Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA Report

Title	Denosumab (Prolia®) for the treatment of osteoporosis
Authors	Magdalena Moshi, Konstance Nicolopoulos, Danielle Stringer, Virginie Gaget, Ning Ma, Thomas Vreugdenburg Royal Australasian College of Surgeons

Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

Technology	Denosumab (Prolia®)
Date	15 March 2022
Type of Technology	Pharmaceuticals

Conflicts of Interest:

The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

EXECUTIVE SUMMARY

Background

Since 2010, denosumab (Prolia®) has been listed on the Spezialitätenliste for the treatment of osteoporosis in postmenopausal women, men with osteoporosis who have an increased fracture risk, women with breast cancer receiving adjuvant aromatase inhibitor therapy (AAIT), and men with prostate cancer on hormone ablation therapy (HAT). Pharmacovigilance reports in 2017 warned that discontinuation of denosumab therapy in patients with osteoporosis may lead to increased bone turnover, significant bone mineral loss and increased vertebral fracture risk. On the basis of these safety concerns, the Federal Office of Public Health (FOPH) is re-evaluating the available evidence for denosumab.

Objective

The objective of this Health Technology Assessment (HTA) is to evaluate the safety, effectiveness, cost-effectiveness and financial impact of denosumab (Prolia®) compared to placebo, bisphosphonates and selective oestrogen receptor modulators (SERMs) in four subgroups of patients. Legal, social, ethical and organisational impacts have also been considered.

Methods

A systematic literature search was conducted in eight biomedical databases, in conjunction with clinical trial registries and speciality websites. Safety, efficacy and effectiveness outcomes reported by at least two randomised controlled trials (RCTs), which in total reported three or more treatment arms, were evaluated using network meta-analysis; outcomes with only two comparison arms were evaluated using pairwise meta-analysis. Risk of bias of the included RCTs was evaluated using the Cochrane Risk of Bias 2.0 tool, and the overall strength of evidence for key outcomes was evaluated using the GRADE approach.

A discrete event simulation (DES) model was developed to quantify the cost-effectiveness of denosumab versus oral bisphosphonates, intravenous (IV) ibandronate, zoledronate, raloxifene, bazedoxifene and no treatment for the management of osteoporosis in postmenopausal women. This population was chosen as an exemplar population because it represents the largest population in which denosumab is used in Switzerland, and it has the most robust clinical data supporting safety and efficacy of denosumab.

Results

Postmenopausal women: Twelve RCTs (k = 22 publications) with low to high risk of bias were identified. Only risedronate was found to be statistically significant for the prevention of nonvertebral fractures compared to placebo after 12 to 84 months of treatment; risedronate was also ranked as the most effective treatment at preventing nonvertebral fracture, with denosumab ranking as the least effective (of six treatments). In relation to femoral neck (FN) bone mineral density (BMD), alendronate, ibandronate and risedronate were statistically significant relative to placebo at 19 (± 1 SD) months, ranking from first to third at increasing FN BMD, respectively. Denosumab was ranked as the fourth most effective treatment (of eight) at increasing FN BMD. However, the clinical relevance of the increases in BMD findings is unclear, as there is a lack of consensus on minimally clinically important differences (MCID) that associates changes in BMD to fracture risk. Vertebral fracture, mortality, adverse events (AEs), serious adverse events (SAEs) and withdrawal due to treatment-related AEs reported no significant differences for any intervention compared to placebo. Evidence for discontinuation effects related to denosumab use was limited and cannot be used to draw conclusions about possible rebound effects.

Women with breast cancer receiving AAIT: Four RCTs (k = 5 publications) with moderate to high risk of bias were identified. There were no studies evaluating the treatment effects of zoledronate, alendronate, raloxifene or bazedoxifene to directly or indirectly contribute to the network meta-analyses of effectiveness or safety outcomes. Denosumab was associated with statistically significant reductions in vertebral fractures, and increases in BMD, relative to placebo. However, the clinical relevance of the increases in BMD is unclear. No statistically significant difference between denosumab and placebo was detected for nonvertebral fractures, mortality, AEs, SAEs or withdrawal due to treatment-related AEs. Evidence for discontinuation effects related to denosumab use was limited and cannot be used to draw conclusions about possible rebound effects.

Men with osteoporosis: Four RCTs (k = 5 publications) with moderate to high risk of bias were identified. None of the included treatments demonstrated a significant treatment effect compared to placebo in relation to vertebral or nonvertebral fracture. For FN BMD, denosumab and zoledronate were statistically significant relative to placebo at 12 months, ranking first and second at increasing FN BMD, respectively. However, the clinical relevance of these BMD findings is unclear. After 12 to 24 months, alendronate and zoledronate showed a statistically significant increase in risk of AEs relative to placebo in men with osteoporosis who have increased fracture risk (ranked fourth and fifth, respectively, of five treatments). None of the included interventions was statistically significant relative to placebo for mortality, SAEs or withdrawal due to treatment-related AEs. No evidence was

available for AEs upon discontinuation of denosumab (i.e. rebound effect).

Men with prostate cancer undergoing HAT: Ten RCTs (k = 10 publications) with moderate to high risk of bias were identified. There were no studies evaluating ibandronate, raloxifene or bazedoxifene in this population. Denosumab was found to be statistically significant relative to placebo for the prevention of vertebral fracture in men with prostate cancer on HAT, ranked as the most effective treatment (of three treatments). None of the included interventions were statistically significant for nonvertebral fractures after 12 to 36 months of treatment. Denosumab was ranked as the most effective treatment at preventing nonvertebral fractures. For FN BMD, zoledronate, denosumab and alendronate were statistically significant relative to placebo at 12 months, ranking second to fourth (of five treatments) at increasing FN BMD, respectively. However, the clinical relevance of these BMD findings is unclear. None of the included interventions were statistically different to placebo in terms of mortality, AEs, SAEs or withdrawal due to treatment-related AEs. No evidence was available for AEs upon discontinuation of denosumab (i.e. rebound effect).

Sensitivity analysis on a combined population: A sensitivity analysis combining all four populations was conducted to investigate how grouping the four populations together affects the precision of the analysis. When populations were combined, only the results associated with denosumab changed from being nonsignificant in many groups to statistically significant in relation to vertebral fracture, nonvertebral fracture and FN BMD.

Costs and cost-effectiveness

Time-to-fracture distributions for hip, clinical vertebral and non-hip nonvertebral (NHNV i.e. forearm, humeral) fractures—derived from Swiss-specific FRAX® (fracture risk assessment tool) probabilities of major osteoporotic fracture (MOF) in women of postmenopausal age at various risk levels—formed the backbone of the economic model. Reductions in the risk of vertebral and nonvertebral fracture due to treatment were informed by the network meta-analysis, while real-world adherence data were obtained from the literature. Cost-effectiveness was determined via cost-effectiveness frontier analysis. Additionally, pairwise comparisons between denosumab and each comparator were made.

At a hypothetical willingness-to-pay (WTP) threshold of Swiss francs (CHF)100,000, IV ibandronate was the most cost-effective option in women aged 60 years at very high risk, and in women aged 70 or 80 years at any risk level. In women aged 60 years at lower risk levels, zoledronate was the most cost-effective option.

Whilst cost-effectiveness frontier analysis did not find denosumab to be the most cost-effective

antiresorptive therapy, some of the incremental cost-effectiveness ratios (ICERs) from pairwise comparisons between denosumab and individual comparators were below the hypothetical WTP threshold of CHF100,000. In women aged 70 years at high fracture risk, denosumab had ICERs of CHF15,927, CHF23,135, CHF86,776, CHF107,460, CHF166,451 and CHF615,149 when compared with no treatment, bazedoxifene, raloxifene, zoledronate, oral bisphosphonates and IV ibandronate, respectively. The higher intervention costs, smaller reduction in the risk of hip fracture and shorter duration of residual benefit associated with denosumab have contributed to the high ICER values seen in pairwise comparisons with oral bisphosphonates and IV ibandronate.

The budget impact analysis explored the potential costs of denosumab from 2021 to 2024. In the base case, it was assumed that use of denosumab would continue to decline by 1.6% per annum, which reflects the average annual decline in use over the period 2018 to 2020. Under this assumption, the payer cost of denosumab was estimated to be CHF 26.6 million in 2024, representing a decrease of CHF 1.6 million compared to 2020 (CHF 28.2 million). While the utilisation of denosumab has declined in recent years, uptake of bisphosphonates has increased, suggesting a substitution may be occurring in practice. Crude analyses indicated the potential for cost savings through the natural substitution of denosumab with bisphosphonates (CHF0.36 million in 2021, increasing to CHF1.43 million in 2024).

Social, legal, ethical and organisational issues

No literature related to the legal implications of denosumab use was identified. Studies reported strong patient preferences and adherence to denosumab compared to bisphosphonates. Efforts to improve adherence would need to be considered if the reimbursement status of denosumab was altered.

Conclusion

Denosumab reported similar treatment effects and safety profile compared to comparator interventions in most populations; however, the analyses were largely limited by statistical imprecision due to the limited evidence in the four specific populations defined in the policy question. The evidence base investigating rebound effects in the Swiss policy context was severely limited and cannot be used to draw meaningful conclusions around the probability and severity of rebound effects upon discontinuation of denosumab therapy. Cost-effectiveness frontier analysis did not find denosumab to be the most cost-effective antiresorptive therapy; however, denosumab was found to be cost-effective over some comparators in pairwise comparisons.

