

# Cost-effectiveness of bazedoxifene versus raloxifene in the treatment of postmenopausal women in Spain

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**Background:** The purpose of this study was to assess the cost-effectiveness of bazedoxifene and raloxifene for prevention of vertebral and nonvertebral fractures among postmenopausal Spanish women aged 55–82 years with established osteoporosis and a high fracture risk.

**Methods:** A Markov model was developed to represent the transition of a cohort of postmenopausal osteoporotic women through different health states, ie, patients free of fractures, patients with vertebral or nonvertebral fractures, and patients recovered from a fracture. Efficacy data for bazedoxifene were obtained from the Osteoporosis Study. The perspective of the Spanish National Health Service was chosen with a time horizon of 27 years. Costs were reported in 2010 Euros. Deterministic results were presented as expected cost per quality-adjusted life-year (QALY), and probabilistic results were represented in cost-effectiveness planes.

**Results:** In deterministic analysis, the expected cost per patient was higher in the raloxifene cohort (€13,881) than in the bazedoxifene cohort (€13,436). QALYs gained were slightly higher in the bazedoxifene cohort (14.56 versus 14.54). Results from probabilistic sensitivity analysis showed that bazedoxifene has a slightly higher probability of being cost-effective for all threshold values independent of the maximum that the National Health Service is willing to pay per additional QALY.

**Conclusion:** Bazedoxifene was shown to be a cost-effective treatment option for the prevention of fractures in Spanish women with postmenopausal osteoporosis and a high fracture risk. When comparing bazedoxifene with raloxifene, it may be concluded that the former is the dominant strategy.

**Keywords:** osteoporosis, bazedoxifene, raloxifene, vertebral, nonvertebral, fracture, efficacy, costs

## Introduction

Osteoporosis is a frequently occurring disease in postmenopausal women, characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in increased bone fragility and fracture risk.<sup>1,2</sup> Osteoporotic fractures commonly occur at the hip, spine, and forearm, with vertebral fractures being the most frequent.<sup>3</sup> Of all patients who sustain a vertebral fracture, it is estimated that 20% will suffer a new vertebral fracture within 1 year.<sup>4</sup> Of all osteoporotic fractures, hip fractures are the most serious, with an elevated mortality risk as well as a high hospital burden in Spain.<sup>5</sup>

Osteoporosis has been a growing economic issue due to the increased number of fractures during the last 20 years, combined with the development of novel agents for the prevention and treatment of osteoporosis.<sup>6</sup> Aside from the economic

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consequences, osteoporosis also has a negative impact on quality of life for the affected individual.<sup>7</sup> The high impact of these socioeconomic consequences makes osteoporosis a high priority health problem.

Over the last decade, various new treatments for the prevention of osteoporotic fractures have been developed and approved. Although existing therapies for postmenopausal osteoporosis have been shown to be effective, they may not be appropriate for all women because of concerns related to safety and/or tolerability.<sup>8,9</sup> One of the currently available therapies is raloxifene, a selective estrogen receptor modulator (SERM) that has been shown to reduce the risk of vertebral fractures in postmenopausal women.<sup>10</sup> Another selective estrogen receptor modulator, bazedoxifene, has been shown to prevent bone loss and to decrease bone turnover, with a favorable endometrial, ovarian, and breast safety profile in a 2 year, Phase III study of postmenopausal women at risk for osteoporosis.<sup>11–13</sup> A 3 year, global Phase III study in osteoporotic women aged 55 years, ie, the Osteoporosis Study,<sup>14</sup> compared bazedoxifene with placebo and raloxifene. Bazedoxifene and raloxifene both reduced the risk of new vertebral fractures compared with placebo. In a post hoc subgroup analysis of patients at higher risk, bazedoxifene significantly reduced the risk of nonvertebral fractures compared with placebo and raloxifene.<sup>14</sup> Higher-risk patients were defined as women with a femoral neck T score  $\leq -3.0$  and/or at least a moderate to severe vertebral fracture or multiple mild vertebral fractures. Many participants in the Osteoporosis Study participated in a 2 year extension study in which bazedoxifene showed sustained efficacy in preventing fractures over 5 years of therapy.<sup>15</sup>

Approximately two million women were estimated to have osteoporosis in Spain in 2010.<sup>16</sup> It is important to evaluate both clinical and economic implications with the introduction of a new treatment, given that treating this population is associated with a high socioeconomic burden. Clinical aspects are normally investigated in clinical trials within a controlled setting and a limited time frame. In the case of osteoporosis, economic modeling is necessary to study the long-term consequences of fracture risk reduction beyond the time frames of clinical trials.

