Cost-Effectiveness of Sequential Abaloparatide/Alendronate in Men at High Risk of Fractures in the United States

PharmacoEconomics

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Electronic Supplementary Material

Section 1: Additional information on the model

A. LIST OF KEY MODEL COMPONENTS/ASSUMPTIONS ALONG WITH THE RATIONALE FOR EACH ASSUMPTION.

Model component/assumption	Rationale
Cost-effectiveness analysis using QALY as outcome	QALY offers the advantage to take morbidity and mortality gains into account
Markov microsimulation model	Allow to track patient disease history (number of fractures and time since fractures) and avoid unnecessary transition restrictions
6-month cycle length	As fractures effects could be different for the periods 0-6 and 7-12 months
1,000,000 of first-order trials for the deterministic analysis and 200 times first order 50,000 simulations for the probabilistic sensitivity analyses	Number of simulations sufficient to guarantee the stability of results
Hip, vertebral, and nonhip nonvertebral 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 type of fractures
Fracture risk adjustment within the model after fracture events	In line with studies suggesting an increased fracture risk after fracture [1, 2]
Excess mortality after hip and vertebral (first and subsequent years)	In line with studies suggesting an excess mortality after hip and clinical vertebral fractures; no excess mortality after nonhip nonvertebral fractures was shown in men [3-5]
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
Men at high risk of fractures (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 [6]
Health care perspective	In line with US guideline for economic evaluations [6]. All health care costs included.

Long-term costs of fractures	Based on a recent study reporting adjusted incremental costs of fractures (per type) for year 2 up to year 5 in the US [7]
Utility decrements following fractures by fracture site (first year and subsequent years)	In line with data currently available [8]
Additional effects of multiple fracture on costs and utility	In line with previous studies suggesting a relationship between fracture costs and the number of fractures [7]
Treatment duration	In line with clinical practice
Effects of ABL/TPTD on hip fractures derived from the estimated fracture risk reduction for nonvertebral fractures	In the absence of hip specific data, the estimate for nonvertebral fractures is more conservative than the estimate for major fractures
Effects after treatment discontinuation: - ALN: linear decrease of the effects for a duration similar to the duration on therapy. - ABL/TPTD: two years maintenance of effects following by a linear decline in the third year	In line with clinical studies assessing the effects of therapies after discontinuation
Drug cost was adjusted by the average drug adherence level from the trial	To consider that all drugs were not taken drug the trial
The therapy costs include the cost of one physician visit per 6 months and the cost of one DXA every two years (similar assumption for all therapies)	In line with clinical practice
Real-world medication adherence	In line with real-life settings and potential impact of adherence on cost effectiveness
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 ACTIVExtend trial
In case of sequential therapy, the effects of both treatments are considered	Realistic assumption in line with previous economic studies of sequential therapies [9, 10]

B. FRACTURE RISK ADJUSTMENT ACCORDING TO BMD

We used the method developed by Kanis et al to adjust the fracture risk according to bone mineral density (BMD) [11]. 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 [12]. 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) [13]. BMD was derived from the recommended NHANES III [14] database and the US Caucasian female BMD reference database was used to derive T-scores in men [15]. The estimated relative risks for men with BMD T-score ≤−2.5 are provided in Table 1.

Table 1. Estimates of the relative risk of fracture for men with BMD T-score ≤−2.5

Age range (years)	Hip	Vertebral	NHNV
50-59	9.817	3.542	2.815
60-69	5.887	2.990	2.457
70-79	4.334	2.702	2.264
80-100	2.307	2.144	1.879

NHNV nonhip nonvertebral

C. BASELINE MORTALITY RATES

Mortality rates for US men (estimated in 2019) according to age are available from official estimates (NCHS, National Vital Statistics System). They are summarized in Table 2.

