

Effects of long-term strontium ranelate treatment on vertebral fracture risk in postmenopausal women with osteoporosis

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Abstract

Summary Vertebral fractures are a major adverse consequence of osteoporosis. In a large placebo-controlled trial in postmenopausal women with osteoporosis, strontium ranelate reduced vertebral fracture risk by 33% over 4 years,

confirming the role of strontium ranelate as an effective long-term treatment in osteoporosis.

Introduction Osteoporotic vertebral fractures are associated with increased mortality, morbidity, and loss of quality-of-life (QoL). Strontium ranelate (2 g/day) was shown to

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prevent bone loss, increase bone strength, and reduce vertebral and peripheral fractures. The preplanned aim of this study was to evaluate long-term efficacy and safety of strontium ranelate.

Methods A total of 1,649 postmenopausal osteoporotic women were randomized to strontium ranelate or placebo for 4 years, followed by a 1-year treatment-switch period for half of the patients. Primary efficacy criterion was incidence of patients with new vertebral fractures over 4 years. Lumbar bone mineral density (BMD) and QoL were also evaluated.

Results Over 4 years, risk of vertebral fracture was reduced by 33% with strontium ranelate (risk reduction=0.67, $p<0.001$). Among patients with two or more prevalent vertebral fractures, risk reduction was 36% ($p<0.001$). QoL, assessed by the QUALIOST®, was significantly better ($p=0.025$), and patients without back pain were greater ($p=0.005$) with strontium ranelate than placebo over 4 years. Lumbar BMD increased over 5 years in patients who continued with strontium ranelate, while it decreased in patients who switched to placebo. Emergent adverse events were similar between groups.

Conclusion In this 4- and 5-year study, strontium ranelate is an effective and safe treatment for long-term treatment of osteoporosis in postmenopausal women.

Keywords Bone densitometry · Menopause · Osteoporotic fracture · Osteoporosis treatment · Strontium ranelate

Introduction

Vertebral fractures are one major adverse clinical consequences of osteoporosis [1]. Most vertebral fractures are precipitated by everyday activities rather than falls [2], and occurrence of a vertebral fracture is a powerful risk factor for future fractures [3]. Vertebral fractures are associated with increased mortality, long-term morbidity [4], and considerable health care costs [5] that are predicted to increase markedly over the period to 2020 [6].

Vertebral fractures, even those not recognized clinically, are also associated with substantial back pain and functional limitation [7, 8] and significant loss of quality-of-life (QoL). Both mental and physical domains of quality of life may be affected, and impairment is directly related to both severity and number of fractures [9, 10].

Strontium ranelate is an oral anti-osteoporotic drug that has been shown to prevent bone loss and increase bone strength in experimental studies [11]. Strontium ranelate increased 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 (CaR) and an

increase in the OPG/RANKL ratio [12]. In postmenopausal women with osteoporosis, strontium ranelate 2 g/day increased bone mineral density (BMD) in a placebo-controlled, 2-year dose–response study in 353 patients [13]. The Spinal Osteoporosis Therapeutic Intervention (SOTI) trial was designed to evaluate efficacy of strontium ranelate (2 g/day) in reducing vertebral fractures. Over the first year and first 3 years of treatment, strontium ranelate treatment was associated with reductions of 49% ($p<0.001$) and 41% ($p<0.001$), respectively, relative to placebo, in the risk of vertebral fractures [14].

Strontium ranelate has also shown significant efficacy against peripheral fractures and hip fractures in patient at risk over 3 years [15] and 5 years [16]. The purpose of the present article is to present results from the SOTI trial relating to vertebral fracture risk, changes in BMD and QoL for the 4-year initial treatment period, and also BMD results from the fifth-year treatment-switch period.

Methods

Patients

Post-menopausal (≥ 5 years) women were ambulatory Caucasian, ≥ 50 years of age with at least one prevalent osteoporotic vertebral fracture. Mean lumbar BMD had to be ≤ 0.840 g/cm² [17]. Exclusion criteria were described elsewhere [18] and were mainly concomitant pathologies or treatment potentially interfering with bone metabolism.