In Spain, several studies have investigated the socioeconomic impact of treatment of osteoporosis to the Spanish National Health Service, as well as for patients.<sup>17–20</sup> Cost-effectiveness analyses of osteoporosis vary considerably between countries.<sup>18</sup> Different tools are being used to estimate fracture risk, which can significantly impact the cost-effectiveness of treatment. A recent cost-effectiveness analysis comparing bazedoxifene with placebo used the FRAX<sup>®</sup> tool (World Health Organization

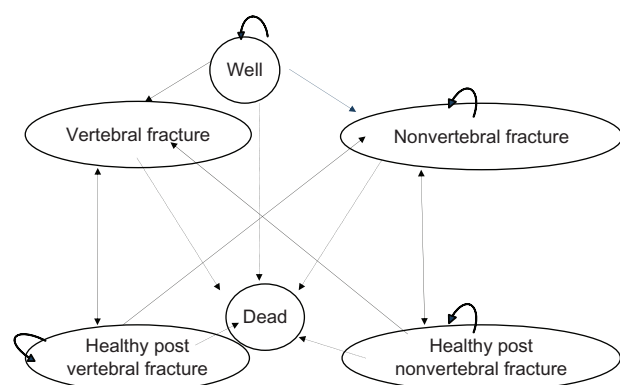
Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK) that provides fracture probabilities for specific populations.<sup>18</sup> Although FRAX can be used to predict the probability of hip or other major osteoporotic fractures, the criteria should not be generalized to other countries having different fracture incidence rates and health care costs.<sup>21</sup> Therefore, when comparing the cost-effectiveness of bazedoxifene with raloxifene in Spanish women with osteoporosis, it is important to take into account that the incidence of fractures is different between southern European countries and countries in the Scandinavian region.<sup>22,23</sup> The objective of this study was to compare the cost-effectiveness of bazedoxifene and raloxifene in the prevention of vertebral and nonvertebral fractures in women diagnosed with osteoporosis. The analysis is based on the Osteoporosis Study<sup>14</sup> and applied to the Spanish setting.

## Materials and methods

### Model specifications

The computer simulation model in Microsoft<sup>®</sup> (Microsoft Corporation, Redmond, WA, USA) Excel used to calculate cost-effectiveness was an updated Markov model that has been used previously to estimate the cost-effectiveness of bazedoxifene incorporating the FRAX algorithm from a European perspective.<sup>18</sup> The model represented the transition of a cohort of postmenopausal women with osteoporosis and aged 55 years through various health states with occurrence of events based on yearly probabilities. The starting age was based on women recruited for a 3 year clinical study of bazedoxifene.<sup>14</sup> The analysis was performed from the health care perspective, following all patients from initiation of treatment until they were 82 years of age and had received bazedoxifene or raloxifene for this 27-year time period. It was assumed that no patient discontinued treatment because of adverse effects.

The model consisted of six health states. All patients began in the “well health” or “no event state”. In each cycle, a patient had a probability of sustaining a fracture, remaining healthy, or dying. After 1 year in any fracture state, the patient had a risk of sustaining a new fracture or dying. If a patient died, she would move to the dead-health state and remain there for the rest of the simulation. After 1 year, the patient moved to the corresponding post-fracture state if no additional fracture occurred. The patient would automatically remain in the post-fracture state (shown as a circular arrow in Figure 1) if she did not die or sustain a new fracture. Fractures could be vertebral or nonvertebral, with half consisting of hip fractures and half consisting of wrist fractures. After a nonvertebral fracture, it was possible



**Figure 1** Graphic representation of the model.

to sustain a vertebral fracture or another nonvertebral fracture.

## Target patient groups, efficacy, and side effects

The Osteoporosis Study<sup>14</sup> was a 3-year, randomized, double-blind, placebo-controlled and active-controlled trial including 7,492 healthy postmenopausal osteoporotic women aged 55–82 years. All women were at least 2 years postmenopausal and had osteoporosis. Osteoporosis was defined as low bone mineral density with a T score between  $-2.5$  and  $-4.0$ , or radiographically confirmed vertebral fractures and lumbar spine and femoral neck bone mineral density T scores not worse than  $-4.0$ . Women were excluded if they had diseases that may affect bone metabolism, conditions that could interfere with bone mineral densitometry, pathologic vertebral fractures, vasomotor symptoms requiring treatment, or serious conditions (endometrial hyperplasia or carcinoma, abnormal vaginal bleeding, malignancy within 10 years of the study, endocrine disorders requiring treatment, or untreated malabsorption disorders). Women with an active or past history of deep vein thrombosis, pulmonary embolism, or retinal vein thrombosis were also excluded, as were subjects with elevated fasting total cholesterol or triglyceride levels ( $\geq 310$  mg/dL or  $\geq 300$  mg/dL, respectively). Use of androgens, systemic estrogen (except for estriol 2.0 mg/day), topical estrogen (more than three times per week), progestagens, selective estrogen receptor modulators, bisphosphonates, calcitonin, parathyroid hormone, and cholecalciferol ( $> 50,000$  IU/week) was prohibited within 6 months of screening.

