Strontium Ranelate Reduces the Risk of Nonvertebral Fractures in Postmenopausal Women with Osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study

J. Y. Reginster, E. Seeman, M. C. De Vernejoul, S. Adami, J. Compston, C. Phenekos, J. P. Devogelaer, M. Diaz Curiel, A. Sawicki, S. Goemaere, O. H. Sorensen, D. Felsenberg, and P. J. Meunier

Department of Epidemiology (J.Y.R.), Public Health and Health Economics, University of Liège, 4020 Liège, Belgium; Endocrine Department (E.S.), Hospital University of Melbourne, 3084 Melbourne, Australia; Institut National de la Santé et de la Recherche Médicale Unité 606 and Fédération of Rheumatologie (M.C.D.V.), Lariboisiere Hospital, 75010 Paris, France; Centro Ospedaliero Clinicizato di Medicina, Riabilitiva e Preventiva di Valeggio (S.A.), 37067 Valeggio Sul Mincio, Italy; Department of Medicine (J.C.), University of Cambridge, Cambridge, CB2 2QQ United Kingdom; Department of Endocrinology (C.P.), Red Cross Hospital, 11526 Athens, Greece; Department of Rheumatology (J.P.D.), Catholic University of Louvain, 1200 Brussels, Belgium; Fundacion Jiménez Diaz (M.D.C.), Servicio de Medicina Interna, Unidad de Metabolismo Oseo, 28040 Madrid, Spain; Warszawskie Centrum Osteoporozy (A.S.), 00-632 Warszawa, Poland; Unit for Osteoporosis and Metabolic Bone Diseases (S.G.), Ghent University Hospital, 9000 Gent, Belgium; The Osteoporosis Research Center (O.H.S.), Department 545, Hvidovre University Hospital, 2650 Hvidovre, Denmark; Universitätklinikum Benjamin Franklin (D.F.), 12200 Berlin, Germany; Department of Rheumatology and Bone Diseases (P.J.M.), Edouard Herriot Hospital, 69372 Lyon, France

Background: Strontium ranelate, a new oral drug shown to reduce vertebral fracture risk in postmenopausal women with osteoporosis, was studied in the Treatment of Peripheral Osteoporosis (TROPOS) study to assess its efficacy and safety in preventing nonvertebral fractures also.

Methods: Strontium ranelate (2 g/d) or placebo were randomly allocated to 5091 postmenopausal women with osteoporosis in a double-blind placebo-controlled 5-yr study with a main statistical analysis over 3 yr of treatment.

Findings: In the entire sample, relative risk (RR) was reduced by 16% for all nonvertebral fractures ($P = 0.04$), and by 19% for major fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle, humerus) ($P = 0.031$) in strontium ranelate-treated patients in comparison with the placebo group. Among women at high risk of hip fracture (age ≥ 74 yr and femoral neck bone mineral density T score ≤ -3, corresponding to -2.4 according to NHANES reference) (n =

1977), the RR reduction for hip fracture was 36% ($P = 0.046$). RR of vertebral fractures was reduced by 39% ($P < 0.001$) in the 3640 patients with spinal x-rays and by 45% in the subgroup without prevalent vertebral fracture.

Strontium ranelate increased bone mineral density throughout the study, reaching at 3 yr ($P < 0.001$): +8.2% (femoral neck) and +9.8% (total hip).

Incidence of adverse events (AEs) was similar in both groups.

Conclusion: This study shows that strontium ranelate significantly reduces the risk of all nonvertebral and in a high-risk subgroup, hip fractures over a 3-yr period, and is well tolerated. It confirms that strontium ranelate reduces vertebral fractures. Strontium ranelate offers a safe and effective means of reducing the risk of fracture associated with osteoporosis. (*J Clin Endocrinol Metab* 90: 2816–2822, 2005)

FEW STUDIES HAVE examined the effect of drug therapy on nonvertebral fractures as a primary end point even though nonvertebral fractures may be considered to be more serious consequences of osteoporosis than vertebral fractures in terms of morbidity, mortality, and cost (1). Trauma is a greater contributor to nonvertebral fractures than it is to vertebral fractures, and therefore, study designed to assess the efficacy of an agent in terms of preventing such fractures is likely to be more difficult (2, 3).

Nevertheless, bone fragility contributes to the pathogen-

esis of nonvertebral fracture, and is the outcome of age- and menopause-related bone loss resulting from an imbalance in the volume of bone resorbed and formed within each of the many multicellular foci eroding bone on its inner or endosteal surface. The remodeling imbalance results from a reduction in bone formation as well as an increase in bone resorption at the cellular level (4).

