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Cost-effectiveness of sequential treatment with abaloparatide vs. teriparatide for United States women at increased risk of fracture

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ABSTRACT

Objectives: There is emerging evidence supporting sequential therapy with an osteoanabolic followed by an antiresorptive in patients at high-risk of fragility fractures. This study assessed the cost-effectiveness of sequential treatment with abaloparatide (ABL) followed by alendronate (ALN) [(ABL/ALN)] compared with teriparatide (TPTD) followed by ALN (TPTD/ALN).
Methods: A previously validated Markov microsimulation model was adapted to estimate the cost-effectiveness of sequential ABL/ALN compared with sequential TPTD/ALN and no treatment with a lifetime horizon from the US payer perspective. Patients were assumed to receive ABL or TPTD for 18 months followed by 5 years of ALN in line with clinical recommendations. The effects of ABL on fracture risk were derived from the ACTIVExtend trial. The effects of TPTD were assumed to be maintained during subsequent ALN treatment, consistent with ACTIVExtend findings for ABL. Evaluation was completed for patients, aged 50–80 years with a BMD T-score ≤ -3.5 or with a T-score between -2.5 and -3.5 and a history of $\geq$ one osteoporotic fracture.
Results: In all simulated populations, sequential ABL/ALN therapy was dominant (lower costs, higher QALYs) compared with sequential TPTD/ALN therapy, resulting from the improved efficacy and lower drug price of ABL. Probabilistic sensitivity analyses suggested that ABL/ALN was dominant in at least 99% of the simulations. Compared to no treatment, the cost per QALY gained of ABL/ALN was always below $130,000.
Conclusions: Sequential ABL/ALN therapy is a cost-effective (dominant) strategy compared with sequential TPTD/ALN therapy for the treatment of US women at increased risk of fractures.

Introduction

Osteoporosis is an increasingly major health problem around the world [1,2]. It is a disease characterized by low bone mass with microarchitectural disruption and increased skeletal fragility, leading to increased fracture risk. In 2010, osteoporosis and low bone mass at the femoral neck or lumbar spine affected an estimated 53.6 million older US adults [3]. Osteoporotic fractures result in significant morbidity, excess mortality and reductions in health-related quality of life [4,5], and are associated with an increased risk of subsequent fractures [6,7]. They also impose a significant financial burden on healthcare systems [1]. In the US, more than 2 million incident osteoporotic fractures occurred in the year 2015 [8]. The total costs of osteoporosis-related fractures were estimated at more than 19 billion US dollars in 2005 [2]. Fractures in women accounted for 71% of fractures and 75% of costs overall, while 72% of all costs are related to hip fractures [2]. With an aging population and increasing life expectancy, annual fractures and associated costs are projected to rise by almost 50% by 2025 [2].

Antiresorptive agents (especially oral bisphosphonates) have frequently been used to treat osteoporosis. However, patients have become concerned about two rare but serious adverse events associated with the use of bisphosphonate therapy, i.e., osteonecrosis of the jaw and atypical femoral fractures. This could potentially explain the 50% decrease observed in the use of oral bisphosphonates in the US between 2008 and 2012 [9]. Poor adherence to oral bisphosphonates due to instructions for use and gastro intestinal side effects is another major concern. Approximately 75% of women who initiate oral bisphosphonates were shown to be non-adherent within 1 year and 50% discontinued therapy by this time [10], leading to a substantial decrease of the potential benefits of the drugs. Further, according to a

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study by Imel et al. [11], 35% of patients adherent to bisphosphonate had either fracture, decreases in bone mineral density (BMD), or persistent osteoporotic BMD.

There are several other drugs approved for osteoporosis that also decrease bone resorption including intravenous bisphosphonates (zoledronic acid administrated yearly and ibandronate administrated every 3 months) and RANKL inhibition with denosumab (administrated subcutaneous every 6 months, DMAB). Persistence at one year remain however suboptimal, respectively 59% for zoledronic acid and between 68 and 82% for DMAB in US patients [12,13]. Recent studies also suggest that discontinuation with DMAB may lead to an increased risk of multiple vertebral fractures [14]. Teriparatide (TPTD), an anabolic agent, was the first drug approved by the FDA for the treatment of osteoporosis that works primarily by increasing bone formation rather than decreasing bone resorption. High cost and poor adherence are however concerns. Noncompliance has been shown to be associated with a 20% higher risk of any fracture (odds ratio, 1.2; 95% CI, 1.07–1.35) and greater medical costs (cost ratio, 1.13; 95% CI, 1.06–1.21) [15]. Given the limitations of currently available therapies and existing unmet medical need new treatments are needed.

The anabolic therapy abaloparatide (ABL), a PTHrP therapy, represents a novel therapeutic option for fracture risk reduction. The Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) [16] trial showed that the use of subcutaneous ABL for 18 months was well tolerated, increased BMD and resulted in significantly reduced risk of vertebral (86%), nonvertebral (43%), and major osteoporotic fractures (70%) compared with placebo and significantly reduced risk of major osteoporotic fractures compared with TPTD [16]. An extension of the ACTIVE trial (called ACTIVExtend) [17], which enrolled patients who had completed 18 months of ABL or placebo in ACTIVE and received up to 24 additional months of open-label alendronate, suggested that the use of ABL for 18 months followed by alendronate (ALN) for 24 months maintained the increases in bone mineral density and reduction of the risk of vertebral and nonvertebral fracture observed after 18 months of ABL. Anabolic therapy followed by an antiresorptive agent seems thus to be an attractive treatment strategy for patients with osteoporosis. Based on the outcomes of ACTIVE and ACTIVExtend trials, on 28 April 2017, ABL was approved by the FDA for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

For healthcare decision makers, it is also important to know whether sequential therapy with the initiation of ABL first followed by an oral bisphosphonate is cost-effective compared with the current alternative treatments. Cost-effectiveness studies are increasingly required for pricing and reimbursement decisions. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has launched a special task force report on US Value Assessment Frameworks seeking a role for health economics [18]. This task force further suggests consideration of variation in risk and treatment response along with budget impact with cost-effectiveness evaluation. The aim of this study was therefore to estimate the cost-effectiveness of sequential treatment with ABL followed by alendronate (ABL/ALN) compared with TPTD followed by ALN (TPTD/ALN) and compared with no treatment in US women at high risk of fractures.

Methods

A previously validated Markov microsimulation model [19–21] was adapted to estimate the cost-effectiveness of ABL/ALN compared to TPTD/ALN and to no treatment with a lifetime horizon from the US payer perspective. Patients were assumed to receive ABL or TPTD for 18 months followed by 5 years of ALN in line with clinical recommendations based on the 2016 American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guideline for osteoporosis [22].

The model was built up using TreeAge Pro 2017 (TreeAge Pro Inc., Williamston, MA, USA) and was conducted in line with the US PHS Panel recommendations [23] and with the Academy of Managed Care Pharmacy (AMCP) format for submission of economic evaluation [24]. This study also adheres to recent recommendations for the conduct of economic evaluations in osteoporosis [25] and to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [26]. Additional detail regarding our model could be found in Appendix A. Table 1 contains a list of key model components and assumptions along with the rationale for each assumption, and data are included in Table 2. Appendix D includes the new Osteoporosis-specific checklist for reporting economic evaluations in osteoporosis.

Model structure

A Markov microsimulation model was used to allow tracking patient characteristics and individual disease histories (e.g. fractures and residential status) and avoid unnecessary transition restrictions. The model health states were no fracture, death, hip fracture, clinical vertebral fracture, wrist fracture and other fracture. The 'other fracture' state includes other osteoporotic fractures as defined by the IOF-EFPIA report [1]. We used a lifetime horizon and a 6-month cycle. Patients could experience multiple fractures at the same site or multiple sites. Discount rate of 3% for both costs and health benefits were used as recommended by the US PHS Panel recommendations [23].

Populations

Consistent with the current utilization management criteria for major payers in the US for the use of anabolic agents, evaluation was done for women 50–80 years of age at increased risk of fractures i.e., women with a BMD T-score ≤ -3.5 and no fracture history or with a BMD T-score between -2.5 and -3.5 and a history of at least one osteoporotic fracture.

Probabilities

The incidences of hip, clinical vertebral and wrist fractures in the US were derived from the study of Ettinger et al. [27] that was used to develop the US FRAX® Tool. This study used hospital discharge data from 38 states for non-Hispanic white women from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) for the year 2006. For the incidence of other fractures, we used estimates of a previous similar study using 2001 HCUP NIS data and combined incidence data for pelvic and other fractures [2].