Subjects were assigned to treatment using a computerized randomization/enrolment system, which assigned unique randomization and package numbers. Randomization was stratified by prevalent vertebral fracture status to ensure a

similar distribution of subjects with and without vertebral fractures across the treatment groups.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the clinical ethics research committee or institutional review board at each institution.

Patients were randomly assigned to each treatment group and received at least one dose of study medication, ie, bazedoxifene 20 mg daily ( $n = 1886$ ), bazedoxifene 40 mg daily ( $n = 1872$ ), raloxifene 60 mg daily ( $n = 1849$ ), or placebo ( $n = 1885$ ) for 36 months. From the total number of eligible patients, the proportion of patients completing the study was 66% for those receiving bazedoxifene 20 mg or 40 mg daily, 68% for those receiving bazedoxifene 60 mg daily, and 67% for those receiving placebo. Approximately 56% of participants in each treatment group had at least one vertebral fracture at baseline, and the majority had one mild vertebral fracture. The base-case populations in this study for the comparison of bazedoxifene and raloxifene were based on a subgroup of high-risk patients with a T score  $\leq -3.0$  or at least one moderate fracture or multiple mild vertebral fractures. Patients receiving bazedoxifene 20 mg daily or raloxifene 60 mg daily were compared.

For osteoporotic patients without fractures, a relative risk reduction for vertebral fractures of 35% (95% confidence interval [CI] 0.32–1.30) was seen in patients treated with bazedoxifene versus 41% (95% CI 0.29–1.21) for those treated with raloxifene (Table 1). Relative risk reductions were 45% (95% CI 0.32–0.94) for bazedoxifene versus 43% (95% CI 0.34–0.97) for raloxifene in patients with previous vertebral fractures (Table 1). No differences in the incidence of nonvertebral fractures were observed between either treatment in women without prior fractures, although the reduced relative risk in high-risk patients with previous fractures was 46% with bazedoxifene and 8% with raloxifene.

Bazedoxifene and raloxifene were associated with a number of adverse events, including leg cramps, venous thrombotic events such as deep vein thrombosis, and breast cysts/fibrocystic breast disease.<sup>14</sup> To account for these adverse events, costs and utilities for each health state were corrected based on their incidences. The incidence of leg cramps was significantly different between the groups, with an incidence of 10.9% on bazedoxifene versus 11.7% on raloxifene ( $P < 0.01$ ). The incidence of deep vein thrombosis was 0.4% in both groups and the incidence of breast cysts/fibrocystic breast disease was 0.7 in the bazedoxifene group and 1.7% in the raloxifene group ( $P < 0.05$ ).

**Table 1** Transition probabilities for bazedoxifene 20 mg/day and raloxifene 60 mg/day

Bazedoxifene	Well	Vertebral fracture	Nonvertebral fracture	Healthy nonvertebral fracture	Healthy nonvertebral fracture	Dead
Well	0.94479 <sup>a</sup>	0.00901 <sup>b,c</sup>	0.024 <sup>b,d</sup>	0	0	0.022 <sup>e</sup>
Vertebral fracture	0	0	0	0.9768120 <sup>a</sup>	0	0.023188 <sup>e</sup>
Nonvertebral fracture	0	0	0.1384667 <sup>b,f</sup>	0	0.8351333 <sup>a</sup>	0.0264 <sup>g</sup>
Healthy vertebral fracture	0	0.0275706 <sup>b,h</sup>	0.1986292 <sup>b,i</sup>	0.7506122 <sup>a</sup>	0	0.023188 <sup>l</sup>
Healthy nonvertebral fracture	0	0.0103615 <sup>b</sup>	0.0528313 <sup>h</sup>	0	0.9126072 <sup>a</sup>	0.0242 <sup>k</sup>
Dead	0	0	0	0	0	1
Raloxifene	Well					
Well	0.944994 <sup>a</sup>	0.008806 <sup>b,c</sup>	0.024 <sup>b,d</sup>	0	0	0.022 <sup>e</sup>
Vertebral fracture	0	0	0	0.9768120 <sup>a</sup>	0	0.023188 <sup>e</sup>
Nonvertebral fracture	0	0	0.1897467 <sup>b,f</sup>	0	0.7838533 <sup>a</sup>	0.0264 <sup>g</sup>
Healthy vertebral fracture	0	0.0271577 <sup>b,h</sup>	0.2287228 <sup>b,i</sup>	0.7209315 <sup>a</sup>	0	0.023188 <sup>l</sup>
Healthy nonvertebral fracture	0	0.0100682 <sup>b</sup>	0.0608356 <sup>h</sup>	0	0.90489624 <sup>a</sup>	0.0242 <sup>k</sup>
Dead	0	0	0	0	0	1