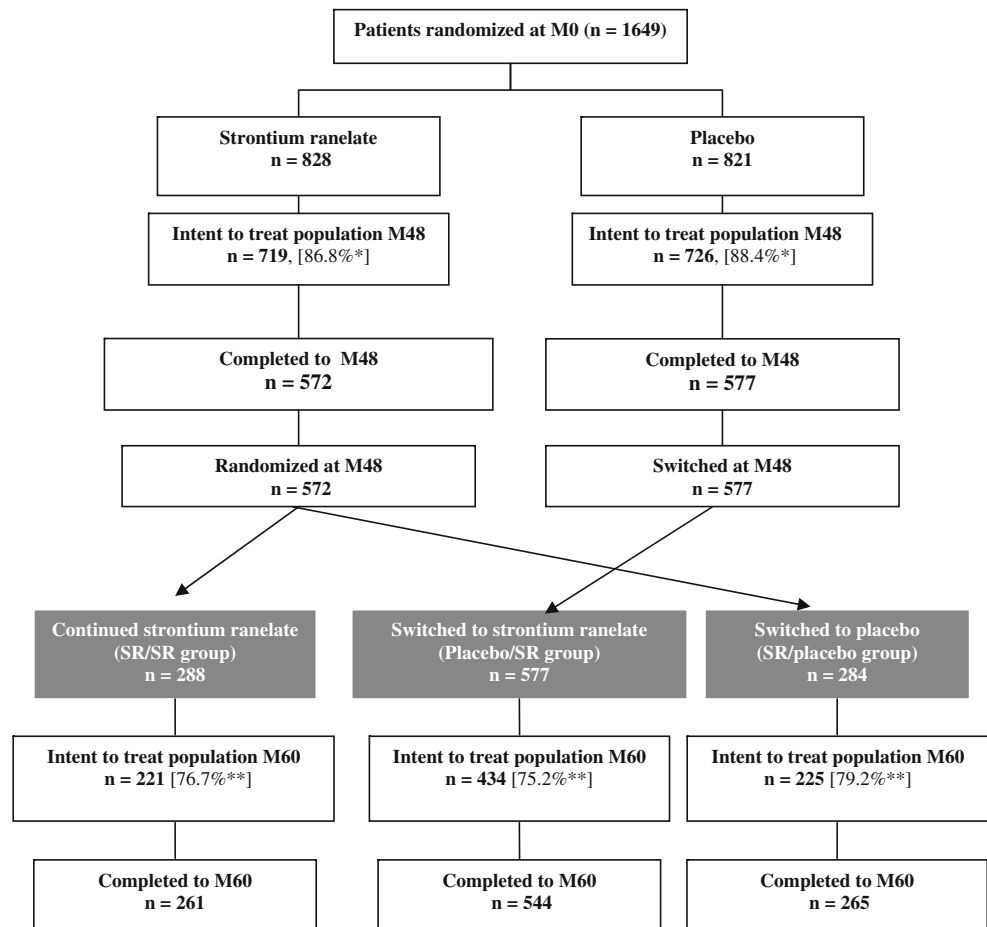
Study design

Methodological details have been described previously [18]. In brief, this was an international, randomized, double-blind, placebo-controlled trial. Previous to and during the study, patients were supplemented in vitamin D and calcium according to their need [18].

Patients were randomized (1:1) to receive strontium ranelate 2 g/day or placebo orally for 4 years, followed by a 1-year period in which patients in the strontium ranelate group were randomized either to switch to placebo (50%, SR/placebo group) or to continue on strontium ranelate 2 g/day (50%, SR/SR group), while all patients in the placebo group were switched to strontium ranelate 2 g/day (placebo/SR group; Fig. 1).

Outcome measures

For the 4-year treatment period, the pre-planned primary efficacy criterion was the incidence of patients experiencing a new vertebral fracture. Secondary criteria included new clinical vertebral fractures, osteoporotic peripheral fractures,

Fig. 1 Flow of patients through the study

* of randomized population at M0

** of randomized population at M48

changes in body height, L_2 – L_4 BMD, total hip and femoral neck BMD, bone turnover markers, and quality-of-life.

For the fifth-year treatment-switch period, the primary efficacy criterion was L_2 – L_4 BMD. Secondary criteria included total hip and femoral neck BMD, new vertebral fractures, and bone turnover markers.

Vertebral fractures were determined from radiographs taken at baseline (M0) and annually thereafter. Radiographs were analyzed semi-quantitatively [19], with a new vertebral fracture defined as a change from grade 0 to grade 1 or higher [19]. Clinical vertebral fractures were defined as new or worsening fractures with back pain and/or body height loss of ≥ 1 cm. Radiographs were assessed centrally (CEMO, France; Pr C. Roux).

Peripheral osteoporotic fractures were determined by investigators from radiographs or hospital reports [20]. Standing body height was standardized and measured by Harpenden stadiometer at all visits.

Total hip, femoral neck, and lumbar BMD were measured by dual-energy X-ray absorptiometry (DXA) using Hologic devices at baseline and every 6 months

post-baseline. A cross-calibration program was performed throughout the study [21], and all scans were analyzed centrally. Strontium distributes in bone and absorbs X-rays to a greater extent than calcium. The presence of strontium may account for approximately 50% of BMD increases measured by DXA with strontium ranelate treatment [22].

Bone turnover markers were assessed at baseline, after 3 and 6 months of treatment, and then annually during 4 years; during the fifth year, they were assessed only in patients treated for 4 years with strontium ranelate and after 51 and 60 months of treatment. Bone alkaline phosphatase (bALP) was assayed by immunoradiometric assay (Tandem[®]-R Ostase[®], Beckman Coulter, formerly Hybritech, San Diego, CA, USA), and serum C-telopeptide cross-link of type I collagen (sCTX) was assayed using an enzyme-linked immunosorbent assay (serum CrossLaps[®]ELISA—Nordic Bioscience Diagnostic, formerly Osteometer Bio-Tech, Herlev, Denmark).

