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## Bazedoxifene, the 3rd generation SERM for the treatment of postmenopausal osteoporosis

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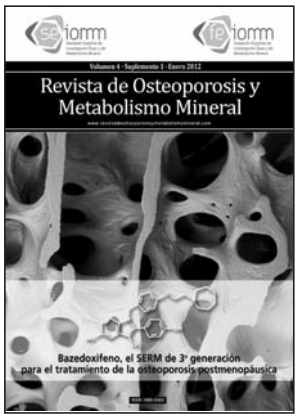


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# SUMMARY

**Vol. 4 (Supl 1) January 2012**

**5** **Bazedoxifen and osteoporosis: systematic review**
Gómez de Tejada Romero MJ, Corral-Gudino L

**17** **Cost of postmenopausal osteoporosis**
Del Pino Montes J

**23** **Role of bazedoxifen in the treatment of postmenopausal osteoporosis**
Sosa Henríquez M, Cancelo Hidalgo MJ

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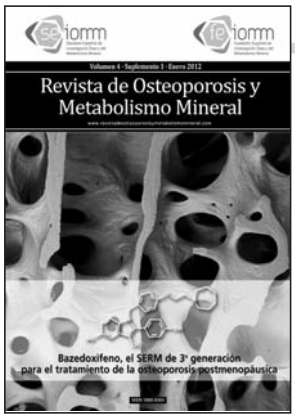


**Vol. 4 (Supl 1) January 2012**

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# Bazedoxifene and osteoporosis: systematic review

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## Summary

History: Osteoporosis is characterised by a deterioration in bone microarchitecture which puts the bone at risk of suffering fractures. Bazedoxifene is a third generation selective estrogen receptor modulator which has been approved for the treatment of postmenopausal osteoporosis.
Objectives: To evaluate the efficacy of bazedoxifene in the primary and secondary prevention of osteoporotic fractures in postmenopausal women.
Search strategy: Searches were carried out on MEDLINE, Cochrane Central, registers of clinical trials and books of summaries to find random controlled trials published between 2000 and 2011.
Selection criteria: Randomised clinical trials aimed both at the primary and secondary prevention of osteoporosis were selected. Studies were chosen which compared women who received bazedoxifene with those given other drugs for osteoporosis or a placebo.
Compilation and data analysis: The selection of studies and the extraction of data was carried out by two researchers working together. A meta-analysis of the results of fracture and the secondary effects was carried out, establishing the relative risk. The quality of the studies was evaluated on the basis of the criteria proposed by the Cochrane collaboration.
Principal results: Five trials were included in the review (13,543 patients): 3 were concerned with primary prevention (5,622) and two with secondary prevention (7,921). Only those studies of secondary prevention evaluated the fractures as principal objective.
Compared with the placebo bazedoxifene reduced the number of new vertebral fractures detected in the follow up at three years in women with osteoporosis: with a dose of 20 mg the number of patients necessary to treat (NNT) was 56 (CI 95%, 34-146), and at a dose of 40 mg the NNT was 63 (CI 95%, 37-231). In the meta-analysis the relative risk compared with the placebo was 0.59 (CI 95%, 0.44-0.79). There was no difference in the number of symptomatic vertebral fractures or in the number of non-vertebral fractures in the analyses predicted at the start of the study. We found no data on the effect of bazedoxifene on the number of fractures in primary prophylaxis.
For the adverse effects, the meta-analysis did not confirm an increase in the risk of deep vein thrombosis which was seen in the reference study (RR: 8.53). There was an increase in episodes of hot flushes (RR:1.88) or muscular cramps (RR:1.32). No reduction in the incidence of breast cancer was observed, nor in endometrial cancer or endometrial hyperplasia with treatment with bazedoxifene compared with the placebo.
Authors' conclusions: Bazedoxifene is an efficacious drug in the reduction in the risk of asymptomatic vertebral fractures in primary prophylaxis. In addition, it has been shown to reduce the loss of bone mineral density and to slow bone remodelling in the primary and secondary prevention of osteoporosis. New studies which analyse the risk of non-vertebral fractures and compare the drug with others in the first line of treatment of osteoporosis are necessary in order to understand the true power of their antifractural effect.

**Key words:** *Osteoporosis. Bone fractures. Selective estrogen receptor modulators. Primary prevention. Secondary prevention.*

## Introduction

Osteoporosis (OP) is characterised by a deterioration in bone microarchitecture such that it puts the bone at high risk of fractures[1]. In the absence of curative treatment, up until now therapeutic efforts have been aimed at reducing this risk of fracture by improving the quality and quantity of bone tissue.

Various drugs are being used to this purpose. The objective is to act on bone remodelling with an antiresorptive (such as the biphosphonates, calcitonin) or osteoformative (teriparatide and PTH 1-84) action, or both (strontium ranelate).

The SERMs (selective estrogen receptor modulators) are drugs which have an estrogen agonist/antagonist action depending on the type of hormonal receptors present in each tissue. Their investigation began with the search for a substance with anti-estrogenic action for the prevention and treatment of breast cancer, tamoxifen, which, it was shown, produced an estrogen agonist effect in bone tissue. However, in spite of increasing bone mineral density (BMD)[2], it did not reduce the risk of fractures[3]. In addition, its stimulant action on the endometrium limited its clinical use in OP. Additional advances in molecular biology and pharmacology identified a new compound in this group, raloxifene, considered, therefore, to be a second generation SERM. Its action is estrogen agonist in acting on the receptors of the bone tissue, reducing the resorption favoured by the lack of that hormone (falling within, therefore, the group of drugs with an antiresorptive action), having been demonstrated to increase BMD and reduce the risk of vertebral fractures[4], but not with non-vertebral fractures[5]. It also exerts this agonist action in the mammary tissue, which is why it is associated with a significant decrease in estrogen-dependent breast cancer[6]. It improves the lipid profile by reducing blood levels of cholesterol, this being another agonist action[7]. As an antagonist action, endometrial stimulation does not result[7], all of which allows its use in the treatment of postmenopausal OP. However, it has adverse effects, such as an increase in the risk of thromboembolism and leg cramps[8], which limit its use. Although it improves the lipid profile, it not been shown to reduce the risk of cardiovascular events[9], and is associated with an increase in the vasomotor symptoms of the menopause (breathlessness, flushes, etc)[8].

In recent years new compounds have been investigated within the SERM group which may be an improvement on raloxifene: these are what are called the third generation SERMs. Two of these, bazedoxifene[10] and lasofoxifene[11] have been approved for treatment of postmenopausal OP.

In this work we have carried out a systematic review focusing on those articles published and carried out with bazedoxifene (BZD) for the treatment of postmenopausal OP concerning its tolerance and safety.

The main objective was the evaluation of the efficacy of BZD for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. As secondary objectives its effects on bone mineral density (BMD), the markers for bone remodelling (MBR) and data on the tolerance and safety of the drug were evaluated.

## Material and method

The objective of the systematic review was to evaluate the efficacy of BZD in the prevention of new vertebral or non-vertebral fractures in postmenopausal women with or without OP.

The review was carried out in accordance with the PRISMA consensus guidelines for systematic reviews and meta-analyses[12].

### Selection criteria

Randomised clinical trials were selected which included postmenopausal women. The inclusion was accepted of those trials aimed at both primary and secondary prevention. A comparison was made between groups treated with BZD at any dose and with other drugs for the treatment of OP (biphosphonates, parathyroid hormone, SERM or strontium ranelate) or a placebo. If calcium or vitamin D were used it would have to have been administered to all the treatment groups being compared. As the most appropriate metric for the measurement of the efficacy of the drug, the incidence of vertebral and non-vertebral fractures was evaluated. Changes in levels of BMD and in the MBRs were evaluated as additional results.

