# Efficacy and Safety of Strontium Ranelate in the Treatment of Osteoporosis in Men

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**Context:** Strontium ranelate reduces vertebral and nonvertebral fracture risk in postmenopausal osteoporosis.

**Objective:** The objective of this study was to determine the efficacy and safety of strontium ranelate in osteoporosis in men over 2 years (main analysis after 1 year).

**Design:** This was an international, unbalanced (2:1), double-blind, randomized placebo-controlled trial (MALEO [MALE Osteoporosis]).

**Setting:** This international study included 54 centers in 14 countries.

**Participants:** Participants were 261 white men with primary osteoporosis.

**Intervention:** Strontium ranelate at 2 g/d (n = 174) or placebo (n = 87) was administered.

**Main Outcome Measures:** Lumbar spine (L2–L4), femoral neck, and total hip bone mineral density (BMD), biochemical bone markers, and safety were measured.

**Results:** Baseline characteristics were similar in both groups in the whole population (age, 72.9 ± 6.0 years; lumbar spine BMD T-score, −2.7 ± 1.0; femoral neck BMD T-score, −2.3 ± 0.7). Men who received strontium ranelate over 2 years had greater increases in lumbar spine BMD than those who received placebo (relative change from baseline to end, 9.7% ± 7.5% vs 2.0% ± 5.5%; between-group difference estimate (SE), 7.7% (0.9%); 95% confidence interval, 5.9%–9.5%; $P < .001$). There were also significant between-group differences in relative changes in femoral neck BMD ($P < .001$) and total hip BMD ($P < .001$). At the end of treatment, mean levels of serum cross-linked telopeptides of type I collagen, a marker of bone resorption, were increased in both the strontium ranelate group (10.7% ± 58.0%; $P = .022$) and the placebo group (34.9% ± 65.8%; $P < .001$). The corresponding mean changes of bone alkaline phosphatase, a marker of bone formation, were 6.4% ± 28.5% ($P = .005$) and 1.9% ± 25.4% ($P = .505$), respectively. After 2 years, the blood strontium level (129 ± 66 μmol/L) was similar to that in trials of postmenopausal osteoporosis. Strontium ranelate was generally well tolerated.

**Conclusions:** The effects of strontium ranelate on BMD in osteoporotic men were similar to those in postmenopausal osteoporotic women, supporting its use in the treatment of osteoporosis in men. **(*J Clin Endocrinol Metab* 98: 592–601, 2013)**



Osteoporosis in men is an important and expanding health care problem (1, 2), with serious consequences in terms of fracture risk, morbidity, mortality, and economic cost (3, 4). In a recent study of men admitted for long-term rehabilitation (5), nearly one-third (31%) had osteoporosis (lumbar spine, total hip, or femoral neck T-score <−2.5). Mortality after osteoporotic vertebral, nonvertebral, and hip fractures is even higher in men than in women (6). Despite the fact that osteoporosis in men is increasingly recognized as a public health issue, the disease remains underdiagnosed and undertreated (7–9). A recent analysis in an American community–based male cohort

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Abbreviations: b-ALP, Bone alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DXA, dual x-ray absorptiometry; EMA, European Medicines Agency; QOL, quality of life; s-CTX, serum cross-linked telopeptides of type I collagen.

found that if National Osteoporosis Foundation criteria for treatment were applied, more than one-third (34%) of white US men older than 65 years and nearly one-half (49%) of white US men older than 75 years would be candidates for osteoporosis drug therapy (9).

Pharmacological and nonpharmacological options exist for osteoporosis in men. As for osteoporosis in women, nonpharmacological options include restoration of muscle function and strength, fall prevention, and discontinuation of smoking and excess alcohol consumption (2). Current pharmacological treatments for osteoporosis in women—alendronate, risedronate, zoledronate, and teriparatide—have been demonstrated to be effective in men, using surrogate endpoints such as bone mineral density (BMD) and bone turnover markers (10–15). It would seem, therefore, that the response to current treatments is independent of sex.

Strontium ranelate reduces vertebral and nonvertebral fracture risk in a wide range of postmenopausal women with documented osteoporosis (16–18), irrespective of age (19, 20) or severity of the underlying disease (21). A strong link between increased BMD and reduced fracture risk was also demonstrated in postmenopausal women treated with strontium ranelate (22). Although its molecular mechanism of action is yet to be fully elucidated, in preclinical and clinical studies, strontium ranelate has been shown to promote osteoblastic cell differentiation in vitro and to improve bone architecture and tissue quality in vivo (23–25). In addition, it directly inhibits osteoclastic differentiation and activity and modulates the OPG-RANK-RANK ligand system in vitro (26).

MALEO (MALE Osteoporosis) is the first randomized placebo-controlled trial in men designed to investigate whether treatment with strontium ranelate is effective and safe in increasing BMD in men with osteoporosis. The protocol of this bridging study was established in compliance with the European Medicines Agency (EMA) guidelines (27). Regulatory approval of an osteoporosis drug for use in men, both from the US Food and Drug Administration and the EMA, requires evidence from bridging studies of treatment effects on intermediate endpoints such as BMD similar to those shown to reduce fracture risk in postmenopausal women. The primary objective of this 2-year study (main analysis at 1 year) was to investigate whether 2 g/d strontium ranelate had similar efficacy with regard to lumbar spine BMD in a male population with fracture risk comparable to that in postmenopausal women in pivotal strontium ranelate studies (16, 17).