Parathyroid hormone was assessed with an immunoradiometric assay (N-tact[®]PTH SP IRMA, Diasorin, USA).

QoL was assessed using self-administered questionnaires: the Short-Form 36 (SF-36®), a widely used generic 36-item instrument [23], and QUALIOST®, a disease-specific 23-item instrument designed to complement the SF-36® in postmenopausal patients with vertebral osteoporosis [24]. Both questionnaires were completed every 6 months throughout the trial. In the SF-36®, items are grouped into eight dimensions, which were further combined into summary scores for mental and physical components. In each case, scores range from 0 to 100, with higher scores indicating better QoL. QUALIOST® contains two dimensions, physical (10 items) and emotional (13 items). Scores again range from 0 to 100, higher scores indicate greater impairment of QoL. One QUALIOST® item (physical dimension item 6) relates specifically to back pain. The QUALIOST® cross-cultural validity and responsiveness have been validated using earlier (3-year) data from the present (SOTI) trial [25].

Statistical analysis

Randomized assignment of treatment was stratified by country and performed using permutation blocks with a fixed size of four.

All these pre-planned efficacy analyses were performed in accordance with the intention-to-treat (ITT) principle. For the M0–M48 period, ITT population for fracture incidence analysis was defined as all randomized patients who took at least one sachet of study drug and with (at least two) X-ray assessments between M0 and M48. For the M48–M60 period, ITT population was defined as all patients who performed the M48 visit, took at least one sachet of study drug between M0 and M48 and after M48, with validated L₂–L₄DXA measurements at M0 and M48, and post M48. The ITT population for QoL analysis comprised patients from the ITT population who had at least one assessable SF-36® (i.e., <50% missing data) and one assessable QUALIOST® completed at baseline, plus at least one assessable SF36® and one assessable QUALIOST® completed post baseline (>12 months, until 4 years of treatment).

For the 4-year analysis, the incidence over time of patients with at least one new osteoporotic vertebral fracture and new clinical vertebral fracture were analyzed by Kaplan–Meier method. Analysis of osteoporosis-related vertebral fractures was therefore carried out on all available data (under treatment or not) up to the cutoff date of the new vertebral fracture, whatever the date of the last study visit for the patients considered. Consequently, as the population selection bias phenomenon increases year after year, any isolated yearly statistical comparison regarding fracture occurrence would provide biased (as well as inaccurate) estimates and would lead to misleading clinical interpretation. Therefore, treatment groups were compared using the Cox model over 4 years.

The incidence of vertebral fractures was adjusted for age, country, prevalent vertebral fractures, and L₂–L₄BMD and incidence of non-vertebral fractures was adjusted for age, country, body mass index, and femoral neck BMD. A log-rank non-parametric test was used to confirm results of the Cox model. Between-group comparisons of BMD and bone markers were performed using covariance analysis with baseline value as covariate and two-tailed Student's *t* tests. Between-group comparison of body height was performed on the change from baseline using a covariance analysis adjusted on height at baseline and prevalent vertebral fracture. The number of patients in each group with a body height loss of ≥ 1 cm was compared using the chi-squared test.

For the fifth-year treatment-switch period (M48 to M60), annual incidence of new vertebral fracture was estimated using a within-group 95% confidence interval of the estimates with Kaplan–Meier method. Within-group comparisons of BMD were performed using the Student's *t* test for paired samples and between-group comparisons using the same test for independent samples. Bone markers were analyzed using descriptive statistics. At entry in the fifth year, a between-group comparison on BMD (lumbar and femoral neck level) and on corresponding *T* scores was performed using a two-sided Student's *t* test for independent samples.

Between-group comparisons of the SF-36® and QUALIOST® total and component scores at each time point were performed using a repeated-measures analysis (mixed model), followed, in the case of non-significant treatment \times time interaction, by Fisher's test. Analysis was first performed on raw data and confirmed by repeating with imputation of missing data. Missing data were replaced, taking into account fracture status of each patient. For example, for patients who had experienced a fracture and for whom the questionnaire was missing after they had their fracture, the average change in score seen in patients after they experienced a fracture was added to the last available score for that patient. Missing items within questionnaires had already been taken into account when calculating scores, with dimension scores being calculated as the mean of non-missing items only if at least half of the items in that dimension had been answered. An analysis of covariance (ANCOVA), with baseline score as covariate, was performed to compare between groups the changes between baseline and last value and between baseline and last value on treatment. The number of patients free from back pain (QUALIOST® item 6) in each group was compared using Poisson regression.

The type I error rate was set at 5% throughout.

Statistical analyses were performed by Servier, and the study was organized under the control of independent advisory and steering committees.

