

Relationships Between Changes in Bone Mineral Density or Bone Turnover Markers and Vertebral Fracture Incidence in Patients Treated with Bazedoxifene

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Abstract We analyzed the relationships between bone mineral density (BMD) or bone turnover marker (BTM) changes and vertebral fracture incidence in women treated with bazedoxifene using a post hoc analysis from a 3-year randomized, placebo-controlled study evaluating the effect of bazedoxifene (20 or 40 mg) on fracture risk reduction. BMD was assessed at baseline and every 6 months for 3 years. Osteocalcin and C-telopeptide of type I collagen were assessed at baseline and at 3, 12, and 36 months. Vertebral fractures were assessed with a semiquantitative visual assessment. Data were available for 5,244 women, of whom 3,476 were treated with bazedoxifene. Using a logistic regression analysis and the classical Li approach, the proportion of fracture incidence explained by BMD change after 3 years of bazedoxifene treatment was 29 % for the total hip and 44 % for the femoral neck. The proportion of treatment explained by lumbar BMD change could not be quantified accurately because of the significant interaction between treatment and change in BMD. With the same model, the 12-month BTM changes explained up to 29 % of the fracture risk reduction observed with the two forms of bazedoxifene. In women treated with bazedoxifene, changes in femoral neck BMD, hip BMD, or BTMs

explained a moderate proportion of the fracture risk reduction observed during the 3 years of follow-up. However, BMD or BTM changes cannot be recommended for individual monitoring of women treated with bazedoxifene.

Keywords Bone turnover marker · DEXA · Fracture · Bazedoxifene

Osteoporosis is a skeletal disorder characterized by compromised bone strength that predisposes affected persons to an increased risk of fracture. Numerous pharmacological treatments are now available to reduce the risk of fracture in these patients. However, it is well known that the response to treatment may differ between individuals [1]. There is still a need to find monitoring modalities of anti-osteoporotic treatments to predict efficacy [2, 3].

Because fractures occur infrequently, clinicians must rely on surrogates to assess response to therapy. The most widely used surrogate is bone mineral density (BMD). Although low BMD is a strong risk factor for fracture in untreated populations [4–7], the usefulness of serial bone mass measurements during treatment is uncertain [8]. Indeed, among women treated for osteoporosis, the strength of the relationship between changes in bone mass and subsequent fractures varies considerably [9–20], suggesting that other factors may be important or that techniques for assessing changes in bone mass lack the precision required to quantify this relationship accurately. Other potential surrogates of fracture are bone turnover markers (BTMs). A number of studies have reported the ability of BTMs to predict the fracture risk in an untreated patient population [21]. However, as for BMD, clinical studies have shown a high diversity of BTMs to predict the

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response of an individual to an antiosteoporosis pharmacological intervention [22–30].

Bazedoxifene (BZA) is a novel selective estrogen receptor modulator (SERM) that has shown tissue-selective activities to confer favorable effects on bone and lipid metabolism without adversely affecting uterine or breast tissue [31, 32]. Preclinical and clinical studies have suggested that BZA could prevent bone loss, decrease bone turnover, and decrease fracture incidence without adverse effects on breast and uterine tissue [33–39].

The objective of this study was to analyze the association between changes in BMD or BTMs and vertebral fracture risk during 3 years of treatment with BZA.

Materials and Methods

Study Design

A post hoc analysis was performed on data from a previous published study [39]. This international, multicenter, double-blind, randomized, placebo- and active-controlled phase 3 trial was conducted at 206 sites in Asia–Pacific countries, Canada, Europe, Latin America, South Africa, and the United States. The design and methodology of this study were fully described in the original study report. Briefly, subjects were randomly assigned to receive BZA 20 or 40 mg, raloxifene 60 mg, or placebo, taken orally once daily. All subjects received daily oral calcium (up to 1,200 mg) and vitamin D (400–800 IU) supplements. Patients were eligible for the study if they were healthy women between the ages of 55 and 85 with at least 2 years since menopause and with osteoporosis, defined as low BMD or radiographically confirmed vertebral fractures. Subjects without prevalent vertebral fracture were required to have lumbar spine or femoral neck BMD T scores between -2.5 and -4.0 (inclusive), whereas subjects with prevalent vertebral fracture (at least one mild vertebral fracture) were required to have lumbar spine and femoral neck BMD T scores not worse than -4.0 . All patients from this study were included in this analysis.