## Materials and Methods

### Trial description

This international, multicenter, unbalanced (2:1), randomized, double-blind, placebo-controlled study involved patients with primary osteoporosis from 54 active centers in 14 countries in South Africa, Australia, Europe, and North America and lasted 2 years. An unbalanced 2:1 randomization ratio in favor of strontium ranelate was chosen for ethical reasons to reduce the number of patients exposed to placebo. The main study analysis took place after 1 year and a secondary analysis after 2 years. Ethical approval was received, and all patients gave written informed consent at selection. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki of 1964 (amended in Tokyo in 2004). The trial is registered on http://www.controlled-trials.com (2006-006086-16).

### Patients

The study population consisted of ambulatory white men aged ≥65 years with low lumbar spine (L2–L4) BMD (≤0.840 g/cm$^2$ with a Hologic dual x-ray absorptiometry [DXA] device or ≤0.949 g/cm$^2$ with a GE Lunar DXA device; T-score, ≤−2.5) and/or low femoral neck BMD (≤0.600 g/cm$^2$ Hologic or ≤0.743 g/cm$^2$ GE Lunar; T-score, ≤−2.4) and at least one risk factor for osteoporotic fracture (including age >75 years, prevalent grade 1 vertebral fracture, previous low trauma fracture, family history of osteoporotic fracture, smoking >15 cigarettes/d, known low BMD, and low body mass index [BMI] <20 kg/m$^2$). BMD cutoffs corresponded to those used in the large-scale pivotal randomized controlled trials of strontium ranelate in postmenopausal osteoporotic women (16, 17). Criteria for exclusion at the selection visit included a history of or increased risk for venous thromboembolism, severe hypogonadism, skeletal diseases (such as secondary osteoporosis, Paget disease, osteomalacia, hyperparathyroidism, and hypoparathyroidism), and previous treatment acting on bone metabolism (including long-term oral or inhaled glucocorticoid treatment in the previous year, bisphosphonate injection in the previous year or tablets in the previous 18 months, calcitriol and 1$\alpha$-vitamin D in the previous 6 months, and parathyroid hormone or derivatives, ie, teriparatide). Patients were not included if they had severe osteoporosis (T-score <−4.0 at any site), >2 prevalent mild (grade 1 using the Genant semiquantitative scoring method) and/or moderate (grade 2) osteoporotic vertebral fractures, or any severe osteoporotic vertebral fracture (grade 3). The first patient visit was on December 11, 2007, and recruitment ended on March 2, 2009. The last patient visit was on March 4, 2011.

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### Treatments

Randomization via an interactive voice system was stratified by country and unbalanced (2:1) in favor of strontium ranelate. Patients were allocated to 2 g/d strontium ranelate or placebo orally (1 sachet daily with water at bedtime) for 2 years. Patients and investigators were blinded to treatment allocation, and the study treatments were identically packaged and labeled. All patients (except those with hypercalciuria >4 mg/kg/24 h) received calcium and vitamin D supplementation (1 g + 800 IU daily) for 2 years from the selection visit.

### Endpoints

The primary endpoint was lumbar spine (L2–L4) BMD at 1 year. Secondary endpoints included lumbar spine BMD at 2 years and hip (femoral neck and total hip) BMD, biochemical bone markers (bone alkaline phosphatase [b-ALP] and serum cross-linked telopeptides of type I collagen [s-CTX]), quality of life (QOL), and safety (including fracture assessment by systematic spinal x-ray at 2 years) at both 1 year and 2 years.

### Measurements

DXA was used to measure BMD at baseline and every 6 months thereafter (or earlier if patients withdrew before 6 months), using two types of DXA device (Hologic and GE Lunar). Quality control monitoring of DXA devices was done on a daily basis. For both types of device, the uncorrected average coefficient of variation was 0.4% ± 0.1%. Each device was cross-calibrated using an external, standardized phantom (European Spine Phantom) to obtain optimal concordance between measurements from different centers (28). The lumbar spine was scanned in an anterior-posterior projection. Both hips were also scanned in an antero-posterior position at baseline, and thereafter only the hip with the lowest BMD at baseline (or the intact hip in cases of hip fracture or prosthesis) was scanned. DXA scans were analyzed at a central reading center (Qualim, Geneva, Switzerland). Hologic male reference values were used to calculate lumbar spine (L2–L4), femoral neck, and total hip T-scores. BMD data from GE Lunar DXA devices were converted using standardized formulas (29, 30).

Serum markers of bone turnover, b-ALP (a marker of bone formation) and s-CTX (a marker of bone resorption), were measured at baseline and at 3, 6, 12, 18, and 24 months (fasting blood sample). QOL was evaluated by assessing back pain and its impact on daily life, using corresponding questions from the QUALIOST questionnaire at baseline and every 6 months thereafter (31). Each patient was asked 4 questions: Have you had pain in the middle or upper part of your back?; Have you had pain when walking or climbing stairs?; Have you experienced discomfort when staying in the same position for a long time (sitting, standing)?; and Has pain interfered with your sleep? Adverse events were monitored, as were clinical and laboratory parameters (including blood strontium levels). Safety evaluation included recording of clinical fracture at selection, at 3 months, and every 6 months thereafter and vertebral x-ray assessment of thoracic/lumbar vertebral fracture using the Genant method at a central reading center (CEMO, Hôpital Cochin, Paris, France) at selection and at 24 months. Prevalent fracture was identified by the existence of any vertebral fracture–induced deformity (grade 1 [mild deformity] or greater) at baseline. Incident fracture was defined as fracture that occurred in vertebrae that were normal (grade 0) at baseline.