Strontium ranelate is a new orally active drug that may dissociate bone formation and bone resorption by allowing continued production of bone while decreasing bone resorption (5, 6, 7). In a recent clinical trial, the Spinal Osteoporosis Therapeutic Intervention (SOTI) study, involving 1649 postmenopausal women with established vertebral osteoporosis, strontium ranelate (2 g/d) orally reduced the relative risk (RR) of new vertebral fractures by 49% at 1 yr and by 41% over 3 yr (8). Treatment of Peripheral Osteoporosis (TROPOS), a randomized, double-blind, placebo-controlled clinical trial, was designed to assess the effectiveness of stron-

tium ranelate in preventing nonvertebral fractures in post-menopausal women with osteoporosis and also to assess its tolerability.

Subjects and Methods

Study subjects

Ambulatory postmenopausal women were recruited at 75 centers in 11 European countries and in Australia.

Women were eligible in the study: 1) if they had a femoral neck bone mineral density (BMD) 0.600 g/cm^2 or less (measured with Hologic instruments), corresponding to a T-score less than -2.5 according to the centralized normative data (D. O. Slosman); 2) and were 74 yr or older, or aged between 70 and 74 yr but with one additional fracture risk factor (*i.e.* history of osteoporotic fracture after menopause, residence in a retirement home, frequent falls, or a maternal history of osteoporotic fractures of the hip, spine, or wrist).

Exclusion criteria were: diseases interfering with bone metabolism or use of anti-osteoporotic treatments (bisphosphonates taken for more than 14 d within the previous year; estrogen, calcitonin, fluoride salts, calcitriol, or 1-α-vitamin D taken for more than 1 month during the previous 6 months).

After receiving information from the investigator (full explanation of the nature, purpose, and duration of the study and that the patient would be free to withdraw from the study at any time, without affecting the standard of care received), and being able to ask questions regarding all aspects of the study, all participants gave written informed consent before enrollment. The study was approved by the Institutional Review Boards.

Treatment and follow-up of the study

Before inclusion in the TROPOS study, patients were subjected to a run-in study to initiate normalization of their calcium and vitamin D status. The duration of this run-in study was 2 wk to 6 months, depending on the severity of calcium and 25-OH vitamin D (25-OH D) deficiency. All enrolled women received daily supplements of up to 1000 mg of elemental calcium adapted to their needs according to their dietary intake (0, 500, or 1000 mg to reach a total daily intake above 1000 mg), and vitamin D according to their serum 25-OH D levels (800 IU for patients having serum 25-OH D lower than 45 nmol/liter and 400 IU for all the others). For patients with severe vitamin D deficiency (25-OH D lower than 30 nmol/liter) the duration of the run-in period was at least 3 months.

At the end of the run-in period, patients were included in TROPOS. Patients were randomly assigned to receive either 2 g/d strontium ranelate or placebo powder for 5 yr (Fig. 1). Subjects were instructed to take the study drug once daily at bedtime or twice daily (one sachet half an hour before breakfast, and one at bedtime). Around 90% of the patients chose the once-daily regimen, at bedtime. Calcium and vitamin

D supplementation was prescribed throughout the study with the dosage determined during the run-in period.

The predetermined main evaluation criterion was the incidence of nonvertebral fractures. The main analysis was performed on all data obtained until the last patient completed 3 yr of follow-up, to comply with international guidelines (9, 10). The patients were followed at 3-month intervals during the first 6 months, then every 6 months.

During the study, nonvertebral fractures were reported by study investigators based on written documentation provided and documented in the source document (radiograph, radiological report, copy of the hospitalization/emergency department report). Only documented nonvertebral fractures were taken into account in the statistical analysis. Fractures of the coccyx, skull, jaw, face, phalanx (fingers and toes), and ankle were not regarded as being related to osteoporosis and were not considered.

Major nonvertebral osteoporotic fractures, defined as fractures of hip, wrist, pelvis and sacrum, ribs-sternum, clavicle, or humerus, were analyzed as a predetermined secondary end point decided by an Advisory Board during the study and well before breaking the code. They are the most relevant sites for osteoporosis-related fractures and important in terms of disability and pain duration.

Nonvertebral (primary end-point), major osteoporosis-related and hip fractures were individually analyzed in the TROPOS study.

Vertebral x-rays were performed at baseline and annually thereafter, according to standardized procedures. All radiographs were analyzed at a central facility using a semiquantitative visual assessment (method of Genant *et al.*; Ref. 11). Vertebral x-rays were not mandatory in TROPOS study (secondary criterion) but were obtained for the largest possible number of patients in agreement with the study protocol; they were not performed in some cases (due to technical or logistical problems), or following investigator decision according to the individual patient's status. In total, a subgroup of 3640 patients (71%) were followed by means of baseline and yearly vertebral x-rays.

BMD was measured by dual energy x-ray absorptiometry at baseline and at 6-month intervals at the proximal femur. All scans were analyzed centrally. A quality control program, including serial measurements of a spine phantom and daily quality controls, was conducted throughout the study (12).