**Notes:** <sup>a</sup>Residual probability; <sup>b</sup>Silverman et al<sup>14</sup>; <sup>c</sup>Felsenberg et al<sup>23</sup>; <sup>d</sup>Marin et al<sup>24</sup>; <sup>e</sup>Ministerio de Sanidad, Política Social e Igualdad (MSP)<sup>25</sup>; <sup>f</sup>Christodoulou and Cooper<sup>45</sup>; <sup>g</sup>Sociedad Navarra de Medicina de Familia y Atención Primaria. Documento para el Manejo de la Osteoporosis en Atención Primaria (SNAMFAP)<sup>27</sup>; <sup>h</sup>Sociedad Española de Investigaciones Óseas y Metabolismo Mineral (SEIOMM)<sup>7</sup>; <sup>i</sup>Naves et al<sup>46</sup>; <sup>j</sup>Agència d'Informació, Avaluació i Qualitat en Salut. (AIAQS)<sup>26</sup>; <sup>k</sup>Borgstrom et al<sup>33</sup>. All probabilities without notes are based on assumption.

## Incidence and fracture risk

Country-specific and age-specific normal population incidences were used when possible. A vertebral fracture can be classified as a clinical fracture (ie, symptomatic fractures that come to clinical attention) or as a morphometric fracture, which includes all fractures, both symptomatic and asymptomatic. The morphometric definition of a fracture was used for this study because it provided more specific incidence data, with an age-standardized incidence ratio of 10.2 (95% CI 4.7–15.7) per 1000 habitants for the female southern European population because clinical fracture data were lacking.<sup>23</sup>

Incidence rates for nonvertebral fractures (ratio 24.2 [95% CI 21.70–26.70]) nonvertebral fractures per 1,000 female inhabitants) were obtained from Marin et al<sup>24</sup> and consisted mostly of wrist fractures (36.7%) and hip fractures (14.9%). Population fracture incidence rates were adjusted to reflect the risk in each treatment group.

The probability of having a new fracture, a second fracture, or remaining healthy was determined by the relative risk of vertebral or nonvertebral fractures affected by treatment with bazedoxifene or raloxifene based on the Osteoporosis Study<sup>14</sup> (Table 1).

## Mortality

Age-specific normal population mortality rates were obtained from the Spanish National Statistics Agency.<sup>25</sup> These were adjusted in the model to take into account mortality associated with fractures.<sup>18</sup> In this analysis, we derived estimates of the excess mortality after vertebral fractures from a study based on Spanish patients which showed an increase in mortality

of 20%–34% within 5 years of the fracture.<sup>26</sup> The relative risk in the year after a vertebral fracture was estimated at 5.4 and was similar in subsequent years. The relative risk of mortality in the year after a nonvertebral fracture was 20.<sup>27</sup> The relative risk of excess mortality in the years subsequent to a nonvertebral fracture were estimated at 30, mostly attributable to hip fractures, although there are studies which claim there is little or no relationship between comorbid conditions and post-fracture mortality.<sup>17</sup> Based on this study, a relative risk of 10 was assumed for patients who sustained a nonvertebral fracture in subsequent years, because these not only included hip fractures but also wrist fractures.

## Quality of life

Utility weights were derived from a global longitudinal study of 57,141 postmenopausal osteoporotic women aged 55 years and older that examined health-related quality of life in women who sustained fractures and the effect of fracture location on their quality of life.<sup>28</sup> Utility values were elicited using the EQ-5D<sup>®</sup> and Short-Form 36 subscales mapped to a country-specific preference-based value. The reduction in quality of life after a vertebral fracture was 38% lower than that observed in a healthy individual. Reduction in quality of life after a nonvertebral fracture estimated based on reductions for hip and wrist fractures was 39%, of which 55% was caused by hip fractures. Reduction in quality of life in the years following a vertebral fracture was 9% lower than that of a healthy individual. A 6% reduction in quality of life was estimated for hip and wrist fractures in the years following a nonvertebral fracture.

Venous thrombolytic events, primarily deep vein thrombosis, were assumed to be associated with a 10% utility loss per year based on assumptions in previous publications.<sup>29,30</sup> No appropriate estimate was found for utility loss due to leg cramps and breast cysts/fibrocystic breast disease. A similar 10% decrease in quality of life was assumed for leg cramps and breast cysts/fibrocystic breast disease as for deep vein thrombosis in all health states. Based on the incidence rates of adverse events for both treatments, utilities were corrected for the decrease in quality of life associated with adverse events (Table 2).