### Statistical methods

Sample size was estimated based on the relative change in lumbar spine BMD from baseline to the last available postbaseline value over 12 months for an estimated difference between strontium ranelate and placebo, using a 2-sided Student *t* test for independent samples with 5% type I error. A common SD of 6% was assumed. To establish a statistically significant between-group difference of ≥3% with ≥90% power, 191 patients were needed (127 strontium ranelate and 64 placebo). When the 15% withdrawal/protocol violation rate expected during the first year was factored in, 221 patients were needed (147 strontium ranelate and 74 placebo). The statistical analysis plan for the 24-month analysis was finalized before study unblinding. The randomized set was defined as all included patients who were randomly assigned to therapy (N = 261). The full analysis set was defined as all randomly assigned patients who took at least 1 dose of study treatment from inclusion to 24 months, had at least 1 baseline lumbar spine BMD value, and had at least 1 postbaseline lumbar spine BMD value up to 24 months.

Baseline characteristics are presented as descriptive statistics with numbers and percentages for qualitative data or as means ± SDs for quantitative data. The efficacy analysis was done on the full analysis set and was based on intention to treat. Intergroup differences in the relative change from baseline to end were analyzed using a general linear model with country as covariate to produce an estimate (E) of the treatment group difference, SE of the estimate with the associated 95% confidence interval (CI) and *P* value. A sensitivity analysis on the primary endpoint was done using a general linear model adjusted for age and prevalent vertebral fracture. The treatment effect on secondary endpoints was studied using a general linear model with country (and baseline value when the change from baseline was studied) as covariate and using a nonparametric approach (Hodges-Lehmann estimator) for the bone markers (nonnormal distribution). The same models were provided for the relative change from baseline to each visit. The safety set was defined as all patients who took at least one dose of the study treatment from inclusion to 24 months. Results were analyzed by the Methodology and Clinical Data Analysis Division of Institut de Recherches Internationales Servier using SAS software (version 9.1).

## Results

The trial profile is shown in Figure 1. Of the 384 patients selected, 261 were included and randomly assigned (174 strontium ranelate and 87 placebo). Most patient withdrawals were due to adverse events (33 of 174 [19%] with strontium ranelate and 13 of 87 [15%] with placebo, respectively) or nonmedical reasons (19 of 174 [11%] with strontium ranelate vs 11 of 87 [13%] with placebo); 117 patients completed 24 months of treatment on strontium ranelate versus 63 with placebo. There were 243 patients in the full analysis set (93% of the randomized set). Patients excluded from the full analysis set (13 of 174 [8%] strontium ranelate and 5 of 87 [6%] placebo) were missing either a baseline lumbar spine BMD value or a postbaseline lumbar spine BMD value. There were 260 patients in

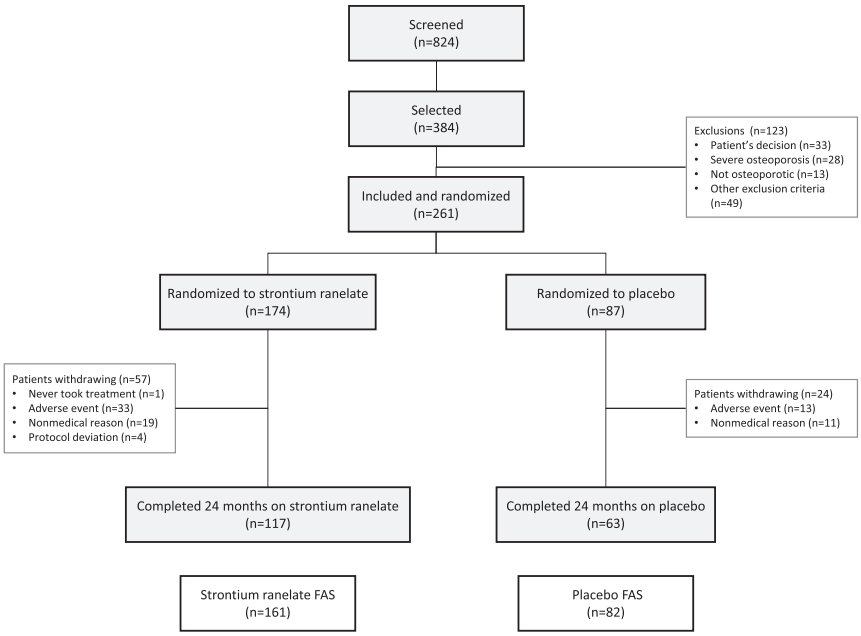


**Figure 1.** Trial profile. FAS, full analysis set.

the safety set (1 patient was excluded because he never took the treatment).