Initial probabilities were then adjusted to accurately reflect the fracture risk in the target population in comparison with that of the general population using previously validated methods [6,28]. Fracture risk was also adjusted when a new fracture occurred during the simulation process in line with studies suggesting an increased risk after previous fractures [6,7,29] (see Appendix A for more explanation).

Baseline mortality rates for age-stratified US women (estimated in 2014) were obtained from official estimates (National Vital Statistics System) [30]. We assumed an increased mortality after hip fracture and clinical vertebral fracture in line with previous economic studies [20], and a (smaller) increased mortality after wrist and other fractures [31]. Because excess mortality may also be attributable to comorbidities, we further took into account that only 25% of the excess mortality following fractures was attributable to the fractures themselves [32,33] (see Appendix A for more explanation).

The probability (not age-dependent) of admissions to nursing home after a hip fracture was derived from the study of Leibson et al. [34]. Admission to nursing home after non-hip fractures was not assumed.

Table 1
Key model components and assumptions

Model components/assumption	Rationale
Cost-effectiveness analysis using quality-adjusted life years (QALY) as outcome	QALY offer the advantage to take morbidity and mortality gains into account
Markov microsimulation model	Allow to track patient characteristics and individual disease histories (e.g. fractures and residential status) and avoid unnecessary transition restrictions
6-month cycle length	Because fractures effects (such as mortality excess) could be different for the periods 0–6 and 7–12 months
1,000,000 of trials for the deterministic analyses and 200 times 25,000 simulations for the probabilistic sensitivity analyses	Number of simulations sufficient to guarantee the stability of results
Hip, clinical vertebral, wrist and other fractures	Most common fracture types with sufficient data (e.g. incidence, costs, utility, excess mortality) to be included as separate health states
Lifetime horizon (until the age of 100 years)	To capture the long-term costs and benefits of interventions
Patients could experience multiple fractures at the same site or multiple sites	Real-world patients may experience any types of fractures
Fracture risk adjustment within the model after fracture events	In line with studies suggesting an increased fracture risk after fracture [29]
Excess mortality after hip, vertebral and non-hip non-vertebral fractures (first and subsequent years)	In line with studies suggesting an excess mortality after all fractures types [4,31,58]
Excess mortality attributable to fracture (25%)	Because excess mortality may also be attributable to comorbidities, we conservatively assumed that only 25% of the excess mortality following a hip or vertebral fracture could be directly or indirectly attributable to the fractures themselves
Two populations of high risk patients (aged over 50 years)	Based on utilization management criteria currently in place in large health plans in the US
Discount rates: 3%	In line with US guideline for economic evaluations [23]
Healthcare perspective	In line with US guideline for economic evaluations [23]
Long-term costs of hip fractures based on the proportion of patients being institutionalized following the fracture	Long-term hip fracture costs are mostly attributable to admission to nursing home
No long-term costs for non-hip fractures	Conservative assumption in the absence of appropriate data
Utility decrements following fractures by fracture site (first year and subsequent years)	In line with data currently available [41]
Additional effects of multiple fracture on costs and utility	In line with previous studies suggesting a relationship between fracture costs and disutility, and the number of fractures [37,59]
Treatment duration	In line with clinical recommendations
Treatment effects: - ABL: ACTIVExtend - TPTD: ACTIVE - ALN: NICE meta-analysis	RCT comparing ABL and TPTD, and meta-analysis for ALN
Effects of ABL/TPTD on hip fractures derived from the estimated fracture risk reduction for non-vertebral fractures	In the absence of hip specific data, the estimate for non-vertebral fractures is more conservative than the estimate for major fractures
Drug cost was adjusted by the average drug adherence level from the trial	To take into account that all drugs were not taken drug the trial
The therapy costs include the cost of one GP visit per 6 months and the cost of one DXA every two years (similar assumption for all therapies)	In line with clinical practice
All comparators' adherence rates were 100% in base case analysis	Lack of real-world adherence data for ABL, and on the impact of lower adherence on efficacy for ABL and TPTD
Most important drug side effects are included	Although of limited impact on the cost-effectiveness of osteoporosis medications, including side effects reflects real-life situations
In case of sequential therapy, the effects of ABL/TPTD are maintained during ALN intake	In line with the ACTIVExtent trial
In case of sequential therapy, the effects of the two treatments are taken into account	Realistic assumption in line with previous economic studies of sequential therapies [49]

ABL Abaloparatide, ALN Alendronate, GP General physician, QALY Quality-adjusted life years, RCT Randomized controlled trial, TPTD Teriparatide.

Fracture costs

In line with the AMCP format for submission of economic evaluation, we used a health care decision maker perspective. All costs were expressed in US$2017 using the US consumer price index for medical care when needed [35].

The study of Bonafente [36] including data from 90,396 US women over age 50 between July 2005 and December 2007 was used to derive the cost of hip, vertebral and other fractures for commercial (up to the age of 64 years) and Medicare patients (for fractures occurring in patients $\geq$ 65 years). This study provided detailed data for each fracture states for both Medicare and commercial patients, and the cost of hip fracture is rather similar than the more recent study of Weaver et al. [37]. The cost of wrist fracture was derived from Tosteson et al. [38]. An incremental cost was assumed for a recurrent fracture at the same location in line with the study of Weaver et al. [37].

Long-term hip fracture costs were based on the proportion of patients being institutionalized following the fracture. The cost of nursing home was derived from the median national costs for semi-private and private rooms [39] and was reduced by 10% to take into account that patients could be institutionalized later in their life irrespective of fracture events.

Utility values

Data from the Report of Nationally Representative Values for the Noninstitutionalized US Adult Population for Five Health-Related Quality-of-Life Scores [40] was used for baseline health utility (data from 2006 using EQ-5D).

The effects of fracture on utility were derived from the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) study [41]. This study is the largest study assessing the quality of life of patients with fractures from 11 countries including 2808 patients (1273 hip, 987 distal forearm and 548 vertebral fracture). US-specific data from ICUROS of EQ-5D health state utility values were quite similar at 18 month post-fracture to overall ICUROS data (for hip and vertebral fractures). Since other fractures were not included in the ICUROS study, we used estimate from a previous systematic review [42]. An additional effect on utility after multiple fractures was modeled (see Appendix A).

Table 2
Key model data

Parameter	Data		
Incidence (annual rate per 100) of fracture [2,26]			
Hip	0.029 (50–54 years), 0.057 (55–59 years), 0.105 (60–64 years), 0.203 (65–69 years), 0.394 (70–74 years), 0.793 (75–79 years), 1.447 (80–84 years), 2.606 (85 +)		
CV	0.064 (50–54 years), 0.132 (55–59 years), 0.124 (60–64 years), 0.233 (65–69 years), 0.473 (70–74 years), 0.523 (75–79 years), 0.622 (80–84 years), 1.095 (85 +)		
Wrist	0.291 (50–54 years), 0.430 (55–59 years), 0.808 (60–64 years), 0.822 (65–69 years), 0.824 (70–74 years), 0.835 (75–79 years), 0.870 (80–84 years), 0.849 (85 +)		
Other	0.529 (50–54 years), 0.910 (55–59 years), 0.789 (60–64 years), 0.900 (65–69 years), 1.282 (70–74 years), 1.887 (75–79 years), 2.386 (80–84 years), 3.074 (85 +)		
Probability of admission to nursing home [33]			
	0.122		
Mortality excess			
Hip (0–6 m / 7–12 m / subs. year)	4.53 (3.56–5.88) / 1.75 (1.42–2.16) / 1.78 (1.33–2.39)		
CV (0–6 m / 7–12 m / subs. year)	4.53 (3.56–5.88) / 1.75 (1.42–2.16) / 1.78 (1.33–2.39)		
Wrist	1.43 (1.07–1.92)		
Other	1.38 (1.18–1.62)		
% attributable to Fx	25%		
Cost of a first fracture (estimated in $2017) [35,36]			
Hip	42,033 (50–64 years), 30,458 (65 +)		
Hip, yearly long-term costs	10,059		
Clinical vertebral	26,421 (50–64 years), 13,713 (65 +)		
Wrist	4866 (50–64 years), 4909 (65 +)		
Other	12,085 (50–64 years), 12,544 (65 +)		
Health state utility values [39,40]			
Baseline utility	0.837 (50–59 years), 0.811 (60–69 years), 0.771 (70–79 years), 0.724 (80 +)		
Hip (1st year / subs. year)	0.55 (0.53–0.57) / 0.86 (0.84–0.89)		
CV (1st year/ subs. year	0.68 (0.65–0.70) / 0.85 (0.82–0.87)		
Wrist (1st year / subs. year)	0.83 (0.82–0.84) / 0.99 (0.97–1.00)		
Other (1st year / subs. year)	0.91 (0.88–0.94) / 0.99 (0.97–1.00)		
Effects on fracture (expressed as relative risk compared to placebo) of medications [17,42]			
	ABL	TPTD	ALN
Hip	0.63 (0.41–0.98)	0.72 (0.42–1.22)	0.62 (0.40–0.98)
CV	0.16 (0.06–0.42)	0.20 (0.08–0.47)	0.56 (0.46–0.68)
Wrist	0.63 (0.41–0.98)	1.13 (0.56–2.25)	0.67 (0.34–1.31)
Other	0.42 (0.25–0.70)	0.67 (0.39–1.14)	0.81 (0.68–0.97)
Drug cost ($ per month) [46]			
	1625	3248	10

ABL abaloparatide, ALN alendronate, CV clinical vertebral, M Months, TPTD teriparatide, Y years.