Contents

Tables

Figures

Abbreviations and acronyms

95% CI	95% confidence interval
95% CrI	95% credible interval
AAIT	Adjuvant aromatase inhibitors therapy
ABCSG-18	Austrian Breast and Colorectal Cancer Study Group, adjuvant denosumab in breast cancer study
ADAMO	A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of denosumab vs placebo in males with osteoporosis
ADT	Androgen deprivation therapy
AE	Adverse event
AFF	Atypical femur fracture
ALN	Alendronate
B-ALP	Bone-specific alkaline phosphatase
BAZ	Bazedoxifene
BIS	Bisphosphonates
BMD	Bone mineral density
BMI	Body mass index
BTM	Bone turnover marker
CHF	Swiss francs
CRF	Clinical risk factor
CTX	C-terminal telopeptide of type 1 collagen
DALY	Disability-adjusted life year
DAPS	Denosumab Adherence Preference Satisfaction study
DEN	Denosumab
DES	Discrete event simulation
DIC	Deviance formation criterion
DSA	Deterministic sensitivity analysis
DXA	Dual-energy X-ray absorptiometry
EUnetHTA	European Network for Health Technology Assessment
FN	Femoral neck
FOPH	Federal Office of Public Health
FRAX®	Fracture risk assessment tool
FREEDOM	Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAT	Hormone ablation therapy

HORIZON-PFT	HORIZON-Pivotal Fracture Trial
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IBN	Ibandronate
ICER	Incremental cost-effectiveness ratio
ICUROS	International Cost and Utilities Related to Osteoporosis fractures Study
IHE	Institute of Health Economics
INAHTA	International Network of Agencies for Health Technology Assessment
IV	Intravenous
LHRH	Luteinising hormone-releasing hormone
LOS	Length of stay
LS	Lumbar spine
MCID	Minimum clinically important difference
MCMC	Markov chain Monte Carlo
MD	Mean difference
MOF	Major osteoporotic fracture
MORE	Multiple Outcomes of Raloxifene Evaluation
NA	Not applicable
NHNV	Non-hip nonvertebral
NR	Not reported
NTX	N-terminal telopeptide of type 1 collagen
OL	Open-label
ONJ	Osteonecrosis of the jaw
OPAQ	Osteoporosis assessment questionnaire
p.a.	Per annum
P1NP	Procollagen type 1 N propeptide
PICO	Population, intervention, comparator, outcome
PL / PLB	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSRF	Potential scale reduction factor
QALY	Quality-adjusted life year
Q^{het}	Cochran's Q-statistic for heterogeneity
Q^{inc}	Cochran's Q-statistic for inconsistency
QoL	Quality of life
Qualeffo-41	Quality of life questionnaire of the European Foundation for Osteoporosis
RANKL	Receptor activator of nuclear factor kappa-B ligand

RCT	Randomised control trial
RIS	Risedronate
RLX	Raloxifene
RoB2	Cochrane Risk of Bias 2.0 tool
RR	Risk ratio
SAE	Serious adverse event
SD	Standard deviation
SERM	Selective oestrogen receptor modulator
SUCRA	Surface under the cumulative ranking curve
SVGO	Schweizerische Vereinigung gegen die Osteoporose (Swiss Association against Osteoporosis)
TH	Total hip
TRAP	Tartare-resistant acid phosphatase
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay
York CRD	University of York Centre for reviews and dissemination
ZOL	Zoledronate

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, and legal, social, ethical and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

In Switzerland, denosumab (Prolia®) is covered by mandatory health insurance for the treatment of osteoporosis in postmenopausal women, men with osteoporosis who have an increased fracture risk, women with breast cancer receiving adjuvant aromatase inhibitor therapy (AAIT), and men with prostate cancer on hormone ablation therapy (HAT) with an increased fracture risk.

Pharmacovigilance reports in 2017 warned that discontinuation of denosumab therapy in patients with osteoporosis can lead to increased bone turnover, significant bone mineral loss (in some cases below baseline levels) and increased vertebral fracture risk.[1] Such complications have not been observed after discontinuation with other osteoporosis therapies.

Because of these safety issues and the existence of similarly effective therapeutic alternatives with potentially fewer side effects, the Federal Office of Public Health (FOPH) wishes to re-evaluate the available evidence for denosumab in osteoporotic patients.

The HTA aims to perform an assessment of the safety, efficacy/effectiveness, cost, cost-effectiveness and budget impact of denosumab compared to all other available osteoporosis therapies in Switzerland.

2 Research question

This HTA report aims to address the following research questions:

- What is the efficacy/effectiveness, safety, cost, cost-effectiveness and budget impact of denosumab (Prolia®) compared to bisphosphonates and selective oestrogen receptor modulators (SERMs) for the treatment of osteoporosis in postmenopausal women, women with breast cancer receiving AAIT, men with osteoporosis who have an increased fracture risk, and men with prostate cancer on HAT with an increased fracture risk?
- Are there any legal, social, ethical or organisational issues associated with denosumab (Prolia®) therapy?

These research questions are operationalised in greater detail in ***Section 6***.

3 Medical background

3.1 Medical context

Osteoporosis is a bone disorder that decreases bone mass and density, increasing skeletal fragility and the risk of fracture.[2 3] It can occur in any bones, but spine, hip and wrist are the most commonly affected areas. Osteoporosis is characterised by imbalanced bone turnover. Bones go through constant cycles of formation and breakdown by cells called osteoblasts and osteoclasts, respectively. In osteoporotic patients, bones break down faster than they are formed.

Osteoporosis can be classified into two types: primary osteoporosis typically results from ageing and is not caused by any other underlying condition;[4] secondary osteoporosis can be caused by lifestyle factors (e.g. smoking), pharmaceuticals (e.g. corticosteroids, AAIT, HAT) or underlying conditions such as hypoestrogenemia or hypogonadism.[5 6]

The severity of osteoporosis can be influenced by pre-existing or ageing issues, such as peak bone mass during adolescence, postmenopausal oestrogen deficiency intensity in women, and/or bone loss attributed to ageing.[7] While research has yet to completely establish the mechanisms behind bone loss, oestrogen deficiency appears to be linked to disease development.[5] It has also been demonstrated that bone loss can occur via systemic abnormalities (i.e. low levels of oestrogen, vitamin D and/or calcium fixation resulting in secondary hyperparathyroidism) or osteoblast dysfunction.[7-9]

3.2 Symptoms, natural course, and diagnostic pathway

Osteoporosis is associated with the following symptoms that typically develop in the sixth decade of life:

- back pain caused by fractured or collapsed vertebrae
- height loss over time
- stooped posture
- increased fracture recurrence

The risk of developing osteoporosis increases proportionately with age. Without treatment and preventive measures (e.g. lifestyle changes such as reducing smoking and alcohol consumption, fall prevention), the disease progresses over time by gradually reducing bone mineral density (BMD) and accumulating fragility fractures, particularly in the spine, resulting in deformity and an increased number of fractures. In the absence of a fracture and other risk factors, osteoporosis can go undiagnosed. Moreover, a cascade effect exists with osteoporosis, defined as the increased risk of subsequent

fractures with each new fracture. About 50% of people with one fracture due to osteoporosis will experience another fracture within the next 12 months.[10]

The diagnosis of osteoporosis follows two main approaches:

- The World Health Organization (WHO) has defined criteria for the identification of osteoporosis based on BMD T-scores,[11] corresponding to the number of standard deviations (SD) between a patient‘s BMD test result and the mean BMD peak value in a cohort of healthy younger individuals.[12] T-scores are calculated based on BMD values measured by dual-energy X-ray absorptiometry (DXA) at several skeletal sites.[13] [14] The International Society for Clinical Densitometry and the WHO consider DXA of the hip or spine as the preferred measurement for the diagnosis of osteoporosis. A T-score of -2.5 is the diagnostic threshold for osteoporosis, and a T-score between -1.0 and -2.5 is the diagnostic threshold for osteopenia.[11] T-score or BMD measurements can be used to determine the risk ratio of fracture.[11]
- The fracture risk assessment tool (FRAX®) is an online tool that calculates the risk of fracture based on clinical risk factors (CRFs) such as age, sex, weight, height, glucocorticoid intake, smoking status, alcohol intake, medical history and femoral neck (FN) BMD of a given patient, and returns a probable absolute fracture risk for the coming 10 years.[15] Since 2009, Swiss epidemiological data can be used to assess fracture risk. FRAX® results are more accurate for individual fracture assessment than T-scores alone,[15] as they encompass a range of factors in addition to BMD.[16] However, fracture risk calculation, according to FRAX®, doesn’t take into account an increased rate of bone loss, falls or reduced mobility, and is only applicable from the age of 40.[17]

In Switzerland, BMD is measured using DXA. The Schweizerische Vereinigung gegen die Osteoporose (SVGO, Swiss Association against Osteoporosis) reports discrepancies between BMD measured in the spine versus the FN, suggesting that a correction factor (10%) be used to amend the results. In addition to BMD measurements, the SVGO recommends that a diagnosis be established based on medical history (i.e. general condition, risk factors, fracture or fall history, and illness or medications impacting bone metabolism or fall risk) and clinical examination (i.e. blood serum tests for calcium and vitamin D, decreased body mass index [BMI], indications for secondary osteoporosis, and evaluation of fall risk).[18] [19] SVGO also recommends measuring the 10-year fracture risk with FRAX®. The association advises the use of adjustment factors to FRAX® results depending on the dose of glucocorticoids consumed, to better assess the risk of fracture in patients with probable secondary osteoporosis (***Table 1***).