Fracture Assessment

Prevalent and incident vertebral fractures were identified using the semiquantitative methodology, as previously reported [40]. If an incident vertebral fracture was identified by semiquantitative methodology, a quantitative morphometric assessment was used to confirm the fracture, which was defined as a decrease in vertebral height of 20 % or more and 4 mm or more. In cases of disagreement between the two methodologies, a binary semiquantitative

assessment by an independent radiologist was conducted to adjudicate the discordant results.

BMD Assessment

BMD of the lumbar spine and other skeletal sites was measured using DXA at baseline and at 6, 12, 18, and 24 months. Those subjects who consented to participate in the extension of the initial study had DXA at 36 months. Consequently, only part of the study population had BMD at 36 months. All DXA scans and vertebral fracture assessments were evaluated at a central analysis facility (Synarc, San Francisco, CA).

BTM Assessment

From fasting blood sample, osteocalcin (OC) and C-telopeptide of type I collagen (CTX-I) were assessed at baseline and at 3, 12, and 36 months. Blood samples with hemolysis were excluded. BTMs were analyzed at a central analysis facility (Synarc, Lyon, France).

Statistical Analysis

Patients were included in this particular analysis only if they had vertebral X-rays and BMD performed at baseline and after at least one follow-up evaluation, independently of drug compliance. A total of 5,244 patients (from the BZA and placebo group) reached these inclusion criteria. For this particular analysis, we used the changes in BMD observed after 36 months and the changes in BTMs observed after 12 months because they were the most important at these times. The association between changes in BMD and fracture incidence was assessed only in the BZA-treated group through a logistic regression analysis with age, body mass index, number of prevalent vertebral fractures, and baseline BMD or BTMs as covariates. The proportion of treatment effect explained by BMD changes was assessed with a logistic regression model that included, besides the effects for treatment and end points, the fixed effects of age, body mass index, baseline BMD or BTMs, and number of prevalent vertebral osteoporotic fractures at the beginning of the follow-up. The proportion was computed as the ratio of the risk reduction explained by the surrogate alone to the overall risk reduction by treatment and surrogate [41]. We also used a new method to assess the proportion of treatment effect explained by the surrogate, i.e., the structural equation models. In these models, variables can be treated as both independent and dependent variables, and alternative hypotheses regarding the causal relationships between these variables can be tested. Here, we hypothesized that treatment has both direct and indirect effects on the occurrence of new vertebral fractures.

Direct effects are the influences of the treatment unmediated by any other variable in the model. Indirect effects are the effects of the treatment that are mediated by its effects on the biomarker (i.e., BMD or BTMs). The Sobel test was used to determine whether this effect was significantly different from null. Most assumptions of the structure equation models were met (e.g., sample size sufficiently large, independence of observations, no correlation between independent variables), but the assumption of normality was violated. Therefore, we used polychoric correlations and weighted least squares estimates for the parameters. Polychoric correlation is a technique for estimating the correlation between two theorized normally distributed continuous latent variables from two observed ordinal variables. If structural equation models were saturated, they were compared to the corresponding logistic and linear models (SAS procedures; SAS Institute, Cary, NC) and trimmed to make the estimates unique.

Results

Data were available for 5,244 women, of whom 3,476 were treated with BZA. Baseline characteristics of this study population are presented in Table 1. No significant differences were observed between the placebo and BZA groups. After 3 years of follow-up, the incidences of new vertebral fractures in subjects who received BZA 20 mg, BZA 40 mg, or placebo were 2.3, 2.5, and 4.1 %, respectively.

