will appear to be reduced. The same phenomenon also occurs when nonvertebral fractures are considered; therefore, we performed comparisons between groups over similar periods of followup since the beginning of the study.

Strontium ranelate produced significant increases in lumbar spine, femoral neck, and total hip BMD relative to placebo. Importantly, increases at all 3 sites were seen during the final year of treatment, indicating that improvements in BMD continued to occur with long-term treatment. After 5 years of treatment, the safety profile of strontium ranelate remained unchanged compared with the 3-year findings, with no new types of AEs noted.

The present study has strengths as well as limitations. This is the first report of a preplanned analysis assessing the efficacy of an antiosteoporotic treatment in preventing nonvertebral and vertebral fractures over a 5-year followup period. As discussed previously, data on treatments for vertebral fractures studied over 4 years (18,19) have been reported, but there have been no published reports of data obtained over 5 years in studies designed with fracture assessment as the primary end point. Furthermore, no previous study has shown data from a preplanned analysis over 5 years regarding nonvertebral fractures.

Data on hip fractures in the present study were obtained through post hoc analysis. While this may be considered a limitation of the study, it should be noted that no other study has demonstrated that a treatment was efficacious in preventing hip fractures in the long term, even in a subset of subjects who are at risk. It must be stressed that at the time of the design of the present study, the primary end point considered was the occurrence of nonvertebral fractures, as required then in the guidelines. The analysis of efficacy in preventing hip fractures was therefore performed later as a post hoc analysis, following the requirements of the EMEA.

Another possible limitation is the proportion of patients included who did not complete the entire 5-year duration of the study. Of the 5,091 patients who were initially randomized, 65% completed the first 3 years of the study (11), and 53% completed the entire 5 years. The total dropout rate over 5 years was ~47%, which could be considered relatively high; however, it compares favorably with the 42% dropout rate in a 3-year trial of risedronate in a population roughly the same age as that in the present study (20). Since there have been no published studies of a 5-year preplanned followup of the same initial population, a direct comparison with our study is not possible.

Published extension studies after the main 3-year followup have usually included data from only a subset of the subjects who remained in the study after 3 years, so no dropout rate can be calculated on the basis of the original randomized population. However, data from extension studies show that the dropout rate over 2 years is close to ours when similar populations are addressed. Hence, in our study, of the 3,320 patients entering the fourth year of followup, 2,714 completers at 5 years represents an 18% dropout rate over these 2 final years, which is in the same range as the 17% dropout rate that occurred over the 2-year extension period in the risedronate study (20).

In conclusion, long-term treatment with strontium ranelate at 2 gm/day for 5 years produced significant reductions in the incidence of nonvertebral, hip, and vertebral osteoporotic fractures in postmenopausal women with osteoporosis. Strontium ranelate represents a safe and effective first-line treatment for postmenopausal women with osteoporosis over the long term.

#### AUTHOR CONTRIBUTIONS

Dr. Reginster had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study design.** Reginster, Diez-Perez, Brandi, Spector, Delmas, Meunier.  
**Acquisition of data.** Reginster, Felsenberg, Diez-Perez, Rizzoli, Spector, Brixen, Goemaere, Cormier, Balogh, Meunier.

**Analysis and interpretation of data.** Reginster, Boonen, Rizzoli, Brandi, Brixen, Goemaere, Cormier, Balogh, Delmas, Meunier.

**Manuscript preparation.** Reginster, Boonen, Diez-Perez, Rizzoli, Brixen, Goemaere, Cormier, Balogh, Delmas, Meunier.

**Statistical analysis.** Reginster, Balogh.

**Manuscript review.** Felsenberg, Spector.

**Study Task Force Committee member.** Balogh.

#### ROLE OF THE STUDY SPONSOR

Servier provided assistance in study design and statistical analysis. All of the authors agreed on the submission of the manuscript, approved the final version, and were given the opportunity to fully review the document.