Treatment

In the sequential ABL/ALN strategy, the fracture risk reduction with ABL was taken from the full ACTIVE/ACTIVExtend ITT at 43 months and assumed to be maintained during ALN intake. As compared with placebo, ABL reduces the risk of vertebral fracture by 84% (relative risk (RR) 0.16; 0.06–0.42) and the risk of major osteoporotic fracture by 58% (RR 0.42; 0.25–0.70) used for other fractures within the model [17]. In the absence of specific data at the hip, in line with previous economic studies, we assumed that the effects of ABL on nonvertebral fractures could be extrapolated to hip fractures. So, it was assumed that ABL reduce the risk of hip fracture and of wrist fracture by 37% (RR 0.63; 0.41–0.98) [17]. When ALN treatment was started, we assumed that fracture risk decreased in the same proportion as it would in a treatment naive patient using estimates from the meta-analysis the NICE appraisal (TA160) [43]. By example, we assumed a RR of hip fracture of 0.63 for ABL and of 0.62 for ALN compared with usual care. We assumed that subsequent ALN therapy would therefore result in a RR of vertebral fracture of 0.39 (i.e., 0.63 × 0.62).

Patients taking TPTD during ACTIVE trial were not enrolled in the extension phase (ACTIVExtend). In line with a previous study suggested the value of ALN after TPTD [44]. and with the ACTIVExtend suggesting that the effects of a bone forming agent (i.e., ABL) is maintained after switching to an antiresorptive drug (i.e., ALN), we used the treatment effects of TPTD from the ACTIVE trial for the sequential therapy TPTD/ALN. Two scenarios were conducted regarding medication adherence: full medication adherence was assumed in base-case and a sensitivity analysis assuming real-world adherence was tested (see later).

It was assumed that the effects of ABL and TPTD on fracture risk remain constant during ALN intake and then linearly decrease during one additional year after ALN discontinuation. The effects of ALN after discontinuation was assumed to linearly decline to zero during a period similar to treatment duration in line with previous economic evaluations [45] and a clinical study [46].

The drug prices were derived from the Online Red Book (WAC price, December 2017) [47]. To take into account that all drugs were not taken within the ACTIVE trial, total drug cost was multiplied by the average drug adherence level from the trial, estimated at 81.5% and 86.8% for ABL and TPTD, respectively [16]. We also assigned the cost of one general physician visit ($117.71) every 6 months of treatment and the cost of one bone density measurement ($112.73) every two years, in line with Medicare reimbursement for DXA scan [48].

We included the cost of hypercalcemia ($130 [49]), a side-effect of treatment. The incidence of hypercalcemia was 0.37%, 3.41% and 6.37% for no treatment, ABL and TPTD in the ACTIVE trial, respectively. The risk of gastrointestinal effects with ALN was also considered in line with the assumptions previously used by the NICE [43,50]. It was assumed that patients treated with ALN required 0.041 extra GP consultations during the first cycle (6 months) and 0.021 GP consultations during the following cycles on treatment, as well as a proton-pump inhibitor for each visit.

Analyses and sensitivity analyses

A total of 1,000,000 trials were run for the deterministic and each one-way sensitivity analysis. Total healthcare costs, number of fractures prevented and QALYs were estimated for each treatment. Incremental cost-effectiveness ratios (ICER) were computed as the difference between ABL/ALN and the comparator treatment in terms of total costs (expressed in $2017) divided by the difference in terms of QALYs.

In the US, there is no single cost-effectiveness threshold; however, using the same approach as other countries cost-effectiveness threshold can be assumed to be two to three times the GDP (around ($100,000 or $150,000)) [51]. The Institute for Clinical and Economic Review suggests that therapies with cost per QALY ranging from $50,000 to $100,000 are considered high care value (if no other substantial benefits exist), or from $100,000 to $150,000 if they offer substantial other benefits [52].

Multiple scenarios were conducted to assess the economic value of ABL including the two high-risk populations at different ages (50–80 years). In addition, one-way and probabilistic sensitivity analyses were performed to test the robustness of the model results. One-way sensitivity analyses were conducted on varying fracture costs (±25%), fracture disutilities (±25%; using estimates from a previous systematic review [42]), on discount rates (5%), mortality after fractures (assuming excess mortality attributable to fracture equal 0% and 50%) and model time horizon (10 year horizon). Additional one-way sensitivity analyses were conducted on treatment characteristics, including estimate for TPTD/ALN hip fracture efficacy (derived from the treatments effects on major fractures), drug price of ABL (premium/discount of 20/50/100%), drug price of TPTD (discount of 25/50%) and considering the fracture risk reduction for TPTD from the Fracture Prevention Trial (i.e., relative risks of 0.35 for vertebral fracture and of 0.47 for other types of fractures including hip using the estimation from non-vertebral fracture) [53]. Two additional assumptions on offset time were also tested for both ABL and TPTD (i.e., a gradual linear decrease in the 3 years following treatment discontinuation and a 2-year maintenance of the effects after discontinuation followed by a linearly decline in the next three years). Another sensitivity analysis limited the number of hip fractures in the model to 2 and the number of vertebral, wrist or other fractures to 4. Finally, real-world adherence was considered for all medications using the methodology proposed by Liu et al. (see Appendix A for more information).

Probabilistic sensitivity analyses were undertaken to examine the effect of the joint uncertainty surrounding the model variables. Nearly all parameters were varying simultaneously over plausible range of values, following guidelines [54]. A description and explanation of the distributions is provided in Appendix B. For each probabilistic sensitivity analysis, the model was run 200 times based on runs of 25,000 patients per treatment arm. Results were presented in the form of cost-effectiveness acceptability curves that show the probability of being cost effective as a function of the decision maker's willingness to pay per QALY gained.

Results

Base-case analysis

Table 3 presents the lifetime costs, number of fractures, QALYs and the ICER (expressed in cost ($) per QALY gained) of sequential ABL/ALN therapy compared with TPTD/ALN and with no treatment in US women aged 70 years with a BMD T-score ≤ −3.5 or with BMD T-scores between −2.5 and −3.5 and history of ≥ one osteoporotic fracture. In both populations, the sequential ABL/ALN therapy was shown to be dominant (lower costs, more QALYs) compared with TPTD/ALN. In women with BMD T-score ≤ −3.5, the sequential ABL/ALN therapy was also cost-saving compared to no treatment, meaning that the averted costs of osteoporotic fractures are higher than the treatment costs. In women with BMD T-score between −2.5 and −3.5 and history of ≥ one osteoporotic fracture, the cost per QALY gained of sequential ABL/ALN therapy compared to no treatment was estimated at $38,763.

In Table 4, the ICERs of ABL/ALN compared to TPTD/ALN and no treatment are presented for other ages ranging from 50 to 80 years. Compared to TPTD/ALN, sequential ABL/ALN therapy was always dominant (less costs, more QALYs). In women with BMD T-score ≤ −3.5, sequential ABL/ALN therapy was cost-saving compared to no treatment for women aged over 70 years and, in women under the age of 70 years, the cost per QALY gained of sequential ABL/ALN therapy compared with no treatment always falls under $80,000. Appendix C Tables C1 and C2 provide the lifetime costs, number of fractures and QALYs for all these age-specific simulations.

