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Long-term treatment of postmenopausal osteoporosis with strontium ranelate: Results at 8 years

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ABSTRACT

Objectives: Strontium ranelate 2 g/day has proven efficacy against vertebral and nonvertebral fracture over 5 years in postmenopausal osteoporosis, though many women require longer-term treatment. This article describes the efficacy, safety, and tolerability of this agent over 8 years.
Methods: Postmenopausal osteoporotic women having participated in the 5-year efficacy trials SOTI and TROPOS were invited to enter a 3-year open-label extension study. The results presented here focus on patients who received strontium ranelate for 8 years.
Results: At the extension baseline, the population treated for 8 years ($n = 879$; 79.1 ± 5.6 years) had femoral neck T-score of -2.61 ± 0.71. The cumulative incidences of new vertebral and nonvertebral fractures (13.7% and 12.0%, respectively) over years 6 to 8 were non-statistically different from the cumulative incidences in the first 3 years of the original studies (11.5% and 9.6%). Lumbar spine, femoral neck, and total hip bone mineral density (BMD) increased throughout the 8-year period. Annual relative change in BMD was significant at every visit, except the 8-year visit for femoral neck and total hip BMD. Strontium ranelate was safe and well tolerated over 8 years.
Conclusions: Long-term treatment with strontium ranelate 2 g/day in postmenopausal osteoporotic women leads to continued increases in BMD at all sites. The data also provide some evidence for a sustained antifracture efficacy.

Introduction

Postmenopausal osteoporosis is a chronic disease requiring long-term management. Most antiosteoporotic treatments have been tested in 3- to 5-year studies, though the optimal treatment duration may be much longer [1]. It is therefore vital to assess the long-term safety and efficacy of antiosteoporotic agents. To date, only three antiosteoporotic drugs have published long-term (beyond 5 years) follow-up data. The antifracture efficacy trials for the bisphosphonates risedronate [2] and alendronate [3] were extended to 7 and 10 years, respectively, while the selective estrogen receptor modulator raloxifene has been evaluated over 8 years [4]. These studies demonstrated continued gains in bone mineral density (BMD), and maintenance of safety profiles, but remained inconclusive regarding long-term antifracture efficacy. Additionally, a 5-year re-randomized double-blind trial (FLEX) conducted in patients assigned to alendronate in the FIT trial demonstrated that women who discontinued alendronate for 5 years showed a moderate decline in BMD but no higher fracture risk other than clinical vertebral fractures [5].

Strontium ranelate is an oral antiosteoporotic drug that has been shown to increase bone formation *in vitro*, enhancing pre-osteoblastic cell replication and osteoblastic differentiation and decreasing abilities of osteoblasts to induce osteoclastogenesis via the calcium sensing receptor and an increase in the OPG/RANKL ratio [6,7]. Independently from these effects on osteoblasts, strontium ranelate decreases bone resorption by inhibition of osteoclast resorbing activity and osteoclastic differentiation [8]. This dual mode of action of strontium ranelate [9,10] results in a rebalance in bone turnover, and therefore in an improvement of bone microarchitecture and strength [11]. Results on iliac crest bone biopsies in postmenopausal osteoporotic women from a phase III study have demonstrated some improvement of both trabecular and cortical bone microstructure after 3 years of treatment [12]. Oral administration of strontium ranelate 2 g/day to postmenopausal osteoporotic women significantly reduces the risk of new vertebral fracture as demonstrated in the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial [13]. In the

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TReatment Of Peripheral Osteoporosis Study (TROPOS), strontium ranelate significantly reduced the risk of vertebral, nonvertebral, and hip fracture in patients at risk with parallel increases in BMD [14–16]. The populations of SOTI and TROPOS having completed the 5-year double-blind phase were invited to enter a 3-year, open-label, extension phase to analyze the long-term effect of the drug on fracture risk, BMD, and safety. Results described here focus on the subgroup of patients treated with strontium ranelate from the beginning of the initial trials.

Materials and methods

Study design and population

The population for this open-label extension study was pooled from the treatment arms of SOTI and TROPOS (study design in Fig. 1) [13,14,17].