Using logistic regression analysis and the classical Li approach, the proportion of fracture incidence explained by BMD change after 3 years of BZA treatment was 29 % for the total hip and 44 % for the femoral neck (Table 2). The proportion of treatment explained by lumbar BMD changes could not be quantified accurately because of the significant interaction between treatment and changes in BMD. With the same model, the 12-month BTM changes explained 14–18 % of the fracture risk reduction observed with BZA (Table 2). However, in subjects treated with BZA 40 mg, the proportion of fracture incidence explained by BTM changes was higher (i.e., >25 %).

Table 1 Baseline characteristics of the study population

	BZA 20 mg	BZA 40 mg	Placebo
Age	66.5 (6.5)	66.2 (6.8)	66.5 (6.8)
Body mass index	26.6 (3.8)	26.5 (3.9)	26.3 (3.8)
Lumbar spine BMD T score	-2.4 (1.2)	-2.4 (1.2)	-2.4 (1.2)
Femoral neck BMD T score	-1.7 (0.9)	-1.7 (0.9)	-1.8 (0.9)
Patients with prevalent vertebral fracture (%)	56.1	55.9	56.4

Table 2 Proportion of vertebral fracture incidence explained by 3-year BMD change or 12-month BTM, using logistic regression analysis and classical Li approach

	BZA 20 + 40 mg	BZA 20 mg	BZA 40 mg
Lumbar BMD	Not assessable	38 (0, >100)	Not assessable
Femoral neck BMD	44 (0–>100)	44 (19–70)	39 (0–>100)
Total-hip BMD	29 (6–52)	36 (20–55)	24 (0–66)
C-telopeptide of type I collagen	18 (3–41)	20 (4–44)	25 (3–68)
Osteocalcin	14 (0–46)	4 (0–21)	29 (0–85)

Values are percentages (95 % confidence interval)

Table 3 Proportion of vertebral fracture incidence explained by 3-year BMD change or 12-month BTM, using structural equation model

	BZA 20 + 40 mg	BZA 20 mg	BZA 40 mg
Lumbar BMD	5 (3–7)	21 (17–26)	0 (0–4)
Femoral neck BMD	22 (17–26)	10 (8–12)	22 (17–27)
Total-hip BMD	14 (11–16)	27 (10–43)	13 (9–17)
C-telopeptide of type I collagen	16 (8–39)	14 (6–22)	25 (5–45)
Osteocalcin	6 (4–8)	0 (0–2)	19 (16–22)

Values are percentages (95 % confidence interval)

With another statistical method using structural equation models, the proportion of fracture incidence explained by 3-year BMD changes was 29 and 43 % for total hip and femoral neck, respectively (Table 3). Using the same methodology, BTM changes after 12 months explained up to 76 % of fracture incidence, but the proportion of treatment effects explained by BTM was different in the BZA 20- and 40-mg groups (Table 3). Interestingly, BMD changes after 1 year of therapy explained 8–15 % of the fracture incidence observed during 3 years of treatment.

Discussion

We have shown, in the present study, a significant association between the changes in BTMs or BMD and vertebral fracture incidence in patients treated with BZA for 3 years. Applying the methodology recently used for antiresorptive agents [42, 43], we calculated that, during a 3-year treatment with BZA, the changes in BMD or BTM account for up to 44 % of the vertebral fracture risk reduction.

Studies exploring the association between BMD changes and fracture reduction have been mainly conducted

