Introduction
The current definition of osteoporosis, which considers the disease to be a systemic alteration characterised by low bone resistance, indicates also that this resistance basically depends on the integration of two variables: the quantity and quality of the bone. Whilst the quantity is directly related to the mineral density of the bone tissue, the quality depends on variables such as the chemical composition of the organic and inorganic materials which make up its matrix (material properties) and the resulting spatial structure of these materials (structural properties), all of which factors depend to a greater or lesser degree on bone remodelling.

Starting from this definition, the ideal therapeutic profile for an anti-osteoporotic drug would be one which on the one hand is shown to increase bone resistance (increasing the BMD and correcting osteoporotic material and structural alterations) and on the other hand, would reduce the incidence of fractures related to fragility of this kind in the axial and peripheral skeleton, be they the first or successive.

These days there is a series of medications which, by means of different action mechanisms and effects on bone remodelling, are capable of mitigating and/or repairing the physiopathological changes which osteoporosis induces in the determinants of bone resistance.

Among these, and depending on the mechanism or type of action which they exert on remodelling, the determinants of resistance and their effector cells, are found the anticatabolics or antiresorptives and the anabolics or bone formers. Whilst the first [oestrogens, modulators of the oestrogen receptors (SERMs), calcitonin and biphosphonates] are characterized as being capable of reducing accelerated bone remodelling by reducing the number of newly activated basic multicellular units (BMU) and the level of their osteoclastic activity, the second type (PTH 1-34 and PTH 1-84) increase bone remodelling by increasing the number of newly activated BMUs and the level of their osteoblastic activity.

However, nowadays, in addition to these large groups of anti-osteoporotic drugs, a third group of medicines should be considered with a mixed anticatabolic-anabolic action mechanism, which in some way combine the effects of antiresorptive drugs with those which form bone.

Strontium ranelate (SR), an oral medicine active against osteoporosis, acts with this combined effect on bone metabolism, on the one hand diminishing resorption, while on the other, increasing bone formation, for which reason it is considered to be a dual action bone agent.

Action mechanism
One of the most significant characteristics recently discovered concerning the action mechanism of SR seems to indicate that this medicine stimulates the receptor sensitive to calcium (CaSR) expressed in the osteoblasts, thus inducing in them the production of inositol 1,4,5-triphosphate and the activation of the mitogenic protein-kinase signalling pathway, a situation which promotes cellular proliferation. Experiments carried out with rats with a genetic absence of CaRS, have also been able to demonstrate the involvement of different CaRS receptors in the stimulatory effect of SR on the replication of the pre-osteoblasts.

However, in addition to this action, recent data indicates that SR can also activate osteoprotegerin (OPG), a cytokine which impedes the conversion of macrophages into osteoclasts. This activation of OPG reduces the expression of the ligand bound to the receptor activator of nuclear kappa B factor.
(RANK-L), the trans-membrane receptor implicated in the differentiation and maturation of the osteoclasts, so suggesting that SR can reduce bone resorption by modulating the RANK/RANK-L/OPG system, essential for osteoclastogenesis11.

Even more recently, through the cultivation of specific cell lines, the role that SR plays in the differentiation of the osteoblasts and osteoclasts has become clearer. For example, Bonnelye and collaborators have shown that SR stimulates the differentiation of the osteoblasts and the formation of bone nodules already from the 5th day of culture, whilst in the control cultures this does not happen until at least 22 days have passed. At the same time the authors show that in cultures of osteoclasts SR achieves a diminution in cellular differentiation in a dose-dependent way, resulting, with this drug, in a lower number of cells than in the controls at 8 days of cultivation. In addition to this diminution, its resorptive action on the osteoid matrix also appears to reduce in a dose-dependent way11.

All these characteristics of the action mechanism of SR, mediated therefore through a series of effects on the osteoblasts (stimulation of the differentiation of the pro-osteoblasts, increase in the proliferation of osteoblasts, increase in osteoblastic activity and increase in the synthesis of the bone matrix) and on the osteoclasts (inhibition of cellular differentiation, reduction in osteoclastic resorptive activity and increase in osteoclast apoptosis)3 rebalancing bone turnover in favour of bone formation, a situation which results analytically in statistically significant increases in the markers for bone formation (bone alkaline phosphatase) and decreases, also significant, in markers for resorption (C-telopeptide), while quantitatively this is characterised by increases in bone mineral density (BMD) and qualitatively by an improvement in the structural and material properties of bone11.