The baseline characteristics of the two groups were similar (Table 1). Mean age was 72.9 ± 6.0 years, mean BMI was 25.5 ± 3.7 kg/m$^2$, and mean time since diagnosis was 26.6 ± 48.6 months in the whole population. Mean lumbar spine BMD T-score was −2.7 ± 1.0, and mean femoral neck BMD T-score was −2.3 ± 0.7. Fewer than one-third of patients (29%) had a prevalent osteoporotic vertebral fracture at baseline, whereas a small minority (11%) had a previous peripheral osteoporotic fracture. Almost one-third of patients (32%) reported at least one previous treatment that could have modulated bone metabolism, the most common of which were mineral supplements, ie, calcium (23%), vitamins (12%, mainly vitamin D and analogs [>11%]), and drugs for the treatment of bone disease (12%, principally bisphosphonates [>11%]).

Levels of 25-hydroxyvitamin $D_3$ were similar in the strontium ranelate (62.2 ± 17.2 nmol/L) and placebo (62.8 ± 18.6 nmol/L) groups at baseline, and 76% of patients had a level of 25-hydroxyvitamin $D_3$ ≥50 nmol/L. Levels of testosterone were also similar in the two groups (18.2 ± 5.9 and 18.6 ± 6.9 nmol/L, respectively), and 97% of patients had a level of testosterone ≥8.6 nmol/L. Levels of bone markers were also comparable; mean levels of b-ALP were 13.0 ± 5.0 ng/mL (median, 12.1 ng/mL; minimum, 10.0 ng/mL; maximum, 14.8 ng/mL) and

**Table 1.** Baseline Characteristics[a]

| Parameter | Strontium Ranelate | Placebo | All | *P* Value[b] |
|---|---|---|---|---|
| Randomized set | | | | |
| n | 174 | 87 | 261 | |
| Age, y | 73.1 ± 6.1 | 72.6 ± 5.7 | 72.9 ± 6.0 | .54 |
| Height, cm | 169 ± 7 | 171 ± 7 | 170 ± 7 | .12 |
| BMI, kg/m$^2$ | 25.2 ± 3.6 | 26.0 ± 4.1 | 25.5 ± 3.7 | .11 |
| Time since diagnosis of osteoporosis, mo | 24.5 ± 45.3 | 30.8 ± 54.6 | 26.6 ± 48.6 | .35 |
| Prevalent vertebral osteoporotic fracture | 53 (31)[c] | 22 (25) | 75 (29) | .38 |
| Previous peripheral osteoporotic fracture | 20 (12) | 9 (10) | 29 (11) | .78 |
| Drugs for treatment of bone disease[d] | 22 (13) | 9 (10) | 31 (12) | .59 |
| Current smokers | 16 (9) | 13 (15) | 29 (11) | .16 |
| Current alcohol consumption | 91 (52) | 53 (61) | 144 (55) | .19 |
| Full analysis set | | | | |
| n | 161 | 82 | 243 | |
| Lumbar spine BMD | 161 (100) | 82 (100) | 243 (100) | |
| BMD, g/cm$^2$ | 0.81 ± 0.10 | 0.83 ± 0.13 | 0.82 ± 0.11 | .11 |
| T-score | −2.8 ± 0.9 | −2.6 ± 1.2 | −2.7 ± 1.0 | |
| Femoral neck BMD | 154 (96) | 78 (95) | 232 (95) | |
| BMD, g/cm$^2$ | 0.62 ± 0.09 | 0.62 ± 0.10 | 0.62 ± 0.09 | .80 |
| T-score | −2.3 ± 0.6 | −2.3 ± 0.7 | −2.3 ± 0.7 | |
| Total hip BMD | 154 (96) | 78 (95) | 232 (95) | |
| BMD, g/cm$^2$ | 0.78 ± 0.12 | 0.79 ± 0.12 | 0.78 ± 0.12 | .82 |
| T-score | −1.7 ± 0.8 | −1.6 ± 0.8 | −1.7 ± 0.8 | |

[a] Values are mean ± SD or n (%).

[b] *P* value for strontium ranelate vs placebo (Student *t* test).

[c] Assessment for 1 patient was missing.

[d] Mainly bisphosphonates (97%).

13.3 ± 4.6 ng/mL (median, 12.4 ng/mL; minimum, 9.8 ng/mL; maximum, 15.6 ng/mL) in the strontium ranelate group (n = 158) and placebo group (n = 79), respectively, at baseline. Mean levels of s-CTX were 0.5 ± 0.3 ng/mL (median, 0.4 ng/mL; minimum, 0.3 ng/mL; maximum, 0.6 ng/mL) and 0.4 ± 0.2 ng/mL (median, 0.4 ng/mL; minimum, 0.3 ng/mL; maximum, 0.5 ng/mL) in the same groups. There were no relevant differences between the randomized set and full analysis set.

Mean treatment duration was 19.2 ± 8.4 months. Compliance was 91% ± 15% with strontium ranelate vs 92% ± 11% with placebo.

The analysis over 1 year showed that lumbar spine (L2–L4) BMD, the primary endpoint, was significantly greater in men who received strontium ranelate (from 0.82 ± 0.10 g/cm$^2$ at baseline in that group to 0.88 ± 0.11 g/cm$^2$ at end) than in men who received placebo (from 0.85 ± 0.14 g/cm$^2$ to 0.86 ± 0.13 g/cm$^2$). The relative changes for the two groups were 7.1% ± 6.0% with strontium ranelate vs 1.7% ± 4.4% with placebo, from baseline to end, and the between-group difference E was 5.3% (SE, 0.8%; 95% CI, 3.9%–6.8%; $P < .001$).