Table 1 Adjustment factors for FRAX® depending on glucocorticoid dosage and fracture type

Dose of glucocorticoids	Major fractures [a]	Hip fracture
Low (<2.5 mg)	-20%	-35%
Medium (2.5–7.5 mg)	0%	0%
High (>7.5 mg)	+15%	+20%

Abbreviations:
mg: miligrams.
Notes:
[a] Vertebrae, hip, wrist, proximal humerus.
Source:
Schweizerische Vereinigung gegen die Osteoporose[19]

3.3 Prevalence and burden of disease

3.3.1 Prevalence

Osteoporosis is a common disorder in the elderly population. In Switzerland, 15.1% of the population age 50 years and above had osteoporosis in 2010, with an estimated 368,685 women and 89,862 men affected by this bone disorder and a total population at risk of 3,041,000 people.[20 21] One third of Swiss older than 65 years are likely to experience a fall.[20] Additionally, in Switzerland one in two women and one in five men will sustain a fragility fracture after the age of 50.[22] Consequently, in 2010 there were an estimated 74,000 new fractures in Switzerland, with hip, spine, forearm and other fractures amounting to 14,000, 11,000, 13,000 and 36,000, respectively.[21] Approximately 70% of these fractures occurred in women.[21]

Similar statistics have been observed in countries neighbouring Switzerland. In France in 2010, 2,784,198 women over age 50 and 691,112 men were diagnosed with osteoporosis from 22,645,000 people in this age group, representing 15.4% of the at-risk population. Similarly, in Germany in 2010, from 33,010,000 people over age 50 there were 4,017,060 women and 1,006,652 men recorded as living with osteoporosis, representing 15.2% of the at-risk population at the time.[23] In the same year, around 22 million women and 5.5 million men within the European Union had osteoporosis, which corresponded to 3.5 million new fragility fractures, including 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1.8 million other fractures.[23] The annual number of fragility fractures is estimated to rise to 4.5 million in 2025, corresponding to a 28% increase, due to changes in population demography.

Globally, it is estimated that over 200 million people currently have osteoporosis,[24] with one in three women and one in five men age 50 or older presenting with osteoporotic fractures.[25] It is projected that 1.6 million hip fractures occur annually worldwide, which is expected to increase to 6.3 million by 2050.[24]

3.3.2 Burden of disease

In general, the burden of disease attributed to osteoporosis corresponds to an increased risk of fracture and the resulting loss of quality of life (QoL). The overall burden of disease can be measured using disability-adjusted life years (DALYs), which combine the years of life lost due to a fracture with the disability resulting from the fracture in surviving individuals. One DALY is equivalent to one year lost due to ill-health, disability or early death.[26]

The burden of osteoporosis depends not only on the prevalence of the disease but also on the risk of falls in the population at risk. In Switzerland, a study aimed at demonstrating the burden of several conditions on the elderly population highlighted that 3% of men and 5% of women had fallen in the 6 months preceding the study, with falls being more common in women over 69 years of age and in men over age 76.[27] The same study showed that, for women, the fear of falling increased with age, from 4% at age 55 to 25% at age 83, compared to men at 1% at age 55 and 17% at age 83. This difference could be explained by an increased likelihood for women to develop osteoporosis in their old age and therefore for a fall to result in a fracture.

In Switzerland, the cost of osteoporotic fractures was estimated to range from Swiss francs (CHF) 34,374–38,871 for hip, CHF19,790–36,622 for spine and CHF7,000–25,454 for wrist depending on the age of the patient.[28] It is anticipated that the population over 50 years of age will increase by 26% in Switzerland between 2010 and 2025, resulting in a 33% increase in the total number of fractures. Consequently, the cost of osteoporosis in Switzerland, including the value of quality-adjusted life years (QALYs) lost, is forecast to reach CHF6.7 billion by 2025, representing an increase of 39% in men and 20% in women compared to 2010.[21] The variation between genders is due to a difference in total calculated QALYs lost due to fracture in men (36%) and women (18%). In the rest of Europe, osteoporosis causes the loss of 2 million DALYs each year.[23]

Globally, the economic burden of this disease is far greater than the projected financial burden of stroke, breast cancer, diabetes or chronic lung disease.[29] In 2000, 5.8 million DALYs were associated with osteoporotic fractures globally, representing 0.83% of the combined burden of non-transmittable diseases.[26]

3.4 Treatment pathway

Osteoporosis can be managed using pharmaceutical or non-pharmaceutical approaches, or a combination of the two.[30-32]

In the absence of obvious signs of osteoporosis, the best approach is to reduce the risk of developing the condition. This includes lifestyle changes (e.g. reducing smoking and alcohol consumption) and

prophylactic supplementation. Various associations around the world recommend adjusting patient nutrition to contain sufficient daily intake of calcium, vitamin D and protein.[26 33] Low BMI is associated with a higher fracture risk while obesity is linked to vitamin D deficiency, therefore maintaining a normal BMI through good nutrition and exercise is suggested. Regular exercise is also recommended because it can reduce the incidence of fractures.[33]

Non-pharmaceutical management of osteoporosis consists of lifestyle changes (i.e. reduction in smoking and alcohol consumption) and fall prevention. Measures such as surface preparation or provision of a walking frame represent the primary management tools for patients presenting a low risk of fracture and/or BMD close to the normal range.[32]

For patients presenting with a low BMD or increased risk of fracture, practitioners usually recommend pharmaceutical treatment in addition to the lifestyle changes listed above.[32] There are multiple classes of anti-resorptive drugs available, including bisphosphonates, SERMs and denosumab (see ***Section 4.1*** and ***4.2***).[30 31] The specific treatment chosen may depend on the severity of osteoporosis. SVGO's recommendations on osteoporosis treatment defined four risk subgroup categories: low, moderate, high and very high/imminent.[22] These recommendations delineate which drugs should be used to initiate therapy according to the fracture risk level in Switzerland.[22]

Treatment follow-up usually encompasses repeated measures of BMD (after two years), and also assessing markers of bone formation or resorption (three to six months after treatment initiation), which also informs the duration for antiresorptive treatment.[17]

4 Technology

4.1 Technology description

Denosumab (Prolia®) is a monoclonal antibody used to treat osteoporosis by inhibiting the activation of cells responsible for bone resorption (osteoclasts). Throughout this HTA, mention of denosumab always refers to the Prolia® formula, unless otherwise indicated. Osteoporosis disturbs the process of bone remodelling by disrupting the fine balance between bone formation conducted by osteoblasts and bone breakdown conducted by osteoclasts, leading to a progressive loss of BMD. Denosumab aims to slow down osteoclast activity thereby reducing bone breakdown.[34]

Osteoclasts are activated by the binding of the receptor activator of nuclear factor kappa-B ligand (RANKL) to its receptor. Osteoblasts produce osteoprotegerin, which controls bone breakdown by interacting with RANKL, thus preventing its attachment to the receptor. Denosumab mimics the role of osteoprotegerin by binding to RANKL and reducing the activation of osteoclasts.[34]

Denosumab is administered as a biannual subcutaneous injection of a 60 mg/mL solution for a minimum of three years.[30] [32] It is recommended that patients also take vitamin D supplements when on denosumab therapy. It is important to note that the use of denosumab in Switzerland is limited to adults as the evidence for paediatric patients is insufficient.[35] Similarly, it is recommended that calcaemia is monitored closely in cases of severe kidney failure (i.e. creatinine clearance <30 mL/min) or for patients undergoing dialysis.[35]

Denosumab is contraindicated in cases of hypocalcaemia (<2.1 mmol/L) or in cases of intolerance or allergy to the medication components (i.e. denosumab, sodium acetate, sorbitol, polysorbate 20) (***Table 2***).[35] It is generally well tolerated by patients and adverse events (AEs) are rare. Known side effects of denosumab therapy include skin infection (cellulitis) near the point of injection, back pain, arm and leg pain, urinary tract infection, constipation and rash.[36] A less common side effect is a reduction in blood calcium. Because of this, if the patient has kidney failure or is following a dialysis treatment calcaemia should be monitored closely. Finally, rare cases of osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) have been reported.[18]

As denosumab acts as an antagonist of RANKL and is not a compound that will remain within bones or the body, the positive impact of denosumab disappears after discontinuation. Several studies looking at the impact of denosumab discontinuation highlighted a possible rebound effect, whereby BMD reduces to below-baseline values after the drug is discontinued.[37-39] This rebound effect creates a higher risk of vertebral fractures. Evidence of the impact of denosumab discontinuation on BMD and general health outcomes is of key interest when evaluating the safety of this medication.

Prolia® is the only denosumab pharmaceutical available in Switzerland for the treatment of osteoporosis. Xgeva® is a denosumab formulation indicated for the treatment of patients with solid tumours presenting with bone metastases, or patients with giant-cell tumours of the bone. This formulation was not included in the present assessment.[40] [41] Dosage and indications/contraindications associated with Prolia® are summarised in ***Table 2***.