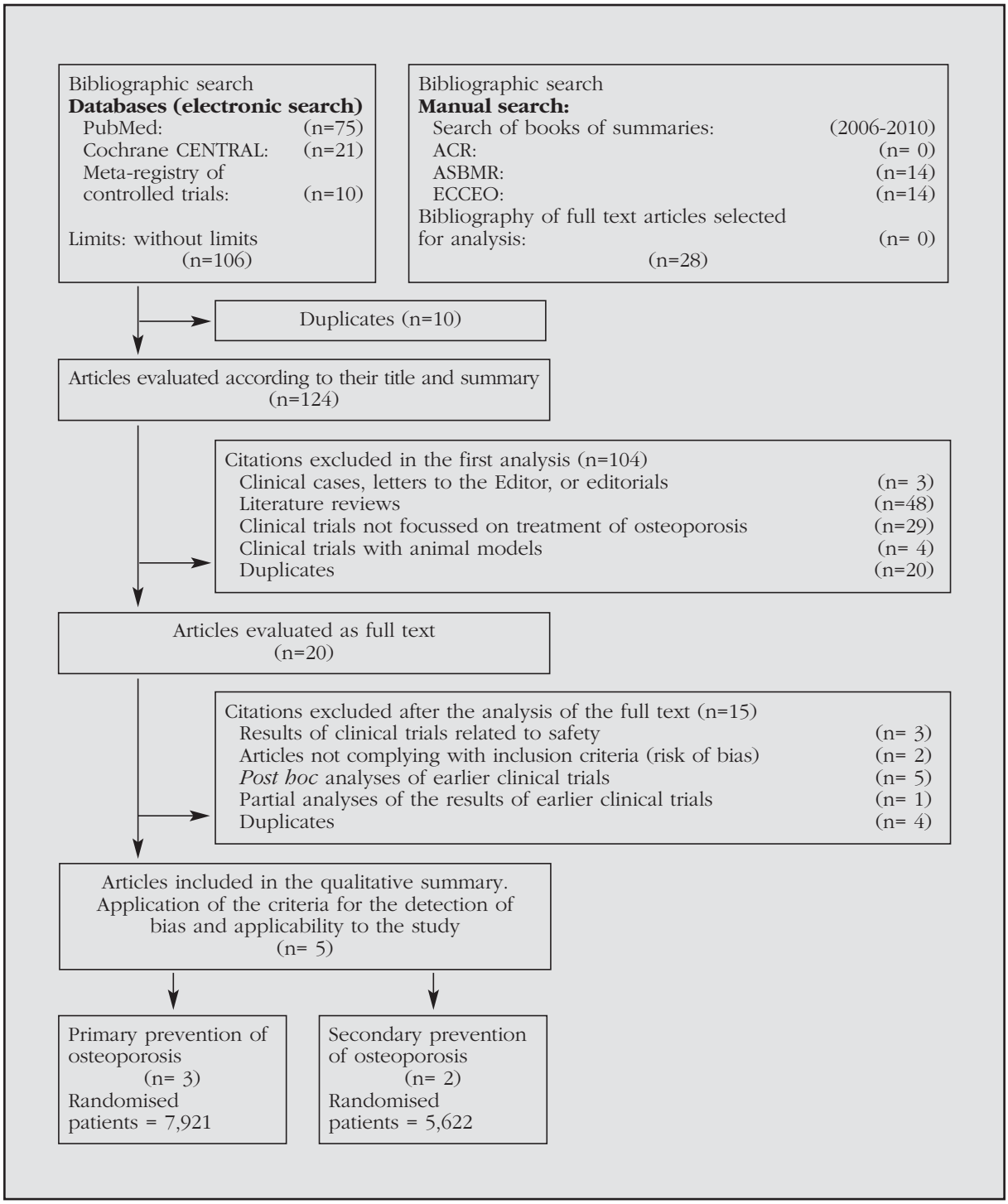
### Information sources

The studies were identified by means of a search of the PubMed MEDLINE database (January 2006 to June 20011). No language limits were used. The following search strategy was used: (("osteoporosis, postmenopausal" [MeSH Terms] OR ("osteoporosis" [All Fields] AND "postmenopausal" [All Fields]) OR "postmenopausal osteoporosis" [All Fields] OR "osteoporosis" [All Fields] OR "osteoporosis" [MeSH Terms]) OR ("bone density" [MeSH Terms] OR ("bone" [All Fields] AND "density" [All Fields]) OR "bone density" [All Fields])) AND ("bazedoxifene acetate" [Supplementary Concept] OR "bazedoxifene acetate" [All Fields] OR "bazedoxifene" [All Fields]). Additional studies were found through a search in Cochrane Central and in records of clinical trials (http://www.controlled-trials.com/mrct/) with the term “bazedoxifene”. Lastly, the search was widened to summaries presented at conferences most relevant to the field of osteoporosis: the American Society for Bone and Mineral Research (ASBMR), the European Congress on Osteoporosis and Osteoarthritis (ECCEO), the International Osteoporosis Foundation (IOF) and the American College of Rheumatology (ACR). The period of publication was limited to the period from 2006 to July 2011. The final search of the different sources was carried out on the 21st June 2011.

### Selection of studies

Two reviewers (MJ.G.T.R and L.C.G) examined each title and summary generated by the search and identified those articles which were potentially eligible, which were then obtained in full text.

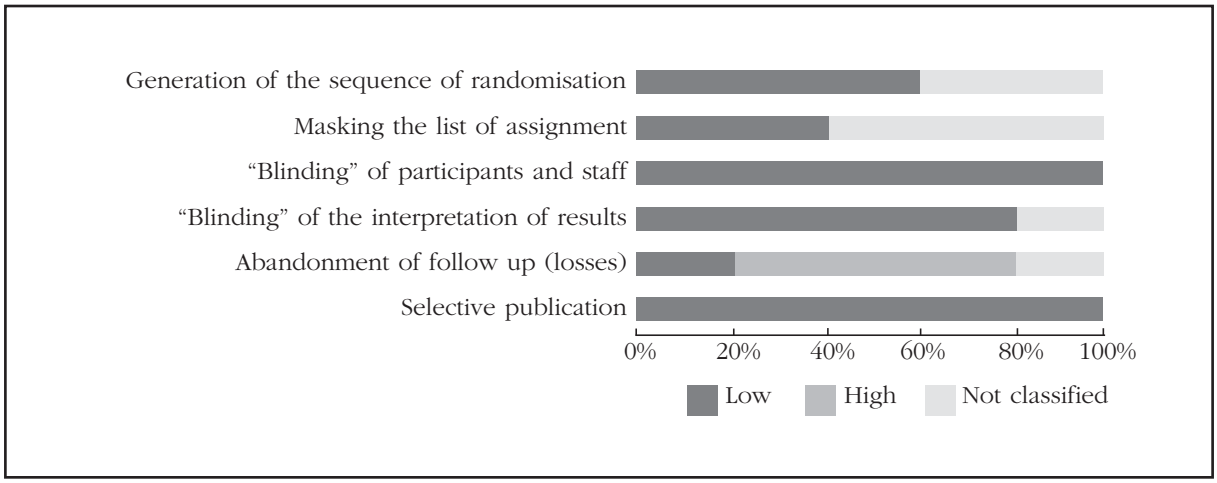
Figure 1. Flow diagram for the selection of articles




Strategy for quality evaluation

The methodological validity of the articles finally selected was evaluated in accordance with the list of questions proposed in the Cochrane collaboration manual, version 5.1.0[13]. This evaluation consists of the detection of six types of bias: selection (bias due to defects in the generation of the sequence of randomisation and masking of the assignment list), trial performance (bias due to defects in the blinding of the participants in the study and of the health personnel treating them), detection (bias due to defects in the blinding of the evaluation of the results), abandonment or attrition (bias due to the presentation of incomplete results) and information (bias due to selective publication of results). Two reviewers (MJ.G.T.R. and L.C.G) evaluated the quality of each eligible clinical trial, having to indicate whether the risk of bias was high, low, or not possible to evaluate, in accordance with the methodological criteria proposed.

Figure 2. Evaluation of risk of bias in the selected articles




Collection and analysis of data

Two reviewers (MJ.G.T.R. and L.C.G) tabulated the information and data. A summary was created which included information on the methodological aspects of the design of the studies, the characteristics of the participants and the results evaluated (fractures, BMD, MBR, adverse or secondary effects). For the fracture data, all those of which the researchers were informed were considered (whether symptomatic or detected through radiology).

For the results referring to the variation in the incidence of new fractures the necessary number of patients to treat was calculated as well as its confidence interval at 95%. In cases in which when calculating the confidence interval one of the extremes had a negative value, only the lower limit of the confidence interval was established with the positive value calculated[14].

A meta-analysis was carried out of the most significant results using the Review Manager software programme (RevMan) version 5.1, developed by the Nordic Cochrane centre (Copenhagen), of the Cochrane collaboration, 2011. For the results regarding fractures or changes in BMD or in the MBRs, the grouping of the data from postmenopausal patients with OP (secondary prevention) with those of the patients without OP (primary prevention) was not permitted in the meta-analysis. This was due to the fact that it was assumed that the percentages of fractures or the values of bone markers or of mineral density before inclusion in the study would differ between the two groups of women. But the joint meta-analysis of women with or without menopause for drug-related secondary effects was permitted. It was assumed that the presence or absence of OP would not influence those secondary effects derived from the selective blocking of estrogen receptors.

## Results

134 articles were found in the systematic literature search. The process of their analysis and selection is described in figure 1. Five articles were selected: one phase 2 clinical trial 15 and four in phase 3[10,16-18] sponsored by Wyeth (Pfizer). Four of the articles compared BZD[10,15-17] and the other a combination of BZD and estrogens combined (EC)[18]. Three of the articles evaluated the effect in postmenopausal women without OP but with risk factors for its development (primary prevention)[16-18]. In these three studies, the principal results studied were changes in BMD in the lumbar spine. The other two articles[10,15] included women with OP (secondary prevention) and in both, the number of new vertebral fractures was evaluated, in the second as the main result and in the first as a secondary result. The numbers of symptomatic vertebral fractures and of non-vertebral fractures were evaluated in both studies as secondary results. A more detailed study of other characteristics of the design of the studies and of the participants in the clinical trials are given in tables 1 and 2. Apart from the original articles which detail the results in relation to OP, three of the clinical trials had published additional articles with results regarding safety[19-23]. In two of the clinical trials a sub-analysis was carried out of the results of the study regarding the seriousness[24,25] or the characteristics of the patients[26] (table 1). The reference study on fractures in secondary prevention was extended by two years[27,28]. In this prolongation, a complete arm of the study (raloxifene) was suspended.

Figure 2 shows the critical evaluation of the clinical trials according to the methodology proposed in the Cochrane collaboration manual. The item most penalised was that corresponding to the risk of bias due to attrition or loss of patients. This was due to the fact that the abandonment rate was very high (around 30% in the studies at 2 and 3 years), with significant differences in the motives for abandonment between the different groups in one of the studies[10,15].