Blood and urine samples were collected at baseline, 3 months, 6 months, then at 6-month intervals, stored (-80 C) and centrally analyzed. Biochemical tests were performed using standard methods. Serum concentrations of PTH was measured with an immunoradiometric assay (N-tact; DiaSorin) (laboratory reference range: 10–65 pg/ml), 25-OH D with a RIA (DiaSorin, Still Water, MN) (laboratory reference range: 7.5–101.0 nmol/liter) and 1,25(OH)$_2$ vitamin D with a radioreceptor assay (DiaSorin).

Statistical analysis

Safety was studied in patients having received at least one sachet of treatment. Anti-fracture efficacy was analyzed on an intention-to-treat (ITT) basis. The ITT was defined as randomized patients having taken at least one sachet of treatment, and with at least one postbaseline assessment of nonvertebral fracture occurrence (first assessment at M3). The ITT analysis was the main statistical analysis.

Nonvertebral (primary end-point), major osteoporosis-related and hip fractures were individually analyzed in TROPOS study.

The TROPOS trial was set up in 1996, *i.e.* more than 1 yr before the release of but in line with the first European Committee for Medicinal Products for Human Use (CHMP) guideline on osteoporosis in 1997 and the Food and Drug Administration guideline issued in 1994 and was powered to evaluate the RR of nonvertebral fractures between groups (primary endpoint). However, nonvertebral fractures including hip and major fractures were documented separately (preplanned analyses) as requested in the CHMP guideline issued in 2001 (CPMP/EW/552/95 rev 1). Therefore, this study was neither designed nor powered to demonstrate an antifracture efficacy at each individual site (*i.e.* hip level).

Moreover, a *post hoc* subgroup of particular medical interest (*i.e.* with a high risk of hip fracture) was analyzed to complete TROPOS efficacy data at the hip site, to comply with CHMP guideline issued in 2001 (CPMP/EW/552/95 rev 1). This subgroup was defined by age 74 yr or older (as the incidence of hip fracture rises exponentially after 74 yr; Ref. 13), and a femoral neck BMD T-score -3 SD or less (defined according
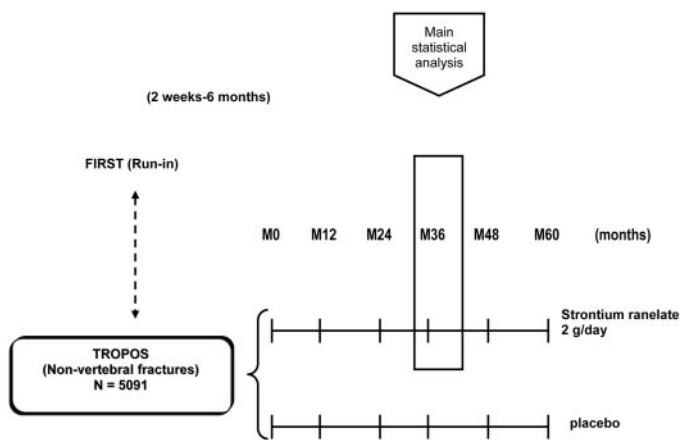

FIG. 1. Study design.

to the centralized normative data, which corresponded to a T-score of −2.4 sp according to the Third National Health and Nutrition Examination Survey data), as previously used as an inclusion criteria for the Hip Intervention Program study (15).

The incidence of patients experiencing nonvertebral fractures was estimated according to the Kaplan-Meier method, and a Cox model was used to compare groups and to estimate the RR and its 95% confidence interval (95% CI). Simultaneous adjustments for influential covariates were carried-out on age, femoral neck BMD, body mass index, and country; type one error rate was set at 5% (two sided). The incidence of patients with new vertebral fractures was calculated each year according to Kaplan Meier method and an unadjusted Cox model was used to estimate the RR and its 95% CI.

For BMD percentage changes at each visit from baseline, a stepdown hierarchical procedure was performed (based on the increasing treatment effect over time). The two groups were compared using a one-sided Student's *t* test at each visit with a type one error rate of 2.5%. The *P* values presented correspond to a two-sided *t* test at the 5% threshold (one-sided *P* values were doubled).