One-way sensitivity analysis

In all one-way sensitivity analyses, sequential ABL/ALN therapy was dominant (lower costs, more QALYs) compared to TPTD/ALN (Table 5), including a 50% discount of TPTD cost or a doubling of the cost of ABL. When considering fracture risk reduction for TPTD from the Fracture Prevention Trial, sequential TPTD/ALN therapy was associated with slightly higher QALY (±0.0125) than ABL/ALN, but the cost per QALY gained for TPTD/ALN was very high ($2,249,927) and ABL/ALN remained the cost-effective strategy. Variations in treatment offset time, treatment cost and fracture costs had a moderate impact

Table 3
Lifetime costs, QALYs, number of fractures and incremental cost-effectiveness ratio (ICER) of ABL/ALN compared with TPTD/ALN and no treatment at the age of 70 years

	ABL/ALN	No treatment	TPTD/ALN	*ABL/ALN* vs. *TPTD/ALN*
BMD T-score ≤ −3.5				
Total costs	83,304	85,004	116,685	−33,381
Healthcare costs	58,376	85,004	61,260	−2884
Treatment costs	24,928	0	55,425	−30,497
QALYs	8.638	8.284	8.602	0.036
Number of fractures	2.021	2.675	2.146	−0.125
ICER *(cost in $ per QALY gained)*		Cost-saving	Dominant	
BMD T-score between −2.5 and −3.5 and history of one osteoporotic fracture				
Total costs	62,749	51,909	95,066	−32,317
Healthcare costs	37,825	51,909	39,658	−1833
Treatment costs	24,924	0	55,408	−30,484
QALYs	8.792	8.513	8.756	0.036
Number of fractures	1.565	2.039	1.683	−0.118
ICER *(cost in $ per QALY gained)*		38,763	Dominant	

ABL abaloparatide, ALN alendronate, BMD bone mineral density, ICER incremental cost-effectiveness ratio, QALY quality-adjusted life-years, TPTD teriparatide.

Table 4
Incremental cost-effectiveness ratio (expressed in cost in $ per QALY gained) of ABL/ALN compared with TPTD/ALN and no treatment at different age

	ABL/ALN vs. no treatment	ABL/ALN vs. TPTD
BMD T-score ≤ −3.5		
50 years	76,181	Dominant
55 years	48,748	Dominant
60 years	41,832	Dominant
65 years	14,089	Dominant
70 years	Cost-saving	Dominant
75 years	Cost-saving	Dominant
80 years	Cost-saving	Dominant
BMD T-score between −2.5 and −3.5 and history of one osteoporotic fracture		
50 years	125,493	Dominant
55 years	91,394	Dominant
60 years	81,865	Dominant
65 years	51,906	Dominant
70 years	38,763	Dominant
75 years	31,390	Dominant
80 years	28,086	Dominant

ABL abaloparatide, ALN alendronate, BMD bone mineral density, QALY quality-adjusted life-years, TPTD teriparatide.

on the ICER of ABL/ALN compared to no treatment. The ICERs of ABL/ALN were always below $20,000 per QALY gained, at the exception of the analysis with a 10 year time horizon where the cost per QALY gained increased to $62,861. Appendix C Table C3 includes the effect of changes in drug costs on the ICER of ABL/ALN compared with TPTD/ALN and no treatment in all simulated populations.

Probabilistic sensitivity analyses

The cost-effectiveness acceptability curves suggest that ABL/ALN was cost-effective compared to TPTD/ALN in at least 99% of the simulations in women with a BMD T-score ≤ −3.5 (Fig. 1). When compared to no treatment, ABL/ALN was cost-effective at a threshold of $100,000 per QALY gained in 86%, 97.5%, 100% and 100% of the simulations at the ages of 50, 60, 70 and 80 years, respectively. The cost-effectiveness planes are included in Appendix C Fig. C1.

Probabilistic sensitivity analyses were also conducted in US women with BMD T-scores between −2.5 and −3.5 and history of ≥ one osteoporotic fracture aged 60, 70 and 80 years (see Appendix C Fig. C2). Sequential ABL/ALN therapy was dominant (more QALYs, lower costs) compared to TPTD/ALN in 100% of the simulations for any threshold up to $200,000 per QALY gained. Compared to no treatment, ABL/ALN was cost-effective, at a threshold of $100,000 per QALY gained, in 81.5%, 99.5% and 100% of the simulations at the ages of 60, 70 and 80 years, respectively. In the other probabilistic sensitivity analysis considering fracture risk reduction for TPTD from the Fracture Prevention Trial, the cost-effectiveness acceptability curve (Appendix C Fig. C3) suggests that sequential ABL/ALN therapy is cost-effective in at least 98.5% of the simulations compared to TPTD/ALN.

Table 5
One-way sensitivity analyses on the incremental cost-effectiveness ratio (expressed in cost ($) per QALY gained) of ABL/ALN compared with TPTD/ALN and no treatment in US women with BMD T-score ≤ −3.5 at the age of 70 years

	ABL/ALN vs. no treatment	ABL/ALN vs. TPTD/ALN
Base case	Cost-saving	Dominant
Fracture cost −25%	14,525	Dominant
Fracture cost + 25%	Cost-saving	Dominant
Fracture disutilities −25%	Cost-saving	Dominant
Fracture disutilities + 25%	Cost-saving	Dominant
Fracture disutilities from another review [37]	Cost-saving	Dominant
Discount rates 5%	8775	Dominant
Excess mortality = 0%	3450	Dominant
Excess mortality = 50%	Cost-saving	Dominant
10-year time horizon	62,861	Dominant
ABL/TPTD other hip fracture efficacy	Cost-saving	Dominant
ABL cost + 100%	60,415	Dominant
ABL cost + 50%	27,808	Dominant
ABL cost + 20%	9275	Dominant
ABL cost −20%	Cost-saving	Dominant
ABL cost −50%	Cost-saving	Dominant
TPTD cost −25%	–	Dominant
TPTD cost −50%	–	Dominant
TPTD fracture risk estimates from fracture prevention trial	Cost-saving	2,249,927*
ABL/TPTD offset: linear decline during 3 years	2552	Dominant
ABL/TPTD offset: 2 years maintenance + 3 years linear decline	Cost-saving	Dominant
Maximum number of fractures	11,393	Dominant
ABL/TPTD real-world adherence	Cost-saving	Dominant

ABL abaloparatide, ALN alendronate, QALY quality-adjusted life-years, TPTD teriparatide.
* ICER of TPTD/ALN compared to ABL/ALN.

Discussion

This study suggests that sequential therapy beginning with ABL followed by ALN is a cost-effective strategy for US women at increased risk of fractures consistent with current utilization management criteria in US health plans. Sequential ABL/ALN was shown to be dominant (more QALYs, less costs) compared with sequential TPTD/ALN, resulting from the improved efficacy and lower drug price of ABL. These findings were robust and persisted in all the one-way and probabilistic sensitivity analyses. Even when incorporating efficacy data of TPTD from the Fracture Prevention Trial, sequential therapy with ABL/ALN remains the cost-effective treatment alternative. When compared to no treatment, sequential ABL/ALN is cost-effective for women aged 60 years and over, and the ICER was between $100,000 and $150,000 in women aged 50 years. In addition, sensitivity analyses on drug prices suggested that ABL/ALN would remain dominant compared to TPTD/ALN even if TPTD price would be reduced by half.

To our knowledge, this study is the first economic analysis of ABL, and one of the first assessing the cost-effectiveness sequential therapy in osteoporosis. There is evidence now supporting the concept of sequential therapy with the initiation of anabolic therapy first followed by an antiresorptive to improve health outcomes in osteoporosis [55] and the current evaluation reinforces the economic value of this strategy. A previous study conducted by Liu et al. [49] suggested sequential therapy with TPTD/ALN to be less cost-effective compared with alendronate monotherapy. Our study suggests that a sequential therapy starting with ABL provided at lower costs (about half of TPTD WAC price), and having an improved risk reduction of major osteoporotic fracture, is a dominant strategy compared a sequential therapy starting with TPTD and results in more favorable cost-effectiveness ratios compared to no treatment. Interestingly, in comparison to previous monotherapy economic evaluations [20], health outcomes of sequential therapy ABL/ALN is becoming substantial (lifetime gain of 0.3 QALY per patient), leading to high potential benefits for patients.