Effects of SR on bone quantity
The effects of SR on the quantity of bone, have been testified to in different preclinical and clinical studies.

In experimental animals (female rats), and in a dose dependent way (225, 450 and 900 mg/kg/day), treatment over 2 years with SR increased significantly (p<0.05), BMD in the lumbar spinal column and femoral neck9.

In clinical trials in humans, SR has also demonstrated a significant increase in BMD, both in the lumbar spinal column and in the femoral neck, statistically significant increases even after adjusting the mineral density due to the content and molecular weight of strontium. This adjustment was considered necessary since, due to the homogeneous distribution of this element in bone and its greater absorption of X rays, the values of BMD obtained by means of dual photon densitometry become magnified by at least 50%10.

In the SOTI (Spinal Osteoporosis Therapeutic International) study, a clinical trial, phase III, in which 1,649 postmenopausal women over 50 years of age with osteoporosis (BMD of lumbar spinal column ≤ 0.84 g/cm²) and at least one vertebral fracture, SR at a dose of 2 g/day over 3 years, participated, there was a significant increase (p<0.001 in comparison with the placebo) in the non-adjusted BMD in the lumbar spinal column (DBMD: 14.4%), in the femoral neck (DBMD: 8.3%) and in the whole hip (DBMD: 9.8%)10.

The TROPOS (Treatment of Peripheral Osteoporosis) study, a clinical trial in which the anti-non-vertebral fracture effect of the administration of 2 g/day of SR in osteoporotic women (BMD <-2.5 DE) older than 73 years, or between 70 and 74 years old with an additional risk factor was evaluated, found at three years of treatment an increase in non-adjusted BMD with respect to the placebo both in the spinal column (DBMD: 14.7%) and in the total hip (DBMD: 8.2%) (adjusted DBMD in LV: 4.1%; adjusted DBMD in FN: 4.9%).

A prolongation of the same study has shown that at 5 years of treatment SR maintains to a statistically significant extent its positive effect on BMD both in the femoral neck (DBMD: 1.8%) and in the total hip (DBMD: 2%)10.

Effects of SR on bone quality
SR has shown equally, in different animal experimentation models and in clinical studies in humans, its capacity to improve all hierarchical levels of bone, the structural characteristics and the material properties, contributing in such a way as to the augment its resistance and, as such, to reducing the risk of fractures16.

SR and structural properties
At the macrostructural level, SR has shown itself capable of increasing the cortical thickness and the area of transversal section of osteoporotic bone, both in experimental animals10 and in humans10.

Thus, recently Briot and collaborators analysed, using Hip Structural or Strength Analysis (HSA), the proximal extremity of the femur of 483 women with postmenopausal osteoporosis (BMD ≤ -2.6 DE) and with an average age of 75.9 years, all of whom were part of the prolongation to 5 years of the TROPOS study. The authors showed that, as opposed to the controls, in patients treated with SR, a significant decrease in the endocortical diameter (ØEC) and significant increases in cortical thickness (CTh), of the area of transversal section (AST), of the moment of inertia of the transversal section (MI), of the area of transversal section of osteoporotic bone, both in experimental animals10 and in humans10.

At the microstructural level, various animal experimentation studies have demonstrated that SR improves to a significant degree the trabecular microarchitecture. Thus, Ammann and collaborators, in intact rats, have shown through histomorphometry of the proximal tibia, that the adminis-
tration of SR over 2 years has a favourable effect on the trabecular and cortical microarchitecture, inducing a significant increase in bone volume (BV/TV), and in the number (TbN) and the thickness of the trabeculae (TbTh), without it implying a significant increase in the thickness of the osteoid, which appears to indicate a neutral effect of the molecule on bone mineralisation. Equally, in their study the authors showed that due to these microarchitectural changes the biomechanical resistance of the vertebral bodies and of the femur of the rats increased significantly with respect to the controls14.

The same group of authors showed in ovariectomised rats (the model which most simulates postmenopausal osteoporosis) that the administration of SR mitigates the physiopathological changes induced by an accelerated bone remodelling, preserving both the bone mass and the microarchitectural properties of the bone20.