with antiresorptive agents [1–3]. However, they provide contradictory results [12–15, 17]. Among women taking alendronate, Hochberg et al. [16] found that larger increases in total-hip and spine BMD were associated with a lower risk of new vertebral fractures. However, another study using a meta-analytical approach showed that the percentage of the reduction in vertebral fracture risk attributable to increases in spine BMD after alendronate treatment was only 16 % [12]. Moreover, it has recently been shown that women losing BMD at the lumbar spine (0–4 %) while on alendronate still had a reduction in vertebral fracture risk compared to their counterparts in the placebo group [44]. With raloxifene, increases in femoral neck BMD after treatment have been shown to account for only 4 % of the effect on vertebral fracture risk [17]. More recently, increases in lumbar spine and femoral neck BMD have been shown to account for only 18 and 11 %, respectively, of the effect of risedronate on vertebral fracture incidence [43]. However, risedronate-treated patients whose BMD decreased were at a significantly greater risk of sustaining a vertebral fracture than patients whose BMD increased. Meta-analytical approaches pooling different antiresorptive agents produced also conflicting results. It has been shown that trials that reported larger increases in BMD tended to observe greater reductions in vertebral fracture risk [18]. Using a Poisson regression, the authors showed that the model predicts a reduction of 54 % of the fracture risk if the treatments increase the spine BMD by 8 % and that most of the total effects of the treatments was explained by the increase in BMD [18]. It has also been reported, in a meta-analysis, that the risk of nonvertebral fractures decreased in patients whose BMD increased during treatment with antiresorptive agents [15]. Reanalyzing these data, although using the same statistical methods but correcting for discrepancies in the reported BMD and person-year data, suggested that the magnitude of the reduction in fracture risk was not associated with the increase in BMD [14]. Thus, there is limited evidence to support the use of BMD increases during antiresorptive therapy as a reliable indicator of fracture risk reduction [13, 42]. Very few studies have assessed the association between BMD changes and fracture reduction with bone-forming agents. One study showed that the proportion of teriparatide-mediated vertebral fracture risk reduction attributable to a 0.09 g/cm² increase in BMD ranged from 30 to 41 % [11]. Using strontium ranelate, it was shown that BMD changes at the level of the hip, but not the spine, accounted for a substantial (i.e., about 75 %) proportion of fracture risk reduction [9, 10]. Recently, using denosumab, it was shown that the change in total-hip BMD may explain 35–51 % of risk reduction of new or worsening vertebral fractures [20]. Interestingly, the change in total-hip BMD appears to explain about 80 % of the reduction in risk of nonvertebral fracture [20].

Previous studies have assessed the potential role of bone marker changes to monitor response to treatment. Eastell et al. [25] found that, among risedronate-treated women, greater reductions in CTX and NTX were associated with fewer spine and nonspine fractures. Another study found that greater reductions in bone-specific alkaline phosphatase (BALP) with alendronate therapy are associated with fewer hip, nonspine, and vertebral fractures [27]. In women treated with teriparatide, Chen et al. [22] found that the increases in C-terminal propeptide of type I procollagen (PICP) at 1 month and N-terminal propeptide of type I procollagen (PICP) at 3 months were the most sensitive and accurate predictors of the lumbar spine BMD changes. With another SERM, i.e., raloxifene, Reginster et al. [24] determined that a 1-year decrease in PINP, BALP, or OC, but not CTX, was predictive of the 3-year vertebral fracture risk reduction with raloxifene therapy. Another study showed that among raloxifene-treated women greater 1-year reductions in BALP and OC were associated with fewer incident vertebral fractures [26]. Short-term changes in biochemical markers of bone formation (BALP, PICP), but not bone resorption (CTX I and NTX I), were associated with long-term BMD changes, but not with fracture incidence, in women treated with strontium ranelate [30].

In our study, as with other antiresorptive agents, the proportion of treatment effects explained by BTM or BMD changes is not sufficiently large to allow prediction of BZA treatment on fracture risk reduction at the individual patient level. However, since we have found a significant association between changes in BMD or BTM and fracture risk reduction with BZA treatment, it could be of clinical relevance to inform the patient about positive BMD or BTM changes. Indeed, as recently demonstrated, feedback of such results to patients could increase compliance with therapy [45].

In our study, the proportion of fracture incidence explained by lumbar BMD changes was either lower than the BMD at other sites or not assessable because of a significant interaction between treatment and BMD changes. However, the clinical value of the assessment of lumbar BMD in the elderly population is a matter of debate. Indeed, in elderly subjects, the worsening of degenerative conditions of the spine can skew the lumbar spine BMD measurement [46–48].