Over 2 years, the average increase in lumbar spine BMD was significantly greater in men who received strontium ranelate than in men who received placebo. The relative changes for the two groups were 9.7% ± 7.5% with strontium ranelate vs 2.0% ± 5.5% with placebo, from baseline to end; the between-group difference E was 7.7% (SE, 0.9%; 95% CI, 5.9%–9.5%; $P < .001$) (Table 2). The sensitivity analysis confirmed the results (E, 7.6%; SE, 0.9%; 95% CI, 5.8%–9.5%; $P < .001$). At every visit (12 and 24 months), there were greater increases in mean relative changes in lumbar spine, femoral neck, and total hip BMD with strontium ranelate than with placebo, which were significant from 12 months onward (all $P < .001$) (Figure 2 and Table 2). Lumbar spine, femoral neck, and total hip BMD increased by 9.8%, 3.3%, and 3.7% after 24 months in men treated with strontium ranelate vs placebo (all $P < .001$) (Table 2).

Mean levels of s-CTX were lower in the strontium ranelate group than in the placebo group from 3 months onward ($P < .001$). The relative change from baseline to end was 10.7% ± 58.0% ($P = .022$) in the strontium ranelate group vs 34.9% ± 65.8% ($P < .001$) in the placebo group (estimate of the adjusted means between-group difference, −22.2%; 95% CI, −33.3% to −8.3%; $P < .001$) (Table 3). Meanwhile, the relative changes from baseline to end of b-ALP were 6.4% ± 28.5% ($P = .005$) in the strontium ranelate group vs 1.9% ± 25.4% ($P = .51$) in the placebo group (estimate of the adjusted means between-group difference, 5.4%; 95% CI, −0.9% to 11.3%; $P = .10$). Blood strontium levels had reached a steady state in the strontium ranelate group by 3 months (137 ± 65 μmol/L), and levels were maintained up to 24 months (138 ± 69 and 129 ± 66 μmol/L at the 12- and 24-month visits).

There was a trend toward a better QOL (ie, a decrease in score) with strontium ranelate from baseline to study end (E, −0.13; 95% CI, −0.27 to 0.01; $P = .072$ vs placebo) (Table 4). Moreover, there was a significant improvement in QOL with strontium ranelate from baseline to 24 months ($P = .009$). More patients receiving stron-

**Table 2.** Mean Percentage Changes in BMD From Baseline to 12 Months, 24 Months, and Study End in Men Receiving Strontium Ranelate or Placebo

| Site | Mean % Change in BMD (95% CI) | | % Treatment-Placebo Difference (95% CI)[a] | *P* Value[b] |
|---|---|---|---|---|
| | Strontium Ranelate (*n* = 161) | Placebo (*n* = 82) | | |
| Baseline to 12 mo | | | | |
| Lumbar spine | 8.2 (7.1 to 9.2) | 1.9 (0.9 to 3.0) | 6.3 (4.7 to 7.9) | <.001 |
| Total hip | 3.0 (2.2 to 3.9) | 1.0 (0.4 to 1.6) | 2.1 (0.9 to 3.2) | <.001 |
| Femoral neck | 3.5 (2.6 to 4.3) | 0.4 (−0.8 to 1.5) | 3.2 (1.8 to 4.6) | <.001 |
| Baseline to 24 mo | | | | |
| Lumbar spine | 11.9 (10.6 to 13.2) | 2.1 (0.6 to 3.6) | 9.8 (7.8 to 11.9) | <.001 |
| Total hip | 3.7 (2.7 to 4.8) | <0.1 (−1.1 to 1.2) | 3.7 (2.0 to 5.3) | <.001 |
| Femoral neck | 4.4 (3.4 to 5.5) | 1.1 (−0.4 to 2.6) | 3.3 (1.5 to 5.1) | <.001 |
| Baseline to study end[c] | | | | |
| Lumbar spine | 9.7 (8.5 to 10.9) | 2.0 (0.8 to 3.2) | 7.7 (5.9 to 9.5) | <.001 |
| Total hip | 3.2 (2.3 to 4.0) | <0.1 (−0.9 to 1.0) | 3.1 (1.8 to 4.5) | <.001 |
| Femoral neck | 3.8 (2.9 to 4.6) | 1.0 (−0.3 to 2.2) | 2.8 (1.3 to 4.2) | <.001 |

[a] Analysis of covariance with treatment and baseline BMD as covariates (intention to treat population) where difference is the least squares mean.

[b] *P* value for strontium ranelate vs placebo (Student *t* test, general linear model).

[c] Value at the last postbaseline visit (until 24 mo) with treatment. When there was no postbaseline visit (until 24 mo) with treatment, the end value corresponds to the first available value.