The results of the current economic model have to be interpreted within the context of some limitations. First, the current model does not provide cost-effectiveness estimates for all available therapies. Instead comparisons were limited to TPTD/ALN and no treatment given the available data on these comparators from the ACTIVE trial. Comparison to other antiresorptive drugs should be made with caution since antiresorptives and osteoanabolic agents have different mechanisms of action and are indicationed for different patient populations. Second, the ACTIVE and ACTIVExtend trials did not have enough statistical power to specifically detect risk reduction for hip fracture. Thus, we assumed the risk reduction for hip fracture would be similar to risk reduction of nonvertebral fractures. This assumption was conservative compared to the effects of major osteoporotic

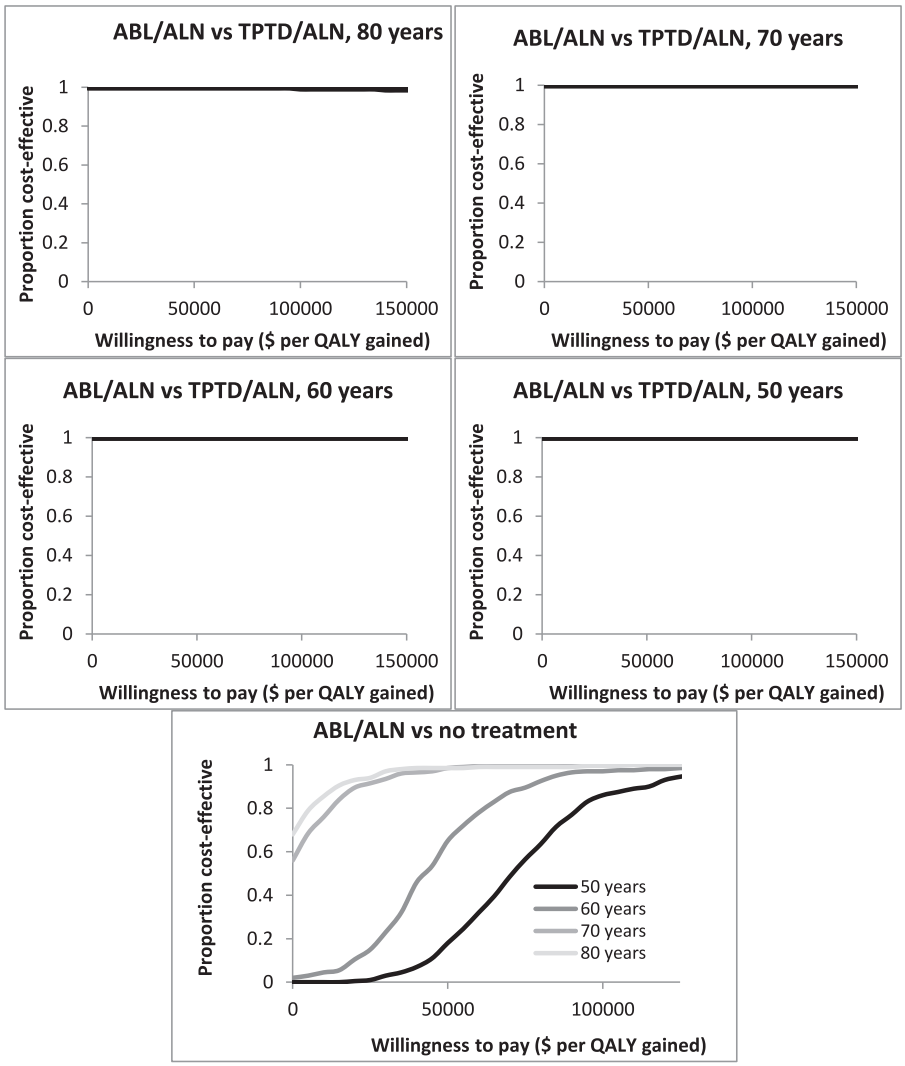

Fig. 1. Cost-effectiveness acceptability curves of ABL/ALN compared to TPTD/ALN and no treatment in women with BMD T-score ≤ −3.5 aged 50, 60, 70 and 80 years. *ABL abaloparatide, ALN alendronate, QALY quality-adjusted life-years, TPTD teriparatide.*

fractures fracture and implemented in previous cost-effectiveness analyses of osteoporosis treatments [49,56]. It should also be acknowledged that patients taking TPTD during ACTIVE trial were not enrolled in the extension phase (ACTIVExtend). Third, the ACTIVExtend trial suggests that the effects of ABL are maintained during bisphosphonate intake for a period of 2 years. Extrapolation of this finding for a 5 year bisphosphonate intake would require further investigation. Sensitivity analyses were conducted on the maintenance of treatment effect after ABL discontinuation. It was conservatively assumed that the effect of ABL after discontinuing ALN in the sequential treatment ABL/ALN rapidly decline to zero. Fourth, another important limitation of this study is the extrapolation of trial efficacy to a simulated patient population. Recently, data from observational studies confirmed that TPTD significantly reduced the risk of clinical vertebral fracture and non-vertebral fractures, although the observed reductions were slightly lower than those reported in the pivotal Fracture Prevention Trial [57]. The effects of ALN in real-life settings as well as real-world adherence to ABL is currently unknown. In a sensitivity analysis, using the methodology designed by Liu et al. [49], adjusting for real-world adherence had limited effects on the ICERs. Given the similar model of intake and frequency of intake, we assumed real-world adherence for ABL is similar to real-world adherence with TPTD. It would be important in the future to collect ABL efficacy data from observational studies, to assess real-life adherence to ABL and to assess the effect of adherence on ABL treatment efficacy. Fifth, efficacy data of oral bisphosphonates was derived from a meta-analysis of several studies and the populations of those may be lower risk than the population of the ACTIVE and ACTIVExtend studies. Other potential limitations are related to the model and data. The most important are availability of data. Although data used to construct the model were based on US literature whenever possible, some data were derived from other countries. In particular, the effects of fracture on utility were not derived from a US study. However, we used an international multinational study (ICUROS), the largest study worldwide assessing the effects of fractures on quality of life. US-specific data from ICUROS of EQ-5D health state utility values were quite similar at 18 month post-fracture to overall ICUROS data (for hip and vertebral fractures), supporting our selection of overall ICUROS data. In addition, in line with previous economic evaluations [21,49], the probability to enter a nursing home after a fracture was restricted to hip fractures and was not age-specific.

Conclusion

This study supports cost-effectiveness of sequential therapy with ABL/ALN compared with sequential therapy with TPTD/ALN therapy for the treatment of US women at increased risk of fractures aged over 50 years. ABL/ALN leads to improved outcomes for less total healthcare costs than TPTD/ALN.

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Conflict of interest

Mickael Hiligsmann has received research grant through institution from Amgen, Radius Health, Inc., and Teva; lecture fees from Radius Health, Inc.; and paid advisory board from UCB. Setareh Williams, Lorraine Fitzpatrick and Richard Weiss are employees and shareholder of Radius Health, Inc. Stuart Silverman has received grant support from Amgen, Radius Health, Inc., and Lilly; consulting fees from Amgen and Radius Health; has served on scientific advisory boards for Lilly and Amgen; and has served on speakers bureaus for Amgen, Lilly and Radius Health, Inc. Jean-Yves Reginster has received consulting fees or paid advisory boards from IBSA-Genevrier, Mylan, Radius Health, Pierre Fabre, Teva; lecture fees when speaking at the invitation of sponsor: IBSA-Genevrier, Mylan, CNIEL, Dairy Research Council, Teva; grant support from industry (all through institution) from IBSA-Genevrier, Mylan, CNIEL, Radius Health, Inc.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2019.01.006.

Appendix A: Additional information on the model

A. Model structure

Because osteoporosis is a chronic disease characterized by a recurrence of events (fragility fractures) and the fracture risk is continuous (but not the same depending on history of fractures and treatment effects) over time, a Markov modeling technique is appropriate. The structure of the developed model can be found on Fig. A1.

The Markov model was evaluated by Monte-Carlo microsimulation (first-order trials) also known as individual-level simulation models where a single run of the model simulates the health care of many thousands of individual patients [60]. This approach presents some major advantages over cohort-based models, increasing the reliability of results and being largely compatible with the existing state of the art, evidence-based literature . By simulating patients one by one, this approach allows to track patient characteristics and individual disease histories (e.g. fractures and residential status) by so-called 'tracker variables'.

The model health states are no fracture, death, hip fracture, clinical vertebral fracture, wrist fracture, other fracture and the corresponding post-fracture states. The 'other fracture' state includes other osteoporotic fractures as defined by the IOF-EFPIA report (i.e. fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures). A 6-month cycle length was used, meaning that every transition could occur every six months. A half-cycle correction was used to allow transitions occurring on the middle of each cycle on average. Post-fracture states were created as some parameters (e.g. fracture disutility) were only estimated over a 1-year period. The model follows the patients until they are dead or they reach the age of 100 years to capture the long-term quality and quantity of life and costs effects of preventing fractures.