Table 1. Characteristics of the studies included in the systematic review

| Nº of register (Denomination) | NCT00205777 | NCT00481169 | NCT00238745 | NCT00384072 | NCT00675688 (SMART 1) |
|---|---|---|---|---|---|
| Study design | Secondary prevention of osteoporosis | Primary prevention of osteoporosis | Secondary prevention of osteoporosis | Primary prevention of osteoporosis | Primary prevention of osteoporosis |
| Type of study | Randomised clinical trial | Randomised clinical trial | Randomised clinical trial | Randomised clinical trial | Randomised clinical trial |
| "Blinding" | Double blind | Double blind | Doble ciego | Double blind | Double blind |
| Phase of study | Phase 3 | Phase 3 | Phase 2 | Phase 3 | Phase 3 |
| Participating centres | 206 centres in countries in the regions of Asia-Pacific, Canada, Europe, Latin America, South Africa and the United States | 101 centres in Canada, Europe and the United States | 17 centres in Japan | Multicentric: China, South Korea and Taiwan | 94 centres in the United States, Europe and Brazil |
| Duration of study | 3 years | 2 years | 2 years | 6 months | 2 years |
| Treatment groups | 1. BZD 20 mg<br>2. BZD 40 mg<br>3. Raloxifene 60 mg<br>4. Placebo | 1. BZD 10 mg<br>2. BZD 20 mg<br>3. BZD 40 mg<br>4. Raloxifene 60 mg<br>5. Placebo | 1. BZD 20 mg<br>2. BZD 40 mg<br>3. Placebo | 1. BZD 20 mg<br>2. Placebo | 1. BZD 10 mg/EC 0.625 mg<br>2. BZD 10 mg/EC 0.45 mg<br>3. BZD 20 mg/EC 0.625 mg<br>4. BZD 20 mg/EC 0.45 mg<br>5. BZD 40 mg/EC 0.625 mg<br>6. BZD 40 mg/EC 0.45 mg<br>7. Raloxifene 60 mg<br>8. Placebo |
| Principal objective | New vertebral radiological fractures (D4 a L4) | Changes in BMD in the lumbar spine | Changes in BMD in the lumbar spine (L1-L4) | Changes in BMD in the lumbar spine | Changes in BMD in the lumbar spine |
| Secondary objectives | Symptomatic vertebral fractures.<br>Non-vertebral fractures.<br>Changes in BMD in the lumbar spine, femoral neck and hip.<br>Changes in MBR. | Changes in BMD in femoral neck, trochanter and hip.<br>Changes in MBR.<br>Variations in lipids. | Changes in BMD in femoral neck, trochanter and hip.<br>Changes in MBR.<br>Variations in lipids.<br>Vertebral or non-vertebral fractures. | Changes in BMD in femoral neck, trochanter and hip.<br>Changes in MBR.<br>Variations in lipids. | Changes in BMD in hip.<br>Cambios en MBR. |
| [Reference] publication | [10]Fracture results.<br>[19]Safety data. | [16]Results BMD.<br>[20]Reproductive tract data. | [15]Results BMD | [17]Results BMD | [18]Results BMD.<br>[22]Reproductive tract data.<br>[23]Menopause symptoms. |
| [Reference] Additional studies | [27]Extension to 5 years, safety data.<br>[28]Extension to 5 years, fracture results.<br>[24]High risk subgroup *post hoc* analysis.<br>[25]*Post hoc* analysis of BMD data and risk of fracture.<br>[21]Sub-study of reproductive tract safety. | [26]Sub-analysis of Afro-American women | Unpublished | Unpublished | Unpublished |

BZD: Bazedoxifene; BMD: Bone Mineral Density; EC: Combined Estrogens; MBT: Markers for Bone Turnover; SMART: Selective estrogen Menopause And Response to Therapy.

Fractures

Two studies analysed the number of new fractures in patients with OP[10,15]. In the reference study at 3 years[10], the number of new vertebral fractures detected in the radiological follow up at 3 years was lower in those patients who had received 20 mg BZD (NNT, 56; CI 95%, 34-146 patients) or 40 mg BZD (NNT, 63; CI 95%, 37-231 patients) than in those patients who received a placebo. There were no differences with the group which received 60 mg raloxifene (NNT, 56 patients in relation to the placebo; CI 95%, 35-158 patients). There were no differences between the four groups in the number of symptomatic vertebral fractures. The results were similar in the prolongation to 5 years of the original study[28]. In the study carried out in Japan[15] the difference between the rate of new vertebral fractures detected in the radiological follow up at 2 years did not reach statistical significant levels. The meta-analysis of both studies shows a reduction in the risk of vertebral radiological fractures for those groups in treatment with BZD (figure 3).

There were no statistically significant differences in either of the two studies when the numbers of non-vertebral fractures were compared (figure 4).

*Post hoc* studies were carried out on the reference study at 3 years[10] to attempt to define subgroups in which the treatment with BZD was most efficient in the prevention of new fractures. In the original article itself[10] there was a sub-study (24% of the patients initially randomised) selecting non-randomly those patients defined as high risk (femoral T-score ≤ -3 or the presence of at least one serious or moderate fracture or minor multiple fractures at the start of the study). This subgroup showed a reduction in non-vertebral fractures in the BZD group compared with raloxifene (NNT, 37; CI 95%, >16 patients) or a placebo (NNT, 29; CI 95%, >15 patients). The same authors, in the prolongation of the original study to 5 years[28], set up a subgroup of 4,216 patients, and, eliminating the branch treated with raloxifene, did not obtain a significant reduction in the appearance of new non-vertebral fractures in high risk patients treated with 20 mg f BZD (37%; p=0.06). In combining the data on both doses, a reduction of 34% ($p<0.05$) was observed. Kanis et al.[24] carried out a *post hoc* study on the whole sample applying the FRAX tool for the evaluation of the risk of fracture, excluding the branch of patients who took raloxifene. The risk reduction of BZD as opposed to a placebo achieved statistical significance for new vertebral fractures diagnosed in the radiological follow up above the 25th percentile of probability of osteoporotic fracture at 10 years, according to the FRAX scale. For symptomatic vertebral fractures this only reached statistical significance above the 75th percentile.

Bone mineral density

The five studies selected provided data regarding the variation in BMD in different locations (lumbar, hip, femoral neck, trochanter), which was favourable to the treatment groups (BZD, BZD/EC or raloxifene) as against a placebo in all cases (see tables 3 and 4). No differences were found when comparing different doses of BZD. Statistically significant differences were found between BZD and raloxifene in the values of BMD in the hip, in favour of raloxifene in one study[10] and, on the contrary, in favour of BZD as against raloxifene in the values of BMD in the lumbar region in some of the treatment groups in the study of the BZD/EC combination (table 4)[18]. The study by Miller et al.[16] did not find differences in the changes in BMD produced by BZD (20 mg and 40 mg) and raloxifene in either of the locations (lumbar and proximal femur).

Makers for bone remodelling

The five studies selected[10,15-18] showed data on the variation in the parameters for bone formation (osteocalcin) and resorption (C-telopeptide). One study[15] analysed also the variations on N-telopeptide in blood and in urine. The results were favourable to the treatment groups (BZD, BZD/EC or raloxifene) as against the placebo in all cases. In the comparison of BZD/EC with raloxifene[18] the majority of the treatment combinations were superior to raloxifene. There were no differences in the rest of the studies in the comparison of BZD with raloxifene.

Lipid profile

Three studies[15-17] analysed the changes in lipid profile. All of these showed a statistically significant reduction in total cholesterol and in LDL cholesterol in the treatment groups (BZD or raloxifene). Some of the studies showed a statistically significant increase in HDL cholesterol in the groups treated with 10 mg and 20 mg of BZD[16]. In another, the values of lipoprotein (a) was reduced to a statistically significant extent in the groups treated with 20 mg and 40 mg of BZD[15].

Adverse effects

Four studies included results regarding the safety of the drug in the original article[15-17,19]. The analysis of four articles highlighted three most significant and frequent adverse effects in the groups in treatment with BZD: a) episodes of deep vein thrombosis (DVT), with a statistically significant difference in relation to the use of BZD in the study which included the greatest number of patients and the longest follow up period[10], but which was not confirmed in the rest of the studies, nor in the meta-analysis (figure 5). The BZD/EC combination did not have a greater frequency of episodes of DVT[23]; b) the presence of vasodilation and flushing (figure 6); and c) leg cramps (figure 7). In the meta-analysis the last two had a higher risk of occurrence in the group in treatment with BZD as against the placebo. The comparison of the three adverse effects with the raloxifene group had no significant differences[10]. In the case of vasodilation/flushing the combination of BZD and EC reduced the number of episodes compared with the placebo[23].