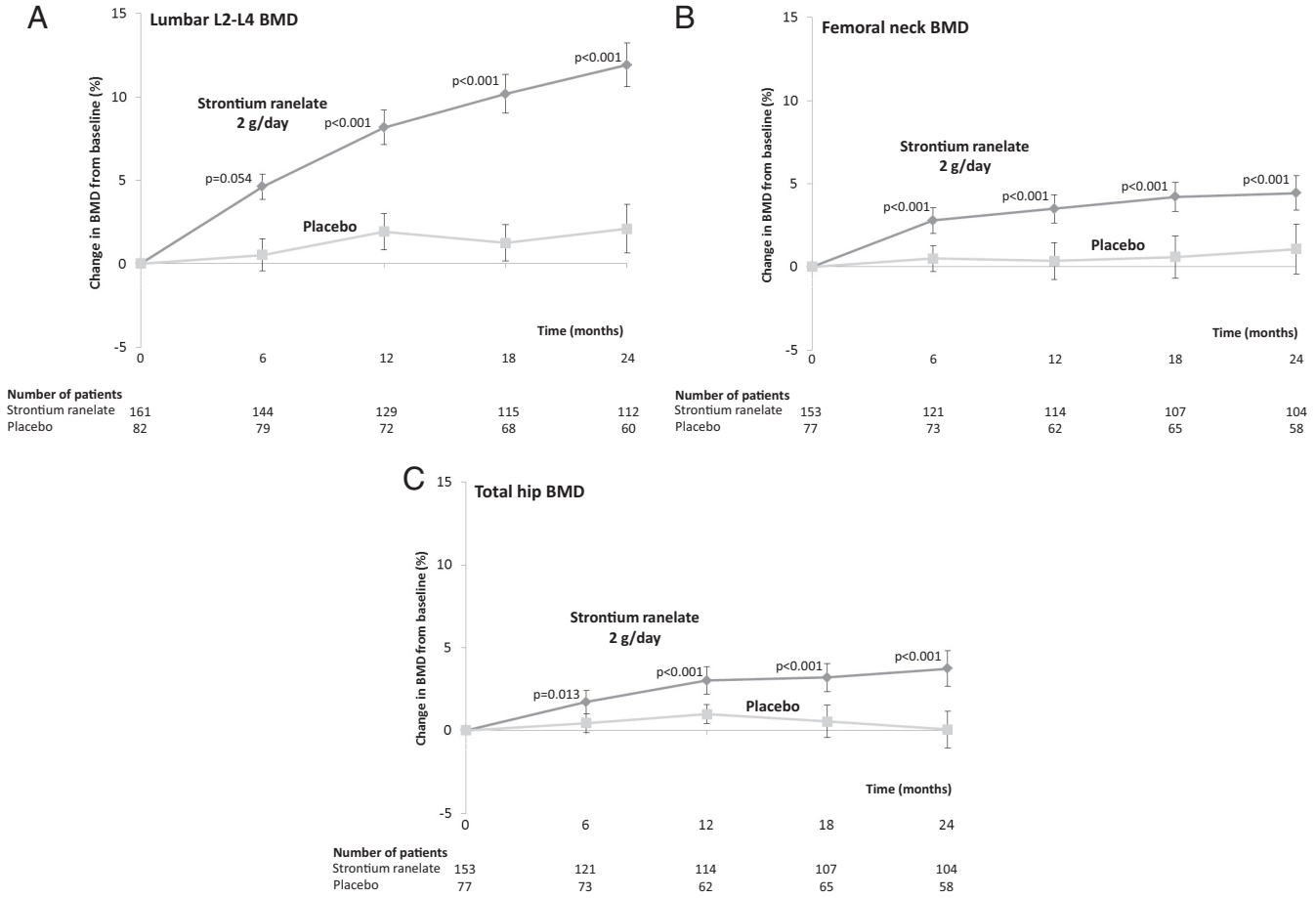


**Figure 2.** Relative change in lumbar spine (A), femoral neck (B), and total hip (C) BMD of the strontium ranelate and placebo groups over 2 years in the full analysis set. Bars are 95% CI.

tium ranelate had improvement in pain in the middle/upper part of back (32% vs 23%; $P = .28$), pain when walking/climbing stairs (23% vs 15%; $P = .39$), and discomfort in the same position (35% vs 27%; $P = .36$) than patients receiving placebo; this improvement was significant for pain interfering with sleep (17% vs 4%; $P = .019$).

The safety set included 173 men receiving strontium ranelate and 87 men receiving placebo. Fewer patients reported at least one emergent adverse event with strontium ranelate (88%) than with placebo (97%) ($P = .03$) (Table 5). The most frequently reported treatment-related adverse event during the study was hypertension (18 of 173 [10.4%] vs 10 of 87 [11.5%]). Although there appeared to be some imbalance in the incidence of coronary artery disorders (angina pectoris and coronary artery disease) between the strontium ranelate and placebo groups (15 of 173 [8.7%] vs 4 of 87 [4.6%]), it should be noted that there was a similar imbalance in the relevant medical histories between the groups (21% in the strontium ranelate group vs 16% in the placebo group), in particular for myocardial ischemia (10.3% vs 3.4%). Comparable incidences of gastrointestinal disorders were reported in both groups (30.1% with strontium ranelate group vs 29.9% with placebo). No participants in either group reported DRESS (drug rash with eosinophilia and systemic symptoms), Stevens-Johnson syndrome, or toxic epidermal necrolysis. Two cases of deep vein thrombosis (including 1 treatment-related case in the first year) and 1 case of nontreatment-related pulmonary embolism (in the second year) were reported with strontium ranelate. All patients had recovered at the end of the study. Overall, the incidence of adverse events considered to be drug-related was similar in both groups (56 of 173 [28.9%] vs 26 of 87 [29.9%]). Most adverse events in each treatment group were either mild or moderate; severe adverse events were reported by 5.4% of men receiving strontium ranelate vs 7.4% of men receiving placebo. More adverse events leading to drug withdrawal were reported by men in the strontium ranelate group (31 of 173 [17.9%] vs 12 of 87 [13.8%]). However, these generally occurred within the first 6 months of treatment and corresponded to gastrointestinal disorders or skin and subcutaneous disorders, which are known side effects of strontium ranelate (32). In the case of skin reactions, it is recommended that treatment be stopped. Four deaths were reported during the