Safety evaluation

Adverse events reported spontaneously by patients or elicited during interview were recorded at each study visit. Blood and urinary calcium and blood phosphorus were assessed at each visit. Hematology and biochemistry tests were performed at M0, M6, M12, and then annually. Adverse events were reviewed by a safety committee, independent from the sponsor and from the other study committees.

Results

Patients

A total of 1,649 patients were randomized: 828 to strontium ranelate and 821 to placebo. Of these, 1,149 patients (69.7%) completed the 4-year treatment period (strontium ranelate, 572 patients; placebo, 577 patients) and entered the fifth-year treatment-switch period. All placebo-treated patients were switched to strontium ranelate, and strontium ranelate-treated patients were randomized either to continue with strontium ranelate (SR/SR group, $n=288$) or to switch to placebo (SR/placebo group, $n=284$; Fig. 1). The proportion of randomized patients included in the ITT population at M48 was 87.6%. At M60, 1,070 patients completed the study; however, 880 patients, representing 76.6% of those who entered the fifth year, were included in the ITT population at M60. The reasons for exclusion of these 190 patients were absence of treatment from M48 and absence of assessable lumbar BMD at baseline, M48, or after M48.

Demographic and clinical characteristics of randomized patients are shown in Table 1. There were no relevant between-group differences. At entry to the fifth-year treatment-switch period, BMD values and corresponding T -scores were lower in patients on placebo during the 4-year treatment period. In addition, a slight between-group difference was observed for patients having taken concomitant treatment for osteoporosis during the study (4.2% and 2.1% patients in the SR/SR and SR/placebo groups versus 6.4% in the placebo/SR group). No other relevant between-group differences were observed for the remaining baseline characteristics.

Efficacy

Vertebral fractures and BMD

Four-year treatment period The risk of new vertebral fracture over the M0 to M48 period was reduced by 33% with strontium ranelate, relative to placebo [risk reduction (RR), 0.67; 95% CI (0.55, 0.81), $p<0.001$]. The number of patients needed to treat for 4 years to prevent one new vertebral fracture was 11 [95% CI (7, 24)]. Among severely affected patients (with two or more prevalent vertebral fractures at baseline), risk reduction with strontium ranelate was 36% (RR, 0.64; 95% CI (0.50, 0.81), $p<0.001$). The total number of new vertebral fractures was significantly lower in the strontium ranelate group (275) than in the placebo group (421; $p<0.001$). The risk of new clinical vertebral fracture was reduced by 36% with strontium ranelate relative to placebo [RR, 0.64; 95% CI (0.49, 0.83), $p<0.001$] (Fig. 2).

Table 1 Baseline characteristics at year 0 and at year 4 of the M48 and M60 ITT populations, expressed as mean±standard deviation unless otherwise stated

	Year 0		Year 4		
	Strontium ranelate, $N=719$	Placebo, $N=726$	SR/SR, $N=221$	SR/placebo, $N=225$	Placebo/SR, $N=434$
Age, years	69.4±7.2	69.3±7.3	72.1±6.9	72.1±6.7	72.1±6.9
Time since menopause (years)	22.1±8.8	21.7±8.8	24.5±8.5	25.0±8.7	24.3±8.3
One or more prevalent vertebral fracture, n patients (%)	628 (87.5)	626 (86.3)	192 (86.9)	197 (87.6)	372 (86.1)
Number of prevalent vertebral fractures	2.5±2.0	2.5±2.1	2.7±2.2	2.8±2.1	3.1±2.7
Lumbar BMD (g/cm^2)	0.731±0.125	0.720±0.118	0.849±0.158*	0.862±0.163*	0.717±0.127
Lumbar T -score	-3.52±1.30	-3.64±1.23			
Femoral neck BMD (g/cm^2)	0.591±0.086	0.590±0.093	0.655±0.888*	0.643±0.087*	0.581±0.094
Femoral neck T -score	-2.78±0.77	-2.79±0.84			
bALP (ng/mL)	12.3 ±4.5	12.8±4.9			
sCTX (ng/mL)	0.51±0.24	0.52±0.24			

* $p<0.001$ for the difference SR/SR–placebo/SR or SR/placebo–placebo/SR (two sided Student's t test for independent samples)

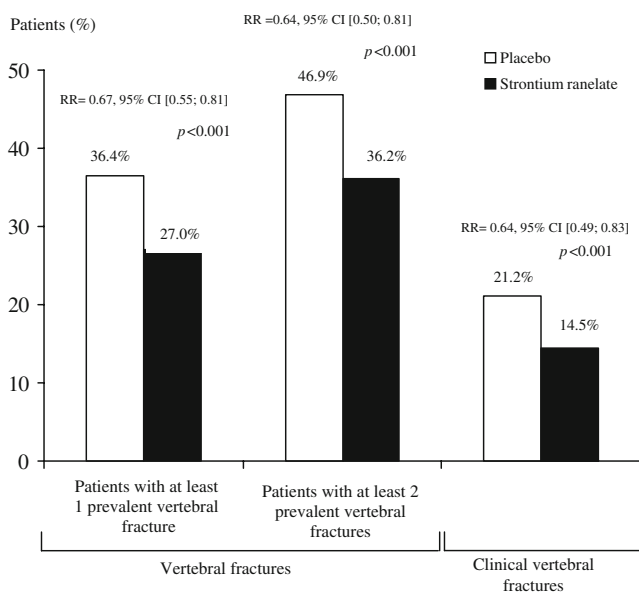


Fig. 2 The proportion of patients who experienced new vertebral fracture(s) during the M0–M48 period

The risk of peripheral fracture was not significantly different over 4 years between the two groups [RR=0.92, 95% CI (0.72, 1.19)].