Table 2. Characteristics of patients included in the studies

| Nº of register (Denomination) | NCT00205777 | NCT00481169 | NCT00238745 | NCT00384072 | NCT00675688 (SMART 1) |
|---|---|---|---|---|---|
| Inclusion criteria | Postmenopausal women between 55 and 85 years of age. BMD T-score of -2.5 to -4 or patients with fractures and T-score <-4. | Postmenopausal (>1 year) women >45 years of age BMD T-score of -1 to -2.5 and ≥1 risk factor for osteoporosis. | Postmenopausal women <85 years with intact uterus. Value of BMD in the lumbar region <70% of the average for Young adults or <80% in patients with non-traumatic fractures. | Postmenopausal (>1 year) women >45 years BMD T-score of -1 to -2.5 and ≥1 risk factor for osteoporosis. | Postmenopausal women of 40 to 75 years, with intact uterus, BMI ≤ 32 kg/m². BMD T-score from -1 to -2.5 and 1 risk factor for osteoporosis. Sub-study 1; > 5 years men. Sub-study 2; 1-5 years men. |
| Exclusion criteria | Bone diseases which alter bone metabolism. Changes which affect the measurement of BMD, pathological vertebral fractures or serious diseases. Women with thromboembolic disease. Having received treatment in the previous 6 months with androgens, estrogens, progesterone, biphosphonates, PTH, SERMs, calcitonin or colecalciferol. | Bone diseases which alter calcium metabolism. Alterations which affect the measurement of BMD, at least one osteoporotic fracture, breast cancer, thromboembolic disease, BMI >32 kg/m², endometrial hyperplasia. Having received treatment between 6 months and two years previously with biphosphonates, PTH, SERM, calcitonin or corticoids. | Diseases which may cause secondary osteoporosis, bone diseases. Alterations which affect the measurement of BMD. ≥6 vertebral fractures or ≥2 lumbar fractures. Endometrial hyperplasia. Endocrine and thromboembolic diseases, laboratory changes. Having received previous treatment with vitamin D, vitamin K, biphosphonates, PTH, SERMs, calcitonin or corticoids. | Bone disease which alter calcium metabolism. Alterations which affect measurement of BMD, at least one osteoporotic fracture, breast cancer, thromboembolic disease, BMI >32 kg/m², endometrial hyperplasia. | History or presence of estrogens dependent neoplasm, thromboembolic disease, CVD, IscC, some types of neoplasms. |
| Number of participants | Examined: 26,749<br>Randomized: 7,492 | Examined: Not listed<br>Randomized: 1,583 | Examined: 808<br>Randomized: 429 | Examined: 950<br>Randomized: 495 | Examined: 10,511<br>Randomized: 3,544<br>Sub-study 1: 1,454<br>Sub-study 2: 861 |
| Dropouts | BZD 20 mg: 34%<br>BZD 40 mg: 34%<br>Raloxifene 60 mg: 32%<br>Placebo: 33% | BZD 10 mg: 32%<br>BZD 20 mg: 30%<br>BZD 40 mg: 30%<br>Raloxifene 60 mg: 28%<br>Placebo: 27% | BZD 20 mg: 27%<br>BZD 40 mg: 23%<br>Placebo: 31% | BZD 20 mg: 7.7%<br>Placebo: 7.5% | Do not figure in the article. |

BZD: Bazedoxifene; IscC: Ischemic Cardiopathy; BMD: Bone Mineral Density; CVD: Cerebral Vascular Disease; BMI: Body Mass Index; men: menopause; SERM: selective estrogen modulator receptors; PTH: Parathyroid Hormone. SMART: Selective estrogen Menopause And Response to Therapy.

Table 3. Changes in bone mineral density. Trials which use bazedoxifene (BZD)

| Reference | [10]¡ | | | | [16]¡¡ | | | | | [15]¡ | | | [17]¡ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Years of monitoring | 3 years | | | | 2 years | | | | | 2 years | | | 6 months | |
| Groups treatment | BZD 20 mg | BZD 40 mg | Ralox 60 mg | Placebo | BZD 10 mg | BZD 20 mg | BZD 40 mg | Ralox 60 mg | Placebo | BZD 20 mg | BZD 40 mg | Placebo | BZD 20 mg | Placebo |
| L1-L4 (%) | 2.21‡ | 2.38‡ | 2.96‡ | 0.88 | 1.08‡ | 1.41‡ | 1.49‡ | 1.49‡ | 0 | 2.43‡ | 2.74‡ | -0.65 | 0.41‡ | -0.32 |
| Total hip (%) | 0.27‡ | 0.50‡ | 0.90‡† | -0.83 | 1.29‡ | 1.75‡ | 1.60‡ | na | 0 | 1.10‡ | 0.93‡ | -0.97 | -0.03‡ | -0.77 |
| Femoral neck (%) | - | - | - | - | na | na | na | na | nd | 1.73‡ | 1.16‡ | -1.14 | -0.08‡ | -0.69 |
| Trochanter (%) | - | - | - | - | na | na | na | na | nd | 1.73‡ | 1.58‡ | -1.14 | 0.50‡ | -0.23 |

na: Not available in the text of the original article; Ralox: Raloxifene: ¡: Shows changes with respect to the values at the start of the study; ¡¡: Shows changes with respect to the values of the placebo group; ‡: Statistically significant differences in comparison with the placebo; †: Statistically significant differences in the comparison between BZD and raloxifene.

Table 4. Changes in bone mineral density in the lumbar region L1-L4 (%)

| Reference | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Years of monitoring | 2 años | | | | | | | |
| Groups treatment | EC 0.625 mg | EC 0.625 mg | EC 0.625 mg | EC 0.45 mg | EC 0.625 mg | EC 0.625 mg | | |
| Groups treatment | BZD 10 mg | BZD 20 mg | BZD 40 mg | BZD 10 mg | BZD 20 mg | BZD 40 mg | Ralox 60 mg | Placebo |
| >5 years of menopause | 1.49‡† | 1.04‡ | 0.57‡ | 1.59‡† | 0.94‡ | 0.51‡ | 0.79 | -1.08 |
| 1-5 years of menopause | 1.60‡† | 0.55‡ | 0.77‡† | 1.13‡† | 1.01‡† | 0.62‡ | -0.07 | -1.41 |

‡: Statistically significant differences in comparison with the placebo; †: Statistically significant differences in the comparison between BZD/EC and raloxifene; BZD: Bazedoxifene; EC: combined estrogens.

Other secondary effects were monitored in the cardiovascular area (myocardial infarction, retinal vein thrombosis or cerebral vascular disease), which showed no difference between BZD and placebo.

In terms of data on safety with respect to the female reproductive system, no reduction in the incidence of breast cancer was observed, nor any increase in endometrial cancer or endometrial hyperplasia with the BZD treatment as opposed to the placebo[15,17,19,20]. In the study of Christiansen et al. the incidence of the diagnosis of fibrocystitis of the breast was significantly higher in the raloxifene group than in the BZD group[10,19]. The combination of BZD and EC did not produce endometrial hyperplasia. With regard to the reference study at 3 years of secondary prevention of OP, a second clinical trial was registered with a sample of patients on whom had been carried out transvaginal ultrasound. This work showed that treatment with BZD had no effect on changes in endometrial thickness, on the incidence of hyperplasia or endometrial carcinoma, on the presence ovarian cysts or carcinoma, or on the number of episodes of uterine or vaginal haemorrhage.

## Discussion

At present, the primordial objective for understanding how efficacious a drug is in the treatment of OP is the reduction in the number of incident fractures. No drug has received this indication without having demonstrated such an efficacy. Of the clinical trials studied, only one had this analysis as its principal objective[10]. The remaining trials consisted of *post hoc* studies[24,25], or studies in which the incidence of fractures was a secondary objective (the primary objectives being changes in BMD and the MBRs)[15-17], or was simply not observed[18].

Figure 3. Meta-analysis regarding radiological vertebral fractures

| Study or Subgroup | BZD 20/40 mg Events | BZD 20/40 mg Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Itabashi 2011 | 8 | 283 | 6 | 142 | 7.7% | 0.67 (0.24, 1.89) |
| Silverman 2008 | 90 | 3758 | 77 | 1885 | 92.3% | 0.59 (0.43, 0.79) |
| **Total (95% CI)** | | **4041** | | **2027** | **100.0%** | **0.59 (0.44, 0.79)** |
| Total events | 98 | | 83 | | | |

Heterogeneity: Tau²=0.00; Chi²=0.06, df=1 (P=0.81); I²=0%
Test for overall effect: Z=3.57 (P=0.0004)

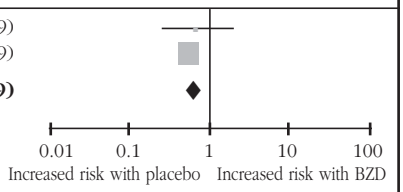



Figure 4. Meta-analysis regarding non-vertebral fractures

| Study or Subgroup | BZD 20/40 mg Events | BZD 20/40 mg Total | Placebo Events | Placebo Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Itabashi 2011 | 8 | 283 | 4 | 142 | 4.0% | 1.00 (0.31, 3.28) |
| Silverman 2008 | 174 | 3758 | 99 | 1885 | 96.0% | 0.88 (0.69, 1.12) |
| **Total (95% CI)** | | **4041** | | **2027** | **100.0%** | **0.89 (0.70, 1.12)** |
| Total events | 182 | | 103 | | | |

Heterogeneity: Tau²=0.00; Chi²=0.04, df=1 (P=0.83); I²=0%
Test for overall effect: Z=1.01 (P=0.31)

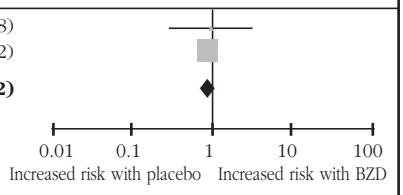



Figure 5. Meta-analysis regarding deep vein thrombosis

| Study or Subgroup | BZD 20/40 mg Events | BZD 20/40 mg Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Itabashi 2011 | 0 | 283 | 0 | 142 | | Not estimable |
| Miller 2008 | 2 | 633 | 1 | 310 | 45.7% | 0.98 (0.09, 10.76) |
| Silverman 2008 | 17 | 3758 | 1 | 1885 | 54.3% | 8.53 (1.14, 64.03) |
| Xu 2011 | 0 | 248 | 0 | 239 | | Not estimable |
| **Total (95% CI)** | | **4922** | | **2576** | **100.0%** | **3.17 (0.35, 28.63)** |
| Total events | 19 | | 2 | | | |