**Table 3.** Mean Percentage Changes in b-ALP and s-CTX From Baseline to Each Visit in Men Receiving Strontium Ranelate or Placebo[a]

| Change from Baseline | Strontium Ranelate (n = 161)[b] | Placebo (n = 82)[b] | Treatment-Placebo Difference (95% CI)[c] | *P* Value[d] |
|---|---|---|---|---|
| Mean change in b-ALP (%) | | | | |
| 3 mo | −1.3 ± 19.9 (n = 146, *P* = .44) | −5.6 ± 16.8 (n = 79, *P* = .004) | 4.2 (−0.5 to 8.2) | .07 |
| 12 mo | −2.5 ± 22.1 (n = 125, *P* = .22) | −5.1 ± 23.2 (n = 71, *P* = .071) | 3.1 (−2.0 to 8.3) | .23 |
| 24 mo | 8.1 ± 31.7 (n = 110, *P* = .008) | 4.7 ± 24.7 (n = 59, *P* = .153) | 2.4 (−5.3 to 10.1) | .57 |
| Study end | 6.4 ± 28.5 (n = 158, *P* = .005) | 1.9 ± 25.4 (n = 79, *P* = .51) | 5.4 (−0.9 to 11.3) | .10 |
| Mean change in s-CTX (%) | | | | |
| 3 mo | −5.4 ± 42.2 (n = 146, *P* = .12) | 11.8 ± 54.5 (n = 78, *P* = .059) | −14.3 (−25.0 to 0.0) | <.001 |
| 12 mo | −2.7 ± 53.9 (n = 125, *P* = .58) | 23.8 ± 70.9 (n = 71, *P* = .006) | −25.0 (−33.3 to −8.3) | <.001 |
| 24 mo | 11.3 ± 54.4 (n = 110, *P* = .032) | 40.9 ± 69.1 (n = 59, *P* < .001) | −25.0 (−41.7 to −10.0) | .001 |
| Study end | 10.7 ± 58.0 (n = 158, *P* = .022) | 34.9 ± 65.8 (n = 79, *P* < .001) | −22.2 (−33.3 to −8.3) | <.001 |

[a] Values are means ± SD.

[b] *P* values indicated are for within-group changes vs baseline (Student *t* test).

[c] Hodges-Lehmann estimator for the difference between group means.

[d] Mann-Whitney-Wilcoxon test.

treatment period: 3 (1.7%) in the strontium ranelate group (septic shock, sudden death, and death of unknown cause in patients who had a strong history of cardiac disorders) and 1 (1.1%) in the placebo group (cerebral hemorrhage). None were considered to be related to study medication. Radiographic vertebral fracture was reported in 7 of 120 (5.8%) men receiving strontium ranelate vs 5 of 64 (7.8%) men receiving placebo (nonsignificant).

## Discussion

MALEO is the first randomized placebo-controlled clinical study to evaluate the efficacy and safety of strontium ranelate in a population of treatment-naive osteoporotic men with low BMD. Our study population has the typical features of a population of men with osteoporosis in terms of age, BMI, and T-score at baseline (5). Treatment with strontium ranelate in this population was associated with significant increases in BMD at the lumbar spine, femoral neck, and total hip throughout the study compared with placebo. These changes in BMD were comparable in magnitude to those observed previously in postmenopausal osteoporotic women treated with strontium ranelate (16, 17).

All previously approved pharmacological treatments of osteoporosis in men, ie, bisphosphonates and teriparatide,

**Table 4.** QOL in Patients Who Had QOL Assessment in the Full Analysis Set[a]

| | Strontium Ranelate (n = 161) | Placebo (n = 82) |
|---|---|---|
| QUALIOST score | | |
| Baseline | 1.62 ± 0.73 | 1.51 ± 0.60 |
| End | 1.36 ± 0.58 | 1.45 ± 0.62 |
| Change from baseline to end | −0.26 ± 0.71 | −0.05 ± 0.54 |
| E (SE) [95% CI] | −0.13 (0.07) [−0.27 to 0.01], *P* = .072[b] | |
| Patients with improvement in QUALIOST item[c] | | |
| Pain in middle/upper part of back | 47 (32) | 18 (23) |
| Pain when walking/climbing stairs | 34 (23) | 12 (15) |
| Discomfort in the same position | 52 (35) | 21 (27) |
| Pain interfering with patient sleep | 25 (17)[d] | 3 (4) |

[a] Values are mean ± SD or n (%).

[b] *P* value for strontium ranelate vs placebo (Student *t* test; general linear model).

[c] For patients with available data (n = 149 strontium ranelate and n = 78 placebo).

[d] *P* = .019 vs placebo (Cochran-Mantel-Haenszel test).