Main analyses of SOTI and TROPOS were performed over 3 years [13,14]. Data for patients in the treatment arms at 3 years are presented here for the purposes of comparison. Details of this population have been described elsewhere [18]. The double-blind, placebo-controlled phases of both trials lasted for 5 years. Patients were thus invited to participate in a 3-year, open-label extension, in which they were to receive treatment with strontium ranelate 2 g/day (Fig. 1). The criteria for entering the extension study was participation in SOTI or TROPOS for 5 years, or interruption of study treatment or withdrawal within the 6-month period preceding the 5-year visit. Only results in patients continuously treated with strontium ranelate over the whole follow-up period will be presented here.

Incidence of fracture

Procedures used to measure fracture are described in the original reports [13,14]. Clinical peripheral fractures were assessed throughout the study according to radiological evaluation and written documentation (radiological report, hospitalization report) [14]. Fractures of skull, jaw, coccyx, phalanx (fingers and toes), ankle, cervical and thoracic vertebrae (C1 to T4), and of posterior arches of the vertebra were not considered as osteoporosis-related fractures and were excluded from the analysis.

Spinal X-rays were recorded at inclusion and then yearly in all patients recruited from SOTI and TROPOS, according to standardized procedures enabling proper visualization of vertebrae from T4 to L5 [13]. Spinal X-rays were read centrally and incident vertebral fracture detected by semi-quantitative assessment and grading, according to the method of Genant [19]. During the extension study, new fracture was defined as the occurrence of a new vertebral, nonvertebral, or hip fracture during the 3-year extension, regardless of the occurrence of fracture during the main analyses of SOTI and TROPOS.

Bone mineral density

BMD was measured by dual energy X-ray absorptiometry (DXA, Hologic) at lumbar spine, femoral neck, and total hip at entry to the extension study and yearly thereafter. Acquisition and quality control programs were the same as those applied during the original studies [13,14,20].

Safety, tolerability, and compliance

Adverse events were recorded at each 6-month visit. Compliance was also assessed every 6 months by counting the number of sachets returned by the patient.

Statistical analysis

The full analysis set (FAS) was defined as patients having taken ≥1 sachet of strontium ranelate after inclusion into the extension study, having at least one baseline and one post baseline lumbar spine L2–L4 BMD measurement, and at least one evaluation of fracture incidence. The efficacy and safety results presented here focus on the subgroup of patients continuously treated with strontium ranelate for up to 8 years.

The Kaplan–Meier method was used to estimate the cumulative incidences of patients with at least one new vertebral, nonvertebral, or any osteoporotic fracture over the first 3 years of SOTI and TROPOS and the 3 years of the extension study in the subgroup of patients treated with strontium ranelate for up to 8 years.

BMD values are expressed as change and relative change from baseline to each visit and to the last value under treatment. Student *t* test for paired samples was used for within-group comparison of the progression of BMD with the previous year's value. *P* value ≤ 0.05 was considered significant.

The association between changes in BMD and fracture incidence in women treated with strontium ranelate was assessed through a logistic regression analysis after adjusting for covariates. Mann–Whitney test was used to compare changes in BMD after strontium ranelate in patients with and without new fractures.

Statistical analysis was performed using SAS/PC software version 8.2.