Heterogeneity: Tau²=1.26; Chi²=1.99, df=1 (P=0.16); I²=50%
Test for overall effect: Z=1.03 (P=0.30)

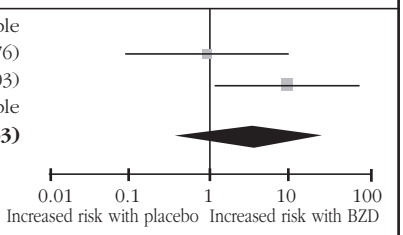



Figure 6. Meta-analysis regarding vasodilation/redness

| Study or Subgroup | BZD 20/40 mg Events | BZD 20/40 mg Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Itabashi 2011 | 6 | 283 | 2 | 142 | 1.0% | 1.51 (0.31, 7.36) |
| Miller 2008 | 144 | 633 | 44 | 310 | 26.9% | 1.60 (1.18, 2.18) |
| Silverman 2008 | 482 | 3758 | 119 | 1885 | 69.1% | 2.03 (1.68, 2,46) |
| Xu 2011 | 11 | 248 | 7 | 239 | 3.0% | 1.51 (0.60 3.84) |
| **Total (95% CI)** | | **4922** | | **2576** | **100.0%** | **1.88 (1.60, 2.21)** |
| Total events | 643 | | 172 | | | |

Heterogeneity: Tau²=0.00; Chi²=1.94, df=3 (P=0.59); I²=0%
Test for overall effect: Z=7.74 (P=0.00001)

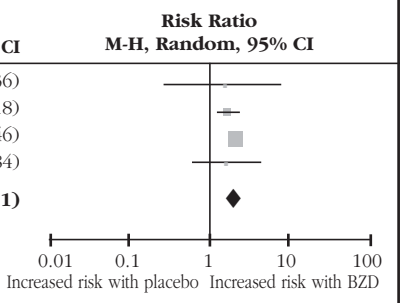
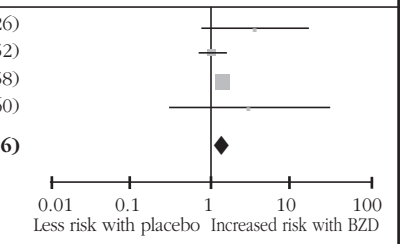



Figure 7. Meta-analysis regarding muscle cramps

| Study or Subgroup | BZD 20/40 mg Events | BZD 20/40 mg Total | Placebo Events | Placebo Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Itabashi 2011 | 13 | 283 | 2 | 142 | 1.8% | 3.26 (0.75, 14.26) |
| Miller 2008 | 77 | 633 | 36 | 310 | 24.7% | 1.05 (0.72, 1.52) |
| Silverman 2008 | 412 | 3758 | 156 | 1885 | 72.7% | 1.32 (1.11, 1.58) |
| Xu 2011 | 3 | 248 | 1 | 239 | 0.8% | 2.89 (0.30, 27.60) |
| **Total (95% CI)** | | **4922** | | **2576** | **100.0%** | **1.28 (1.05, 1.56)** |
| Total events | 505 | | 195 | | | |

Heterogeneity: Tau²=0.01; Chi²=3.32, df=3 (P=0.35); I²=10%
Test for overall effect: Z=2.40 (P=0.002)



The principal variables of the results evaluated in the remaining clinical trials were changes in BMD and the variation in the MBRs. The results obtained in relation to changes in BMD showed an increase in this measure in all locations with the use of BZD as against the placebo. The comparisons with raloxifene in the different trials showed different results[10,16,18]. The MBRs behaved in a similar way, with greater reductions in the groups in treatment with BZD. The combination of BZD with EC obtained even better results than raloxifene[18]. However, when in a clinical trial MBRs or the measurement of BMD are used as its main measure as a substitute for the number of fractures, the results need to be interpreted with care. The relationship between changes in BMD or the MBRs and the reduction in the number of fractures due to antiresorptive treatment is unknown in most cases, and low in those in which it is quantified. The great biological variability which the MBRs possess limit their capacity to individually predict the risk of fracture[29]. Studies carried out with risedronate have concluded that the changes in the levels of BMD do not predict a reduction in the degree of fractures[30,31]. The raised incidence of fractures observed in patients with osteopenia corroborates these conclusions[32].

In the valuation which the authors themselves make in the study of treatment of OP at three years with BZD using logistic regression indicates that the changes in bone mineral density after 1 and 3 years of treatment with BZD would explain 8% and 29% of hip fractures respectively, or 15% and 43% respectively of fractures in the femoral neck[25]. The interpretation of changes in the lumbar region does not figure in the study due to methodological problems.

In our review we have not found one on one comparisons of BZD with other drugs recommended as the treatment of choice for OP having demonstrated to reduce the risk of fractures, both vertebral and non-vertebral in randomised clinical trials[33]: alendronate[34], risedronate[35], zoledronate[36], strontium ranelate[37,38] or teriparatide[39]. Neither at a dose of 20 mg nor at 40 mg did BZD improve the reductive effect on the incidence of vertebral fractures of raloxifene in patients with osteoporosis.

The *post hoc* analysis of BZD has shown a decrease in non-vertebral fractures in osteoporotic patients at high risk of fracture. However, the interpretation of these results is controversial, since for some authors, the results of *post hoc* analysis of subgroups should be interpreted with scepticism and should not be used as definitive proof of the effect of a treatment. The recommendation is that all the analyses of subgroups should be planned before carrying out the study to avoid having to look for results which may be statistically significant[40].

Similarly to that which happens with raloxifene, its safety level appears to be optimum but special attention should be given to its principal adverse effect, the risk of tromboembolism, whose real incidence is not yet clear. More data are necessary to obtain information on its safety. In addition, the high incidence of cramps and breathlessness may be a significant motive for abandonment. The combination with EC could encourage adhesion to treatment by reducing vasomotor symptoms.

The main limitations for the acceptance of the results of our review in terms of the results obtained are: the finding of only one clinical trial which valued as its main objective that which *a priori* was the most suitable measure of results; the poor evaluation of the biases in the selected clinical trials, notably the great losses in the follow up and the lack of clarity in the masking of the assignment list. The carrying out of the meta-analysis with the data published and not with the individual patient data is the fundamental limitation in relation to this review. However, our results are similar to those published previously in an independent systematic review of BZD[41].

Recently, at the 22nd Congress of the North American Menopause Society, the results obtained from a second extension of two years (total of 7 years of treatment) of the original reference study[10] have been presented, in which the raloxifene group has been eliminated and the group on 40 mg of BZD moved to 20 mg, resulting in two branches, 20 mg BZD and placebo. It concluded that in the long term BZD maintained its safety profile and its efficacy in reducing the incidence of vertebral fractures shown in the original study[42,43].

**Implications for practice**

BZD is a drug which is efficacious in the reduction in risk of radiological vertebral fractures in osteoporotic women, but which has not been shown to reduce the number of symptomatic vertebral fractures or non-vertebral fractures. In addition, it is efficacious in reducing the loss of BMD and remodelled bone both in primary and secondary prevention of OP, with a similar action and safety levels as raloxifene. Given that raloxifene is included in the clinical practice guides of the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM), indicated as a first choice drug for menopausal patients under 65 years of age and with a low risk of hip fracture (OP only in the spine, without previous fractures)[44], bazedoxifene should be considered in the same position in the therapeutic algorithm. It is possible that it increases the incidence of deep vein thrombosis, but this is not well established.

**Implications for research**

With respect to the reduction in the incidence of non-vertebral fractures, new clinical trials are necessary whose principal objective is non-vertebral fractures to obtain more conclusive results. In addition, it would be advisable to carry out new studies which compared the use of BZD with a combination of BZD and EC in order to understand which of the two treatments would be most useful in the treatment of OP and which had the better safety profile.

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# Cost of postmenopausal osteoporosis

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## Introduction

Osteoporosis (OP) is a common disease, responsible for a great number of the fractures occurring in people over 50 years of age. Through various pathogenic mechanisms a reduction in bone mass occurs, which is accompanied by an increase in bone fragility. Osteoporotic fractures in the vertebrae, the hip, the forearm and the humerus are the most frequent. They are a massive health problem due to their repercussions, not only on the health and quality of life of the patients, but also due to the economic and social costs of their treatment and aftercare.

Form a conceptual point of view, it is necessary to distinguish between OP as a clinical entity and densitometric OP. With respect to the former, this consists of a systematic bone disorder characterised by a deterioration in bone resistance which predisposes it to fracture, in the light of the fact that bone resistance is the result of an integration of bone density and bone quality[1]. The cause may have an influence on the loss of bone mass or on other elements, such as the bone's microarchitecture, on which the quality of the tissue depends. On the other hand, the latter is an operative definition proposed by the working group of the World Health Organisation (WHO) meeting in 1992[2]. This took into account a number of levels or cut-off points of bone mineral density (BMD) for postmenopausal white women. Thus, considered as normal are those values of BMD above -1 standard deviation (SD) in relation to the average for young adults (T-score > than -1); osteopenia corresponds to values of BMD between -1 and -2.5 SD (T-score between -1 and 2.5); OP, values of BMD lower than -2.5 SD (T-score lower than -2.5); and established OP, when in addition to the above conditions are combined with one or more osteoporotic fractures[2]. This definition is mainly useful as a epidemiological and diagnostic classification criterion, but should not be used in isolation, with other circumstances having to be taken into account such as age, rapidity of bone loss or the frequency of falls[2], since BMD only explains 70% of bone fragility[3].