Very recently, Cattani-Lorentea and collaborators evaluated, by means of computerised microtomography (µ-TC), standard biomechanical trials and techniques of nanoindentation, the capacity of SR, administered in an isolated form or in association with alendronate or PTH, to improve the intrinsic quality of newly-formed bone in intact or ovariectomised rats. After 8 weeks of treatment, the authors found that while the SR-alendronate association was exclusively capable of preserving the bone microstructure, augmenting maximum bone resistance only comparatively with the group of ovariectomised rats, the SR-PTH association was able to increase significantly bone volume (BV/TV) and the thickness of the trabeculae (TbTh), increasing significantly the maximum bone resistance in both intact and ovariectomised rats, at levels also above those obtained with the administration of PTH alone21.

In humans, different types of studies have also been carried out which ratify the favourable effects of this molecule on the microarchitecture of osteoporotic bone.

Arlot and collaborators, in an analysis carried out by µ-TC of trans-iliac biopsies obtained after three years of treatment with SR, found significant changes in trabecular architecture resulting in the treated group in an increase in cortical thickness (DCTh: 18%) and in the number of trabeculae (DTbN: 14%), as well as significantly lower intertrabecular separation (DTbSp: -18%), or, which is the same, a higher trabecular connectivity22, changes noted previously with the same technique by other authors in isolated biopsies of patients participating in randomised double blind clinical trials with SR23.

However, in addition, in Arlot’s study the administration of this drug induced a significant change in the proportions between trabeculae with plaque forms and those with rod forms (DSMI: -22%), which indicates clearly a structural and biomechanical improvement in the trabecular tissue (Figure 1). All these data bring the authors to the conclusion that the decline in the rate of vertebral and non-vertebral fracture experienced by those osteoporotic patients treated with SR is intimately related to an improvement in the microstructural characteristics of the bone22,23.

Very recently, Rizzoli and collaborators, in 88 women with postmenopausal osteoporosis (aged 63.7 ± 7.4 years and T-score in CL and CT: -2.7 ± 0.9 and -2.0 ± 0.8, respectively), compared directly through high resolution peripheral computerised tomography (CTp-AR, XtremCT® Scanco...
Medical) the effects on the microarchitecture of the distal extremity of the tibia induced by 2 g per day of SR or 70 mg per week of alendronate. After one year of treatment, and in comparison with baseline values, SR increased significantly the cortical thickness (DCTh: 5.3%; p<0.001), while in those patients treated with alendronate no significant increase was noted (p= 0.045). In addition, in the group treated with SR significant increases in bone volume (DBV/TV: 2.0%; p= 0.002) and trabecular density (DTb Dens: 2.1%; p= 0.002) were found, while in the alendronate group no significant variations were found (p= 0.725 y p= 0.645, respectively)²⁴ (Table 2).

### SR and material properties

From the point of view of the material properties of bone, SR has been shown in different studies, both experimental and clinical, to be capable of preserving the degree of bone mineralisation and the crystalline characteristics of bone.

Farlay and collaborators, through microanalysis of X-ray diffraction and quantitative microradiographs evaluated in cynomolgus monkeys the effect which SR, at doses of 200-1,250 mg/day, had on bone mineralisation and the physical characteristics of the hydroxyapatite crystals, showing that after 52 weeks of treatment with strontium they are deposited in the cortical and trabecular bone in a dose-dependent way, distributed uniformly in all the bone tissue, already in the remodelling or quiescent phase. In the study, both the characteristics of the crystals, and the average degree of bone mineralisation and index of heterogenicity of the distribution of strontium resulted in being similar to those animals in the control group²⁵.