Mean reduction in body height was less in the strontium ranelate group compared with placebo [estimated between-group difference (SE) (mm), 2.1 (0.8), $p=0.007$], and the proportion of patients with a reduction in body height of ≥ 1 cm was significantly lower in the strontium ranelate group (36.6%) than with placebo (42.1%; $p=0.034$).

BMD increased over time at all sites measured in the strontium ranelate group but decreased slightly in the placebo group. The between-group differences for the change from baseline in BMD at the different sites were 14.6% for the lumbar site, 8.7% for the femoral neck, and 9.8% for the total hip site ($p<0.001$ for each site).

Serum concentration of bALP was higher in the strontium ranelate group than in the placebo group from M3 to M48, with significant between-group difference on the change from baseline to end (change from baseline to end, 2.5 ± 4.5 and 1.9 ± 5.8 ng/mL in the strontium ranelate and placebo groups, respectively; $p=0.031$). Concentration of sCTX was lower in the strontium ranelate group than in the placebo group from M3 to M48, with a significant between-group difference on the change from baseline to end (change from baseline to end, 0.01 ± 0.30 and 0.06 ± 0.27 ng/mL in the strontium ranelate and placebo groups, respectively; $p<0.001$).

Fifth-year treatment period In the SR/SR group, the progressive increase in L_2 – L_4 BMD seen throughout the 4 years of the trial continued during the fifth year, with a further increase of $1.2\pm 5.8\%$ between M48 and end on

treatment (Fig. 3). In the SR/placebo group, the increase in BMD began to reverse after the switch to placebo ($-3.2\pm 5.8\%$) between M48 and end on treatment, although BMD was still substantially higher at M60 (0.819 ± 0.147 g/cm²) compared with M0 (0.734 ± 0.123 g/cm²). Both the increase in L_2 – L_4 BMD in the SR/SR group and the decrease in the SR/placebo group between M48 and end on treatment were significant ($p<0.001$ and $p=0.002$, respectively). BMD in the placebo/SR group increased after switch to strontium ranelate; the increase between M48 and end on treatment ($5.3\pm 7.3\%$) was similar to the increase seen in strontium ranelate-treated patients during the first year (M0–M12) of the trial ($6.4\pm 7.7\%$).

BMD changes at other measured sites were similar to those at the L2–L4 site. Significant differences were seen in the change in BMD between M48 and end over 5 years between the SR/SR group and the SR/placebo group at each site ($p<0.001$ in each case; Table 2).

The decrease in BMD in the SR/placebo group was not associated with a significant between-group difference in the incidence of new vertebral fractures over the fifth year of treatment: 6.9% (14 patients) in the SR/SR group compared with 8.9% (19 patients) in the SR/placebo group ($p=0.463$). However, these results should be interpreted with caution since the number of patients with a fracture is small.

Bone markers (fifth year) After discontinuation of treatment, a significant decrease in bALP from M48 to last observation on treatment (from 15.2 ± 5.2 to 11.6 ± 3.6 ng/mL, $p<0.001$) and an increase in sCTX (from 0.552 ± 0.263 to 0.588 ± 0.225 ng/mL, $p=0.038$) were observed.

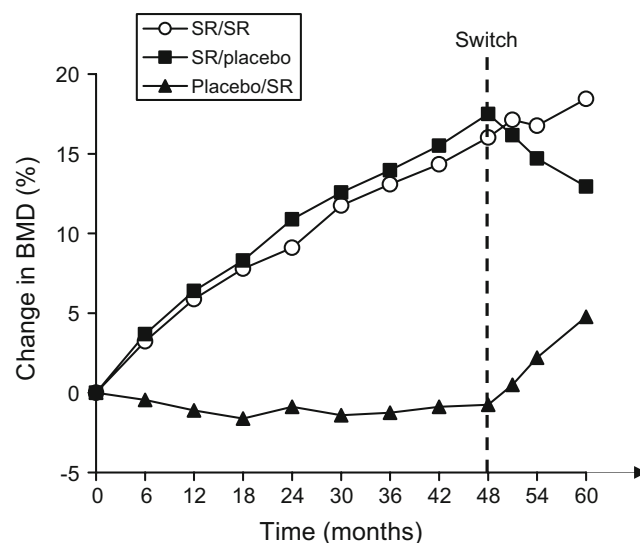


Fig. 3 Changes in bone mineral density (BMD) at the lumbar L2–L4 site with time throughout the trial. Treatment switch at 48 months is indicated by vertical dashed line