## REFERENCES

- Cummings SR, Melton LJ III. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002;359:1761–7.
- Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int* 1997;7:407–13.
- Schwenkglens M, Lippuner K, Hauselmann HJ, Szucs TD. A model of osteoporosis impact in Switzerland 2000–2020. *Osteoporos Int* 2005;16:659–71.
- Puffer S, Torgerson DJ, Sykes D, Brown P, Cooper C. Healthcare costs of women with symptomatic vertebral fractures. *Bone* 2004;35:383–6.
- Seeman E, Delmas PD. Bone quality—the material and structural basis of bone strength and fragility. *N Engl J Med* 2006;354:2250–61.
- Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. *Calcif Tissue Int* 2001;69:121–9.
- Buehler J, Chappuis P, Saffar JL, Tsouderos Y, Vignery A. Strontium ranelate inhibits bone resorption while maintaining bone formation in alveolar bone in monkeys (*Macaca fascicularis*). *Bone* 2001;29:176–9.
- Baron R, Tsouderos Y. In vitro effects of S12911-2 on osteoclast function and bone marrow macrophage differentiation. *Eur J Pharmacol* 2002;450:11–7.
- Marie PJ. Strontium ranelate: a novel mode of action of optimizing bone formation and resorption. *Osteoporos Int* 2005;16 Suppl 1:S7–10.
- Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350:459–68.
- Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of non-vertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90:2816–22.
- 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:S66–76.
- Melton LJ III, Thamer M, Ray NF, Chan JK, Chestnut CH III, Einhorn TA, et al. Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. *J Bone Miner Res* 1997;12:16–23.
- Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993;8:1137–48.
- Slosman DO, Provedini DM, Meunier PJ, Delmas PD, Sebert JL, de Vernejoul MC, et al. The use of different dual x-ray absorptiometry brands in a multicenter clinical trial. *J Clin Densitom* 1999;2:37–44.
- Nielsen SP, Slosman D, Sorensen OH, Basse-Cathalinat B, De Cassin P, Roux CR, et al. Influence of strontium on bone mineral density and bone mineral content measurements by dual X-ray absorptiometry. *J Clin Densitom* 1999;2:371–9.
- Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. *Osteoporos Int* 2004;15:38–42.
- Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al, the Fracture Intervention Trial Research Group. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077–82.
- Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, et al, for the Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomised clinical trial. *J Clin Endocrinol Metab* 2002;87:3609–17.
- Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003;32:120–6.
- Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcif Tissue Int* 2004;75:462–8.
- Black D, Schwartz A, Ensrud K, Cauley JA, Levis S, Quandt SA, et al, for the FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX), a randomized trial. *JAMA* 2006;296:2927–38.
- Ensrud KE, Barrett-Connor EL, Schwartz A, Santora AC, Bauer DC, Suryawanshi S, et al, for the Fracture Intervention Trial long-term extension. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial Long-Term Extension Research Group. *J Bone Miner Res* 2004;19:1259–69.
- Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales A, Menkes CJ, Wasnich RD, et al, for the Phase III Osteoporosis Treatment Study Group. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. *J Clin Endocrinol Metab* 2000;85:3109–15.
- Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al, for the Alendronate Phase III Osteoporosis Treatment Study Group. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004;350:1189–99.
- Siris ES, Harris ST, Eastell R, Zanchetta JR, Goemaere S, Diez-Perez A, et al, for the Continuing Outcomes Relevant to Evista (CORE) Investigators. Skeletal effects of raloxifene after 8 years: results from the Continuing Outcomes Relevant to Evista (CORE) study. *J Bone Miner Res* 2005;20:1514–24.
- Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al, for the Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006;355:125–37.
- Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al, the Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12.
- Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al, for the Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Effects of risedronate treatment on vertebral and non-vertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999;282:1344–52.
- Reginster JY, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al, Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000;11:83–91.