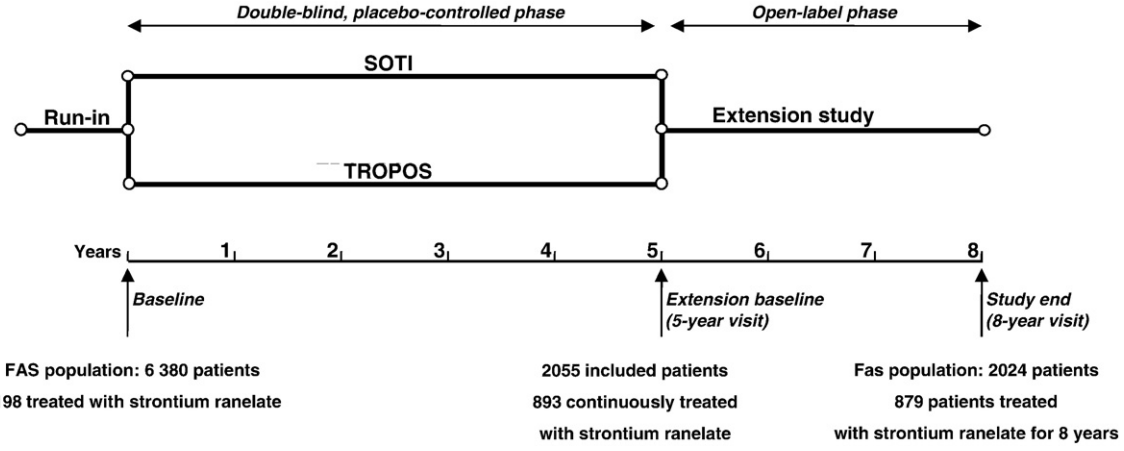

Fig. 1. Study design. Description of the pooled 8-year population from the SOTI and TROPOS studies receiving strontium ranelate 2 g/day. SOTI, Spinal Osteoporosis Therapeutic Intervention; TROPOS, TReatment Of Peripheral Osteoporosis Study.

Results

Characteristics of the population

Out of the 2055 patients included in the extension study in 63 centers, 893 were treated with strontium ranelate from the beginning of SOTI ($n=164$) or TROPOS ($n=739$) studies. Out of them, 892 were included in the safety set and 879 in the FAS, 13 patients having no efficacy assessment either at the baseline or after inclusion in the extension phase being excluded from the FAS. The baseline characteristics of this "8-year" population at inclusion in the initial studies and at entry in the extension phase are presented in Table 1. This population is representative of the whole SOTI TROPOS population. Indeed, in these patients, the severity of the disease at inclusion in the initial study, as assessed by the perentage of patients with prevalent fractures and the BMD values, is similar to that observed in the general SOTI and TROPOS populations [13,14].

Exposure to treatment and compliance

In the patients from the FAS treated with strontium ranelate for 8 years, the mean treatment exposure from first intake to the 8-year visit was 87.6 ± 11.4 months (i.e. 7 years and 4 months). The mean global compliance during the 3 years of the extension study was 86.8 ± 16.8%, which compares well with the overall compliance over the whole 8 years of treatment in the same population (87.9 ± 12.9%) and the values reported in the original studies [13,14].

Fracture rate

In the patients continuously treated with strontium ranelate, the cumulative incidence of patients with at least one new osteoporotic fracture was 28.8% at the inclusion of the extension study and 41.1% over the 8-year treatment with strontium ranelate. In those patients, Fig. 2 shows that the cumulative incidences of any osteoporotic fracture over the 3 years of the extension study and the first 3 years in SOTI and TROPOS were not statistically different. Considering the population, this suggests continued antifracture efficacy of strontium ranelate over 8 years.