As expected, BMD or BTM changes do not explain the entire antivertebral fracture efficacy of BZA. The relationship between BMD changes and fracture risk is confounded by other factors that contribute to the etiology of a vertebral fracture. One of these factors is the change in bone microarchitecture induced by BZA that could also contribute to the reduction of fracture that cannot be captured by BMD measurements [49, 50].

These observations of an association between BMD or BTM changes and fracture risk are supported by preclinical studies. Indeed, in animal models, BZA treatment was shown to maintain or increase BMD, preserve normal histological bone quality, and improve bone compressive strength [32].

This study has limitations. First, heterogeneity between the results of BZA 20 and 40 mg was observed. However, all results were analyzed using two statistical models that showed comparable results. It should also be pointed out that the combination of the two dosages of BZA did not improve the ability of BMD or BTMs to explain the fracture incidence reduction observed with BZA. It may be that the absence of substantial differences in the main results (i.e., in BMD, BTMs, and fracture incidence) observed between the two dosages could partly explain this fact [39, 51]. Second, BTMs and BMD were not assessed at every visit in every patient, mainly because of patient discontinuation from the study. However, the number of dropout patients (about 33 %) is not unexpected for a 3-year study on osteoporosis. Third, our analysis was based on measurements of BMD by DXA. It should also be acknowledged that imprecision in the measurement of BMD could affect the association between changes in BMD and reduction in fracture risk, even though BMD was assessed with strict quality control. Fourth, even if the total number of fractures was low, some fractures could have occurred just before BTM assessments; and it is well known that a recent fracture can influence BMT assessments [52, 53]. Lastly, inpatient variability of BTM measurements limits the transposition of these results in daily practice.

In conclusion, BMD and BTM changes account for a moderate proportion of fracture incidence (treatment effect) in women treated with BZA. However, at an individual patient level fracture risk reduction with BZA treatment cannot be reliably estimated from BTM or BMD changes.

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References

1. Miller PD (2005) Bone density and markers of bone turnover in predicting fracture risk and how changes in these measures predict fracture risk reduction. *Curr Osteoporos Rep* 3(3):103–110
2. Bonnick SL, Shulman L (2006) Monitoring osteoporosis therapy: bone mineral density, bone turnover markers, or both? *Am J Med* 119(Suppl 1):S25–S31
3. Miller PD (2007) Monitoring osteoporosis therapies. *Curr Osteoporos Rep* 5(1):38–43
4. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K et al (1993) Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet* 341(8837):72–75
5. Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL (1993) Long-term fracture prediction by bone mineral assessed at different skeletal sites. *J Bone Miner Res* 8(10):1227–1233
6. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 312(7041):1254–1259
7. Bruyere O, Varela AR, Adami S, Detilleux J, Rabenda V, Hilgsmann M et al (2009) Loss of hip bone mineral density over time is associated with spine and hip fracture incidence in osteoporotic postmenopausal women. *Eur J Epidemiol* 24(11):707–712
8. Seeman E (2007) Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? *Bone* 41(3):308–317
9. Bruyere O, Roux C, Badurski J, Isaia G, de Vernejoul MC, Cannata J et al (2007) Relationship between change in femoral neck bone mineral density and hip fracture incidence during treatment with strontium ranelate. *Curr Med Res Opin* 23(12):3041–3045
10. Bruyere O, Roux C, Detilleux J, Slosman DO, Spector TD, Fardellone P et al (2007) Relationship between bone mineral density changes and fracture risk reduction in patients treated with strontium ranelate. *J Clin Endocrinol Metab* 92(8):3076–3081
11. Chen P, Miller PD, Delmas PD, Misurski DA, Krege JH (2006) Change in lumbar spine BMD and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. *J Bone Miner Res* 21(11):1785–1790
12. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ et al (2002) Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med* 112(4):281–289
13. Delmas PD, Li Z, Cooper C (2004) Relationship between changes in bone mineral density and fracture risk reduction with antiresorptive drugs: some issues with meta-analyses. *J Bone Miner Res* 19(2):330–337
14. Delmas PD, Seeman E (2004) Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. *Bone* 34(4):599–604
15. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD (2002) Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab* 87(4):1586–1592
16. Hochberg MC, Ross PD, Black D, Cummings SR, Genant HK, Nevitt MC et al (1999) Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group. *Arthritis Rheum* 42(6):1246–1254
17. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD (2002) Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. *J Bone Miner Res* 17(1):1–10
18. Wasnich RD, Miller PD (2000) Antifracture efficacy of antiresorptive agents are related to changes in bone density. *J Clin Endocrinol Metab* 85(1):231–236
19. Rabenda V, Bruyere O, Reginster JY (2011) Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression. *Osteoporos Int* 22(3):893–901
20. Austin M, Yang YC, Vittinghoff E, Adami S, Boonen S, Bauer DC et al (2012) Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res* 27(3):687–693
21. Vasikaran S, Eastell R, Bruyere O, Foldes AJ, Garnero P, Griesmacher A et al (2011) Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 22(2):391–420
22. Chen P, Satterwhite JH, Licata AA, Lewiecki EM, Sipos AA, Misurski DM et al (2005) Early changes in biochemical markers of