Very recently, Boivin and collaborators, analysed through the same techniques the deposition of strontium, its focus of distribution and the degree of bone mineralisation in biopsies from patients with postmenopausal osteoporosis treated with SR over more than 3 years, all women, pertaining to phase II or III of the clinical trials. In all the biopsies the total strontium contented was also evaluated. In addition, in some of the cases, the general distribution of strontium in the whole sample was analysed, by means of X-ray cartography, to calculate the percentage of bone surface which contained this element. The authors found that, in a dose-dependent way, the strontium was deposited exclusively in bone newly-formed during the period of treatment, so that a greater concentration was found in the new UBM than in the old, even after 3 years of treatment with the drug. In this study the total content of strontium in the bone reached a plateau at 3 years of treatment with the drug, which for the authors showed that the strontium does not substitute for calcium ions, but that it is absorbed in the bone mineral surface. The cartographic analysis of the samples showed that the bone formation activity during the treatment with SR was greater in the trabecular bone than in the cortical, the degree of bone mineralisation remaining homogeneous during the period of treatment. The authors conclude that due to all these characteristics SR is an efficacious and safe drug from the point of view of bone material quality²⁶.

| Table 1. SR and HSA (Modified by Briot et al. 2009) |
|----------------|----------------|----------------|
| HSA           | SR (n= 251)    | Placebo (n= 232) | Value | p   |
| CTh           | 10,27 ± 11,57  | -4,02 ± 9,33    | < 0,001 |
| ØEC           | -1,93 ± 3,19   | 0,01 ± 3,59     | < 0,001 |
| AST           | 9,05 ± 10,65   | -4,06 ± 8,82    | < 0,001 |
| MIST          | 8,60 ± 14,06   | -4,81 ± 14,63   | < 0,001 |
| MS            | 11,07 ± 14,03  | -4,72 ± 14,77   | < 0,001 |
| Rate          | -10,32 ± 10,08 | 5,93 ± 22,00    | < 0,001 |

| Table 2. SR vs Alendronate in women with postmenopausal osteoporosis (Modified by Rizzoli et al. 2009) |
|----------------|----------------|----------------|
|               | Strontium ranelate | Alendronate                  | #         |
|               | Average | DE     | Average | DE     | considered | 95% CI       |
| Tb. N (N/mm)  | 4,2     | 3,2    | 4,3     | 10,7   | 0,05       | (-4,0;4,2)   |
| Tb. Sp (mm)   | -3,7    | 8,3    | -3,1    | 9,8    | -0,65      | (-4,6;3,3)   |
| C. Th (mm)    | 5,3     | 10     | 1,3     | 6,0    | 3,9        | (0,1;7,7)    |
| Tb. Th        | -1,6    | 8,6    | -2,8    | 8,3    | 1,2        | (-2,6;5,0)   |
| BV/TV         | 2,0     | 5,3    | 0,6     | 3,6    | 1,7        | (0,0;3,3)    |
| Tb. Dens      | 2,1     | 5,2    | 0,6     | 3,8    | 1,8        | (0,1;3,4)    |
| Cort. Dens    | 1,1     | 2,7    | 0,5     | 2,0    | 0,6        | (-0,4;1,7)   |
Effects of SR on bone resistance
In addition to the stated effects of SR on the structural and material properties of bone, the improvement in bone quality which SR can induce in bone resistance has been underlined in different studies and through different types of biomechanical tests.

In animal experimentation models (female rats), treatment over 2 years with SR increased significantly compared to controls (p<0.05) total bone resistance measured both with techniques of biomechanical resistance to vertebral compression (DRO: 20%) and in flexion tests at three points of the femoral diaphysis (DRO: 14%), this increase in the final force of fracture is directly (r= 0.739) and significantly (p<0.0001) related to the increases achieved in DMO14.

Recently Ammann and collaborators, using nanoindentation techniques, showed a significant increase in the elasticity, the toughness, and the capacity to dissipate energy of impact in the trabecular and cortical bony nodes of the vertebrae of rats treated for 104 weeks with different daily doses of SR. For the authors, these results showed for the first time the direct action of SR on the biomechanical quality of bone tissue. This increase in bone resistance induced by SR was responsible finally for the reduction in the risk of fracture in women with menopausal osteoporosis treated with SR15.

Conclusions
SR, a dual action drug capable of dissociating remodelled bone, rebalancing it towards bone formation, acts at the level of each and every one of the determinants of bone resistance, increasing significantly and promptly BMD, improving qualitatively the structure of cortical and trabecular bone, and preserving mineralisation, the size and structure of the mineral crystals, even at high doses. Thus SR, by improving significantly the biomechanical properties of bone, reduces significantly the risk of fractures in women with postmenopausal osteoporosis.

Bibliography