The impact of OP results from its most significant complication, fractures. Therefore, not only should the diagnosis of a reduced BMD be considered, but also an evaluation of the risk of fracture. A series of indices have been developed with this objective, notable among which due to its popularity is that proposed by the WHO study group, called FRAX, which includes a series of clinical parameters, in addition to the BMD, for the evaluation of the risk of fracture[4]. These parameters are independent of the BMD, included among which are previous history of fragility fractures, family history of osteoporotic fractures, thinness and active smoking, alcohol consumption and an increase in bone turnover[5]. It is not surprising that the frequency of falls is also associated with a higher risk of fracture[6].

### Importance and impact of OP

OP has a great impact on the health and the economy of developed countries. Osteoporotic fractures have a sizeable impact from a socioeconomic point of view. Although measures have been proposed to reduce the problem, OP continues to be underdiagnosed, and many patients, even with fractures recognisable as osteoporotic, remain without treatment. Social and political measures are still insufficient to address the prevention of this serious socio- health problem.

OP is a very common disease, which affects 150-200 million people in the world. Approximately half of these patients come from the developed nations of North America, Europe and Japan. In general terms, it is estimated that around 33% of women over 50 years of age have OP. Its prevalence in women increases with age from 15% in the interval between 50 and 59 years, to more than 80% at ages over 80 years[7]. In males the prevalence of OP is lower, 8% according to the data from the NHANES study[8].

In Spain, nearly 2 million women and 800,000 men have OP. The prevalence of densitometric OP is 26.07% (CI 95%, 22.57-29.57%) in women over 50 years of age[9], much higher than that observed in men, 8.1% in those over 50 years of age[10], and 11.3% in those over 70 years of age[11]. Osteoporotic fractures are responsible for the serious clinical and socioeconomic consequences of OP. The disability produced by OP in Europe is greater than the impact of many cancers and other chronic diseases such as rheumatoid arthritis, asthma or the cardiac repercussions of hypertension[12].

Osteoporotic fracture, calculated using data from the year 2000 across the whole world, reached a figure of 9 million fractures, of which more than half occurred in Europe and the United States, with the following distribution: of the hip, 1.6 million; the forearm, 1.7 million; and clinical vertebral (symptomatic) 1.4 million[12]. Current data have been projected into the future and it is estimated that these fractures will increase in the coming decades[13]. There are no direct data regarding the number of fractures in Spain globally, but it is thought that the number may reach 100,000 fractures a year, with direct costs greater than 126 million euros, and indirect costs of 420 million euros.

The prevalence of vertebral fractures is difficult to quantify. More than two thirds are asymptomatic and can only be diagnosed by imaging methods, generally lateral X-ray of the lumbar and dorsal spine[14,15]. The presence of existing fractures in women over 65 years of age multiplies by 7-10 times the risk of suffering another new fracture in the next 5 years[16]. It also increase the probability of suffering non-vertebral fractures, with an estimated risk quotient of 2.8-4.5, and this increases with the number of vertebral deformities.

Vertebral fractures are infrequent before the age of 50 but, as with other fractures, increase with age. Various studies have indicated that their prevalence in women older than 50 is between 18 and 28%[17]. In Europe, data on prevalence come principally from the "European Vertebral Osteoporosis Study" (EVOS), in which has been observed a prevalence of 12.2% for men and of 12% for those between 50 and 79 years of age[18]. The individuals in this study were later included in a prospective study: "European Prospective Osteoporosis Study" (EPOS)[19]. The annual incidence is considered to be 1% in women of 65 years of age, 2% in those of 75 and of 3% in those over 85 years of age. In men over 50 years of age it is between 5.7 and 6.8/1,000 people/year, which is equivalent to approximately half of that observed in women[20]. More recent Spanish data coming from the "Osteoporotic vertebral fracture and associated risk factors" (FRAVOS - "Fractura vertebral osteoporótica y factores de riesgo asociados") study in a population from Valencia, indicates that the prevalence of vertebral fractures in women over 50 years of age is 21.4%, which increases up to 46.3% in those over 75 years of age[21].

Non-vertebral fractures, excluding cranial and cervical fractures, are more numerous than vertebral fractures in the population with postmenopausal OP, and greatly exceed the sum of those in the hip and wrist[22]. Their locations are highly diverse and the frequency in each location is very small, with the exception of those in the hip and the wrist. As we have indicated, hip fractures are notable by their high morbimortality. They are frequent fractures, affecting 1% of the population. Hip fractures make up 10% of all non-vertebral fractures, but their percentage increases with age, reaching 40% after the age of 80 years.

Fractures of the hip are considered, from a prognostic point of view, the most serious due to their high morbimortality. Less than half of these patients will recover to their earlier state, since 25% will need home care and 20% with remain in a continuing state of dependence. The incidence increases exponentially with age, and is double in women compared with men[23]. Most of these fractures occur after a fall from a height equal or less than the patient's own height. The global risk of fracture of the hip from 50 years of age in the United Kingdom is 11.4% and 3.1% for women and men, respectively. The incidence varies substantially from one population to another, and is usually higher in white Caucasian individuals. In Europe, the proportion of hip fractures varies up to 7 times between different countries. Spain is considered to be a zone of moderate incidence[24], while in Norway, Sweden, Iceland, Denmark and the US the incidence is high[25]. In our country the annual incidence is highly variable, varying between 301/100,000 and 897/100,000 patients over 65 years of age per year[26].

Distal fractures of the ulna and radius, or Colles fractures, have a different presentation profile to those previously mentioned. Data is more scarce than for vertebral or hip fractures. Most of the incidence data comes from the Northern hemisphere, principally from the Scandinavian countries, the United Kingdom and the US. There is an increase in incidence in Caucasian women between 40 and 65 years of age, followed by a plateau which remains for the subsequent years[17], which has been related to an alteration in neuromuscular reflexes caused by aging, and to a tendency to suffer falls whose impact the patient automatically attempts to mitigate by extending their arms. This type of fracture appears mainly in women, and mostly after the age of 65. In the United Kingdom the lifetime risk of fracture in women of 50 years of age is 16.6%, while at 70

years of age this risk falls to 10.4%. The incidence in males is significantly lower and does not change much with age (risk during the rest of life of 2.9% at 50 years of age and 1.4% at 70)[27].

**Cost of OP and osteoporotic fractures**

In addition to the personal repercussions due to its high morbimortality, OP generates highly significant socioeconomic costs and the analysis of these costs bring with them great uncertainty, given that their calculation is difficult, with a possibility bias. The information available is incomplete[28], both in relation to the prevalence of fractures and in the data on related costs. The most reliable data come from the analysis of hip fractures, of which is it easy to understand the incidence and the direct hospital costs. The most common analysis of costs are the cost-effectiveness studies of drug interventions. Many of the calculations in cost studies are based on theoretical models which use known epidemiological data. The results are expressed in monetary units or on the basis of the loss of quality-adjusted life years (or QUALY)[28].

The calculation is complex and needs to include the consequences of the impact on the individual (among others, the possibility of death caused by bone diseases) and the impact on the emotional state. The socioeconomic costs are divided into direct and indirect costs. Among the first are those derived from hospitalisation, ambulatory care and drug treatment. These costs may be related to acute, social and hospital care, both short and long term, and the drugs. Included in the non-medical direct costs are social and informal care. Included in the costs of social care are the costs of adaptations of the home, health care received in the home, home care and transport. Lastly, the indirect costs mainly include the loss of production of the patient or of the family members who look after them.

The hospital costs are influenced by the duration of the hospitalisation. In the ambulatory care is included the visits to the orthopaedic surgeon, visits to other doctors, including the general practitioner, visits by the nurse, the physiotherapist, the occupational therapist and the cost of help over the phone.

One of the problems resulting from fractures is disability. Some models of socioeconomic study use an approach in which the costs are calculated as disability-adjusted life years (or DALY)[12]. In addition to the significant economic costs, fractures have a social impact which, although influencing the costs, should be considered independently, in the same way as mortality or morbidity are. Many of the economic studies come from Sweden or the United Kingdom. The annual loss related to fractures in Sweden is 15,930 QUALYs[29]. In stratifying them by risk, which is to say, by age, the value of the loss on one QUALY in the United Kingdom, with reference to 2002, is £103,572 at 50 years, £149,226 at 60 years, £186,818 at 70 years and £488,050 at 80 years[28].

In addition, in fractures, the reduction in the quality of life related with health has a significant individual social cost. In a recent study carried out in the "Canadian Database of Osteoporosis and Osteopenia (CANDOO) cohort, the quality of life is notably reduced in spite of treatment when the Mini-Osteoporosis Quality of Life Questionnaire is used[30].

**Cost of hip fracture**

The cost of hip fractures vary according to the country in which they are considered. The report of the International Osteoporosis Foundation (IOF) from 2008, observed variability in days of hospital stay due to hip fracture between different European countries, which is undoubtedly reflected in the cost[31]. It is probable that these costs will increase in the coming years. According to Spanish data, the frequency of hip fracture appears to increase independently of age[26], a fact which is observed in other countries in our area and, according to the IOF report, it is expected to increase significantly in the next few decades, doubling by 2050.