- bone formation predict BMD response to teriparatide in postmenopausal women with osteoporosis. *J Bone Miner Res* 20(6):962–970
23. Bauer DC, Garnero P, Bilezikian JP, Greenspan SL, Ensrud KE, Rosen CJ et al (2006) Short-term changes in bone turnover markers and bone mineral density response to parathyroid hormone in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 91(4):1370–1375
 24. Reginster JY, Sarkar S, Zegels B, Henrotin Y, Bruyere O, Agnusdei D et al (2004) Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. *Bone* 34(2):344–351
 25. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD (2003) Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res* 18(6):1051–1056
 26. Bjarnason NH, Sarkar S, Duong T, Mitlak B, Delmas PD, Christiansen C (2001) Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. *Osteoporos Int* 12(11):922–930
 27. Bauer DC, Black DM, Garnero P, Hochberg M, Ott S, Orloff J et al (2004) Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. *J Bone Miner Res* 19(8):1250–1258
 28. Garnero P (2008) Biomarkers for osteoporosis management: utility in diagnosis, fracture risk prediction and therapy monitoring. *Mol Diagn Ther* 12(3):157–170
 29. Delmas PD, Munoz F, Black DM, Cosman F, Boonen S, Watts NB et al (2009) Effects of yearly zoledronic acid 5 mg on bone turnover markers and relation of PINP with fracture reduction in postmenopausal women with osteoporosis. *J Bone Miner Res* 24(9):1544–1551
 30. Bruyere O, Collette J, Rizzoli R, Decock C, Ortolani S, Cormier C et al (2010) Relationship between 3-month changes in biochemical markers of bone remodelling and changes in bone mineral density and fracture incidence in patients treated with strontium ranelate for 3 years. *Osteoporos Int* 21(6):1031–1036
 31. Chines AA, Komm BS (2009) Bazedoxifene acetate: a novel selective estrogen receptor modulator for the prevention and treatment of postmenopausal osteoporosis. *Drugs Today (Barc)* 45(7):507–520
 32. Palacios S (2010) Efficacy and safety of bazedoxifene, a novel selective estrogen receptor modulator for the prevention and treatment of postmenopausal osteoporosis. *Curr Med Res Opin* 26(7):1553–1563
 33. Christiansen C, Chesnut CH III, Adachi JD, Brown JP, Fernandes CE, Kung AW et al (2010) Safety of bazedoxifene in a randomized, double-blind, placebo- and active-controlled phase 3 study of postmenopausal women with osteoporosis. *BMC Musculoskelet Disord* 11:130
 34. de Villiers TJ, Chines AA, Palacios S, Lips P, Sawicki AZ, Levine AB et al (2011) Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. *Osteoporos Int* 22(2):567–576
 35. Harvey JA, Holm MK, Ranganath R, Guse PA, Trott EA, Helzner E (2009) The effects of bazedoxifene on mammographic breast density in postmenopausal women with osteoporosis. *Menopause* 16(6):1193–1196
 36. Itabashi A, Yoh K, Chines AA, Miki T, Takada M, Sato H et al (2011) Effects of bazedoxifene on bone mineral density, bone turnover, and safety in postmenopausal Japanese women with osteoporosis. *J Bone Miner Res* 26(3):519–529
 37. Kanis JA, Johansson H, Oden A, McCloskey EV (2009) Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX. *Bone* 44(6):1049–1054