## Costs

Treatment costs for osteoporosis consisted of drug costs, diagnostic and follow-up tests, and physician visits. Costs were represented in 2010 Euros and discounted according to health economic guidelines, resulting in a 3% discount for costs and benefits.<sup>31</sup> Drug tariffs were derived from a Spanish drug cost database.<sup>32</sup> Drug costs for bazedoxifene were assumed to be similar to those for raloxifene. Monitoring of treatment for osteoporosis was estimated to include annual physician visit and annual bone mineral density measurement, based on other studies and expert opinion.<sup>33,34</sup>

Event-related fracture resource utilization was obtained by expert consultation. Vertebral fractures were assumed to be associated with 2 days of hospitalization. Outpatient treatment comprised of two imaging procedures, three specialist visits, and concomitant medication such as analgesics over 90 days. Vertebral fracture costs resulted in approximately €3878 per event.

Nonvertebral fracture costs were assumed to consist of 50% hip fractures and 50% wrist fractures. Hip fractures were associated with 15 hospitalization days and similar

outpatient treatment to that for vertebral fractures, including additional rehabilitation costs during a 40-day period. Wrist fractures included four hospitalization days, surgery costs, and outpatient treatment similar to that for hip fractures, with one less imaging procedure. Nonvertebral fracture costs were estimated at €7,478 per event (Table 3).

Resource utilization associated with the treatment of adverse events such as leg cramps, deep vein thrombosis, and breast cysts/fibrocystic breast disease, was added to all health states based on the treatment-related incidence and expert validation (Table 4). Treatment of leg cramps and breast cysts/fibrocystic breast disease was associated with one diagnostic test and one specialist physician visit per year. Management of deep vein thrombosis included several diagnostic tests, a specialist physician visit, and use of concomitant medication.

**Table 3** Osteoporosis treatment and fractures: resource utilization in units and costs

	Units	Cost (EUR) 2010
<b>Treatment</b>		
Drug costs		287 <sup>a</sup>
Conventional blood test	1	21 <sup>b</sup>
Bone density scan	1	165 <sup>c</sup>
Visit to rheumatologist	1.5	69 <sup>d</sup>
Annual treatment costs		576
<b>Vertebral fracture</b>		
Hospitalization vertebral fracture (average 2 days)		3,513.90 <sup>e</sup>
Radiography	1	32.80 <sup>f</sup>
Bone scan	1	232.34 <sup>g</sup>
Visit to orthopedic surgeon	2	44.10 <sup>d</sup>
Analgesics (2 tablets/day, 90 days)		0.06 <sup>a</sup>
Annual treatment costs		3878
<b>Nonvertebral fracture</b>		
Hip fracture		
Hospitalization hip fracture (average 15 days)		7,956.70 <sup>e</sup>
Visits to orthopedic surgeon	3	44.10 <sup>d</sup>
Radiography	2	32.80 <sup>f</sup>
Rehabilitation (40 days)		52.87 <sup>b</sup>
Analgesics (2 tablets/day, 90 days)		0.06 <sup>a</sup>
Wrist fracture		
Surgery	1	96.97 <sup>h</sup>
Hospitalization wrist fracture (average of 4 days)	4	555.71 <sup>d</sup>
Visits to orthopedic surgeon	3	44.10 <sup>d</sup>
Radiography	3	32.80 <sup>f</sup>
Rehabilitation (40 days)		52.87 <sup>b</sup>
Analgesics (2 tablets/day, during 90 days)		0.06 <sup>a</sup>
Annual treatment costs (50% hip and 50% wrist)		7478

**Table 2** Utilities

Health condition	Utility <sup>a</sup>	Corrected utility for adverse events	
		Bazedoxifene <sup>b</sup>	Raloxifene <sup>b</sup>
Well	1	0.996	0.9954
Vertebral fracture	0.620	0.61752	0.617148
Nonvertebral fracture	0.651	0.647898	0.6475077
Healthy post vertebral fracture	0.910	0.90636	0.905814
Healthy post nonvertebral fracture	0.940	0.9358416	0.93527784
QoL loss due to each adverse event of 10% <sup>c,d,e</sup>	-0.1	—	—

**Notes:** <sup>a</sup>Includes assumption; <sup>b</sup>Adachi et al<sup>28</sup>; <sup>c</sup>Silverman et al<sup>14</sup>; <sup>d</sup>Sobocki et al<sup>29</sup>; <sup>e</sup>Zethraeus et al<sup>30</sup>.

**Abbreviation:** QoL, quality of life.

**Notes:** <sup>a</sup>Vademecum<sup>32</sup>; <sup>b</sup>Hospital Lluís Alcanyis<sup>47</sup>; <sup>c</sup>Hospital de la Esperanza<sup>48</sup>; <sup>d</sup>Instituto Nacional de la Salud (INSALUD)<sup>49</sup>; <sup>e</sup>Finnern and Sykes<sup>50</sup>; <sup>f</sup>Cernuda<sup>51</sup>; <sup>g</sup>Diari Oficial de la Generalitat de Catalunya (DOGC)<sup>52</sup>; <sup>h</sup>DOGC<sup>53</sup>.