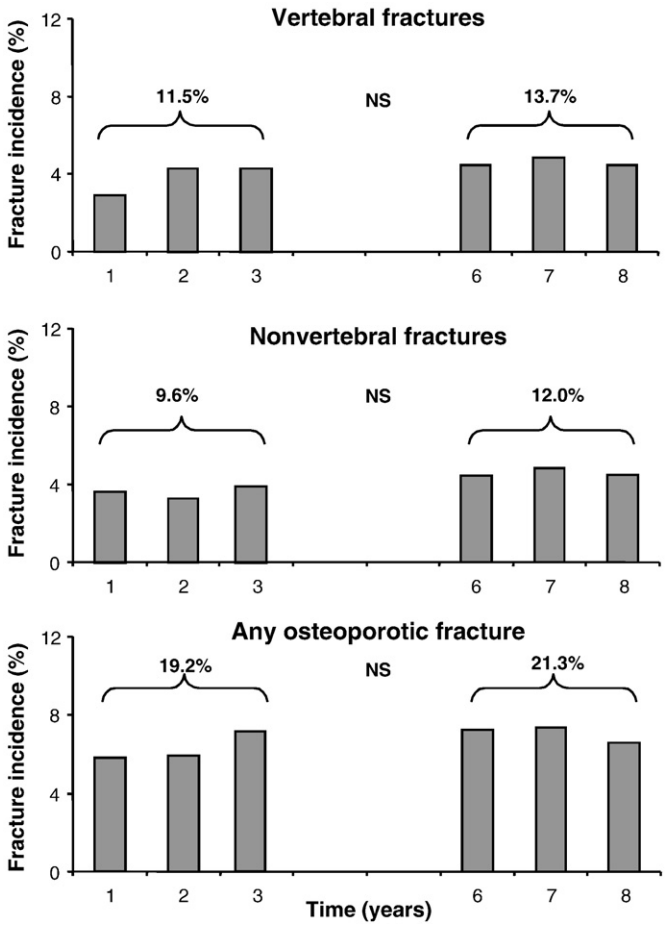

Fig. 2. Incidence of new vertebral fracture, nonvertebral fracture, and any osteoporotic fracture in the extension study population treated with SR for 8 years (FAS, $n=879$). Comparison in this population of the incidence over the first 3 years with the incidence over the 3 years of the extension period (Kaplan–Meier estimates).

Bone mineral density

The absolute values of lumbar spine, femoral neck, and total hip BMD increased in all patients treated with strontium ranelate up to 8 years (Table 2). The annual relative change in BMD was significant at every yearly visit, except for the 8-year visit for femoral neck and total hip BMD (Fig. 3). Lumbar spine BMD rose by 0.04 ± 0.08 g/m^2 during the 3-year extension study, which corresponds to a mean increase of 4.47 ± 8.44%. This is less than half the increase in lumbar BMD in patients in the first 3 years of the SOTI trial (12.7%) [13]. A similar

Table 1
Baseline characteristics of the patients having received strontium ranelate 2 g/day continuously when they entered the extension phase (population "8-year", $n=893$) as compared with the other patients of the SOTI TROPOS studies at inclusion in SOTI TROPOS.

	SOTI TROPOS population without "8-year" population, $N=5847$	Population "8-year" included, $N=893$	Population "8-year" FAS, $N=879$
	M0	M0	Year 5
Age (years)	75.2 ± 6.5	73.9 ± 5.7	79.1 ± 5.6
Body mass index (kg/m^2)	25.6 ± 4.1	25.9 ± 4.2	25.9 ± 4.4
Time since menopause (years)	25.7 ± 8.4	25.7 ± 7.4	30.9 ± 7.4
≥1 prevalent nonvertebral fracture	35.6%	40.1%	49.6%
≥1 prevalent vertebral fracture	44.7%	38.5%	44.2%
Lumbar BMD (g/cm^2)	0.78 ± 0.15	0.77 ± 0.15	0.93 ± 0.20
T-score	-3.00 ± 1.59	-3.11 ± 1.51	−1.42 ± 2.09
Femoral neck BMD (g/cm^2)	0.56 ± 0.08	0.57 ± 0.07	0.61 ± 0.08
T-score	-3.01 ± 0.68	-3.02 ± 0.60	−2.61 ± 0.71
Total hip BMD (g/cm^2)	0.66 ± 0.10	0.67 ± 0.09	0.73 ± 0.10
T-score	-2.65 ± 1.01	-2.51 ± 0.91	−1.90 ± 1.02

Baseline characteristics of the "8-year" FAS population at entry in the extension phase are also presented. Values are means ± SD.

Table 2
Bone mineral density (BMD) at lumbar spine, femoral neck, and total hip in the extension study population (FAS, $n=879$) having received strontium ranelate 2 g/day for 8 years (or last study visit).