Table 2 Technology details

Name (manufacturer)	Dose and Administration	Indications	Contraindications
Prolia® (AMGEN Switzerland AG)	One 60 mg subcutaneous injection administered every 6 months (thigh, abdomen or upper arm)	- Postmenopausal women with T-score values ≤ -2.5 SD - Supplementary to AAIT in women with breast cancer presenting an increased fracture risk - Men with osteoporosis and an increased fracture risk - Supplementary to HAT in men with prostate cancer presenting an increased fracture risk	- Hypocalcaemia (i.e. blood calcium <2.1 mmol/L) - Hypersensitivity or allergy to denosumab, or the listed excipients (i.e. sodium acetate, sorbitol, polysorbate 20)

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **HAT**: hormone ablation therapy; **SD**: standard deviation.
Sources:
Swissmedicinfo[35]

4.2 Alternative technologies

In addition to lifestyle changes and denosumab, two classes of pharmaceuticals are currently recommended for management of osteoporosis in Switzerland. Bisphosphonates and SERMs currently available in Switzerland are summarised in ***Table 3***.

4.2.1 Bisphosphonates

Bisphosphonates represent a commonly prescribed group of compounds used for the treatment of osteoporosis.[31 42] As their name indicates, they contain two phosphonates, giving them a high affinity for bone minerals through the binding to hydroxyapatite (bone mineral) binding sites. Like denosumab, bisphosphonates reduce the activity of osteoclasts; however, unlike denosumab, bisphosphonates are preferentially absorbed in active bone remodelling areas, thus a portion of bisphosphonates are retained in the newly formed bone.[43] Through these actions, bisphosphonates reduce the breakdown of hydroxyapatite within the bone, causing an overall suppression of bone resorption. Although bisphosphonates are used to treat other disorders, they are primarily used for the management of osteoporosis.[43]

In Switzerland, four bisphosphonates are available: alendronate, ibandronate, risedronate and zoledronate (***Table 3***). Bisphosphonates can be administered either orally or through intravenous (IV) infusions. Alendronate is administrated orally once per week at 70 mg (***Table 3***). Similarly, risedronate (Actonel being the only brand available in Switzerland) is administered orally in the form of a 35 mg tablet taken once per week. For osteoporotic patients, zoledronate is administered via a 5 mg IV infusion once per year. Alternatively, for patients with cancer who have an increased risk of fracture, zoledronate is delivered as a 4 mg IV infusion once per year. Ibandronate is administered as a 150 mg tablet once

per month or a 3 mg IV injection every three months for patients with osteoporosis, and as a 6 mg IV injection every three to four weeks for patients with bone metastases.

Finally, some patients may develop AEs or an intolerance to bisphosphonates. One study reported AEs in up to 62.3% of the 839 patients treated with various oral bisphosphonates and serious AEs in 6.8% of the same cohort.[37 44] Published adverse reactions include but are not limited to gastrointestinal (GI) episodes in the upper and lower GI tract, infections, allergic reactions to the medication, cystitis, arthralgia, pain and fractures.[44-47] For these reasons, bisphosphonates are contraindicated for patients presenting with acute inflammation of the GI tract, oesophageal pathologies that could delay medication absorption (if taken orally) and kidney failure, or patients who have a history of allergy to the medication. Moreover, rare cases of ONJ and AFF have also been reported.[18]

4.2.2 SERMs

As mentioned previously, there is growing evidence that a reduction in oestrogen production can contribute to the onset of osteoporosis.[48] SERMs act as either oestrogen agonists or antagonists in different parts of the body. It is their oestrogen agonist (i.e. compounds that can bind to oestrogen receptors) properties that are used in the treatment of osteoporosis. A dose of SERMs mimics oestrogen thereby diminishing the impact that the reduction of this hormone has on bone turnover.[49]

There are two forms of oestrogen agonist SERMs available in Switzerland for management of osteoporosis: bazedoxifene and raloxifene. Raloxifene was the first SERM validated for the treatment of postmenopausal osteoporosis. In Switzerland, raloxifene (Evista®) is administered orally via a daily 60 mg tablet. Bazedoxifene, found in Switzerland under the brand name Conbriza®, is administered as a daily 20 mg tablet (***Table 3***).[50 51] In the Swiss context, both of these medications are exclusively prescribed to postmenopausal women with a T-score ≤-1 SD or who have experienced fractures. (**NOTE**: bazedoxifene (Conbriza®) was removed from the Spezialitätenliste on 01-06-21, during the production of this report)

4.2.3 Other pharmaceuticals for the treatment of osteoporosis

In addition to denosumab, bisphosphonates and SERMs, several other pharmaceuticals are available for the treatment of osteoporosis. However, due to their limited use or lack of availability in Switzerland, these pharmaceuticals were not selected for the present assessment.

For example, hormone replacement therapies are another example of antiresorptive agents that can adjust oestrogen levels and in turn inhibit the detrimental effect of menopause on bone turnover. Hormone replacement therapy can be conducted with oestrogen with or without progesterone.[52] Estalis® is a hormone (oestradiol) currently recommended as a second-line treatment for osteoporosis

(induced by oestrogen deficiency) in Swiss postmenopausal women with a high fracture risk and for women presenting with oestrogen-deficiency symptoms.[53]

Some pharmaceuticals can increase bone formation or BMD, including parathyroid hormones and strontium. A commonly prescribed parathyroid hormone is teriparatide, which has been shown to increase BMD significantly in postmenopausal women.[54] The use of teriparatide is limited in Switzerland to second-line treatment in a) patients with glucocorticoid induced osteoporosis and high fracture risk and in b) patients with progressive osteoporosis (i.e. incident fractures during antiresorptive treatment). Strontium is not licensed in Switzerland.

Calcitonin is a hormone produced by the thyroid that helps regulate serum calcium and phosphate levels, opposing the action of parathyroid hormones. It can provide efficient but short-term pain relief in patients with osteoporotic vertebral fractures. In Switzerland, the use of calcitonin is limited to population subcategories that do not correspond to the population groups selected for this assessment.

Table 3 Alternative technologies available in Switzerland

Type of medication	Active ingredient	Name (manufacturer(s))	Dose and administration	Indications	Contraindications
Bisphosphonate	Alendronate	Alendron Mepha® 70 (Mepha Pharma AG) Alendron D3-Mepha® (Mepha Pharma AG) Alendronat Helvepharm® (Helvepharm AG) Alendronat Zentiva® (Helvepharm AG) Alendronat Sandoz® (Sandoz Pharmaceuticals AG) Alendronate Spirig HC® (Spirig HealthCare AG) Alendronate Streuli® (Streuli Pharma AG) Binosto® (Labatec Pharma SA) Fosamax® (MSD Merck Sharp and Dohme AG) Fosavance® (MSD Merck Sharp and Dohme AG)	One 70 mg tablet once weekly for all alendronate medications	- Documented osteoporosis (reduction of more than 2.5 SD in osteodensitometry or cases of fracture) - Postmenopausal women - Men with osteoporosis and increased fracture risk	- Acute inflammation of GI tract - Symptomatic osteomalacia - Oesophageal pathologies preventing or delaying medication transport to the stomach - Kidney failure (i.e. creatinine clearance <30 mL/min) - Hypocalcaemia - Hypersensitivity or allergy to medication components - Patients unable to maintain vertical position for at least 30 min
Bisphosphonate	Ibandronate (ibandronic acid)	*IV injection:* Bonviva® IV (Future Health Pharma GmbH) Ibandronat Helvepharm® Osteo (Helvepharm AG) Ibandronat Mepha® Osteo IV (Mepha Pharma AG) Ibandronat Spirig HC® IV (Spirig HealthCare AG) Ibandronat Sandoz® IV (Sandoz Pharmaceuticals AG) Bondronat® (Future Health Pharma GmbH) [a]	One 3 mg IV injection every three months One 6 mg IV injection every 3-4 weeks [a]	- Documented osteoporosis (reduction of more than 2.5 SD in osteodensitometry or cases of fracture) - Postmenopausal women with osteoporosis	- Hypersensitivity or allergy to medication components - Untreated hypocalcaemia

Type of medication	Active ingredient	Name (manufacturer(s))	Dose and administration	Indications	Contraindications
Bisphosphonate	Ibandronate (ibandronic acid)	*Oral medications:* Bonviva® 150 mg (Future Health Pharma GmbH) Ibandronat Mepha® 150 mg (Mepha Pharma AG) Ibandronat Spirig HC® 150 mg (Spirig HealthCare AG) Ibandronat Sandoz® 150 mg (Sandoz Pharmaceuticals AG)	One 150 mg tablet once monthly	- Documented osteoporosis (reduction of more than 2.5 SD in osteodensitometry or cases of fracture) - Postmenopausal women with osteoporosis	- Patients with hypersensitivity or allergy to medication components - Untreated hypocalcaemia - Oesophageal pathologies preventing or delaying medication transport to the stomach - Patients unable to maintain vertical position for at least 30 min
Bisphosphonate	Risedronate (sodium risedronate)	Actonel® (Future Health Pharma GmbH)	One 35 mg tablet weekly	- Documented osteoporosis (reduction of more than 2 SD in osteodensitometry or cases of fracture) - Postmenopausal women - Men with osteoporosis and increased fracture risk - Patients presenting with corticosteroid-induced osteoporosis - Patients presenting with Paget's disease of the bone	- Hypersensitivity or allergy to medication components - Untreated hypocalcaemia - Severe kidney failure (creatinine - clearance <30 mL/min) - Patients unable to maintain vertical position for at least 30 min - During pregnancy or lactation