Results

Study subjects

Of the 5091 patients initially recruited, 4932 (97%) comprised the ITT population; 1977 patients (39%) were at least 74 yr and having a femoral neck BMD T-score −3 sp or less (Fig. 2). A total of 3640 patients (71%) had a baseline and at least one follow-up vertebral x-ray taken at yearly intervals. The mean duration of the run-in period was 101 ± 52 d. Baseline characteristics of the placebo and treated groups were similar in the ITT population (Table 1) and in the subgroup of patients who were followed with vertebral x-rays:
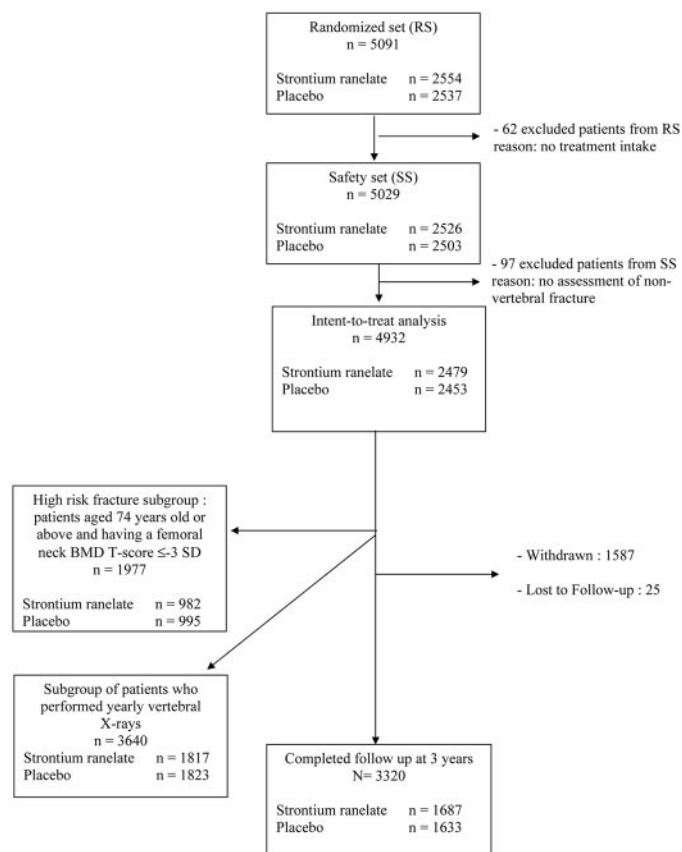

Fig. 2. Study populations.

mean age was 77 yr, mean duration of treatment intake was 906 ± 471 d (mean ± sp), corresponding to a mean global compliance of 82%. In the high-risk fracture subgroup, the baseline characteristics were also comparable between the placebo and treated groups (Table 1), mean age was 80 yr, mean duration of treatment intake was 838 ± 485 d (mean ± sp), corresponding to a mean global compliance of 80%.

Nonvertebral fractures

In the ITT population, strontium ranelate was associated with a 16% RR reduction in all nonvertebral fractures over a 3-yr follow-up period [RR = 0.84; 95% CI (0.702; 0.995); *P* = 0.04] (Fig. 3). 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]. The RR of experiencing a hip fracture in the ITT population was reduced by 15% but this figure did not reach statistical significance, as the study was not designed nor powered for this parameter. In the high-risk fracture subgroup (women ≥74 yr and with femoral-neck BMD T-score ≤−3), treatment was associated with a 36% reduction in risk of hip fracture [RR = 0.64; 95% CI (0.412; 0.997), *P* = 0.046] (Fig. 4).

Vertebral fractures

Yearly vertebral x-rays were performed in 3640 patients (1817 in the strontium ranelate group and 1823 in the placebo group); a reduction in the RR of new vertebral fracture of 39% over 3 yr was observed in the strontium ranelate group [RR = 0.61; 95% CI (0.51; 0.73), *P* < 0.001], and by 45% [RR = 0.55; 95% CI (0.39; 0.77), *P* < 0.001] over the first year of treatment. In these 3640 patients, 66.4% had no prevalent vertebral fracture at inclusion (1230 patients in the strontium ranelate group and 1186 in the placebo group). The risk of experiencing a first vertebral fracture in these patients was reduced by 45% [RR = 0.55; 95% CI (0.42; 0.72), *P* < 0.001]. The incidence of vertebral fractures in the strontium ranelate and placebo groups was 7.7% and 14.0%, respectively, over 3 yr. In the subgroup of patients with at least one prevalent fracture (n = 1224, 587 in the strontium ranelate group and 637 in the placebo group), the risk of experiencing a new vertebral fracture was reduced by 32% [RR = 0.68; 95% CI (0.53; 0.85), *P* < 0.001]. The incidence of vertebral fractures in this instance for the strontium ranelate and placebo groups was 22.7% and 31.5%, respectively, over 3 yr.