 38. Pinkerton JV, Archer DF, Utian WH, Menegoci JC, Levine AB, Chines AA et al (2009) Bazedoxifene effects on the reproductive tract in postmenopausal women at risk for osteoporosis. *Menopause* 16(6):1102–1108
 39. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ et al (2008) Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res* 23(12):1923–1934
 40. Genant HK, Wu CY, van Kuijk C, Nevitt MC (1993) Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 8(9):1137–1148
 41. Li Z, Meredith MP, Hoseyni MS (2001) A method to assess the proportion of treatment effect explained by a surrogate endpoint. *Stat Med* 20(21):3175–3188
 42. Li Z, Chines AA, Meredith MP (2004) Statistical validation of surrogate endpoints: is bone density a valid surrogate for fracture? *J Musculoskelet Neuronal Interact* 4(1):64–74
 43. Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP et al (2004) Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. *J Clin Densitom* 7(3):255–261
 44. Chapurlat RD, Palermo L, Ramsay P, Cummings SR (2005) Risk of fracture among women who lose bone density during treatment with alendronate. *The Fracture Intervention Trial. Osteoporos Int* 16(7):842–848
 45. Solomon DH, Avorn J, Katz JN, Finkelstein JS, Arnold M, Polinski JM et al (2005) Compliance with osteoporosis medications. *Arch Intern Med* 165(20):2414–2419
 46. Liu G, Peacock M, Eilam O, Dorulla G, Braunstein E, Johnston CC (1997) Effect of osteoarthritis in the lumbar spine and hip on bone mineral density and diagnosis of osteoporosis in elderly men and women. *Osteoporos Int* 7(6):564–569
 47. Kleerekoper M, Villanueva AR, Stanciu J, Rao DS, Parfitt AM (1985) The role of three-dimensional trabecular microstructure in the pathogenesis of vertebral compression fractures. *Calcif Tissue Int* 37(6):594–597
 48. Legrand E, Chappard D, Pascaretti C, Duquenne M, Krebs S, Rohmer V et al (2000) Trabecular bone microarchitecture, bone mineral density, and vertebral fractures in male osteoporosis. *J Bone Miner Res* 15(1):13–19
 49. Boonen S, Haentjens P, Vandenput L, Vanderschueren D (2004) Preventing osteoporotic fractures with antiresorptive therapy: implications of microarchitectural changes. *J Intern Med* 255(1):1–12
 50. Borah B, Dufresne TE, Cockman MD, Gross GJ, Sod EW, Myers WR et al (2000) Evaluation of changes in trabecular bone architecture and mechanical properties of minipig vertebrae by three-dimensional magnetic resonance microimaging and finite element modeling. *J Bone Miner Res* 15(9):1786–1797
 51. Miller PD, Chines AA, Christiansen C, Hoeck HC, Kendler DL, Lewiecki EM et al (2008) Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. *J Bone Miner Res* 23(4):525–535
 52. Hashidate H, Kamimura M, Nakagawa H, Takahara K, Ikegami S, Uchiyama S et al (2011) Early changes in bone specific turnover markers during the healing process after vertebral fracture. *Open Orthop J* 5:32–36
 53. Obrant KJ, Ivaska KK, Gerdhem P, Alatalo SL, Pettersson K, Vaananen HK (2005) Biochemical markers of bone turnover are influenced by recently sustained fracture. *Bone* 36(5):786–792