Type of medication	Active ingredient	Name (manufacturer(s))	Dose and administration	Indications	Contraindications
Bisphosphonate	Zoledronate (zoledronic acid)	*Osteoporotic population:* Aclasta® (Novartis Pharma Schweiz AG) Zoledronate Osteo Sandoz® (Sandoz Pharmaceuticals AG) *Cancer population:* Zoledronat Accord® Onco (Accord Healthcare AG) Zoledronat Fresenius® Onco (Fresenius Kabi Switzerland Ltd.) Zoledronat Onco Labatec® (Labatec Pharma SA) Zoledronat Teva® Onco (Teva Pharma AG) Zoledronic acid Onco Sandoz® (Sandoz Pharmaceuticals AG) Zometa® (Novartis Pharma Schweiz AG)	For osteoporosis, it is recommended to infuse a single dose of 5 mg/100 mL of Zoledronate Osteo Sandoz® or Aclasta® intravenously once a year. For those with cancer who have an increased risk of fracture, it is recommended to infuse a single dose of 4 mg/5 mL of zoledronate (all brands) intravenously every 3-4 weeks [b]	- Documented osteoporosis (reduction of more than 2.5 SD in osteodensitometry or cases of fracture) - Postmenopausal women - Men with osteoporosis and increased fracture risk - Patients presenting with corticosteroid-induced osteoporosis - Patients presenting with Paget's disease of the bone	- During pregnancy or lactation - Hypersensitivity or allergy to medication components - Hypocalcaemia (Aclasta, Zoledronate Osteo Sandoz) - Severe kidney failure (creatinine clearance <35 mL/min, Aclasta, Zoledronate Osteo Sandoz)
SERM	Raloxifene (raloxifene hydrochloride)	Evista® (Leman SKL SA)	One 60 mg tablet daily	- Postmenopausal women with increased facture risk (-1 difference in T-score measured by densitometry in the spine or the distal area of the forearm)	- Women of reproductive age - Existing or history of deep vein thrombosis - Hypersensitivity or allergy to components of the medication - Liver failure - Severe kidney failure - Unexplained uterine/vaginal bleeding - Clinical signs of endometrium cancer

Type of medication	Active ingredient	Name (manufacturer(s))	Dose and administration	Indications	Contraindications
SERM	Bazedoxifene (bazedoxifenum/ bazedoxifene acetas)	Conbriza® (Pfizer AG) [c]	One 20 mg tablet daily	- Postmenopausal women with increased facture risk (-1 difference in T-score measured by densitometry in the spine or at the FN)	- Existing or history of deep vein thrombosis - In women for whom postmenopausal status is not clearly established - Clinical signs of endometrium cancer - Unexplained uterine/vaginal bleeding - During breast feeding - Hypersensitivity or allergy to medication components

Abbreviations:
FN: femoral neck; **GI**: gastrointestinal, **IV**: intravenous; **mg**: milligrams; **min**: minute/s; **mL**: millilitres; **SERM**: selective oestrogen receptor modulators, **SD**: standard deviation.
Notes:
[a] Bondronat® which is administered as a 6 mg IV injection every 3-4 weeks has not been considered during the analysis as this dosage is only indicated for those with bone metastases.
[b] Zoledronic acid Onco Sandoz® is also available as a single infusion dosage of 4 mg/100 mL (pre-diluted; ready to infuse) intravenously once a year.
[c] During the production of this report Conbriza® was removed from the Spezialitätenliste
Source:
Swissmedicinfo.ch[55]

4.3 Regulatory status / provider

In Switzerland, denosumab has been approved for use by Swissmedic and is included on the Spezialitätenliste, therefore it is currently reimbursed through mandatory health insurance.[56] Details of the manufacturer, dose and administration, and indications and contraindications of denosumab can be found in ***Table 2***. Physicians can prescribe denosumab without additional training or credentials. It is recommended that the administration of denosumab be performed by an individual with knowledge in injection techniques.[50 57]

Further information was sought on reimbursement practices in other European countries. A search of the Danish Medicines Agency,[58] Norwegian Medicines Agency,[59] the Swedish Dental and Pharmaceutical Benefits Agency,[60] Italian Medicines Agency,[61] Greek Ministry of Health,[62] and the French Ministry of Social Affairs and Health[63] provided information for the reimbursement of denosumab for the treatment of osteoporosis in postmenopausal women and men who are at increased risk of fracture. However, only the Swedish Dental and Pharmaceutical Benefits Agency[60] and Italian Medicines Agency[61] provided information for the use or reimbursement of denosumab for treatment in men with prostate cancer on HAT and an increased fracture risk. Additionally, none of the health agencies searched provided information for the use or reimbursement of denosumab as a supplementary treatment to AAIT in women with breast cancer presenting an increased fracture risk.

Throughout Europe, denosumab (Prolia®) has been granted marketing authorisation from the European Medicines Agency, Committee for Medicinal Products for Human Use.[64] Denosumab (Prolia®) has been approved and marketed in over 80 countries on a prescription basis.[65 66]

5 PICO

5.1 PICO box

Table 4 Study selection criteria

P:	1. Postmenopausal women with osteoporosis (with a reduction of more than 2.5 SD in osteodensitometry or in case of a fracture) 2. Women with breast cancer receiving AAIT and an increased fracture risk [a] 3. Men with osteoporosis and an increased fracture risk [a] 4. Men with prostate cancer on HAT and an increased fracture risk [a] *Exclusion criteria: patients with multiple myeloma, bone metastases (from solid tumours), giant-cell tumours, hypercalcaemia of malignancy refractory to bisphosphonate treatment, patients with kidney disease*
I:	Denosumab (Prolia®) or denosumab (60 mg) *Exclusion criteria: denosumab (Xgeva®) or denosumab (120 mg)*
C:	1. All bisphosphonates available in Switzerland o Alendronate: 70 mg tablet once weekly o Ibandronate: 150 mg tablet once monthly, 3 mg/3 mL infusion trimonthly [b] o Risedronate: 35 mg tablet once weekly o Zoledronate: 4 mg/5 mL or 4 mg/100 mL (i.e. post-dilution) infusion monthly/trimonthly/annually, 5 mg/100 mL infusion annually 2. All SERMs available in Switzerland [b] o Bazedoxifene: 20 mg tablet once daily [a] o Raloxifene: 60 mg tablet once daily 3. Placebo *Exclusion criteria: romosozumab is not listed on the Spezialitätenliste*
O:	**Efficacy/effectiveness**: *Primary* • Fractures (e.g. vertebral fractures, nonvertebral fractures, hip fractures) • Health-related quality of life (HRQoL) (e.g. mean change measured with SF-36, OFDQ, OPTOQLQ, Qualeffo-41, OPAQ). *Secondary* • Bone mineral density (BMD) measured at femoral neck (FN), lumbar spine (LS), total hip (TH) and/or trochanter • Bone turnover markers (BTM) – measured using CTX, NTX, ALP, B-ALP, osteocalcin and/or P1NP • Fracture risk [c] **Safety**: • Mortality • Treatment-related adverse events • Serious adverse events • Withdrawal due to treatment-related adverse events • Adverse events upon discontinuation of denosumab (e.g. rebound effect) [d]

Compliance:

- Adherence to therapy [e]
- Primary non-adherence/non-fulfilment adherence [f]
- Non-persistence [g]
- Non-conforming [h]

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **B-ALP**: bone-specific alkaline phosphatase; **BMD**: bone mineral density; **BTM**: bone turnover markers; **CTX**: C-terminal telopeptide of type 1 collagen; **FN**: femoral neck; **HAT**: hormone ablation therapy; **HRQoL**: health-related quality of life; **LS**: lumbar spine; **mg**: milligrams; **mL**: millilitres; **NTX**: N-terminal telopeptide of type 1 collagen; **OFDQ**: osteoporosis function disability questionnaire; **OPAQ**: osteoporosis assessment questionnaire; **OPTOQLQ**: quality of life questionnaire for osteoporosis; **P1NP**: procollagen type 1 N propetide; **Qualeffo-41**: quality of life questionnaire of the European Foundation for Osteoporosis; **SERMs**: selective oestrogen receptor modulators; **SD**: standard deviations; **SF-36**: 36-item short form health survey; **TH**: total hip.
Notes:
[a] During the production of this report Conbriza® was removed from the Spezialitätenliste and is therefore no longer reimbursed by mandatory health insurance in Switzerland.
[b] Ibandronate and SERMs are only indicated for use in postmenopausal women.
[c] Calculated using: age, BMD, body weight, number of falls in the last year, and number of fractures after age 50 etc.[67]
[d] After stopping denosumab one or more of the following occurs: rate of BMD loss increases above baseline levels, increase in BTM indicates increased bone resorption (i.e. CTX, NTX, DPD), and/or increased rate of vertebral fractures.[68-70]
[e] Adherence: *"the degree to which the person's behaviour corresponds with the agreed recommendation from a healthcare provider", WHO*.[71]
[f] Primary non-adherence/non-fulfilment adherence: Where medication prescribed by the medical practitioner is never fulfilled or initiated by the patient.[72]
[g] Non-persistence: When a patient does not adhere to the medication regimen as prescribed due to miscommunication about the therapeutic plan. There are 2 types of non-persistence: 1) unintentional non-persistence occurs when patients are prevented from implementing the treatment regimen due to resource and capacity limitations (e.g. cost, competing demands); 2) intentional non-persistence occurs when patients do not adhere with the treatment regimen due to their own motivations i.e. attitudes, expectations, and beliefs.[72]
[h] Non-conforming: Where patients do not adhere to the treatment regimen as prescribed (e.g. skipping doses, taking medication at incorrect times, taking more than prescribed dose, taking incorrect doses).[72]

5.2 Population

The populations of interest (***Table 4***) reflect the current restrictions on denosumab in Switzerland (per the Spezialitätenliste). These populations contain patients who have either primary or secondary osteoporosis. Primary osteoporosis occurs in postmenopausal women (T-score ≤ -2.5) and men without underlying disease (cancer, hormonal disorders etc.). Secondary osteoporosis occurs in cancer patients receiving medication, specifically, women with breast cancer receiving AAIT who have an increased fracture risk, and men with prostate cancer on HAT who have an increased fracture risk. Studies reporting only on patients with multiple myeloma, bone metastases (from solid tumours), giant-cell tumours, hypercalcaemia of malignancy due to bisphosphonate treatment, and/or patients with kidney disease were excluded from this review, as these are indications for Xgeva®, a different formulation of denosumab.