	Lumbar spine L2 to L4	Femoral neck	Total hip
BMD at baseline (g/cm^2)	0.77 ± 0.14	0.57 ± 0.07	0.67 ± 0.09
BMD at extension baseline (5-year visit) (g/cm^2)	0.93 ± 0.20	0.61 ± 0.08	0.73 ± 0.10
BMD at last study visit (g/cm^2)	0.97 ± 0.22	0.63 ± 0.09	0.74 ± 0.11
ΔBMD (baseline to last study visit) (g/cm^2)	+0.20 ± 0.14	+0.06 ± 0.07	+0.07 ± 0.07
Relative change (0 to 8 years)	26.7 ± 17.8%	10.3 ± 12.4%	10.7 ± 12.4%
ΔBMD (extension baseline to last study visit) (g/cm^2)	+0.04 ± 0.08	+0.01 ± 0.05	+0.007 ± 0.04
Relative change (5 to 8 years)	4.5 ± 8.4%	2.3 ± 7.9%	0.96 ± 6.12%

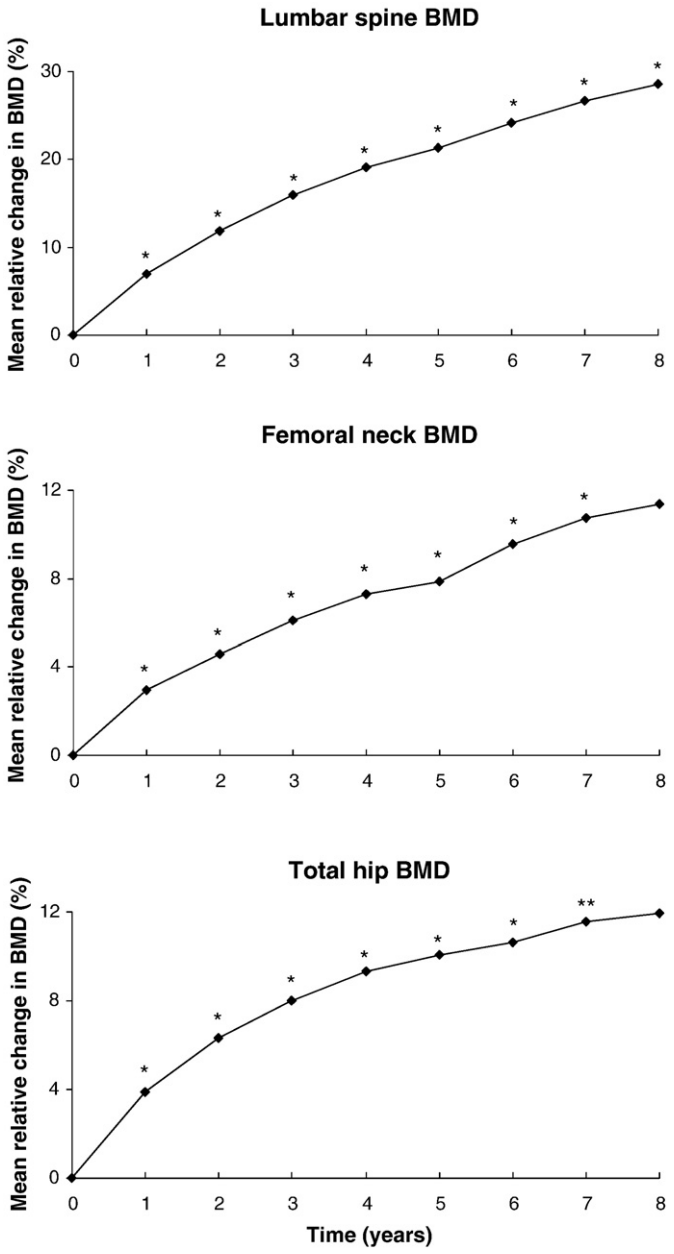

Fig. 3. Relative change in lumbar spine, femoral neck, and total hip bone mineral density (BMD) over 8 years in patients continuously treated with SR (data available in 776 patients for lumbar spine BMD and 720 patients for femoral neck and total hip BMD). *$P<0.001$; **$P<0.05$ versus previous year visit.

trend toward a smaller increase in BMD over 3 years upon long-term treatment was observed for femoral neck and total hip BMD.