Among the circumstance which contribute to expenditure due to hip fractures are, in addition to direct costs, mortality, disability and the need for institutionalisation. The cause of death on many occasions is not directly related to the fracture. It has a biphased pattern of frequency, with an initial peak in the first 4 weeks and another increase later, at between 6 and 12 months. There is a later decrease in frequency, although it remains above expected levels in subsequent years[32]. Mortality is 20-30% in the first year, which means that the risk of death increases by 2 to 10 times of the levels expected in a population with similar characteristics[17]. The excess in mortality is estimated as a risk of 3.35 (CI 95%, 1.5-7.47) compared with the later risk of 1.30 (CI 95%, 0.85-1.98)[33].

Another of the social costs is dependency, which is seen in more than half of the patients who survive after a hip fracture. In the combination of disabilities attributable to osteoporotic fractures, the hip fracture has the greatest costs. 40% of the DALYs lost because of OP are due to fracture of the hip[12]. Due to their situation of dependency many patients have to be institutionalised in order to be cared for, generally in an old people's home. This represents a significant expenditure which is not always taken into account. The clearest information comes from the analysis of costs in the United Kingdom. The percentage of patients institutionalised varies with age, from 4% at 60-79 years, to 12% at 80-89 years and up to 17% above 90 years[33].

The global cost of hip fractures was calculated at 34,800 million dollars in 1990, and this figure will continue to rise, it being calculated to reach 131,500 million dollars in 2050[17]. In the US the cost of hip fractures is estimated to be 19,300 dollars during the first year in women over 65 years of age, and 21,700 dollars for the age range 50 to 65 years. The greatest cost is represented by hospital

stays, which amount to 50% of the total cost. The direct costs vary between European countries. In Sweden it varies between 9,396 euros in patients from 50 to 64 years of age and 25,253 euros in those over 85 years of age. In Belgium it is calculated at 16,624 euros, while in Spain the cost is estimated to be lower than in Sweden, at 6,759 euros[34].

Other costs to be considered are those derived from the care of patients once they have passed the acute period of the fracture. In the United Kingdom they take into account for their calculation various parameters related to the possible outcomes of hip fracture: the most favourable is discharge and return home; the second, less favourable is that the patient becomes incapacitated and is moved to an old people's home or a hospital for the chronically ill; finally, the worst outcome is death in the first year after fracture. These global annual social costs, relating to the year 2002, are estimated at more than 30 million pounds sterling. In this would be included patients who go back to their homes (45%), at £1,750 per patient; those who die in the first year (30%), at £2,964 per person; and those patients who require long term institutionalised care (25%) whose costs rise to £22,218. The total costs due to medical visits to the primary care doctor in the first year is estimated to be 8.5 million pounds.

In the following years the costs varied between those who live at home and those who are institutionalised. Taking this into account, the total costs are £6,635 for patients at home, £27,228 for those who are institutionalised, and lastly, for those who die, £7,772. However, many studies do not normally estimate the costs of later years, which would be 0 for those who die. It is assumed that those who return to their homes (non-complicated fracture) would also have a low cost. However, when they are admitted to private residences there is an additional cost of £18,900 per year (1996 prices)[35].

The cost at 2002 prices of fracture in a patient who returns home is different according to age. The cost would be £4,880 at 50 years of age, and increases to £8,800 for those over 80 years of age. Similarly, younger patients who enter a residence have a cost of £29,620, while this would increase to £32,795 in the group of patients of 80 years of age. In subsequent years, the cost of those patients staying in private residences remains stable at an annual cost of £27,290[28].

In Canada, the direct costs of the treatment of hip fractures is estimated at 28,297 dollars, and the direct medical costs at 17,961 dollars. The expenditure related to the care of the patient during the rest of the first year would be 10,336 dollars. Additional care during successive years would be 7,302 dollars. The indirect costs would increase to 4,218 dollars in patients between 65 and 69 years of age, while they would be 1,158 in those over 75 years of age[36].

In Sweden, the cost of treatment of hip fracture varies between 115,994 Swedish crowns for those in the group between 50 and 64 years of age and 166,232 Swedish crowns in the group over 85 years of age, at 2005 prices[29]. The costs which occur in the period between 12 and 18 months after the fracture of the hip reach 14,360 euros. The cost also varies greatly between age groups, from 527 euros in the 50-64 age group to 4,000 euros in those over 85 years of age. At all ages the cost is higher in men than in women[37].

There are, logically, differences depending on the outcome. Between those who die in the first 4 months and those who die at between 5 and 18 months, and those who survive beyond this time. In those who die in the first few months the cost is 14,115 euros, while in those who survive more than 18 months the cost is 11,350 euros[37].

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# Role of bazedoxifene in the treatment of postmenopausal osteoporosis

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## Introduction. Osteoporosis. Its importance

La Osteoporosis is a disease which does not have a totally satisfactory definition[1]. Since the 50s, when Fuller Albright defined it as "too little bone"[2], an incomplete concept, since it only recognises the quantitative, and not the qualitative aspect of the disease, it has been succeeded by other definitions, such as that of the American National Institute of Health (NIH) which in 1988 referred to osteoporosis as " a condition in which bone mass is reduced, increasing the bone's susceptibility to suffer fractures"[2,3], or that agreed by the Hong Kong Consensus in 1993[4]. In spite of it not being totally satisfactory, nowadays we accept the definition published by the NIH in the year 2001, an update of the 1988 version, which considers osteoporosis to be "a disease of the whole skeleton characterised by low bone mass and an alteration in bone microarchitecture which causes bone fragility, with a consequent increase in the risk of fractures"[5].

Even though the current definition addresses the fundamental problem of osteoporosis (the existence of a greater bone fragility which results in an increase in the risk of suffering fractures), and integrates the loss of quantity (bone mass) with changes in the quality of bone (microstructural changes), this definition of osteoporosis does not have a direct clinical application, because with it we cannot use it to identify those patients who suffer from the disease. Thus in day to day care, the definition of osteoporosis most used is that derived from a densitometric finding of a T-score lower than -2.5, although this has the limitation of being based exclusively on quantitative criteria[6].

## Clinical situations in which the use of bazedoxifene is indicated

Taking into account the premise that bazedoxifene is indicated for treatment of postmenopausal women with osteoporosis, we are able to profile more specifically those women in whom the drug could have a more precise indication.

*a. The patient with densitometric osteoporosis*

Given that osteoporosis does not have symptoms in itself, and that the clinical signs are produced as a consequence of its complications, fractures[1,7], it is necessary to identify and treat the disease before the fractures appear. At the moment we only have available densitometry, which only evaluates the quantitative, and not the qualitative components of bone. According to the World Health Organisation (WHO) densitometric osteoporosis exists when the patient has a value of T lower than -2.5 in any anatomical location where the measurement is taken[6,8,9].

There is a clear relationship between a decrease in bone mineral density and an increased risk of fracture, in such a way that it is accepted globally that for each reduction in the typical deviation the risk of fracture doubles[10]. Therefore, in a woman in whom a diagnosis of osteoporosis has been established by densitometry, it is possible to initiate treatment with bazedoxifene.

should be recommended that it be taken daily at the same time so that the patient does not forget to take it. In the case in which a dose is missed, this should be administered as soon as possible, in order to continue with the normal timetable, thus avoiding double or extra doses[27].

This ease of administration facilitates therapeutic compliance with bazedoxifene, which has been demonstrated in the different clinical trials in which the abandonment rates are similar to those of the placebo[23].

As with the other drugs used for the treatment of osteoporosis, bazedoxifene should be associated with calcium and vitamin D supplements since its efficacy in this association has been demonstrated in clinical trials[12,20-23]. The drug may be taken at the same time as the supplement, there being no interference in its absorption.

## Adverse effects

In general, bazedoxifene is a well-tolerated drug. The adverse effects most frequently observed in the clinical trials were breathlessness and muscle spasms, especially cramps in the legs. Less frequent but more serious are thromboembolic episodes[20].

Other adverse effects report are dry mouth, allergic reactions, increase in triglycerides, peripheral oedema and drowsiness, and an increase in transaminases, although the frequency was similar to that produced with the placebo[20,22,27].

## To whom should bazedoxifene not be prescribed?

Bazedoxifene is only indicated for the treatment of postmenopausal women. It has no indication for use in premenopausal patients. Other contraindications are[27]:

- Personal history of venous thromboembolism or of an increased risk of having this pathology.
- Allergy to bazedoxifene or some of its excipients.
- Its safety in women with endometrial or breast cancer has not been sufficiently studied. There are no data regarding its use concomitant with other treatments used in breast cancer. Its use for the prevention of breast cancer is not recommended.
- Its safety in patients with severe renal and hepatic insufficiency has not been established.
- In those women with moderate of intense vasomotor symptoms it should be born in mind that bazedoxifene does not act on these symptoms, which means that they should be treated, in addition, with other specific associated drugs (for example, estrogens).

## The patient with high risk of breast cancer

In the clinical studies of bazedoxifene it has not been associated with an increase in tension or pain in the breast, benign or malignant pathology, their presence being similar to that with the administration of a placebo[28]. These results are maintained after treatment in the long term over 7 years[34].

A study with digital mammography in women treated for 2 years with bazedoxifene has indicated that the treatment does not affect mammary density and therefore, does not modify the diagnostic interpretation of the mammography[29].