5.3 Intervention

The intervention under investigation is the drug denosumab, a monoclonal antibody that inhibits the attachment of RANKL to its receptors, facilitating an increase in BMD in patients. Denosumab (Prolia®) administered subcutaneously in 60 mg doses was included. Denosumab administered in 120 mg doses (i.e. Xgeva®) was excluded from this review.[40 73]

5.4 Comparator

Three relevant comparators were included (***Table 4***). Bisphosphonates and SERMs are active comparators available in Switzerland.

Bisphosphonates are drugs that inhibit bone remodelling and are commonly used to treat osteoporosis.[74] Only the four types of bisphosphonate available in Switzerland (alendronate, ibandronate, risedronate and zoledronate) have been included as comparators. Additionally, these bisphosphonates were only included at the specific doses available in Switzerland, including alendronate administered orally at a once weekly dose of 70 mg, risedronate administered orally at a once weekly dose of 35 mg, zoledronate administered via an IV infusion delivered at a dose of 5 mg once per year and/or 4 mg administered monthly, trimonthly and/or yearly, and ibandronate administered orally at a once monthly dose of 150 mg and/or a trimonthly IV injection containing 3 mg of the active compound. Per Swissmedic, ibandronate is only indicated for use in postmenopausal women.

SERMs are drugs that can stimulate or inhibit oestrogen receptors. SERMs are used to treat a large variety of postmenopausal conditions (including osteoporosis) because the drug behaves differently in various types of human tissue.[75] Only the two types of SERMs available in Switzerland (i.e. bazedoxifene[1] and raloxifene) were included. Additionally, these SERMS were only included at the specific doses available in Switzerland: raloxifene administered orally via a daily 60 mg tablet and bazedoxifene administered as a daily 20 mg tablet. Per Swissmedic, SERMs are only indicated for use in postmenopausal women.

[1] During the production of this report, bazedoxifene (Conbriza®) was removed from the Spezialitätenliste; however, it will still be included in the analysis per the original project scope.

The final comparator is placebo, which has been included to evaluate the efficacy of the active treatment. A matching placebo which is designed to have no therapeutic benefit and presented as identical (i.e. packaging and appearance) to the active treatment was considered for inclusion.

5.5 Outcomes

5.5.1 Efficacy and effectiveness outcomes

Fracture is a critical outcome. Osteoporotic fractures, including vertebral and nonvertebral fracture, have a substantial impact on QoL.[76-78] They result in morbidity and disability and can cause substantial pain, chronic disability and death. Hip and vertebral fractures are the most prevalent and debilitating types of osteoporotic fractures. Hip fractures (FN and intertrochanteric) can cause substantial pain and decrease mobility, which results in increasing dependence.[76 77] Vertebral fractures (spinal compression) can lead to deformity, chronic back pain, height loss, decreased mobility and decreased pulmonary function.[76 77] Fractures can have a significant impact on a patient's ability to perform daily living activities and live independently.[76-78]

Health-related quality of life (HRQoL) is also a critical outcome.[79-81] HRQoL can be measured using a patient self-reported assessment of physical, social and emotional/mental health. Examples of HRQoL tools used to measure the impact of primary or secondary osteoporosis on patients are the QoL questionnaire of the European Foundation for Osteoporosis (Qualeffo-41) and the osteoporosis assessment questionnaire (OPAQ).[79-81] Qualeffo-41 measures pain; physical, social and mental function; and general health,[82] whereas OPAQ measures physical, emotional and social functioning as well as loss of usual activities.[81]

BMD is an important outcome because it provides a vital indication of bone health via a non-invasive scan (i.e. DXA).[83] BMD measurements can be taken at multiple locations in the body but are most reliably measured at the lumbar spine (LS), FN, total hip (TH) and trochanter.[83-86] BMD scores can show whether a patient is responding to treatment, as well as assist in the calculation of a patient's fracture risk.[67 83 86-88]

Bone turnover markers (BTMs) are commonly used in clinical research to measure either bone formation (e.g. procollagen type 1 N propetide [P1NP], osteocalcin, bone-specific alkaline phosphatase [B-ALP]) or bone resorption (e.g. C-terminal telopeptide of type 1 collagen [CTX], N-terminal telopeptide of type 1 collagen [NTX], tartare-resistant acid phosphatase [TRAP]), and thus determine the efficacy of a treatment (***Table 5****,* adapted from Lane 2006).[89] These markers represent the resulting metabolites of bone formation and resorption released to the blood stream. They are an important outcome as they can help determine whether a patient is responding to treatment, the impact of treatment withdrawal, or

if a specific intervention is causing secondary osteoporosis.[32 90 91] As with BMD, BTMs provide a non-invasive indication of a patient's continuing bone health by blood, serum or urine testing.[90-92]

Table 5 Common BTMs used to measure bone formation and resorption

Marker type	Present in blood serum	Present in urine
Bone formation	• B-ALP • P1NP • Osteocalcin	Nil
Bone resorption	• TRAP • CTX [a] • NTX	• Hydroxyproline • Pyridinolines • Deoxypyridinolines • NTX • CTX [a]

Abbreviations:
B-ALP: bone-specific alkaline phosphatase; **BTM**: bone turnover marker; **CTX**: C-terminal telopeptide of collagen cross-links; **NTX**: N-telopeptide of collagen cross-links; **P1NP**: procollagen type 1 N-terminal propeptide; **TRAP**: tartare-resistant acid phosphatase.
Notes:
[a] CTX is the only BTM used in Switzerland.
Sources:
Lane 2006[89]

Fracture risk is an important outcome for a patient with osteoporosis. It provides an individualised probability of a fracture occurring.[93 94] The most common tool used to calculate fracture risk is the fracture risk assessment tool (FRAX®),[67 87 94] which provides a 10-year probability for major osteoporotic fracture (MOF) (i.e. fractures of the hip, spine, forearm and humerus).[95] FRAX® calculates absolute fracture risk by using both non-skeletal and skeletal risk factors. Non-skeletal factors include smoking status, BMI, vitamin D deficiency, frequency of falls past 50 years of age, physical activity, low calcium intake and excessive alcohol consumption. Skeletal factors include gender (i.e. female), postmenopausal status (i.e. started early), amenorrhoea (primary or secondary), age, ethnicity (i.e. Caucasian), low BMD, BTM (i.e. high resorption markers), long-term glucocorticoid therapy, rheumatoid arthritis, neuromuscular disorders and hypogonadism in men (primary or secondary).[67 87 94]

5.5.2 Safety

Mortality and **adverse events (AEs) upon discontinuation of treatment (i.e. rebound effect)** are both critical outcomes. Mortality will reflect if denosumab has the potential to be fatal to patients,[66 96 97] whereas AEs experienced upon discontinuation of denosumab (i.e. rebound effect) will reflect if stopping the treatment could jeopardise patient health.[68 70 98-100] AEs upon the discontinuation of denosumab may be defined as when one of the following occurs: rate of BMD loss increases above

baseline levels, increase in BTM indicates increased bone resorption (i.e. CTX, NTX, DPD), and/or increased rate of vertebral fractures.[68 70 98 99]

Treatment-related AEs, serious adverse events (SAEs) and withdrawal due to treatment-related AEs are important outcomes. These outcomes will reflect if any patients have been harmed as a result of a denosumab treatment regimen.[97 101 102] All reported treatment-related AEs and SAEs that were identified and classified throughout the included literature have been collated for each intervention/comparator and considered as relevant to the analysis. Examples of treatment-related AEs and SAEs associated with denosumab that may cause a patient to discontinue treatment include, but are not limited to: AFF; dermatological issues (e.g. dryness, peeling blisters); dental issues (e.g. decay, infection, delayed healing); ONJ; pain in muscle, joints, and/or bone; hypocalcaemia; and serious infections.[66 96 102 103]

5.5.3 Compliance

Compliance is a critical outcome for patients with osteoporosis being treated with an anti-resorptive therapy such as denosumab.[104] Primary or secondary osteoporosis is a chronic illness that needs continuous treatment to ensure long-term bone health. The key to achieving this is patient compliance with the treatment regimen.[104-106] For denosumab, it is paramount to ensure that patients continually take their medication as prescribed and routinely present for their scheduled six-monthly subcutaneous injections.[73 104 106] Compliance was measured using:

- Adherence: The degree to which the person's behaviour corresponds with the agreed recommendation from a healthcare provider.
- Primary non-adherence/non-fulfilment adherence: Where medication prescribed by the medical practitioner is never fulfilled or initiated by the patient.
- Non-persistence: When a patient does not adhere to the medication regimen as prescribed, due to a miscommunication about the therapeutic plan.
- Non-conforming: Where patients do not adhere to their treatment regimen as prescribed (i.e. skipping doses, taking medications at incorrect times, taking more than prescribed, taking incorrect doses).