Bone mineral density

Femoral neck BMD and total hip BMD significantly increased from 6 months onwards in the strontium ranelate group. At 3 yr, the BMD in the strontium ranelate group had increased from baseline by 5.7% at the femoral neck and 7.1% at the total hip (*P* < 0.001 for both comparisons with baseline values) corresponding to differences between the placebo and the treatment groups at 3 yr of 8.2% [95% CI (7.7; 8.7), *P* < 0.001] (Fig. 5) and 9.8% [95% CI (9.3; 10.4), *P* < 0.001], respectively. The combined effects of strontium distribution in bone and increased x-ray absorption of strontium compared with calcium leads to an amplification of BMD measurement by dual energy x-ray absorptiometry. These effects

TABLE 1. Baseline characteristics of the ITT population and in high-risk fracture subgroup

Characteristics[a]	ITT		High-risk fracture subgroup	
	Strontium ranclate (n = 2479)	Placebo (n = 2453)	Strontium ranclate (n = 982)	Placebo (n = 995)
Age (yr)	76.7 ± 5.0	76.8 ± 5.0	79.7 ± 4.6	79.5 ± 4.4
Time since menopause (yr)	28.4 ± 7.3	28.5 ± 7.5	31.4 ± 7.0	31.6 ± 7.0
Any prevalent (vertebral or nonvertebral) osteoporotic fracture (%)	55.4	54.2	58.8	57.4
BMD T-score				
Femoral neck	−3.13 ± 0.59	−3.13 ± 0.60	−3.55 ± 0.48	−3.55 ± 0.48
Total hip	−2.70 ± 0.94	−2.70 ± 0.96	−3.24 ± 0.85	−3.28 ± 0.86
Lumbar spine	−2.83 ± 1.63	−2.84 ± 1.62	−3.16 ± 1.60	−3.24 ± 1.53

No significant difference between groups for all baseline characteristics.

[a] Plus-minus values are means ± SD.

of strontium may account for approximately 50% of the measured changes in BMD.

Adverse events

Treatment was well tolerated; the incidence of AEs was well balanced between the two groups (87.9% in the strontium ranelate group and 88.9% in the placebo group), as well as the serious AEs (24.7% in the strontium ranelate group and 24.4% in the placebo group) and withdrawals due to AEs (24.2% in the strontium ranelate group and 21.6% in the placebo group). Nausea (7.2% *vs.* 4.4%), diarrhea (6.7% *vs.* 5.0%), headache (3.4% *vs.* 2.4%), and dermatitis and eczema (5.5% *vs.* 4.1%) were reported more commonly in the strontium ranelate group, but only during the first 3 months of treatment; after 3 months there was no difference between groups concerning nausea and diarrhea. Upper gastrointestinal symptoms were comparable between the two groups (incidence of gastritis, 2.3% in the strontium ranelate group and 2.7% in the placebo group).

In the strontium ranelate group, serum calcium decreased (2.39 ± 0.12 mmol/liter at baseline *vs.* 2.33 ± 0.12 mmol/liter at end point (last available evaluation) for the strontium ranelate group; 2.39 ± 0.13 mmol/liter at baseline *vs.* 2.39 ± 0.11 mmol/liter at end point for the placebo group) and serum phosphorus increased (1.22 ± 0.18
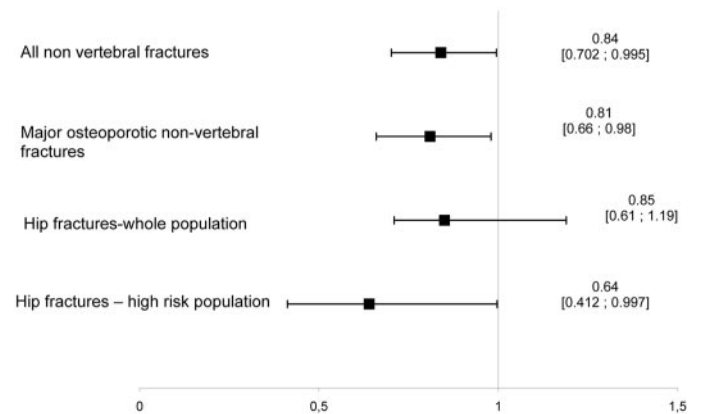
mmol/liter at baseline *vs.* 1.32 ± 0.17 mmol/liter at end point for the strontium ranelate group; 1.22 ± 0.17 mmol/liter at baseline *vs.* 1.21 ± 0.15 mmol/liter at end point for the placebo group). A slight decline in serum PTH was observed in both groups, more pronounced in the strontium ranelate group (33.24 ± 14.53 pg/ml at baseline *vs.* 29.81 ± 14.32 pg/ml at end point for the strontium ranelate group; 33.15 ± 14.41 pg/ml at baseline *vs.* 32.22 ± 15.87 pg/ml at end point for the placebo group). These changes in serum Ca, P, and PTH were without clinical consequences. No changes were observed for serum 25-OH D (69.1 ± 23.5 nmol/liter at baseline *vs.* 64.3 ± 20.4 nmol/liter at end point for the strontium ranelate group; 69.4 ± 21.9 nmol/liter at baseline *vs.* 65.1 ± 20.4 nmol/liter at end point for the placebo group) and for 1,25(OH)$_2$ vitamin D levels (37.6 ± 11.9 nmol/liter at baseline *vs.* 34.7 ± 10.6
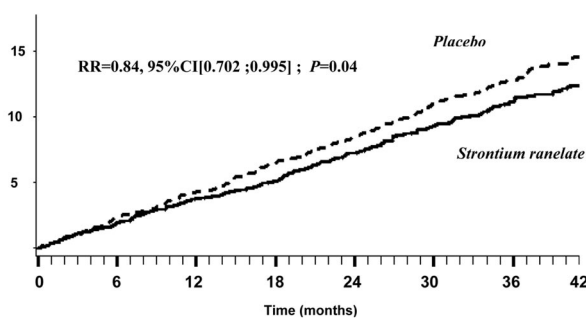
FIG. 3. Incidence over time of patients with at least one incident of osteoporosis-related nonvertebral fracture.