Relationship between changes in bone mineral density and fracture incidence

Relationship between changes in BMD and fracture incidence was studied in the FAS subpopulation treated with strontium ranelate from the beginning of SOTI TROPOS, with available BMD and fracture data at 6 and 8 years ($n=417$). After adjustment for age, body mass index, BMD, number of vertebral fractures at baseline, and from baseline to 5 years, there was no significant association between change in BMD at the lumbar spine from 6 to 8 years and incidence of vertebral fracture over the same period of time. There was however an association between change in BMD at the total proximal femur and incidence of vertebral fracture ($P=0.02$). Each 1% increase in total proximal femur BMD was associated with decreased risk for new vertebral fracture by 5% (95% adjusted confidence interval [CI], 1%–10%). Women with new vertebral fractures between 6 and 8 years had a 0.2% [6.1] decrease in total proximal femur BMD compared with a 1.9% [6.3] increase in women without new vertebral fracture ($P=0.02$). Changes in lumbar spine and total proximal femur BMD were not associated with the incidence of nonvertebral fracture.

Safety and tolerability

In the subgroup of patients treated with strontium ranelate for 8 years (safety set = 892), treatment with strontium ranelate was well tolerated, with similar percentages of patients reporting emergent adverse events in the 3-year extension study (86.2%) as in the original studies (e.g., 87.9% in the treatment arm in the first 3 years of TROPOS versus 88.9% in the placebo group) [14]. The treatment-related adverse events rate was low. The most common emergent adverse events are listed in Table 3, and compared with the values in the pooled population of SOTI and TROPOS at 3 years. No DRESS was reported in SOTI and TROPOS studies as well as in the whole population involved in the 3-year open-label extension phase.

Discussion

In the 879 postmenopausal women with osteoporosis treated with strontium ranelate 2 g/day for 8 years, the incidence of fracture was stable over the 8-year follow-up, and did not show the age-expected increase over the 3-year extension study. Indeed, no statistically significant difference was shown between the occurrence of osteoporotic fracture over the last 3 years versus the first 3 years of treatment. In parallel, the absolute values of BMD at lumbar spine, femoral neck, and total hip rose, though analysis of relative change suggests a slowing of the annual increase in BMD over 8 years. Treatment with strontium ranelate appeared to be safe and well tolerated over 8 years, and compliance was maintained at the levels of the original studies.

The sharp increase of the incidence of fracture with age in normal and osteoporotic women has been confirmed in the huge population of more than 170,000 women aged 50 to 99 years and followed for up to 3 years as part of the National Osteoporosis Risk Assessment (NORA) [21]. A recent population-based, 10-year, prospective study in postmenopausal women found that the relative risk of nonvertebral fracture in women aged 80 to 85 was more than twice that in women aged 70 to 79 (relative risk 1.76 versus 3.81), while the relative risk of vertebral fracture increased nearly threefold (4.59 versus 13.4) [22].

Table 3
Safety of strontium ranelate over 3 years in the extension study population having received strontium ranelate 2 g/day from the beginning of SOTI or TROPOS studies (safety set, $n=892$) and in the first 3 years of SOTI and TROPOS [18].

	Extension population ($n=892$)	SOTI/TROPOS 3 years ($n=3352$)
Nervous system disorders		
• Headache	0.7%	3.0%
• Disturbances in consciousness	1.2%	2.2%
• Memory loss	3.4%	2.1%
• Seizures	0.1%	0.3%
Nervous system disorders		
• Nausea	0.9%	6.6%
• Diarrhea	2.7%	6.5%
Skin and subcutaneous tissue disorders		
• Dermatitis	0.2%	2.1%
• Eczema	0.3%	1.5%
Venous thromboembolism	1.0%/year	0.9%/year

This excess risk is attributable to a drop in BMD with age, but also to other age-related changes (muscle weakness, balance disorders, accelerated calcium, and vitamin D insufficiency). In this context, our observation of similar cumulative fracture incidences in the first 3 years of the study (population aged 75 to 78 years), and in the last 3 years when the population had aged by 5 years, can be considered as indirect evidence for the continued antifracture efficacy of strontium ranelate over up to 8 years of treatment. This is also in line with the reported absence of an impact of age, or indeed any other risk factor at baseline, on the antifracture efficacy of this treatment over 3 years [18].