5.5.4 Minimum clinically important differences (MCIDs) and improvements for outcomes of interest

The selected endpoints used to assess the effectiveness/efficacy of denosumab in comparison to other pre-specified interventions either seek to assess fracture rates/reduction directly or indirectly (i.e. using

hard clinical endpoints or surrogate endpoints). Both BMD and BTM are surrogate endpoints for fracture. Therefore, these indirect measures would not be considered meaningful and are not appropriate or valid surrogates for fracture reduction, as the causal link between these outcomes and fracture have not been proven without a doubt.[107-109] Therefore, no MCIDs have been identified or utilised to aid in the interpretation of the findings in this HTA report.

6 HTA key questions

The following key questions have been addressed, covering the central HTA domains as designated by the European Network for Health Technology Assessment (EUnetHTA) Core Model (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, and legal, social, ethical and organisational aspects):

1. Is denosumab (Prolia®) effective/efficacious compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), SERMs (bazedoxifene, raloxifene) and placebo for the treatment of osteoporosis in postmenopausal women, women with breast cancer receiving AAIT with an increased fracture risk, men with osteoporosis who have an increased fracture risk, and men with prostate cancer on HAT with an increased fracture risk?
2. Is denosumab (Prolia®) safe compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), SERMs (bazedoxifene, raloxifene) and placebo for the treatment of osteoporosis in postmenopausal women, women with breast cancer receiving AAIT with an increased fracture risk, men with osteoporosis who have an increased fracture risk, and men with prostate cancer on HAT with an increased fracture risk?
3. What effect does denosumab (Prolia®) discontinuation (i.e. the rebound effect) have on postmenopausal women, women with breast cancer receiving AAIT with an increased fracture risk, men with osteoporosis who have an increased fracture risk, and men with prostate cancer on HAT who have an increased fracture risk?
4. Are there any compliance issues with denosumab (Prolia®) compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), SERMs (bazedoxifene, raloxifene) and placebo?
5. What are the costs associated with denosumab (Prolia®)?
6. Is denosumab (Prolia®) cost-effective compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), SERMs (bazedoxifene, raloxifene) and placebo for the treatment of osteoporosis in postmenopausal women, women with breast cancer receiving AAIT with an increased fracture risk, men with osteoporosis who have an increased fracture risk, and men with prostate cancer on HAT with an increased fracture risk?
7. What is the budget impact of denosumab (Prolia®)?
8. Are there any legal, social, or ethical issues associated with denosumab (Prolia®) therapy?
9. Are there any organisational issues associated with denosumab (Prolia®) therapy?

7 Effectiveness, efficacy and safety

7.1 Summary statement efficacy, effectiveness and safety

Postmenopausal women: Twelve randomised controlled trials (RCTs) (k = 22 publications) with low to high risk of bias were identified. Only risedronate was found to be statistically significant for the prevention of nonvertebral fractures compared to placebo after 12 to 84 months of treatment. It also ranked as the most effective treatment at preventing nonvertebral fracture, with denosumab ranking as the least effective (of six treatments). In relation to FN BMD, alendronate, ibandronate and risedronate were statistically significant relative to placebo at 19 (± 1 SD) months—ranking from first to third, respectively—at increasing FN BMD. Denosumab was ranked as the fourth most effective treatment (of eight) at increasing FN BMD. However, the clinical relevance of these BMD findings is unclear. Vertebral fracture, mortality, AEs, SAEs and withdrawal due to treatment-related AEs reported no significant differences for any intervention compared to placebo. Evidence for discontinuation effects related to denosumab use was limited and cannot be used to draw conclusions about possible rebound effects.

Women with breast cancer receiving AAIT: Four RCTs (k = 5 publications) with moderate to high risk of bias were identified. There were no studies evaluating the treatment effects of zoledronate, alendronate, raloxifene or bazedoxifene to directly or indirectly contribute to the network meta-analyses of effectiveness or safety outcomes. Denosumab was found to be statistically significant relative to placebo for the prevention of vertebral fracture and increasing BMD; however, the clinical relevance of these BMD findings is unclear. No statistically significant difference between denosumab and placebo was detected for nonvertebral fractures, mortality, AEs, SAEs or withdrawal due to treatment-related AEs. Evidence for discontinuation effects related to denosumab use was limited and cannot be used to draw conclusions about possible rebound effects.

Men with osteoporosis: Four RCTs (k = 5 publications) with moderate to high risk of bias were identified. None of the included treatments demonstrated a significant treatment effect compared to placebo in relation to vertebral or nonvertebral fracture. For FN BMD, denosumab and zoledronate were statistically significant relative to placebo at 12 months—ranking first and second, respectively—at increasing FN BMD. However, the clinical relevance of these BMD findings is unclear. After 12 to 24 months, alendronate and zoledronate showed a statistically significant increase relative to placebo in risk of AEs in men with osteoporosis who have an increased fracture risk (ranked fourth and fifth, respectively, of five treatments). None of the included interventions were statistically significant relative to placebo for mortality, SAEs or withdrawal due to treatment-related AEs. No evidence was available

for AEs upon discontinuation of denosumab (e.g. rebound effect in men with osteoporosis who have an increased fracture risk).

Men with prostate cancer undergoing HAT: Ten RCTs (k = 10 publications) with moderate to high risk of bias were identified. There were no studies evaluating ibandronate, raloxifene or bazedoxifene in this population. Denosumab was found to be statistically significant relative to placebo for the prevention of vertebral fracture in men with prostate cancer on HAT. It ranked as the most effective treatment (of three treatments). None of the included interventions were statistically significant for the prevention of nonvertebral fractures after 12 to 36 months of treatment. Denosumab was ranked as the most effective treatment at preventing nonvertebral fractures. For FN BMD, zoledronate, denosumab and alendronate were statistically significant relative to placebo at 12 months—ranking second to fourth, respectively, (of five treatments)—at increasing FN BMD. However, the clinical relevance of these BMD findings is unclear. None of the included interventions were statistically different relative to placebo in terms of mortality, AEs, SAEs or withdrawal due to treatment-related AEs. No evidence was available for AEs upon discontinuation of denosumab (e.g. rebound effect in men with prostate cancer on HAT who have an increased fracture risk).

7.2 Methodology effectiveness, efficacy and safety

Two systematic literature searches were conducted for this HTA report. The literature searches were conducted in eight biomedical databases (PubMed, Embase, Cochrane Library, Cumulative Index of Nursing and Allied Health Literature [CINAHL], EconLit, University of York Centre for Reviews and Dissemination (York CRD), Ethicsweb, PsycInfo) from inception to 17 February 2021. The search strategy and results are summarised in ***Appendix A***.

The first search identified the literature relevant to denosumab (i.e. the intervention) in patients with osteoporosis. The literature identified from this search was used to: (i) inform a section of the network meta-analysis, which will assist in determining the efficacy, effectiveness and safety of denosumab; (ii) determine the cost-effectiveness and budget impact of denosumab; (iii) review the legal, social, ethical and organisational issues associated with denosumab therapy. Given that the first search was designed to be highly sensitive to capture a total literature base related to denosumab, no methodological filters were applied. The literature from this search was combined with a select number of studies from the second search prior to study selection commencing.

The second systematic search identified literature associated with patients who have osteoporosis in the relevant populations and who were treated with either bisphosphonates or SERMs (i.e. the

comparators). This search string was combined with a methodological filter to limit the literature captured in the search to the RCTs needed for the network meta-analysis. The complete filter is available in ***Appendix A***. The included literature from this search was limited to the network meta-analysis section of this HTA report.

The complete search string and methodological RCT filter for PubMed (MEDLINE) are presented in ***Appendix A***. The search string and filter were adapted to fit the syntax of the other databases as appropriate.

7.2.1 Other sources

Searches were also conducted in five clinical trial registries (ClinicalTrals.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Registry, WHO International Clinical Trials Registry Platform and Australian New Zealand Clinical Trials Registry) to identify ongoing clinical trials related to the treatment of osteoporosis with denosumab. Additional grey literature searches were conducted on specialty websites to highlight any relevant literature that may not have been otherwise identified.

7.2.2 Study selection

Results from the literature search were imported into Rayyan (bibliographic management software). Rayyan functions similarly to EndNote but allows for easy blinding of reviewers and management of study inclusion conflicts.[110] Study selection was limited to English, French, German and Italian language studies. French, German and Italian are three of the four official languages of Switzerland. The fourth language of Romansh was not included because of the limited number of publications available.[111 112] Only studies that met the PICO criteria were considered eligible for inclusion. Only studies based in WHO-Mortality-Stratum A countries were included (i.e. Andorra, Australia, Belgium, Brunei, Canada, Croatia, Cuba, Cyprus, Czech Republic [Czechia], Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, The Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom [UK], and United States of America [USA]). Studies based outside of WHO-Mortality-Stratum A countries were excluded during full-text screening because the cause of death and burden of disease in these countries are not comparable to those in Switzerland.[113]

The search results were screened by title and abstract against predetermined inclusion criteria by three reviewers. To ensure that the predetermined inclusion criteria were interpreted consistently by the three reviewers, two separate training samples (k = 250 and k = 200 citations) were used to establish inter-rater reliability. The first sample was an initial training sample in which all three reviewers selected studies in triplicate, with selections compared between reviewers. Inter-rater reliability was checked via

discordance among reviewers on the second sample (k = 2/200); the calculated Fleiss Kappa score was high (kappa = 0.872). Based on this, screening of the remainder of articles by title and abstract was split between the three reviewers. In cases where a reviewer was unsure, the article was included for further review by full text. All articles deemed potentially relevant were then reviewed in full text by two reviewers independently. Conflicts between reviewers on study inclusion were settled via consensus. If consensus could not be reached, a third reviewer decided whether to include or exclude the citation.