FIG. 4. New nonvertebral fractures for the ITT population and hip fractures in the high-risk fracture subgroup over 3 yr: RR and 95% confidence interval. *, The incidence of major osteoporotic fractures is lower than the sum of each incidence per site, as some patients experienced several types of fracture.
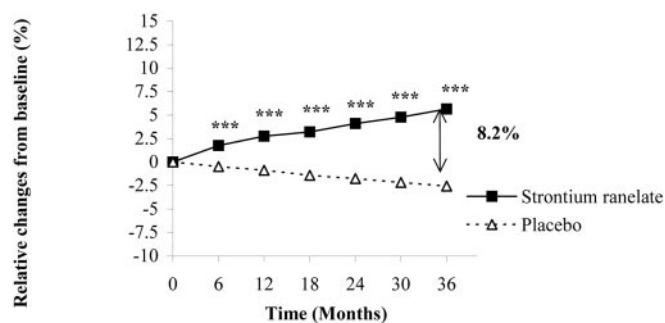
Number of evaluated patients	M0	M12	M24	M36
Strontium ranelate	2243	1851	1596	1393
Placebo	2238	1908	1630	1395

Fig. 5. Femoral neck BMD: relative mean differences between changes from baseline (%). Student's test for independent samples: $P < 0.01$ (hierarchical stepdown procedure).

nmol/liter at end point for the strontium ranelate group; 37.1 ± 11.7 nmol/liter at baseline *vs.* 33.5 ± 10.1 nmol/liter at end point for the placebo group).

Discussion

The aim of any treatment for osteoporosis is to prevent all fractures whatever their type. The phase 3 development program of strontium ranelate consisted of two parallel international clinical studies aimed to evaluate the antifracture effect of strontium ranelate on both vertebral (SOTI study) and nonvertebral fractures (TROPOS study).

The TROPOS study was designed in 1996 with, as primary end-point, the incidence of nonaxial fractures. However, to follow the CHMP guideline issued in 2001 (CPMP/EW/ 552/95 rev 1), nonaxial fractures including hip were documented separately. The study was consequently not specifically designed or powered to demonstrate a reduction of the risk of hip fracture. To address a request from the European authorities, efficacy in reducing hip fractures in a population liable to experience this type of event was analyzed in *post hoc*.

Over 3 yr, daily oral strontium ranelate 2 g per os reduced the risk of all nonvertebral fractures, and that of the major nonvertebral osteoporotic fractures, including hip, humerus, pelvis and sacrum, ribs, clavicle, or wrist fractures in the whole population.

In the subgroup analysis of women at higher risk of hip fracture, those aged 74 yr or over and with femoral neck BMD T-score of −3 SD or less, the risk of hip fractures was reduced by 36%. These high-risk patients were defined according to risk factors for hip fracture. Seventy-four years, which was the main age criterion for inclusion in the study was reported to be the age starting from which incidence of hip fracture rises exponentially (13). This has been confirmed in the placebo group in the pooled data from SOTI and TROPOS studies, which showed that the incidence of hip fracture was 1.1% over 3 yr in patients less than 74 yr old and 4.4% in patients with age 74 yr or older. The threshold for femoral neck BMD of −3 SD or less was defined as this threshold was already used in the HIP study as an inclusion criteria (14). The validity of this threshold was confirmed in the placebo

group in the pooled data from SOTI and TROPOS studies, where the incidence of hip fracture increases in patients with femoral neck BMD T-score −3 SD or less; the incidence of hip fracture over 3 yr was equal to 1.2% in patients with baseline femoral T-score below −3 and 3.1% in patients above this threshold. Moreover, a femoral neck BMD T-score equal to −3.0 SD according to the study normative data, corresponds to −2.4 SD according to the National Health and Nutrition Examination Survey normative range.

Supplementation with calcium and vitamin D has been reported to reduce the risk of hip fracture among women in nursing homes (15), and, therefore for ethical reasons all patients received calcium and vitamin D supplementation.