Table 2. Probabilities of death for US men

Age		Age	
50	0.0049	75	0.0339
51	0.0053	76	0.0371
52	0.0058	77	0.0412
53	0.0064	78	0.0453
54	0.0070	79	0.0500
55	0.0077	80	0.0549
56	0.0083	81	0.0607
57	0.0090	82	0.0675
58	0.0098	83	0.0749
59	0.0106	84	0.0835
60	0.0114	85	0.0936
61	0.0123	86	0.1040
62	0.0132	87	0.1163
63	0.0141	88	0.1298
64	0.0150	89	0.1444
65	0.0160	90	0.1602
66	0.0172	91	0.1772
67	0.0183	92	0.1952
68	0.0196	93	0.2143
69	0.0209	94	0.2343
70	0.0223	95	0.2552
71	0.0239	96	0.2767
72	0.0256	97	0.2987
73	0.0283	98	0.3210
74	0.0307	99	0.3434

Source: 2022 NCHS, National Vital Statistics System. Mortality table 2019

D. Real-world adherence

Treatment effects and costs were reduced and adjusted using formulas from Liu et al. (2006) [9].

Hazard ratios were adjusted to real-world adherence rate as follows:

*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)*

E. 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 utilities based on confidence intervals.

Table 3. Distributions of model parameters for the probabilistic sensitivity analyses

Parameter	Distribution
Fracture risk	
Hip fracture, vertebral fracture and NHNV fracture risk	Beta
Relative risk of a prior fracture on future fracture risk (for age range 60 to 70)	Log normal
Treatment effects	Log normal
Mortality	
Excess mortality after fractures	Log normal
Utility	
Relative risk of the effects of fractures	Beta
Fracture costs	
First year and subsequent year cost of a fracture	Normal (SE = 20% of the mean)

NHNV nonhip non vertebral, SE standard error

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Section B

Table 1. CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Methods
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Methods
Setting and location	6	Provide relevant contextual information that may influence findings.	Methods
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods
Time horizon	9	State the time horizon for the study and why appropriate.	Methods
Discount rate	10	Report the discount rate(s) and reason chosen.	Methods
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods

Topic	No.	Item	Location where item is reported
Rationale and description of model	16	If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.	Methods
Analytics and assumptions	17	Describe any methods for analyzing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Methods
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Methods
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Methods
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	methods
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Results
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	Results
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, public, community, or stakeholder involvement made to the approach or findings of the study	NR
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Funding

Topic	No.	Item	Location where item is reported
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Conflict of interest

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25.

Table 2. ESCEO-IOF Osteoporosis-specific checklist

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
Excess mortality after fractures	2	Describe approaches and data sources used for the excess mortality after fractures	Methods
Fractures costs	3	Describe approaches and data sources used for fractures costs	Methods
Fractures effects on utility	4	Describe approaches and data sources used for the effects of fractures on utility	Methods
Treatment effect during treatment	5	Describe fully the methods used for the identification, selection and synthesis of clinical effectiveness data (per fracture site)	Methods
Treatment effect after discontinuation	6	Describe fully the methods used for the treatment effect after discontinuation	Methods
Medication adherence	7	Describe approaches and data sources used for modelling medication adherence	Methods
Treatment costs	8	Describe approaches and data sources used for therapy costs	Methods
Treatment side effects	9	Describe approaches and data sources used for costs and utilities effects of adverse events	Methods

From: Hiligsmann M et al. Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the US branch of the International Osteoporosis Foundation. Osteoporos Int 2019 Jan;30(1):45-57

Table 3. ESCEO-IOF checklist for the design and conduct of an economic evaluation in osteoporosis