Low total hip or femoral neck BMD is associated with an increased long-term risk of vertebral and nonvertebral fracture [23,24]. European Guidance from the International Osteoporosis Foundation stated that even if further data were needed, BMD monitoring patients treated with bone forming agents appeared to be of greater value than their use with inhibitors of bone resorption [25]. As a plateau of bone strontium content, chemically measured in treated women from phase III studies, is reached after 3 years [26]. It was anticipated to have a less increase in BMD after this time point. In this context, a *post hoc* analysis of women from the treatment arms of SOTI and TROPOS recently demonstrated that the increase in femoral neck and total hip BMD accounted for 76% and 74%, respectively, of the reduction in vertebral fracture risk over 3 years [27]. The same analysis indicated associations between femoral neck and total hip BMD and nonvertebral fracture, though these failed to reach significance. We should note that femoral neck BMD is generally recognized as a better predictor of fracture risk than lumbar spine BMD [25]. Our results over 8 years are in line with these conclusions, i.e., an association between the maintenance of increased BMD and a reduction in both vertebral and nonvertebral fracture risk with long-term strontium ranelate.

We have previously shown that, in women treated for 3 years with strontium ranelate, an increase in hip but not spine BMD was associated with a proportional reduction in vertebral fracture incidence [27]. Each 1% increase in total proximal femur BMD was associated with a 2% (95% CI, 1–4%) decrease in risk for new vertebral fracture. In this analysis, our results are consistent with previous report showing a significant association between the increase in total proximal femur BMD and the vertebral fracture incidence and the lack of statistically significant relationship between increase in spine BMD and decrease in fracture incidence.

As stated above, this is only the fourth study of an antiosteoporotic agent to go beyond 5 years [2–4]. Thus, in a study in which more than 650 women received alendronate for 10 years, there was a continuous increase in lumbar spine BMD, but plateaus for femoral neck and total hip BMD [3]. Similar trends were seen for risedronate treatment in a study in which just 83 patients continued for 7 years [2]. Neither study included the end point of new osteoporotic fracture, and so it was impossible to determine whether an increase in lumbar spine BMD, but not hip BMD (better predictor of fracture risk) [21] would translate into clear results in terms of sustained antifracture efficacy for these bisphosphonates. Another result of these studies was the persistence of treatment effects upon discontinuation, leading to the conclusion that there is no clinical advantage in the administration of bisphosphonates beyond 4 to 5 years [1,28]. The other agent to have been tested long term is raloxifene, for which results over 8 years showed maintenance of the increases in lumbar spine and femoral neck BMD, but failed to demonstrate an effect on nonvertebral fracture risk [4]. The present data on the effects of strontium ranelate over 8 years indicate a stable fracture rate during the complete treatment phase despite the age increase, concomitantly with the maintenance of BMD levels.

Levels of compliance with strontium ranelate over 8 years (87.9%) compare well with those observed in two studies with risedronate treatment over 3 years (86% and 85% of compliance respectively) [29,30] even considering the design of this extension study, in which the patients themselves chose to continue treatment. Poor compliance has been cited as one of the most important factors contributing to often unexpectedly raised fracture rates in patients prescribed antiosteoporotic treatment, notably bisphosphonates [31]. Compliance may therefore play a key role in the maintenance of antifracture efficacy.

The limitations of our study are those inherent to any long-term trial in the management of a chronic disease. The absence of a placebo group prevented any direct comparison of fracture rates, but it was unethical to treat with placebo over this length of time, particularly in an aging osteoporotic population. Our comparison of fracture incidences over 3 years at the beginning and end of the 8-year period does, however, provide indirect evidence of the impact of strontium ranelate on fractures. Second, the population was not randomized and the decision to continue into the extension study was left to the patient. It could be argued that this would eliminate patients with poor compliance or tolerability issues.

To conclude, the effect on BMD appears to be relatively similar during the complete 8-year treatment phase. Furthermore, there is an indication that the fracture rate was stable during the complete treatment phase despite the age increase. The safety profile of patients treated for 8 years is in agreement with previous findings with no new safety signals identified. Thus, although this is an open non-controlled extension, results support a maintained effect and a good safety profile of an 8-year treatment with strontium ranelate in postmenopausal women.

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