All the patients, one at a time, began in the 'no fracture' state and had, every 6-month, a probability of having a fracture of the hip, clinical vertebrae, wrist, or other site or dying. Patient in a fracture state can stay in the same fracture state if they re-fracture, change to another fracture state, die or change in the next cycle to the corresponding post-fracture state. Patients being in any post-fracture states might have a new fracture (all fracture types are again possible), die or move to the 'no fracture' state. Patients could experience multiple fractures at the same site or multiple sites as in real-life.

B. Baseline fracture risk adjustment

Initial probabilities were adjusted to accurately reflect the fracture risk in the target population in comparison with that of the general population using previously validated methods.

We used the method developed by Kanis et al. to adjust the fracture risk according to BMD [61]. This method allows estimating the relative risk (RR) of individuals below a threshold value compared with the fracture risk of the total population of that age, and the RR of individuals at a threshold. One standard deviation decrease in BMD was associated with a relative risk of 1.8, 1.4 and 1.6 respectively for clinical vertebral, forearm and other osteoporotic fracture [62]. The relative risk for hip fracture was shown to decrease with age and ranged from 3.68 (at 50 years) to 1.93 (at 85 years) [63]. BMD was derived from the recommended NHANES III [64] database.

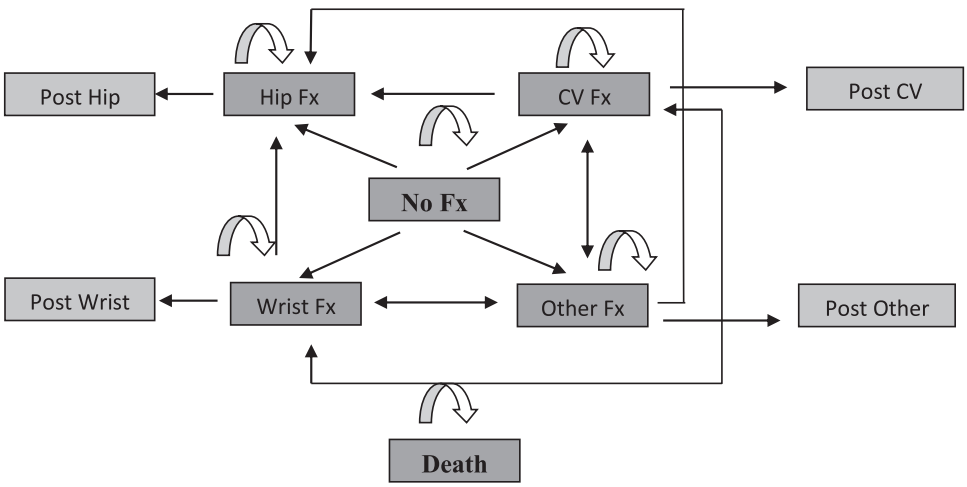

Fig. A1. Model structure. Transitions to death and transitions from post-fracture states to any fractures states, 'death' and 'no fx' were excluded from the graph for simplicity. Patients being in any post-fracture states might have a new fracture, die or move to the 'no fracture' state. FX = fracture; CV = clinical vertebral.

For the presence of a previous osteoporotic fracture (second population), we used the RR from another study of Kanis et al. [65] that used a cohort of 250,000 person-years. The RRs of previous fracture versus no fracture with BMD adjustment were used (50–54 years: 1.91; 55–59 years: 1.83; 60–64 years: 1.94; 65–69 years: 1.99; 70–74 years: 1.98; 75–79: 1.82; 80 + : 1.72).

C. Increased risk during the simulation

Fracture risk was also adjusted when a new fracture occurred during the simulation. Several studies have indeed suggested an increased risk after previous fractures [65–67]. The model incorporates, during the simulation process, an increased risk of subsequent fracture for individuals who have a prior fracture at the same location. These increased relative risks are 4.4 (3.6, 5.4), 2.3 (1.5, 3.7), 3.3 (2.0, 5.3), and 1.9 (1.7, 2.2) for vertebral, hip, wrist and other fractures, respectively [66]. As the underlying risk of fracture may contain prior fracture at other sites and a multiplicative hypothesis could not be supported at this time, we conservatively did not model an increased risk of subsequent fractures at sites different from that of the prior fracture(s), except in the year following the fracture (see below). However, an increased relative risk of 2.3 (2.0, 2.8) is modeled for a hip fracture after a vertebral fracture, because this effect is largely supported by the literature [66]. Since the increased risk after a fracture is shown to decrease with increasing age, we reduced the RR by 10% per each decade above the age of 70 years [65].

Recently, the predictive value of a recent fracture at different sites for future hip fracture was investigated [68]. The analysis was based on an Icelandic population-based cohort of 18,872 men and women aged on average 53 years when recruited between 1967 and 1991. The risk of hip fracture within 2 years after the sentinel fracture for a women aged 75 years varied from 1.6 to 5.0-fold higher than the risk of a hip fracture in the normal population depending on the site of the fracture (respectively 4.7 (3.7–6.0), 5.0 (3.8–6.6) and 1.6 (1.2–2.2) for fractures at the hip, clinical vertebral and for wrist fracture). The RR for wrist fractures was also used for the other fractures within the model. In our model, for technical reasons, we conservatively only modeled these increased risks in the first year following the fracture. No further effect was assumed in subsequent years. This assumption underestimates the effects of fractures on future fracture risk and should be seen as a limitation.

It was also assumed that further fractures of the same type have no additional effect on future fracture risk due to the absence of data providing an accurate relationship between the number of prior fractures and increased risk of fractures. In the population with a history of osteoporotic fractures at baseline that occurred a new fracture during simulation, only the highest increased risk effect of fracture was modeled.

D. Excess mortality after fractures

Excess mortality after hip fracture was derived from a meta-analysis [69]. Based on this study, we assumed that hip fracture increases the probabilities of death in women by 4.535 in the first six months following the fracture (= mean of the impacts estimated in the periods 0–3 and 3–6 months), by 1.755 in the period 7–12 months and by 1.779 in subsequent years.

As the increased mortality following clinical vertebral fractures has been found in many studies to be very similar than those of a hip fracture [70–73], the same impact was assumed after hip and clinical vertebral fractures. Because excess mortality may also be attributable to comorbidities, we conservatively assumed that only 25% of the excess mortality following a hip or vertebral fracture could be directly or indirectly attributable to the fractures themselves [72,74]. The excess mortality after hip or vertebral fracture included in the model are thus estimated at 1.88, 1.19 and 1.20 for the periods 0–6 months, 7–12 months, and subsequent years, respectively.

Recently, the study of Tran et al. suggested an excess mortality after wrist of 1.43 (1.07–1.92) and after other fractures of 1.38 (1.18–1.62) [75]. We therefore included these estimates and again, that only 25% of the excess mortality is assumed to be attributable to the fracture. If a patient had a non-hip non-vertebral fractures and a hip/vertebral fracture, only the excess mortality of the hip/vertebral fracture is incorporated in the model. For patients with both hip and vertebral fracture or with several hip or vertebral fractures, we included only one mortality excess.

E. Effects of multiple fractures on costs and utilities

An increased cost was assumed for a recurrent fracture at the same location in line with the US study of Weaver et al. [76]. The proportion factor (68% and 106% for recurrent fracture in commercial and Medicare) were thus applied for a recurrent fracture at the same location [76].

In line with previous economic evaluations [77], when a second fracture occurred at the same site, the disutility applied to the first fracture event was reduced by 50%. This assumption is supported by recent studies showing that the number of fractures is a significant determinant of quality of life [78].

F. Adherence

One sensitivity analysis was conducted assuming real-world adherence. Treatment effects and costs were reduced and adjusted using formulas from Liu et al. [79]. The US adherence levels for medications from Cheng et al. [80] was used for ALN and TPTD. Similar adherence level than TPTD was assumed for ABL given the similar model of intake and frequency of intake.