Type of economic evaluation	
• Cost-utility analysis using QALY as outcome	YES
Method for the conduct of economic evaluation	
• A model based economic evaluation	YES
Modelling technique	
• Lifetime horizon	YES
• Markov model is appropriate (6 months/1-year cycle length)	YES (6 months)
• Avoid hierarchy of fractures and restrictions after fracture events	YES
• Hip, clinical vertebral, and nonvertebral nonhip fracture	YES
Base-case analysis and population	
• Multiple scenarios: age range, BMD and fracture risk scenarios	YES
• At least a scenario including a 10-year risk of a major osteoporotic fracture equal to 20% or with a BMD T-score ≤−2.5 with or without fractures	YES
• The FRAX® or GARVAN® tools can be used to model fracture risk	NA
• Increased risk after fracture events within the model	YES
Mortality • An additional effect (on costs and/or utility) after multiple fractures	YES
• Excess mortality after hip fractures	YES
• Proportion attribute to the fracture (e.g., 25%-30%)	YES
Fracture costs and utility	
• Societal and/or healthcare payor perspective	YES
Acute fracture costs	
• Long-term costs after hip fracture (attributable to the fracture)	YES
• First year and subsequent years effects of fractures on disutility	YES
• National ICUROS data if available	YES (whole ICUROS study)
Treatment characteristics	
• Treatment duration similar to guidelines or RCTs	YES
• Comparators: no treatment and relevant active osteoporotic agent(s)	YES
• Sequential therapy may be considered as intervention/comparators	YES
• Efficacy data from RCTs, (network) meta-analysis	YES
• In the absence of hip/wrist specific efficacy data, use of nonvertebral or clinical fracture efficacy data	YES
• Treatment effects after discontinuation depending on treatment	YES
• Medication adherence as sensitivity analysis	YES (base case)
• Drug costs and administration/monitoring costs	YES
Adverse events	YES

BMD bone mineral density, ICUROS International Costs and Utilities Related to Osteoporotic Fractures Study, QALY quality-adjusted life year, RCT randomized controlled trial

From: Hiligsmann M et al. Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the US branch of the International Osteoporosis Foundation. Osteoporos Int 2019 Jan;30(1):45-57

Section C: Additional results

Table 1. Lifetime costs, QALYs, number of fractures and incremental cost-effectiveness ratio (ICER) of ABL/ALN compared with alternative treatments in US men with BMD T-score ≤−2.5 and a recent fracture aged ≥50 years

	ABL/ALN	No treatment	Unbranded TPTD/ALN	ALN monotherapy
50 years				
Costs	91,692	82,841	95,363	81,440
QALYs	13.123	13.017	13.090	13.038
Number of fractures (per patient)	2.252	2.422	2.309	2.395
ICER *(cost in US$ per QALY gained)*		**83,383**	**Dominant**	**120,856**
55 years				
Costs	90,219	81,691	93,711	80,086
QALYs	11.744	11.630	11.715	11.654
Number of fractures (per patient)	2.041	2.210	2.093	2.182
ICER (cost in US$ per QALY gained)		**74,702**	**Dominant**	**112,242**
60 years				
Costs	89,636	83,542	93,535	81,380
QALYs	10.273	10.134	10.246	10.169
Number of fractures (per patient)	1.860	2.069	1.921	2.033
ICER *(cost in US$ per QALY gained)*		**43,691**	**Dominant**	**79,366**
65 years				
Costs	87,595	81,042	91,754	79,007
QALYs	8.840	8.711	8.814	8.743
Number of fractures (per patient)	1.664	1.888	1.730	1.848
ICER *(cost in US$ per QALY gained)*		**50,644**	**Dominant**	**88,022**
70 years				
Costs	84,311	79,456	88,560	76,844
QALYs	7.329	7.182	7.304	7.217
Number of fractures (per patient)	1.438	1.689	1.504	1.640
ICER *(cost in US$ per QALY gained)*		**32,901**	**Dominant**	**66,467**
75 years				
Costs	81,315	78,992	85685	75,412
QALYs	5.876	5.726	5.847	5.766
Number of fractures (per patient)	1.223	1.504	1.288	1.443
ICER *(cost in US$ per QALY gained)*		**15,517**	**Dominant**	**53,695**
80 years				
Costs	71,524	69,433	75875	65,944
QALYs	4.538	4.397	4.512	4.434
Number of fractures (per patient)	0.980	1.274	1.043	1.210
ICER *(cost in US$ per QALY gained)*		**14,877**	**Dominant**	**54,012**
85 years				
Costs	67,270	68,778	71,138	63,527
QALYs	3.293	3.112	3.270	3.169
Number of fractures (per patient)	0.794	1.131	0.838	1.040
ICER *(cost in US$ per QALY gained)*		**Dominant**	**Dominant**	**30,184**
90 years				
Costs	53,400	52,512	57,131	48,136
QALYs	2.390	2.252	2.371	2.296
Number of fractures (per patient)	0.598	0.901	0.647	0.820
ICER *(cost in US$ per QALY gained)*		**6,430**	**Dominant**	**56,065**