In breast cancer cell lines, bazedoxifene shows a differentiated pattern of genetic expression with respect to raloxifene and lasofoxifene in more powerfully antagonising the stimulator effect of the estrogens[30].

In the phase III studies the presence of breast cancer was similar for bazedoxifene, raloxifene and placebo, and the incidence of breast cancer turned out to be low and not powerful enough to properly evaluate this aspect[31,32].

## Bazedoxifene and the reproductive tract

Treatment with bazedoxifene over 5 years is not associated with changes in endometrial thickness, the frequency of abnormal uterine bleeding, an increase in benign endometrial pathologies such as polyps endometrial hyperplasia or malignant pathology. Nor did it interfere with cervicovaginal cytology results[27,29,33]. In an extension of the reference study to 7 years, the group treated with bazedoxifene showed an endometrial thickness similar to that with the placebo and lower incidence of endometrial carcinoma than in the placebo group ($p<0.05$), although the number of cases was very low in both groups[34].

In recently postmenopausal women at risk of osteoporosis, treatment with bazedoxifene over two years has shown no differences in relation to the placebo in the measurement of ovarian volume, the number or size of ovarian cysts or in the presence of malign ovarian pathology[35].

Preclinical and clinical studies suggest a different and favourable uterine profile for bazedoxifene compared with other SERMs. The marked antagonist effect on the endometrium has permitted the development of the association of bazedoxifene with the estrogens, since it neutralises more powerfully than raloxifene the proliferative effect induced by the estrogens in the endometrium[36], which suggest a different endometrial profile for this SERM.

## Women with associated pathology

Cardiovascular pathology is the principle cause of dysfunction in postmenopausal women. Hence the effect of an intervention on surrogate markers of cardiovascular disease is seen to have great importance.

In the lipid profile, bazedoxifene has shown a significant reduction in blood cholesterol (-3.75%), cholesterol bonded to low density lipoproteins (-3.6%) and an increase in cholesterol bonded to high density proteins (5.10%), in comparison with the placebo. The effect on the triglycerides was similar to that of the placebo. This favourable effect on the lipid profile is independent of age and has been shown both in the prevention study[28] (average age 57.6 years) and in the study with women with osteoporosis (average 65.9

years)[27]. For this reason, a woman with hypercholesterolemia may be a candidate for treatment[20], with the expectation of an additional beneficial effect of an improvement in their lipid profile.

Arterial hypertension is another important surrogate marker for cardiovascular risk. Treatment over 5 years with bazedoxifene has been shown to be similar to the placebo in its effect on blood pressure. Thus, women with hypertension could use bazedoxifene since, in addition, it does not interact with anti-hypertension drugs. Nor has there been reported to be any influence on the glycemic profile in the follow up at 5 years of treatment with bazedoxifene. Women on anticoagulant treatment, and once they have be evaluated for its indication, could be treated with bazedoxifene since there is no medicinal interaction with anticoagulant drugs like warfarin.

## A new approach to the treatment of osteoporosis. Sequential therapy

One of the problems which we currently find in the treatment of osteoporosis is knowing how long should be maintained.

It should be born in mind that treatment for osteoporosis does not "cure" the disease, rather it reduces the risk of the appearance of fractures. Most of the reference studies designed to demonstrate the effectiveness of drugs in achieving this last 3–5 years. Up until now the available data has been observational, usually with a very low number of patients participating in the study, which does not maintain the methodological rigor observed during the randomised clinical trial. Therefore, in order to be reasonably safe and legally protected, we are authorised to maintain the treatment for the patients for the same time as the clinical trial lasts.

However, what do we usually do with the patients when they complete the 3-5 years? We consider whether to continue with the treatment or to cancel it, this in a patient affected by osteoporosis in whom there remains a high risk of fragility fracture and in whom, by being 3-5 years older, this risk is even higher. Up until now we have adopted individualised positions, with the agreement of the patient, and in many cases the treatment has been maintained for periods longer than those of the clinical trial, due, on the one hand, to the generally good tolerance of the drug, and on the other, the absence of reported of secondary effects or significant complications. This has been the case until relatively recently when there have started to be reports of the presence of atypical diaphyseal femoral fractures in patients in whom the treatment, usually with biphosphonates, had been sustained for a long period[37]. The risk of fracture per 100 patients per year in these patients has been established by some authors at 1.46 (CI 95%: 1.11-1.88)[38], and by others at values as high as 37.4 (CI 95%: 12.9-119, $p<0.001$)[39]. The duration of treatment with biphosphonates appears to be a significant factor in the appearance of these atypical fractures, since when these drugs, especially alendronate, are maintained over 2 years 2 cases for every 100,000 patients treated per year are observed, while when the treatment is prolonged for 8 years, the risk increases to 78 cases per 100,000 patients treated per year[37].

In the light of this we need to rethink what to do in the longer term with those patients affected by osteoporosis, especially when we are going to indicate a treatment for the first time, since, with the current data, it does not seem very advisable to maintain a treatment with powerful antiresorptive drugs beyond 5 years, and besides, we already know that the indication for the anabolic drugs, PTH 1-34 and 1-84, is that they can only be maintained for 2 years. There are no data with respect to this, but in these circumstances, in a patient with postmenopausal osteoporosis, we could consider the possibility of beginning the first years of treatment with an antiresorptive drug such as bazedoxifene which is not as powerful as the biphosphonates or denosumab, in order, some years later, to continue with one of these more powerful drugs, precisely when the patient has the greater risk of fracture by being older. We do not have studies available which support this suggestion, which should be taken only as a personal opinion of the authors.

**In conclusion,** bazedoxifene is a selective estrogen receptor modulator whose prolonged use, for at least 5 years, produces a reduction in the appearance of new vertebral fractures and a decrease in the risk of non-vertebral fractures in those women at high risk, considered to be those who had a BMD in the femoral neck with a T-score lower than -3.0, and/or 1 severe vertebral fracture or two moderate vertebral fractures.

It is a drug with a significant long term safety profile, and has the additional advantage of not increasing the risk of breast cancer and of reducing the risk of endometrial cancer. Therefore, it is a drug which we should consider as the first choice for the treatment of osteoporosis.

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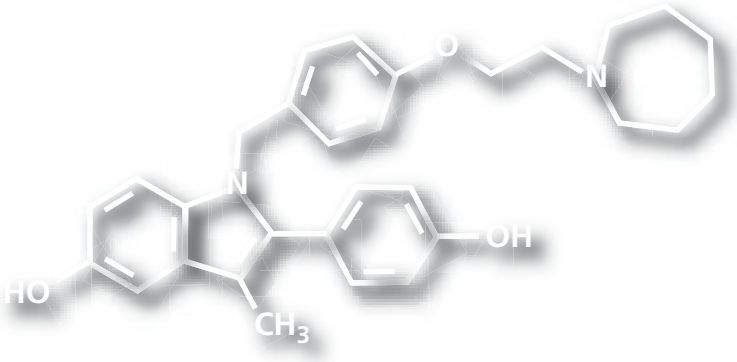


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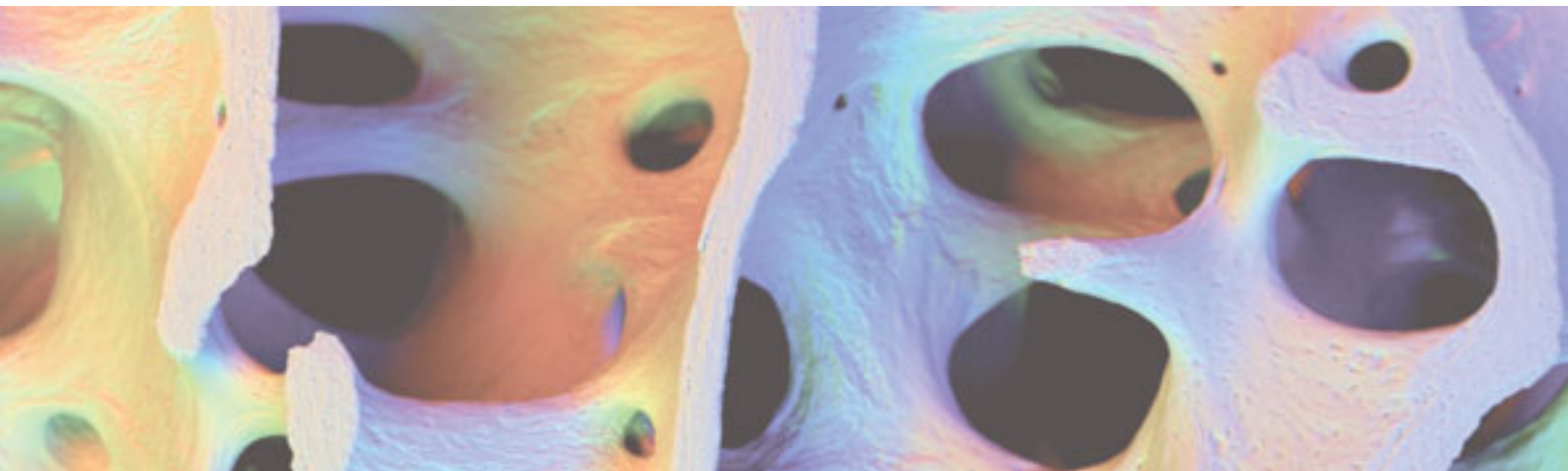
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