Hazard ratios were adjusted to real-world adherence rate:

*Adjusted Hazard Ratio (HR) = (Real-World Adherence Rate) * (HR from the Trial) + (100% - Real-World Adherence Rate) * (HR of the Placebo Group in the Trial.*

Similarly, treatment costs were also adjusted with real-world adherence rate as follows:

*Adjusted Treatment Cost = (Real-World Adherence Rate) * (Treatment Cost) + (100% - Real-World Adherence Rate) * (Treatment Cost of the Placebo Group in the Trial).*

Appendix B: Distributions for probabilistic sensitivity analyses

A beta distribution was used for the incidence of all fracture types. Parameters of the distribution were estimated based on the number of fractures and the population in the age range 70–74 years. Normal distributions, with a standard deviation assumed to be 20% of the mean, were used for fracture cost variables given a standard error was not available for these parameters. Log-normal distributions were assumed for all relative risk parameters, i.e. fracture risk reduction with therapy or the excess mortality following the fracture. Parameters were derived from the 95% confidence intervals of the parameters. A beta distribution was assumed for the effects of fracture on quality-adjusted life years based on confidence intervals. Normal distributions, with a standard deviation assumed to be 15% of the mean, were also assumed for excess mortality attributable to the fracture and for the probability of being admitted to nursing home following a hip fracture. The same PSA parameter samples were used

when running different treatments (except for the effect of oral bisphosphonates) (Table B1).

Table B1
Distributions of model parameters for the probabilistic sensitivity analyses

Parameter	Distribution
Fracture risk	
Hip fracture, CV fracture, wrist fracture and other fracture risk	Beta
Relative risk of a prior fracture on future fracture risk (for age range 60–70)	Log normal
Probability of admissions to a nursing home following hip fractures	Normal (SE = 15% of the mean)
Treatment effects	Log-normal
Mortality	
Excess mortality after fractures	Log-normal
Excess mortality attributable to fracture	Normal (SE = 15% of the mean)
Utility	
Relative risk of the effects of fractures	Beta
Fracture costs	
Cost of a fracture	Normal (SE = 20% of the mean)
Long term cost after hip fracture	Normal (SE = 20% of the mean)

SE standard error.

Appendix C: Additional results

Tables C1—C3

Table C1
Lifetime costs, QALYs, number of fractures and incremental cost-effectiveness ratio (ICER) of ABL/ALN compared with alternative treatments in the US in women with BMD T-score ≤ −3.5 aged between 50 and 80 years

	ABL/ALN	No treatment	TPTD/ALN
50 years			
Discounted costs	98,942	85,120	131,166
Discounted QALYs	15.357	15.175	15.330
Number of fractures (per patient)	3.490	3.813	3.571
ICER (cost in $ per QALY gained)		76,181	Dominant
55 years			
Discounted costs	100,722	89,758	133,421
Discounted QALYs	13.777	13.552	13.739
Number of fractures (per patient)	3.213	3.622	3.320
ICER (cost in $ per QALY gained)		48,748	Dominant
60 years			
Discounted costs	97,645	88,119	130,145
Discounted QALYs	12.099	11.871	12.068
Number of fractures (per patient)	2.860	3.291	2.976
ICER (cost in $ per QALY gained)		41,832	Dominant
65 years			
Discounted costs	93,888	89,715	126,945
DiscountedQALYs	10.396	10.100	10.360
Number of fractures	2.478	3.015	2.595
ICER (cost in $ per QALY gained)		14,089	Dominant
70 years			
Discounted costs	83,304	85,004	116,685
Discounted QALYs	8.638	8.284	8.602
Number of fractures (per patient)	2.021	2.675	2.146
ICER (cost in $ per QALY gained)		Cost-saving	Dominant
75 years			
Discounted costs	74,341	79,073	107,894
Discounted QALYs	6.974	6.620	6.927
Number of fractures	1.599	2.321	1.736
ICER (cost in $ per QALY gained)		Cost-saving	Dominant
80 years			
Costs	57,179	60,926	89,793
QALYs	5.388	5.056	5.349
Number of fractures	1.087	1.847	1.223
ICER (cost in $ per QALY gained)		Cost-saving	Dominant

ABL abaloparatide, ALN alendronate, BMD bone mineral density, ICER incremental cost-effectiveness ratio, QALY quality-adjusted life-years, TPTD teriparatide.

Table C2
Lifetime costs, QALYs, number of fractures and incremental cost-effectiveness ratio (ICER) of ABL/ALN compared with alternative treatments in the US in women with BMD T-scores between −2.5 and −3.5 and history of one osteoporotic fracture aged between 50 and 80 years

	ABL/ALN	No treatment	TPTD/ALN
50 years			
Discounted costs	71,082	52,754	103,133
Discounted QALYs	15.527	15.381	15.508
Number of fractures (per patient)	2.761	3.018	2.836
ICER (cost in $ per QALY gained)		125,493	Dominant
55 years			
Discounted costs	72,081	55,361	104,336
Discounted QALYs	13.944	13.761	13.914
Number of fractures (per patient)	2.529	2.856	2.630
ICER (cost in $ per QALY gained)		91,394	Dominant
60 years			
Discounted costs	70,200	54,395	102,384
Discounted QALYs	12.276	12.083	12.245
Number of fractures (per patient)	2.235	2.593	2.350
ICER (cost in $ per QALY gained)		81,865	Dominant
65 years			
Discounted costs	68,120	54,970	100,592
Discounted QALYs	10.571	10.318	10.542
Number of fractures	1.920	2.339	2.041
ICER (cost in $ per QALY gained)		51,906	Dominant
70 years			
Discounted costs	62,749	51,909	95,066
Discounted QALYs	8.792	8.513	8.756
Number of fractures (per patient)	1.565	2.039	1.683
ICER (cost in $ per QALY gained)		38,763	Dominant
75 years			
Discounted costs	57,128	48,841	89,439
Discounted QALYs	7.109	6.845	7.069
Number of fractures	1.236	1.743	1.357
ICER (cost in $ per QALY gained)		31,390	Dominant
80 years			
Discounted costs	47,670	40,465	79,370
Discounted QALYs	5.471	5.215	5.430
Number of fractures	0.877	1.406	0.991
ICER (cost in $ per QALY gained)		28,086	Dominant

ABL abaloparatide, ALN alendronate, BMD bone mineral density, ICER incremental cost-effectiveness ratio, QALY quality-adjusted life-years, TPTD teriparatide.

Table C3
Effect of changes in drug costs on the incremental cost-effectiveness ratio (expressed in cost ($) per QALY gained) of ABL/ALN compared with TPTD/ALN and no treatment in US women with BMD T-score ≤ −3.5 and in women BMD T-score between −2.5 and −3.5 and history of one osteoporotic fracture

	BMD T-score ≤ −3.5		BMD T-score between −2.5 and −3.5 and history of one osteoporotic fracture	
	ABL/ALN vs. no treatment	ABL/ALN vs. TPTD/ALN	ABL/ALN vs. no treatment	ABL/ALN vs. TPTD/ALN
Age 50 years				
Base case	76,181	Dominant	125,493	Dominant
ABL cost −50%	12,534	Dominant	46,427	Dominant
ABL cost −20%	50,722	Dominant	93,867	Dominant
ABL cost + 20%	101,639	Dominant	157,119	Dominant
ABL cost + 50%	139,827	Dominant	204,558	Dominant
ABL cost + 100%	203,473	Dominant	283,624	Dominant
TPTD −25%	–	Dominant	–	Dominant
TPTD −50%	–	Dominant	–	Dominant
Age 60 years				
Base case	41,832	Dominant	81,865	Dominant
ABL cost −50%	Cost-saving	Dominant	22,052	Dominant
ABL cost −20%	21,547	Dominant	57,940	Dominant
ABL cost + 20%	62,116	Dominant	105,790	Dominant
ABL cost + 50%	92,542	Dominant	141,677	Dominant
ABL cost + 100%	143,253	Dominant	201,490	Dominant
TPTD −25%	–	Dominant	–	Dominant
TPTD −50%	–	Dominant	–	Dominant
Age 70 years				
Base case	Cost-saving	Dominant	38,763	Dominant

(continued)

Table C3 (*continued*)

	BMD T-score ≤ −3.5		BMD T-score between −2.5 and −3.5 and history of one osteoporotic fracture	
	ABL/ALN vs. no treatment	ABL/ALN vs. TPTD/ALN	ABL/ALN vs. no treatment	ABL/ALN vs. TPTD/ALN
ABL cost −50%	Cost-saving	Dominant	Cost-saving	Dominant
ABL cost −20%	Cost-saving	Dominant	22,246	Dominant
ABL cost + 20%	8244	Dominant	55,279	Dominant
ABL cost + 50%	27,808	Dominant	80,054	Dominant
ABL cost + 100%	60,415	Dominant	121,345	Dominant
TPTD −25%	–	Dominant	–	Dominant
TPTD −50%	–	Dominant	–	Dominant
Age 80 years				
Base case	Cost-saving	Dominant	28,086	Dominant
ABL cost −50%	Cost-saving	Dominant	Cost-saving	Dominant
ABL cost −20%	Cost-saving	Dominant	10,079	Dominant
ABL cost + 20%	2622	Dominant	46,093	Dominant
ABL cost + 50%	23,448	Dominant	73,103	Dominant
ABL cost + 100%	58,157	Dominant	118,120	Dominant
TPTD −25%	–	Dominant	–	Dominant
TPTD −50%	–	Dominant	–	Dominant