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

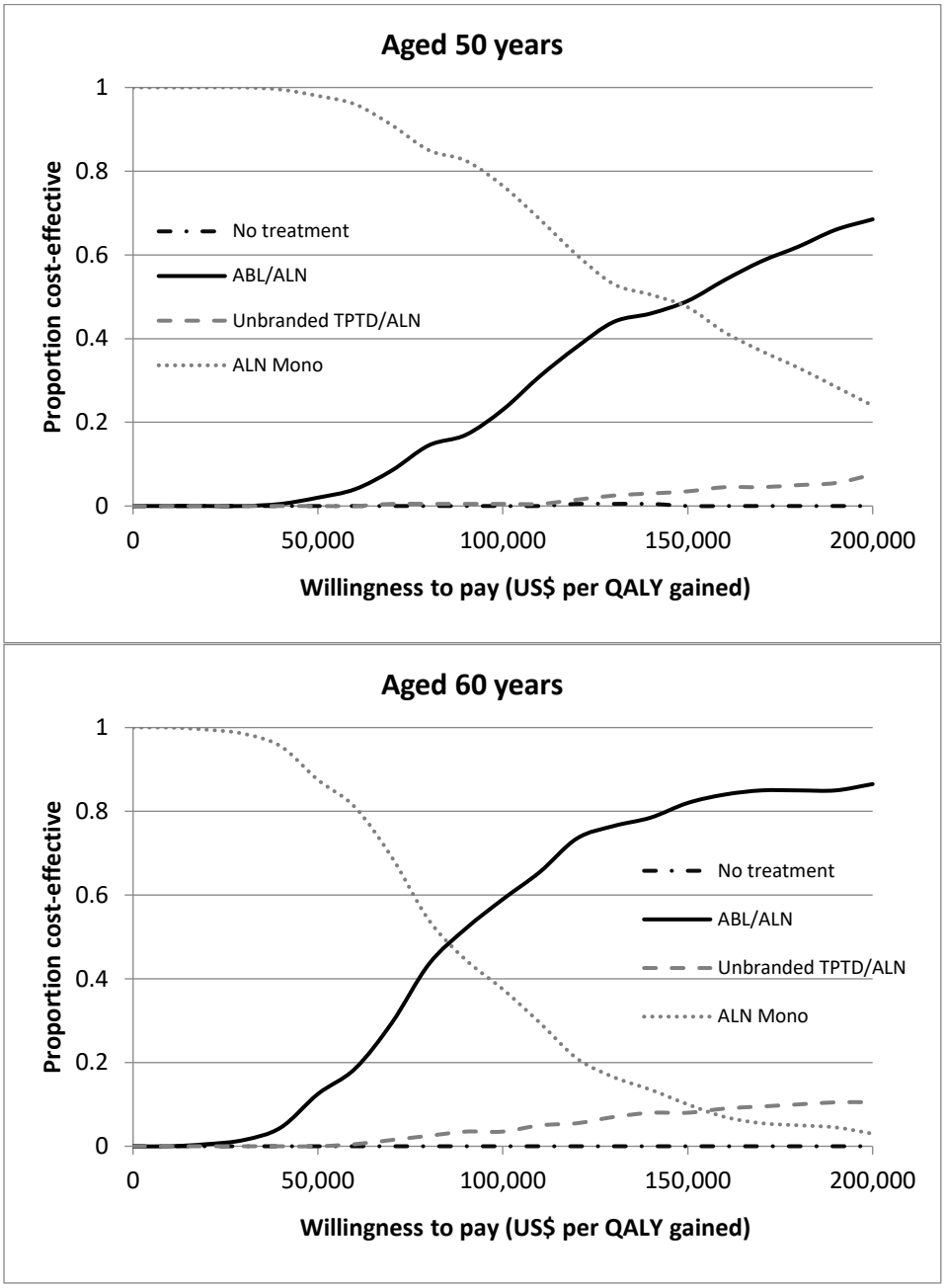
Table 2: One-way sensitivity analyses on the cost (US$) per QALY gained of ABL/ALN compared with alternative treatments in US men with a recent fracture and a BMD T-score ≤−2.5 at the age of 70 years