**Table 4** Adverse events: resource utilization in units and costs

Adverse events	Units	Cost (€) 2010
<b>Leg cramps</b>		
Basic analyses: blood, biochemistry, electrolytes	1	39 <sup>a</sup>
Visit to specialist physician	1	46 <sup>b</sup>
Annual treatment costs		85
<b>Deep vein thrombosis</b>		
Basic analyses: blood, biochemistry, ions	1	39 <sup>a</sup>
Doppler echocardiogram	1	70 <sup>b</sup>
Plethysmography of legs	1	111 <sup>b</sup>
Venography	1	79 <sup>b</sup>
Visit to specialist physician	1	46 <sup>b</sup>
Heparin sodium (injection 5000 UI/mL, 5 days)		1.83 <sup>c</sup>
Warfarin (5 mg/day, 40 days)		2.30 <sup>c</sup>
Annual treatment costs		349
<b>Breast cysts/fibrocystic breast disease</b>		
Mammography	1	128 <sup>b</sup>
Visit to specialist physician	1	46 <sup>b</sup>
Annual treatment costs		174

**Notes:** <sup>a</sup>Diari Oficial de la Generalitat de Catalunya (DOGC)<sup>53</sup>; <sup>b</sup>Boletín Oficial De La Rioja (BOR)<sup>54</sup>; <sup>c</sup>Vademecum<sup>32</sup>.

## Analyses

In this study, quality-adjusted life-years (QALYs) gained was included as an effectiveness measure to allow us to compare the value of the interventions across different disease states. The incremental cost-effectiveness ratio (ICER), which is a measure of the cost per QALY gained in this study, is defined as:

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{C_{\text{bazedoxifene}} - C_{\text{raloxifene}}}{E_{\text{bazedoxifene}} - E_{\text{raloxifene}}}$$

where  $\Delta C$  is the difference in cost between treatment with bazedoxifene and raloxifene and  $\Delta E$  is the difference in effectiveness (QALYs) between each treatment. The ICER could be computed from the main outputs, cost, and QALYs in this model.

The variation in effects, in terms of both reduced fracture risk and utilities, as well as direct health care costs, was included in the probabilistic sensitivity analysis, which was done using statistical distributions to capture parameter uncertainty. We used beta and gamma distributions for probabilities and costs, respectively. The results from 1000 cohort iterations were presented as cost-effectiveness acceptability curves and as a scattered plot in the incremental cost-effectiveness plane.

## Results

The base-case analysis consisted of postmenopausal women with established osteoporosis aged 55 years. Health care

costs for treatment of osteoporosis and fractures per patient were similar for both treatment groups but, corrected for the incidence of adverse events, resulted in a slightly higher event cost for raloxifene than for bazedoxifene (Table 5).

Deterministic results using a 27-year horizon showed that the expected cost per patient was higher in the raloxifene cohort (€13,436) than in the bazedoxifene cohort (€13,381, Table 6). The estimated gain in QALYs was slightly higher in the bazedoxifene cohort than in the raloxifene cohort (14.56 versus 14.54). The ICER showed bazedoxifene to be the dominant treatment strategy, being less costly (by €444) and more effective (+0.03 QALYs) compared with raloxifene.

## Sensitivity analysis

The probabilistic analysis showed a large variation in both costs and effects when introducing uncertainty around the input parameters. Cost-effectiveness acceptability curves showed that treatment with bazedoxifene had a higher probability of being cost-effective than treatment with raloxifene using alternative values up to €50,000 for the maximum willingness to pay for an additional QALY gained by the National Health Service (Figure 2). If taking into account the commonly, albeit not officially, accepted willingness-to-pay threshold of €30,000 for a QALY in the health care sector in Spain,<sup>35</sup> bazedoxifene is a cost-effective option.

The mean incremental QALY and cost gain amounted to 0.16 and –€428, respectively, which showed that bazedoxifene was the dominant treatment strategy (Figure 3). The incremental costs were scattered on both sides of the  $x$  axis, indicating that bazedoxifene generates cost savings (52% of observations were below the  $x$  axis). Fifty-one percent of the observations were located on the right of the  $y$  axis, indicating observations where the gain in QALYs was higher for bazedoxifene. According to the probabilistic sensitivity analysis, bazedoxifene generated greater health benefit in terms of QALYs gained, but at less cost.