**Table 5.** Overall Safety Profile and Most Common (≥5%) Adverse Events in the Strontium Ranelate Group[a]

| Adverse Event | Strontium Ranelate (n = 174) | Placebo (n = 87) | *P* Value[b] |
|---|---|---|---|
| Any emergent adverse event | 153 (88.4) | 84 (96.6) | .03 |
| Emergent adverse events leading to study drug withdrawal[c] | 31 (17.9) | 12 (13.8) | .40 |
| Any drug-related emergent adverse events | 50 (28.9) | 26 (29.9) | .87 |
| Any serious emergent adverse events | 51 (29.5) | 26 (29.9) | .95 |
| Fatal emergent adverse events | 3 (1.7) | 1 (1.1) | 1.00 |
| Adverse events ≥5% in the strontium ranelate group | | | |
| Hypertension | 18 (10.4) | 10 (11.5) | .79 |
| Back pain | 15 (8.7) | 11 (12.6) | .31 |
| Fall | 12 (6.9) | 7 (8.0) | .75 |
| Hypercalciuria | 11 (6.4) | 5 (5.7) | .85 |
| Arthralgia | 10 (5.8) | 10 (11.5) | .10 |
| Bronchitis | 10 (5.8) | 4 (4.6) | .78 |
| Nasopharyngitis | 9 (5.2) | 9 (10.3) | .12 |
| Spinal osteoarthritis | 9 (5.2) | 6 (6.9) | .58 |
| Pruritus | 9 (5.2) | 4 (4.6) | 1.00 |
| Cataract | 9 (5.2) | 2 (2.3) | .35 |

[a] Values are n (%).

[b] *P* value for strontium ranelate vs placebo ($\chi^2$ test if all theoretical frequencies ≥5% and the Fisher test otherwise).

[c] Excluding sudden deaths.

have been investigated in clinical trials with BMD as a surrogate endpoint (10–12, 14). BMD is known to predict osteoporotic fracture in men, independent of age, body weight, or prevalent fracture (33, 34). With regard to strontium ranelate, changes in femoral neck BMD have been linked to a reduction in vertebral and hip fracture risk (22, 35). In postmenopausal osteoporosis, the 3-year increase in BMD with strontium ranelate explains a large part (76%) of the reduction in vertebral fracture rate observed during treatment (22). Our findings suggest that strontium ranelate may have antifracture efficacy in men with osteoporosis.

The dosage of strontium ranelate used in our study (2 g/d) was the same as that used in the trials in osteoporotic women (16, 17). After 2 years, mean levels of blood strontium in the men in the active treatment arm of this study (129 ± 66 μmol/L) were similar to those (118 ± 79 and 134 ± 88 μmol/L) in the strontium ranelate–treated women in those trials, SOTI (Spinal Osteoporosis Therapeutic Intervention) and TROPOS (Treatment of Peripheral Osteoporosis) (16, 17), and, as with those studies, blood strontium levels remained constant during the study.

Although the levels of bone resorption markers appeared to be lower with strontium ranelate than with placebo and those of bone formation markers were maintained, the small sample size made true trends hard to discern. Although there are likely to be differences in the pathogenesis of osteoporosis in men and women (1, 2, 36), the behavior of bone markers in male osteoporotic patients treated with strontium ranelate compared with those in patients treated with placebo was compatible with that observed in postmenopausal osteoporotic women (16). No sex differences were expected with regard to the mechanism of action on bone metabolism, because strontium ranelate is not a hormonal treatment.

BMD treatment responses in studies of bisphosphonates and teriparatide in men with osteoporosis (10–12, 14) are generally similar to those observed in studies of postmenopausal osteoporosis. The present study now extends these findings to show that there is also a similar response in osteoporotic men and postmenopausal women with strontium ranelate. Our findings also confirm those of a previous 1-year open-label study in men (strontium ranelate vs alendronate), which showed that treatment with strontium ranelate increased BMD after 1 year (37). As in postmenopausal osteoporotic women (38), QOL results indicate an improvement in QOL in patients treated with strontium ranelate compared with placebo. The positive trend was confirmed over 24 months, particularly with regard to pain that interfered with sleep.

Strontium ranelate was generally well tolerated, and adverse events reported were similar to those reported in osteoporosis studies in postmenopausal women. A few cases of coronary artery disorders occurred during the study, but these occurred in patients with relevant medical histories of coronary artery disease, which was unevenly distributed between the groups.

Certain limitations are worth discussing. Strontium ranelate has been shown to be safe in general and effective in postmenopausal women up to 10 years (39); the duration of the current study was short in comparison. Only white men were included in this study; however, treatment

with strontium ranelate has also been shown to be effective in non-white women (40). Although the current study was not powered to assess fracture incidence, after 2 years vertebral fracture incidence (central x-ray reading) was lower in the strontium ranelate group than in the placebo group. As discussed earlier, our chosen surrogate primary endpoint, lumbar spine BMD, has been used as a primary endpoint in most randomized controlled trials in osteoporosis in men, and documentation of a link between increased BMD and reduced fracture risk in women treated with strontium ranelate reinforces the use of BMD as a surrogate endpoint (22). The high degree of variability of the biomarker results, particularly in the placebo group, precluded any further conclusion about the mode of action of strontium ranelate beyond current knowledge (26).

In summary, the effects of strontium ranelate on BMD suggest that the impact of strontium ranelate on fracture risk is likely to be sex-independent. Two years of strontium ranelate therapy in men with low BMD was generally well tolerated and increased BMD at all skeletal sites assessed. The effects of strontium ranelate treatment on BMD in this study were similar to those previously shown to be associated with fracture risk reduction in women with postmenopausal osteoporosis (16, 17). Strontium ranelate has recently been approved by the EMA for the treatment of osteoporosis in men at increased risk of fracture (41).

## Appendix

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