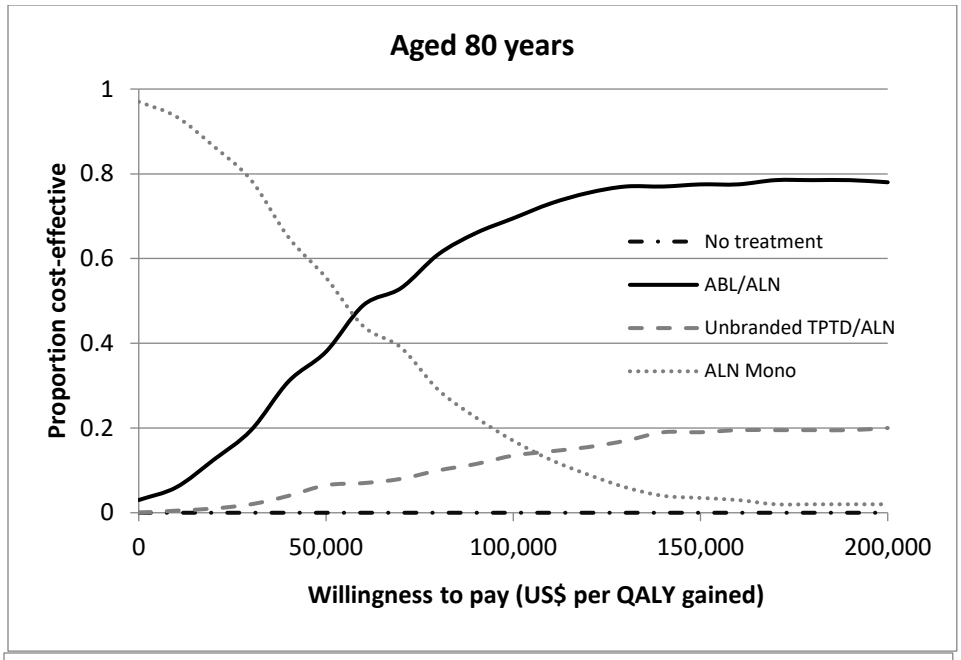
	ABL/ALN vs no treatment	ABL/ALN vs unbranded TPTD/ALN	ABL/ALN vs ALN monotherapy
Base case	32,901	Dominant (incr. costs: −4,250 incr. QALY: 0.026)	66,467
Model data and structure			
Fracture incidence −25%	67,747	Dominant (incr. costs: −3,512 incr. QALY: 0.022)	113,641
Fracture incidence +25%	10,780	Dominant (incr. costs: −4,891 incr. QALY: 0.032)	41,532
Fracture cost −25%	50,872	Dominant (incr. costs: −3,627 incr. QALY: 0.027)	85,690
Fracture cost +25%	15,259	Dominant (incr. costs: −4,880 incr. QALY: 0.025)	49,377
Long-term fracture cost	13,505	Dominant (incr. costs: −4,831 incr. QALY: 0.026)	49,078
Lifetime fracture costs	30,052	Dominant (incr. costs: −4,381 incr. QALY: 0.029)	64,956
Fracture disutilities −25%	41,675	Dominant (incr. costs: −4,264 incr. QALY: 0.019)	87,713
Fracture disutilities +25%	28,601	Dominant (incr. costs: −4,303 incr. QALY: 0.029)	60,437
Discount rates 0%	17,193	Dominant (incr. costs: −4,753 incr. QALY: 0.031)	43,869
Discount rates 5%	46,973	Dominant (incr. costs: −3,957 incr. QALY: 0.022)	88,094
No excess mortality	35,228	Dominant (incr. costs: −4,415 incr. QALY: 0.022)	81,808
10-year time horizon	61,167	Dominant (incr. costs: −4,004 incr. QALY: 0.019)	116,219
T-score ≤−2.5 and no previous fx	132,257	Dominant (incr. costs: −2,856 incr. QALY: 0.016)	189,492