Table 2 Relative changes (%) in bone mineral density between M48 and last observation on treatment in patients continuing on strontium ranelate (SR/SR group) and switching to placebo (SR/placebo group)

	SR/SR group (mean±SD), N=221	SR/placebo group (mean±SD), N=225	Between-group difference (SE) ^a	95% CI	p value
Lumbar L2–L4	1.21±5.78 (n=207)	-3.22±5.79 (n=212)	4.43 (0.57)	3.32; 5.54	<0.001
Femoral neck	0.11±4.16 (n=199)	-2.12±5.79 (n=207)	2.22 (0.50)	1.24; 3.21	<0.001
Total hip	0.41±3.02 (n=199)	-2.53±4.36 (n=207)	2.94 (0.37)	2.21; 3.67	<0.001

^a SR/SR group minus SR/placebo group

Quality of life (fourth year) A total of 1,250 patients (87% of the ITT population) were assessed for QoL (strontium ranelate $n=623$, placebo $n=627$). For the SF-36[®] questionnaire, there were no significant differences between the treatment groups for the mental and physical component summary scores. Among the individual SF-36[®] dimensions, a significant between-group difference on the change from baseline to last value and on the change from baseline to last value on treatment was observed for the General Health Perception dimension ($p=0.043$ and $p=0.012$, respectively).

QUALIOST[®] global scores were lower (indicating better QoL) in the strontium ranelate group than in the placebo group at each post-baseline assessment and significant between-group differences in favor of strontium ranelate in the change from baseline to endpoint (mean change from baseline in the strontium ranelate group = -0.06 and mean change from baseline in the placebo group = 1.92, $p=0.020$) and from baseline to endpoint on treatment (mean change from baseline in the strontium ranelate group = -0.40 and mean change from baseline in the placebo group = 1.63, $p=0.015$) were observed.

When the physical and emotional QUALIOST[®] dimensions were considered separately, a statistically significant between-group difference of the change from baseline to last value and from baseline to last value in treatment in favor of strontium ranelate was observed for both emotional score ($p=0.025$ and $p=0.012$, respectively) and physical score ($p=0.022$ and $p=0.034$, respectively; Fig. 4).

Proportion of patients free of back pain (patients who answered 'not at all' to 'Have you had pain in the middle or upper part of your back?', QUALIOST[®] item 6) after 4 years of treatment was 28% higher in the strontium ranelate group than with placebo ($p=0.005$). Indeed, 14.6% of patients receiving strontium ranelate versus 11.2% of patients receiving placebo were free of back pain [RR, 1.28; 95% CI (1.08, 1.52)].

Safety

In all, over 4 years, 739 patients in the strontium ranelate group (89.5%) and 720 patients in the placebo group (88.5%) reported at least one emergent adverse event under

treatment. Diarrhea (6.3% versus 3.8%, respectively) and nausea (5.2% versus 3.8%, respectively) were more frequently reported in the strontium ranelate group than in the placebo group. Skin disorders were reported similarly in both groups (14.5% in the strontium ranelate group and 15.1% in the placebo group), including dermatitis and eczema (2.1% versus 1.8% and 1.0% versus 1.2%, respectively). Over 4 years, four serious adverse events in each group concerning skin disorders were reported (one dermatitis and one contusion in each group, a pemphigoid and a lichen planus in the strontium ranelate group, and two skin ulcers in the placebo group). None were considered as related to the study drug by the investigators.

Over 4 years, the number of patients reporting an embolism or a venous thrombosis was eight and five in the strontium ranelate and placebo groups, respectively.

In the fifth year, in patients starting strontium ranelate (placebo/SR group), the number of emergent adverse events reported was similar to the SR/SR and SR/placebo groups (55.7% versus 56.7% and 55.5%, respectively). Diarrhea, nausea, and headache were more frequently reported. These events occurred mainly during the first 3 months of

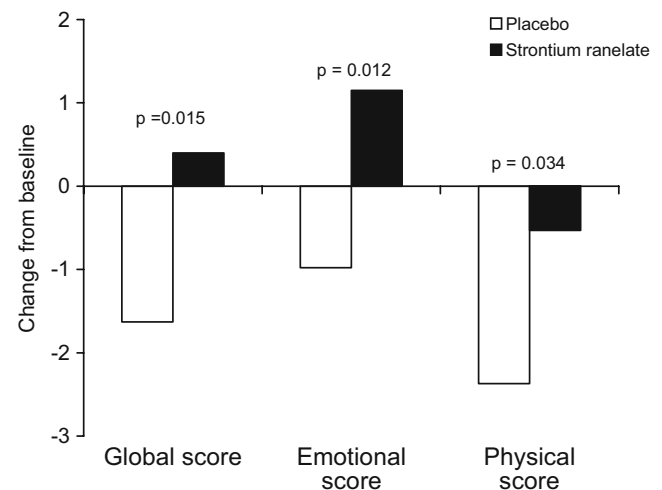


Fig. 4 Changes from baseline to last evaluation (baseline–endpoint) during the M0–M48 treatment period in quality of life assessed by QUALIOST[®] global score, emotional score, and physical score in the ITT population on treatment (ANCOVA). p value difference versus the placebo group