Among the currently registered anti-osteoporotic drugs, the only study in which a nonvertebral site has been assessed as the primary endpoint was the HIP study with risedronate (15). Hip fracture risk was reduced by 30%, and major nonvertebral osteoporotic fracture risk by 20% in the analysis which compared women assigned to risedronate (pooled 2.5 or 5 mg dose) with those assigned to placebo. Risedronate reduced hip fracture (RR reduction: 40%) in the subgroup of women 70–79 yr of age with osteoporosis (femoral neck BMD T-score <−3 SD plus at least one risk factor for hip fracture or <−4 SD) and with prevalent vertebral fracture at baseline (*post hoc* analysis). Nonvertebral fractures (considering fractures of the six following sites: clavicle, humerus, wrist, pelvis, hip, or leg) were also reduced (secondary endpoint) in the Vertebral Efficacy with Risedronate Therapy-North America study but not in the Vertebral Efficacy with Risedronate Therapy-Multinational study (16, 17). In the Fracture Intervention Trial studies with alendronate, there was no significant reduction in the risk of nonvertebral fracture (secondary end point) in the population as a whole but significant reduction was reported in *post hoc* subgroups of patients with prevalent vertebral fracture or femoral neck BMD T-score less than −2.5 (18, 19). In the SOTI study, there was a reduction of the risk of nonvertebral fractures by 10% but this did not reach statistical significance as the study was not specifically designed to demonstrate the nonvertebral anti-fracture effect of strontium ranelate (primary end-point, vertebral fractures).

The RR of vertebral fracture was significantly reduced by 39% which is consistent with results previously published. In the vertebral fracture SOTI study, strontium ranelate reduced vertebral fracture risk by 41% over 3 yr and by 49% in the first year (8). Strontium ranelate increases spinal and femoral BMD in a dose-dependent fashion (20, 21) while achieving a dose-dependent increase in ultimate strength and work to fracture (toughness or the resistance to micro-damage progression) reported in compression tests in specimens from vertebrae and midshaft femur from animal studies (22). Other studies showed that strontium ranelate 2 g/d increased spine and hip BMD, in women with prevalent vertebral fractures (8, 20). In the TROPOS study, the increase in hip BMD was similar to that observed previously (20).

Strontium ranelate given for up to 3 yr to older subjects was well tolerated. These results were consistent with previous studies carried out in younger patients (8, 20, 21). The most common AEs were gastrointestinal disorders (nausea and diarrhea), most of which were reported at the beginning

of treatment and without noticeable difference between groups after 3 months. Upper gastrointestinal symptoms were comparable between the two groups.

The small changes observed in homeostasis parameters (decrease in calcium and PTH serum levels, increase in blood phosphorus) were possibly linked to the activation of the calcium-sensing receptors by strontium as shown in *in vitro* experiments (23, 24), but were not clinically relevant and were not associated with any clinical consequence.

In summary, the results of the study demonstrate that the oral administration of strontium ranelate 2 g/d to postmenopausal women with osteoporosis induces a significant reduction in nonvertebral fractures including in particular hip fractures in a subset of patients highly exposed to the hip fracture risk. Analysis of data gathered on a large subgroup of patients demonstrated that the treatment also significantly reduced the incidence of vertebral fractures. The medication was well tolerated, especially at the upper gastrointestinal level.

Strontium ranelate, being effective in reducing both non-vertebral including hip and vertebral fracture risks, is a new first-line treatment for postmenopausal osteoporosis.