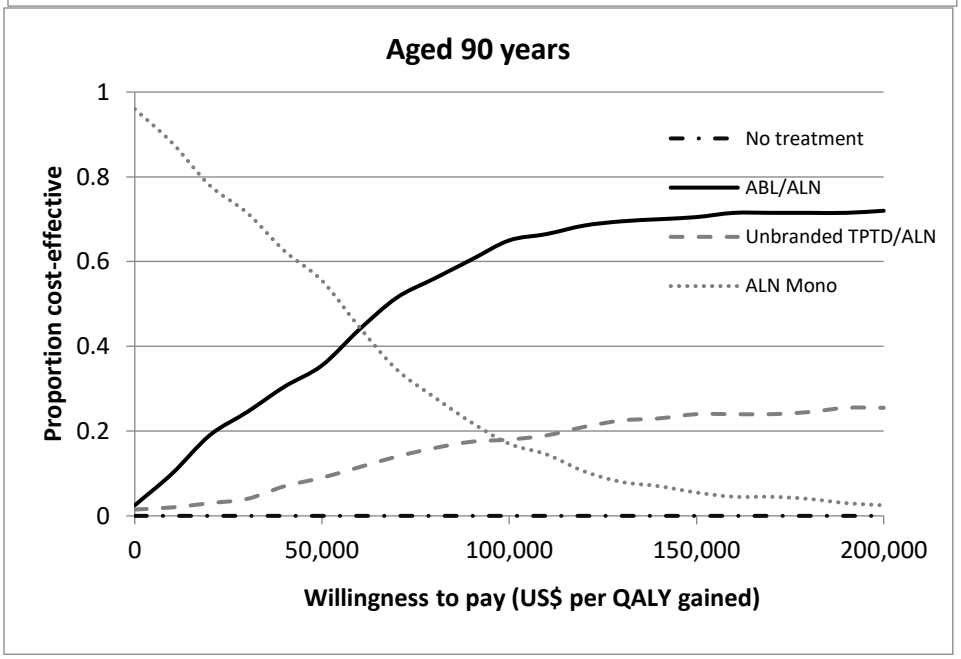
Treatment characteristics			
ABL/TPTD hip fx efficacy	15,168	Dominant (incr. costs: −6,012 incr. QALY: 0.044)	38,994
Network meta-analysis	28,460	Dominant (incr. costs: −3,850 incr. QALY: 0.027)	58,201
ABL cost −20%	9,528	Dominant (incr. costs: −7,715 incr. QALY: 0.027)	35,707
ABL cost +20%	57,482	Dominant (incr. costs: −772 incr. QALY: 0.027)	99,795
ABL cost −50%	Dominant (incr. costs: −3,823 incr. QALY: 0.144)	Dominant (incr. costs: −12,948 incr. QALY: 0.025)	Dominant (incr. costs: −1,270 incr. QALY: 0.109)
ABL cost +50%	92,203	175,441	149,374
Offset time (linear decline 3 y)	56,260	Dominant (incr. costs: −3,585 incr. QALY: 0.025)	111,196
Offset time (2 y + 3 y decline)	19,477	Dominant (incr. costs: −4,715 incr. QALY: 0.027)	46,045
Complete medication adherence	20,605	Dominant (incr. costs: −6,539 incr. QALY: 0.045)	115,391
No adverse events	32,877	Dominant (incr. costs: −4,250 incr. QALY: 0.025)	66,436

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

Figure 1. Cost-effectiveness acceptability curves of ABL/ALN versus alternative treatments in US men with BMD T-score ≤−2.5 and a recent fracture aged 50, 60, 80, and 90 years