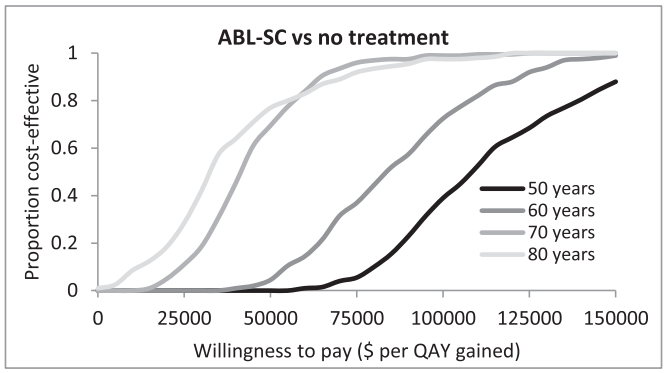

Fig. C2. Cost-effectiveness acceptability curves of ABL/ALN compared to no treatment in US women with BMD T-scores between −2.5 and −3.5 and history of one osteoporotic fracture aged 50, 60, 70 and 80 years. *ABL abaloparatide, ALN alendronate, BMD bone mineral density, QALY quality-adjusted life-years*.

Figs. C1—C3

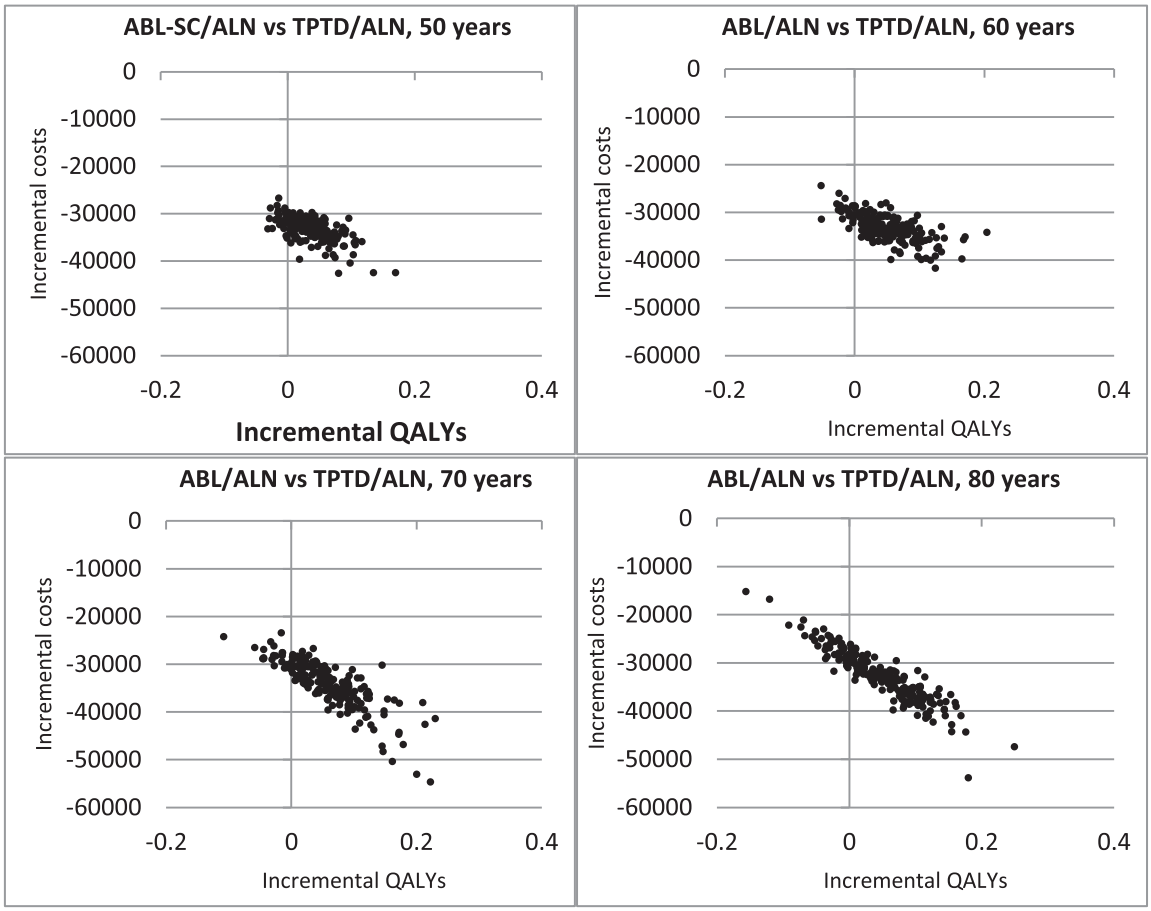

Fig. C1. Cost-effectiveness planes of ABL/ALN versus TPTD/ALN in women with a BMD T-score ≤ −3.5 aged 50, 60, 70 and 80 years. *ABL abaloparatide, ALN alendronate, QALY quality-adjusted life-years, TPTD teriparatide*.

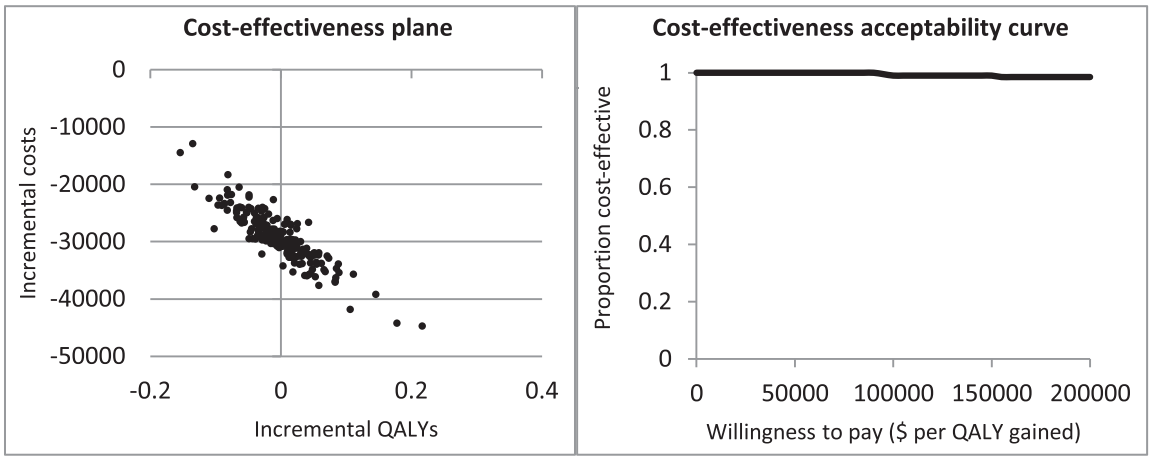

Fig. C3. Cost-effectiveness plane and cost-effectiveness acceptability curve of ABL/ALN compared to TPTD/ALN in US women with BMD T-score ≤ −3.5 aged 70 years: additional scenario considering fracture efficacy from the FPT trial. *ABL abaloparatide, ALN alendronate, BMD bone mineral density, QALY quality-adjusted life-years, TPTD teriparatide*.

Appendix D: Osteoporosis-specific checklist – Specific items to include when reporting economic evaluations on osteoporosis*

Item	Item no.	Recommendation	Reported on page no. / line no.
Transition probabilities	1	Report the transition probabilities and how they were estimated (including increased fracture risk)	Methods section and appendix A (Sections B and C)
Excess mortality after fractures	2	Describe approaches and data sources used for the excess mortality after fractures	Appendix A Section D
Fractures costs	3	Describe approaches and data sources used for fractures costs	Methods section
Fractures effects on utility	4	Describe approaches and data sources used for the effects of fractures on utility	Methods section
Treatment effect during treatment	5	Describe fully the methods used for the identification, selection and synthesis of clinical effectiveness data (per fracture site)	Methods section
Treatment effect after discontinuation	6	Describe fully the methods used for the treatment effect after discontinuation	Methods section
Medication adherence	7	Describe approaches and data sources used for modeling medication adherence	Appendix A Section F
Treatment costs	8	Describe approaches and data sources used for therapy costs	Methods section
Treatment side effects	9	Describe approaches and data sources used for costs and utilities effects of adverse events	Methods section

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