treatment. Skin and subcutaneous disorders were reported similarly in the three groups (5.5% in the SR/SR group, 7.3% in the SR/placebo group, and 4.3% in the placebo/SR group). Two serious adverse events classified as skin disorder occurred: one contusion due to a fall in the placebo/SR group and one in the SR/placebo. None was considered as related to the study drug.

Serum creatinine kinase concentrations increased in some patients starting strontium ranelate. High levels (concentration greater than three times the upper value of the normal reference range) were detected in 0.7% of the patients (three patients), but none reached five times the upper value of the normal reference range.

Concerning calcium homeostasis, over 4 years, mild decreases in calcium and parathyroid hormone (PTH) serum levels were observed in the strontium ranelate group (from 2.38 ± 0.13 mmol/L at baseline to 2.22 ± 0.10 mmol/L at end and from 30.98 ± 12.71 pg/mL at baseline to 28.75 ± 11.60 pg/mL at end, respectively), while blood phosphorus concentration slightly increased (from 1.22 ± 0.19 mmol/L at baseline to 1.31 ± 0.17 mmol/L at end). These changes were of too small magnitude to have clinical relevance. During the fifth year, in the group which stopped strontium ranelate, trends to inverse changes were observed; slight increase in serum calcium concentration (from 2.31 ± 0.93 to 2.36 ± 0.09 mmol/L) and decrease in blood phosphorus concentration (1.31 ± 0.16 to 1.22 ± 0.14 mmol/L).

Discussion

The main result of this pre-planned analysis is that long-term treatment (4 years) with strontium ranelate produced a significant 33% reduction in the risk of vertebral fractures. A similar reduction (36%) was seen in the subset of severely affected patients with ≥ 2 prevalent vertebral fractures at baseline. The reductions in fracture risk were associated with a progressive increase in BMD of the lumbar and hip regions that extended throughout the treatment period.

Few studies of anti-osteoporotic drugs using randomized initial treatment periods of duration comparable to the present trial (4 years) and in the same type of patients are published. In patients without prevalent vertebral fracture, alendronate (10 mg/day) reduced by 44% vertebral fractures over 4 years, but no data were available in patients with prevalent vertebral fracture [26]. Raloxifene reduced vertebral fracture by 34% over 4 years in patients with prevalent vertebral fracture [27]. The 33% risk reduction seen over 4 years in this study is of similar magnitude to these results. No data are available for risedronate for initial randomized periods of 4 years or longer, but a reduction in vertebral fractures of 59% was reported from a smaller (265 patients) 2-year extension to a 3-year study [28].

The reduction in risk of vertebral fractures of 33% over 4 years in the present study is smaller than that seen in the corresponding analysis over 3 years (41%) [14]. An apparent decrease in the size of risk reduction achieved with greater treatment duration has been reported in previous studies of other anti-osteoporotic drugs. For risedronate, risk reductions of 65% and 61% seen at 1 year decreased to 41% and 49%, respectively, over 3 years [29, 30]. Comparisons of cumulative endpoints at different times during a long-term study must therefore be interpreted with caution. The patients at risk of a given endpoint, although well balanced between treatment groups in terms of disease characteristics and level of risk at randomization, become progressively unbalanced (for example, due to censoring of fracture cases, attrition of more severely affected patients, and introduction of concomitant osteoporosis medication) over time if 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 vertebral antifracture efficacy of strontium ranelate over 4 years in this study has also been confirmed over 5 years in the Treatment of Peripheral Osteoporosis study [16].

Many factors contribute to bone fragility that leads to osteoporotic fractures [31]. One important mechanism is the progressive net loss of bone due to a greater degree of bone resorption than formation at focal remodeling sites, leading to an overall deficit in bone formation in later adult life. In postmenopausal women, the rate of net bone loss is accelerated by an increase in the intensity of bone remodeling in response to reduced estrogen levels. Antiresorptive agents such as bisphosphonates and raloxifene reduce the rate of bone remodeling, reflected in decreases in markers of both bone formation and bone resorption [32, 33]. Strontium ranelate appears to have a different mode of operation. In various animal models, strontium ranelate has been shown to prevent bone loss by increasing bone formation and decreasing bone resorption [34]. These *in vivo* results were consistent with *in vitro* data where strontium ranelate has been shown to reduce bone resorption by osteoclasts and to stimulate bone formation by osteoblasts [34, 35]. It has been demonstrated *in vitro* that strontium ranelate is an agonist of the CaR and is able to stimulate the replication of osteoblasts through the activation of CaR [36]. CaR is one of the major molecular determinants involved in controlling the cations concentration through regulation of PTH [37]. The slight decrease in serum calcium and PTH in association with a slight increase in blood phosphorus observed in this study is in agreement with an action mediated through the CaR in postmenopausal women.