**Table 5** Annual cost per health state

Health state	Cost (€) 2010	Corrected costs for adverse events	
		Bazedoxifene	Raloxifene
Well	576	580	581
Vertebral fracture	3878	4458	4459
Nonvertebral fracture	7478	8058	8059
Healthy post vertebral fracture	576	580	581
Healthy post nonvertebral fracture	576	580	581

**Table 6** Total cost, incremental costs, QALY, QALYs gained, and ICER

Treatment	Cost (€)	Incremental costs	QALY	QALYs gained	ICER (€/QALY)
Bazedoxifene	13,436	-444 €	14.56	+0.02	Dominant
Raloxifene	13,881		14.54		

**Abbreviations:** QALY, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio.

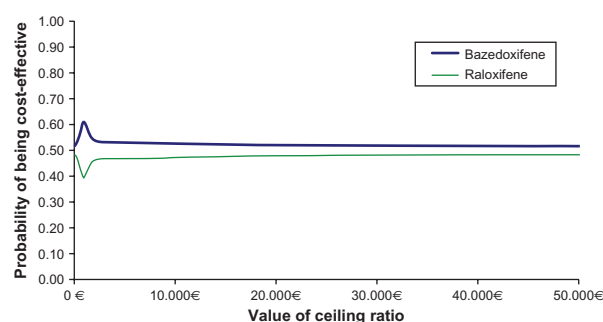
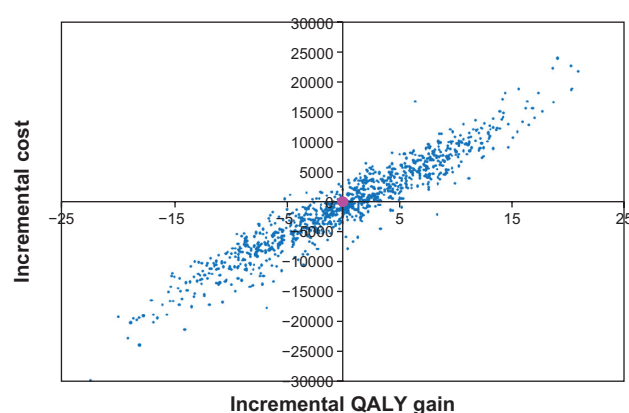
## Discussion

This study investigated the cost-effectiveness of bazedoxifene compared with raloxifene in postmenopausal Spanish women with osteoporosis using effectiveness data from the Osteoporosis Study.<sup>14</sup> The results of this study indicate that bazedoxifene was the dominant treatment strategy compared with raloxifene for the prevention of vertebral and nonvertebral fractures in high-risk postmenopausal osteoporotic women aged 55–82 years.

Probabilistic sensitivity analysis that accounted for parameter uncertainty confirmed the deterministic results. Treatment with bazedoxifene demonstrated a higher probability of being cost-effective than treatment with raloxifene up to a maximum of €50,000 for willingness to pay for an additional QALY gained.

Although no guidelines are available in Spain to determine whether an intervention can be considered cost-effective, a nonofficial threshold of €30,000 for a QALY is considered acceptable, and compares favorably with other medical and surgical procedures.<sup>35</sup> When this threshold is taken into account, bazedoxifene was a cost-effective treatment option compared with raloxifene.

Any conclusions from this study need to be placed into the context of assumptions made for this model. Important issues to consider are the epidemiology, morbidity, and mortality associated with vertebral and nonvertebral fractures, as well as adverse events arising from both treatments. These issues have been addressed as much as possible by assuming

**Figure 2** Cost-effectiveness acceptability curves: bazedoxifene versus raloxifene.**Figure 3** Cost-effectiveness of bazedoxifene versus raloxifene in postmenopausal women with osteoporosis.

**Abbreviation:** QALY, quality-adjusted life-years.

conservative scenarios or by including a probabilistic sensitivity analysis.

The general conclusions of this study are primarily based on vertebral and nonvertebral fracture outcomes and the effect of adverse events associated with both treatments. From our results, it is apparent that the effect of treatment on fracture risk and adverse events related to both treatments are important drivers for cost-effectiveness.

In the base case, treatment effects for the prevention of vertebral fractures and nonvertebral fractures with or without previous fractures were based on a head-to-head comparison of bazedoxifene with raloxifene.<sup>14</sup> Relative risk reductions for vertebral fractures were higher for the raloxifene cohort, although relative risks were lower for patients in the bazedoxifene cohort who had sustained earlier vertebral and nonvertebral fractures. Differences in relative risk reduction for nonvertebral fractures after prior fractures were larger and more favorable for bazedoxifene. No treatment effect was assumed for nonvertebral fractures in patients without fractures because the fracture incidence did not differ significantly from placebo.<sup>14</sup> Similar results were found comparing raloxifene with placebo in the Multiple Outcomes of Raloxifene Evaluation study.<sup>10</sup> If effects on nonvertebral fractures in patients without prior fractures were included, these could further improve cost-effectiveness.