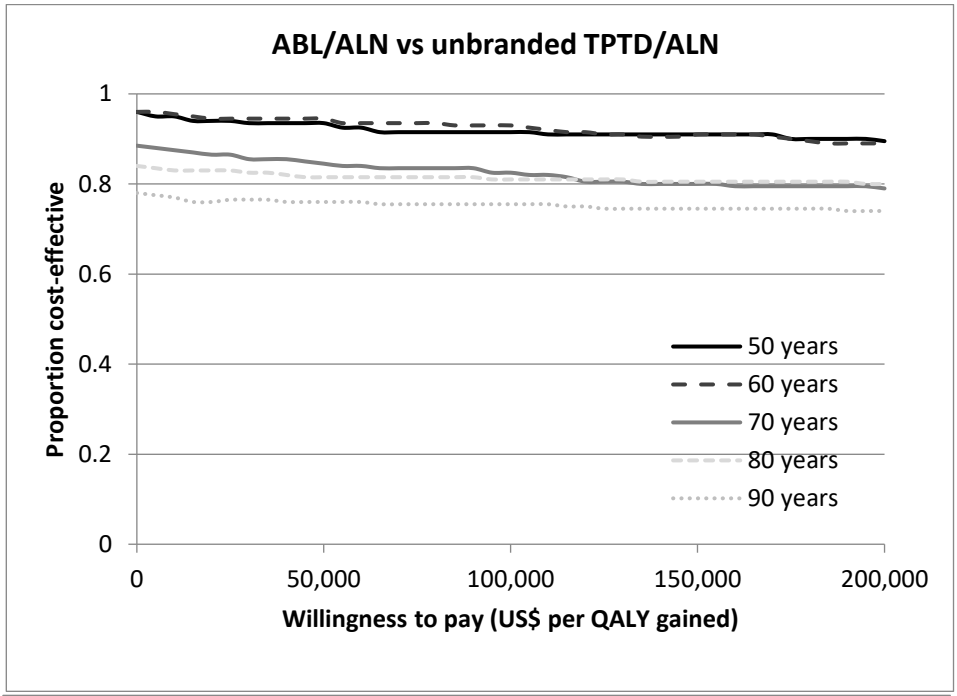


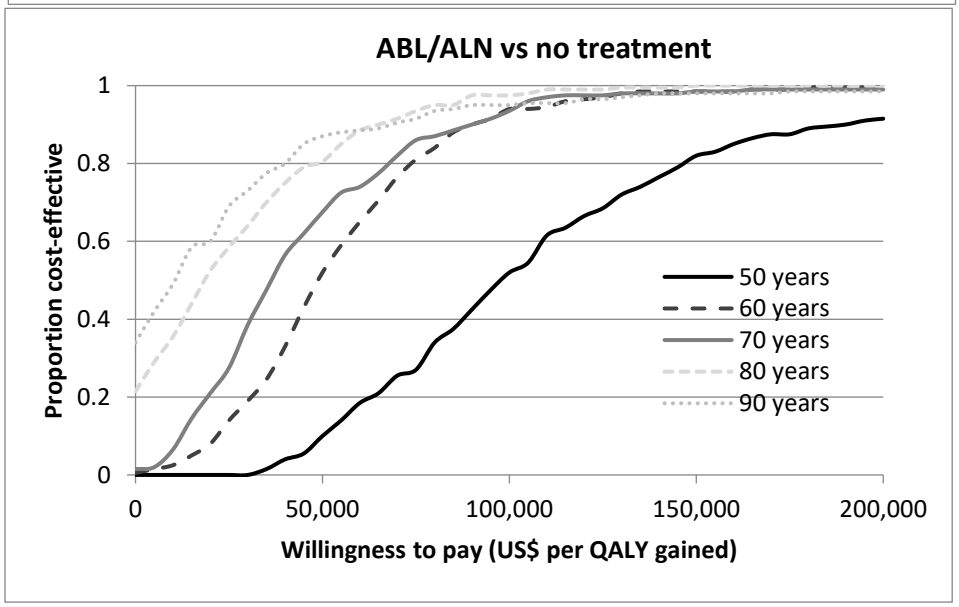




ABL abaloparatide, ALN alendronate, BMD bone mineral density, mono monotherapy, QALY quality-adjusted life year, TPTD teriparatide

Figure 2. Cost-effectiveness acceptability curves of ABL/ALN versus each alternative treatment in US men with BMD T-score ≤−2.5 and a recent fracture aged 50, 60, 70, 80, and 90 years





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