Acknowledgments

List of investigators: **FRANCE:** Prof. P. J. Meunier, Edouard Herriot Hospital, Lyon; Dr. J. P. Aquino, Medical Clinic La Porte Verte, Versailles; Prof. J. Dehais, Pellegrin-Tondu Hospital, Bordeaux; Prof. P. Fardellone, Nord Hospital, Amiens; Prof. G. Werhya, Brabois Hospital, Vandoeuvre; Dr. C. Benhamou, La Madeleine Hospital, Orleans; Prof. M. C. De Vernejoul, Lariboisière Hospital, Paris; Prof. A. Kahan, Cochin Hospital, Paris; Dr. O. Bonidan, E. Muller Hospital, Mulhouse; Prof. C. Marcelli, Regional Hospital and University Centre, Caen; Prof. J. L. Kuntz, Hautepierre Hospital, Strasbourg; Prof. A. Prost, Hôtel Dieu Hospital, Nantes; Prof. P. Bourgeois, Pitié-Salpétrière Hospital, Paris; Prof. F. Blotman, Lapeyronie Hospital, Montpellier; Prof. B. Vellas, La Grave-Casselardit Hospital, Toulouse. **BELGIUM:** Prof. J. Y. Reginster, Centre Hospitalo Universitaire Centre ville, Liege; Prof. J. P. Devogelaer, Catholic University of Louvain, Brussels; Prof. J. M. Kaufman, Ghent University Hospital, Gent; Dr. M. Walravens, Medical Centre, Tessenderloo and Somedi, Heist-op-den-Berg; Dr. F. Raeman, Jan Palfijin Ziekenhuis, Merksem. **DENMARK:** Dr. S. Pors Nielsen, Hillerod Hospital, Hillerod; Dr. O. H. Sorensen, The Osteoporosis Research Center, Hvidovre; Prof. H. Beck-Nielsen University Hospital, M. Osteoporosis Centre, Odense; Dr. P. Charles, Aarhus Amtssygehus, Aarhus C. **ITALY:** Prof. S. Ortolani, Centre Auxologico Italiano, Milano; Prof. S. Adami, Hospital and Clinical Centre of Medecine, Valeggio sul Mincio; Prof. G. Bianchi, Unita Salitaria Locale 3 Hospital "La Colletta", Arenzano; Dr. M. L. Brandi, General Hospital Careggi, Firenze; Prof. D. Cucinotta, S. Orsola Malpighi Hospital, Bologna; Prof. C. Fiore, Medical Clinic, Vittorio Emanuel Hospital, Catania; Prof. C. Gennari, Institute of Medical Clinic, New General Hospital "Le Scotte", Siena; Prof. G. Isaia, University of General Medicine, Torino; Prof. G. Luisetto, Univerity Institute of Semeiotica Medica, Padova; Prof. R. Passariello, Institute of Radiology "La Sapienza" University, Rome; Prof. M. Passeri, Parma University, Parma; Prof. G. Rovetta, E. Bruzzone Institute, Genova; Prof. L. Tessari, San Raffaele Hospital, Milano. **POLAND:** Prof. J. E. Badurski, Center for Osteoporosis and Osteo-Articular Diseases, Bialystok; Dr. K. Hoszowski, Medical Centre, Warsaw; Prof. R. S. Lorenc, Osteoporosis Centre of Krajowe, Warsaw; Dr. A. Sawicki, Warsawian Center of Osteoporosis ad Calcium Metabolism "Osteomed", Warsaw. **HUNGARY:** Dr. A. Balogh, Medical and Health Sciences Centre, University of Debrecen, Debrecen; Prof. R. De Chatel, Semmelweis Orvostudomanyi Egyetem, Budapest/Sote, Budapest. **UNITED KINGDOM:** Dr T. D. Spector, Department of Rheumatology, St. Thomas' Hospital, London; Dr. D. V. Doyle, Silverthorn Centre, Chingford; Dr. P. Ryan, Medway Hospital Trust, Gillingham; Dr. I. G. Smith, SYNEXUS Ltd. Clinical Research Centre, Manchester; Dr. R. Smith, Banbury Clinical Studies Centre, Banbury; Dr. M. Clements, North London Clinical Studies Centre, Mount Vernon Hospital, London. **GREECE:** Dr. C. Phenekos, Red Cross Hospital, Athens. **AUSTRALIA:** Prof. K. W. Ng, St Vincent's Hospital, Fitzroy Victoria; Prof. J. Wark, Royal Melbourne Hospital, Parkville Victoria; Prof. E. Seeman, Austin and Repatriation Medical Centre, Heidelberg Victoria; Dr. J. Prins, Princess Alexandra Hospital, Wooloongabba, Queensland; Prof. R. Prince, Sir Charles Gairdner Hospital, Nedlands, Western Australia; Dr. J. Graham, Ashford Specialist Centre, Ashford, South Australia. **SPAIN:** Dr. A. Diez, El Mar Hospital, Barcelona; Dr. A. Roces Varela, Hospital Nuestra Sra de la Candelaria, Santa Cruz de Tenerife, Canarias; Dr. J. M. Padrino, Hospital 12 de Octubre, Madrid; Dr. J. B. Cannata, General Hospital of Asturias, Oviedo; Dr. J. Gijon/Dr. A. Torrijos, La Paz Hospital/Hospital de Rehabilitacion y Traumatologia, Madrid; Dr. M. Díaz Curiel/Dr. A. Rapado, Jiménez Díaz Foundation, Madrid. **GERMANY:** Prof. E. M. Lemmel, Max Grundig Clinic, Buhl; Dr. D. Felsenberg, Benjamin Franklin Clinical University, Berlin; Prof. J. Hensen, Medical Clinic 1, Erlangen; Dr. G. Stucki, Clinic for Physical Medecine and Rehabilitation, München; Dr. J. Semler, Immanuel Hospital, Berlin; Prof. W. Schmidt, St. Josef-Hospital, Bochum; Prof. H. P. Kruse, Med. Clinical University, Hamburg. **SWITZERLAND:** Prof. J. P. Bonjour/Prof. R. Rizzoli, Geneva University Hospital, Geneva.

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