Adverse events associated with both treatments were obtained from the Osteoporosis Study.<sup>14</sup> The main effect observed was a decrease in quality of life for affected patients and associated treatment costs incurred by patients. Similar findings for loss of quality of life because of adverse events were reported in studies of raloxifene.<sup>10,36</sup> An increased incidence of venous thrombotic events, primarily deep vein thrombosis, was observed in the bazedoxifene and

raloxifene groups, a finding consistent with that reported in earlier studies.<sup>36,37</sup> Further, bazedoxifene was associated with a lower incidence of breast cyst/fibrocystic breast disease compared with raloxifene. All adverse events were assumed to cause a 10% decrease in quality of life in the first year and subsequent years because appropriate estimates for utility loss were lacking in the literature. When the utilities were corrected for decrease in quality of life, the QALY gain was higher for the bazedoxifene cohort, leading to better cost-effectiveness. Other estimates of decrease in quality of life could influence cost-effectiveness ratios.

The incidence of breast cancer in the study reported by Silverman et al<sup>14</sup> was low for bazedoxifene and raloxifene, and no significant differences were observed in the incidence of breast cancer between the treatment groups. In the same study,<sup>14</sup> treatment with bazedoxifene was associated with fewer cases of breast cancer than treatment with raloxifene over a period of 3 years, although these results were not significant. These results contrast with previous reports that raloxifene is associated with a reduction in breast cancer risk.<sup>37–39</sup> Although different studies, as mentioned before, report possible effects of bazedoxifene and raloxifene on risk of breast cancer, any decrease in quality of life due to breast cancer for the second and following years after having breast cancer, as reported by Zethraeus et al,<sup>40</sup> has not been included in this model. Including decrease in quality of life because of breast cancer, might affect the cost-effectiveness ratio, and would improve for bazedoxifene based on the lower number of cases observed, as was seen in the study reported by Silverman et al.<sup>14</sup>

An important strength of this study is that data on incidence of events, post-event mortality, and costs were country-specific. Apart from its strengths, there were also several limitations to the study. We only included patients who sustained a vertebral or nonvertebral fracture, and there were no data included for patients who could have sustained multiple fractures simultaneously. Therefore, the effect of multiple fractures in terms of costs and quality of life could not be determined.

Regarding data on quality of life, a limitation of this study was the lack of references for loss of quality of life as a result of adverse events, such as leg cramps and breast cysts/fibrocystic breast disease. Decrease in quality of life because of deep vein thrombosis was based on assumptions made in previous studies,<sup>28,29</sup> although supportive evidence was lacking.

The effects of poor adherence and persistence were not investigated in this study. Adherence tends to be higher in clinical trials than in clinical practice. Although data on adherence

are available for raloxifene,<sup>41</sup> no data outside of clinical trials are available for bazedoxifene. Overall adherence with treatment for osteoporosis has been shown to be poor.<sup>42,43</sup> As a consequence of nonoptimal persistence, the number of fractures avoided could be reduced, results in less QALY gain for the treatment population. Another effect is the reduction in intervention costs when treatment is stopped before the planned treatment duration. Therefore, less persistence could lead to less effectiveness, which might be compensated for somewhat by lower intervention costs, meaning persistence is likely to have a small effect on cost-effectiveness ratios, which is in line with the results of Jonsson et al.<sup>44</sup>

Whether bazedoxifene is a cost-effective treatment depends largely on the probability of having a nonvertebral fracture, sustaining a subsequent nonvertebral fracture, and decreased quality of life due to adverse events, as well as the amount the Spanish National Health Service is willing to pay for a QALY gained. Bazedoxifene compared with raloxifene in this study was shown to fall below the threshold of €30,000 for an intervention that demonstrates typical benefits in Spain. It is important to recognize that the present study was undertaken in a Spanish setting and that the results are not automatically applicable elsewhere, given that fracture risk, mortality, and costs may differ from country to country.

## Conclusion

Bazedoxifene was shown to be a cost-effective treatment option for the prevention and treatment of fractures in postmenopausal osteoporotic women with a high fracture risk in Spain. When comparing bazedoxifene with raloxifene, it may be concluded that bazedoxifene is the dominant treatment strategy. Results of probabilistic sensitivity analysis show that the choice of the optimal strategy of bazedoxifene is independent of the maximum that the Spanish National Health Service is willing to pay per additional QALY. Bazedoxifene demonstrated a slightly higher probability of being cost-effective for all threshold values.

## Disclosure

Nuria Pérez-Álvarez and Lisette Kaskens are employees of BCN Health Economics and Outcomes Research, Barcelona, Spain, a consultancy hired by Pfizer Inc, to develop the economic model and the manuscript. Josep Darbà was involved as an external advisor hired by Pfizer Inc. from the Universitat de Barcelona and responsible for the development, review of the model, comments and review of the manuscript. Susana Holgado-Pérez reports no conflict



of interest in this work. Jill Racketa was an employee of Pfizer Inc, at the time of this study, and Javier Rejas is an employee of Pfizer SLU. The authors wish to thank Roger Lou, a former employee of Pfizer Inc, for his assistance in the logistic part of the study and comments and review of the manuscript. Additional editorial support was provided by Bo Choi of MedErgy and funded by Pfizer Inc.

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