Consistent with the dual mode of action of strontium ranelate, analysis of serum markers of bone metabolism over the first 3 and 4 years of the SOTI study showed that strontium ranelate treatment was associated with a small but significant increase in bALP and a significant decrease in sCTX, relative to placebo [12]. Following treatment withdrawal, results obtained were in agreement with this dual mode of action as they show a significant decrease in bALP and an increase in sCTX. These changes are already observed 3 months after treatment discontinuation, suggesting a relatively rapid release of strontium from bone.

In the present analysis, patients who continued on strontium ranelate in the main treatment period and in the treatment-switch period showed a progressive increase in BMD throughout the entire 5-year period. The increase in lumbar BMD from M48 to end in the SR/SR group ($1.2 \pm 5.8\%$) is clinically significantly smaller than in the placebo/SR group ($5.3 \pm 7.3\%$). Increase of bone density with strontium ranelate may be due to different effects: increase in bone mass, increase in the degree of mineralization, or artifactual increase of BMD due to the presence of strontium in bone. Studies on bone biopsies have demonstrated that the degree of mineralization is not modified compared to placebo after 3 years of treatment [38]. Regarding the bone strontium content, it has been demonstrated that bone strontium content reached a plateau after 3 years of treatment [39]. This plateau might explain at least partly the smaller increase in BMD after 4 years of treatment compared to the first year of treatment and suggested that strontium ranelate continue to increase bone mass despite the plateau observed in bone strontium content. Furthermore, a strong relationship between the increase in BMD and a subsequent reduction of the risk to have a new vertebral or hip fracture have been demonstrated in strontium ranelate-treated patients indicating that BMD may be of interest to monitor those patients for 3 years [40, 41]. After treatment withdrawal, patients who switched to placebo at 4 years experienced a significant reduction in BMD, showing effects of strontium ranelate to be progressively reversible and reflecting clearance of strontium from bone. Decrease observed after treatment cessation is also suggesting that BMD may be followed up after a treatment with strontium ranelate.

After 3 years, strontium ranelate treatment was associated with significant beneficial effect on QoL, relative to placebo, assessed by QUALIOST[®], a validated disease-targeted QoL instrument [24, 25, 42]. These results are confirmed after 4 years of treatment: Both the emotional and physical components of the global QUALIOST[®] score were improved in comparison to placebo ($p=0.012$ and $p=0.034$, respectively).

Relative to baseline, placebo-treated patients showed an initial improvement in global QUALIOST[®] score at the 6-

month assessment, followed by a progressive worsening throughout the remainder of the 4-year treatment period, with scores at the last four assessments worse than at baseline. The strontium ranelate group showed significant benefits on QoL, relative to baseline, at all assessments, indicating that strontium ranelate prevented or delayed the progressive worsening of QoL with time seen in placebo-treated osteoporotic women.

The magnitude of the difference in the change of QUALIOST[®] total score from baseline to last assessment between the strontium ranelate and placebo groups was clinically relevant as it reached approximately 2.0; this may be compared with the difference of 1.38 observed using the same instrument between patients with one new osteoporotic fracture and patients without new fracture [24]. It is important to note that these changes represent predominantly the long-term effects of fractures on QoL; soon after the occurrence of fracture, the impact on QoL may be larger.

Although the impact of osteoporotic fractures on QoL has been explored in several studies, there have been relatively few studies evaluating the effects of anti-osteoporotic drugs on QoL. One year of treatment with alendronate or calcitonin significantly reduced pain and improved QoL compared with calcium supplementation in a study of 151 patients [43]. Raloxifene treatment had no significant effect, relative to placebo, on QoL over 3 years [44]. A meta-analysis of five studies indicated that teriparatide treatment reduced the risk of new or worsening back pain, although wider QoL was not evaluated [45]. To our knowledge, the present study is the first large, long-term randomized study to demonstrate preplanned beneficial effects of an anti-osteoporotic drug on back pain and QoL.

In conclusion, in this 5-year randomized trial in postmenopausal women with osteoporosis, long-term treatment with strontium ranelate 2 g/day was associated with a 33% reduction in the risk of vertebral fractures, relative to placebo, over a 4-year treatment period. The reduction in fractures was accompanied by a significant improvement in QoL and increase in the number of patients free of back pain. BMD increased progressively throughout 4 and 5 years of strontium ranelate treatment, and began to decline in those patients switched from strontium ranelate to placebo at 4 years. This decrease in BMD following treatment cessation may have reflected strontium elimination from bone. Strontium ranelate represents an effective first-line intervention for long-term treatment in postmenopausal women with osteoporosis.

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