7.2.2.1 Study design

Different types of publications and study designs were considered for selection. RCTs that met the PICO criteria were included to assess the clinical effectiveness and safety of denosumab. Due to the limited amount of evidence available for the effects of denosumab discontinuation, non-randomised and single-arm studies that met the PICO criteria detailed in ***Table 4*** were also included to assess AEs upon discontinuation of denosumab (i.e. rebound effects). Similarly, RCTs and non-randomised studies were considered when identifying evidence for determining the cost-effectiveness of denosumab. Systematic reviews, literature reviews, RCTs, non-randomised studies, single-arm studies, ethnographic studies, phenomenological studies, narrative research and case studies were considered when assessing ethical, social, organisational and legal considerations.

7.2.3 Data extraction

7.2.3.1 Efficacy, effectiveness and safety data extraction

One reviewer independently extracted data (on a trial-arm level) into a standardised template, which was then checked against the original study record by a second reviewer. Disagreements were settled by discussion or utilisation of a third independent reviewer. Data of interest included:

- Trial information: trial-arm, trial identifier, location, date, number of institutions, study design, length of follow-up, inclusion/exclusion criteria, study author.
- Demographic information: number of participants, age, sex, comorbidities, indication.
- Intervention and comparator: type and method of intervention/comparator, concomitant interventions.
- Outcomes of interest: baseline, final or change from baseline scores in any of the aforementioned outcomes (***Table 4***).
- Any noteworthy features (i.e. effect modifiers), limitations or differences in the study.

For the extraction of outcomes, both intention-to-treat and per-protocol information was extracted; however, intention-to-treat data were preferentially utilised in the analysis. Similarly, both adjusted and unadjusted results were extracted, with unadjusted results preferentially utilised in the data analysis.

For studies that reported outcomes graphically, *WebPlotDigitizer* was used to estimate numerical values.[114] When utilising *WebPlotDigitizer*, standard error was calculated by subtracting the upper and lower bounds of the reported error bars from the mean.

7.2.4 Assessment of quality of evidence

The assessment of the quality of evidence was performed by one reviewer and checked by a second reviewer. Any differences were settled via consensus. If consensus could not be reached, a third reviewer was consulted. Study quality and risk of bias was assessed using different tools depending on the trial design. RCTs were evaluated using Cochrane Risk of Bias 2.0 (RoB 2.0),[115] and single-arm trials were evaluated using the Institute of Health Economics (IHE) quality appraisal checklist for case series.[116]

The overall quality of the outcomes was appraised using a modified version of the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach adapted for network meta-analysis, described by Salanti et al. 2014.[117] This modified GRADE approach acknowledges: (i) what each piece of direct evidence contributes to the analysis; (ii) the central role indirect comparisons plays in the analysis; (iii) the prospect of disagreement between indirect and direct evidence; and (iv) how the validity of the network meta-analysis is affected by the assumption of transitivity. The approach is capable of evaluating both the relative treatment effect for the pairwise comparisons as well as the treatment rankings.[117 118]

7.2.5 Data analyses of efficacy, effectiveness and safety outcomes

7.2.5.1 Network meta-analysis methods

Safety, efficacy and effectiveness outcomes reported by at least two RCTs, which in total report three or more treatment arms, were included in network meta-analyses.[119] This minimum threshold was used because it enabled treatment effect measures to be generated in situations where no direct comparative data were available, as well as allowing for treatments to be ranked based on effect.[120 121]

Both the Bayesian and frequentist techniques were used to perform the meta-analyses in the HTA report. The network meta-analysis performed on data extracted from RCTs on postmenopausal women was analysed using a Bayesian method and the output was used to provide data for the health economic modelling.[122] The frequentist approach was used to analyse the data extracted from RCTs on the other

three populations (i.e. women with breast cancer receiving AAIT, men with osteoporosis and men with prostate cancer on HAT) for pragmatic reasons, as this form of analysis does not require prior information and is less time-intensive to run.[121 123] In addition, the data extracted for these populations were less extensive, so health economic evaluations were not conducted for these populations.[121-123]

Geometry of the network

Network diagrams were drawn to illustrate the geometry of the treatment network in each analysis.[118 120] Each node in the diagram represents one of the treatments (i.e. denosumab, alendronate, ibandronate, risedronate, zoledronate, bazedoxifene, raloxifene and placebo). The size of each network node is proportional to the sample size of that node, and the thickness of the lines connecting the nodes is proportional to the number of included trials (i.e. direct evidence).[118 120] Trials that were not connected to the network were excluded from the analysis; point estimates can only be generated if the treatment of interest connects (directly or indirectly) to the referent (reference) comparator. Network graphs were plotted using the igraph package in RStudio.[124]

Statistical analysis

The extracted data were synthesised using both network and pairwise meta-analyses. Random-effects models were used in all network and pairwise meta-analyses conducted in order to account for any variations in the possible effect modifiers (compliance, age, baseline fractures etc.) as well as the variances in the end-of-treatment regimen timepoints. The random-effects model was also used to account for variations in population-based factors and discrepancies in how the intervention and comparators were delivered in the included trials.

Bayesian statistical inference

The Bayesian network meta-analysis was performed in RStudio using the 'BUGSnet (Bayesian inference Using Gibbs Sampling to conduct a Network meta-analysis)' package.[122 125-127] An exemplar copy of the code used to conduct the Bayesian network meta-analysis is presented in the HTA Supplement. The network meta-analysis was performed under the assumption of a consistency model using a random effects model. The referent comparator for each model was placebo, as most of the available direct evidence was reporting treatment effect relative to placebo.[128] Default and non-informative priors with standard normal distributional and sufficiently wide SDs were used to compute the posterior distribution data in the Bayesian network meta-analysis, as it was computationally feasible.[129 130]

<u>Dichotomous outcomes</u>

For dichotomous outcomes, risk ratios (RR) were calculated using the link function *logit* and a binomial family distribution. The total number of events at longest duration of follow-up were extracted and used in the network meta-analysis. Fracture events were analysed as dichotomous outcomes and used to assess the primary effectiveness of the included treatments. Fractures were delineated into vertebral and nonvertebral fractures. Additionally, the safety outcomes of mortality, AEs, SAEs and withdrawals due to AEs were also analysed as dichotomous outcomes.

Continuous outcomes

For continuous outcomes, mean differences (MD) were calculated using the link function *identity* and a normal family distribution. Mean percentage change for BMD and/or BTM were extracted for each reported timepoint. In situations where the mean percentage change was not provided (e.g. T-score, g/cm^2, nmol) in a publication, measurements at baseline and for all reported timepoints were extracted. The percentage change was then imputed from the extracted baseline and timepoint measurements using the formula reported in the section on ***Imputation methods for dealing with missing values***. In trials evaluating BMD across several anatomical locations, measurements taken at the FN, LS, TH and trochanter were extracted preferentially. Similarly, in RCTs that evaluated BTM using a variety of markers, CTX, NTX, P1NP and/or B-ALP were extracted preferentially. Individual network meta-analyses were performed for each preferred BMD measurement location as well as for each selected BTM. The mean follow-up period (± 1 SD of the follow-up period) from all included trials was calculated and results at this timepoint were used in the network meta-analysis. Standardised mean difference was not applied in the Bayesian network meta-analysis as it was not supported by the 'BUGSnet' package.[122 125]

Modelling, convergence and output

For dichotomous outcomes, a burn-in of 70,000 iterations of Markov chain Monte Carlo (MCMC) simulation was used where results were discarded. A burn of 700,000 iterations of MCMC simulations was run to estimate parameters. For the purpose of assessing the consistency assumption an inconsistency model using a random effects model was run. A burn-in of 5,000 iterations of MCMC simulation and an additional 25,000-iteration of MCMC simulations were run to compare the parameter for the assessment of consistency.

For continuous outcomes, a burn-in of 10,000 iterations of MCMC simulation was used where results were discarded. A burn of 100,000 iterations of MCMC simulations was run to estimate parameters. For the purpose of assessing the consistency assumption, an inconsistency model using a random effects

model was run. A burn-in of 5,000 iterations of MCMC simulation and an additional 25,000-iteration of MCMC simulations were run to compare the parameter for the assessment of consistency.

Trace plots and the Gelman-Rubin statistic as defined in Brooks and Gelman (i.e. potential scale reduction factor [PSRF]) were used to assess if convergence in each treatment included in the network meta-analysis model had been reached.[131 132] The statistical threshold used to determine if convergence had been met was any PSRF value between 1 and 1.05.[130] Iterations of MCMC simulations were added in blocks of 100,000 until the PSRFs for each treatment included in the network were under the predetermined threshold of 1.05 and the trace plots showed convergence had been met. The consistency random-effect model was only performed after PSRFs for each treatment were under the predetermined threshold and the trace plots illustrated convergence had been met.

The findings for network meta-analysis are presented as forest plots (mentioned above), network diagrams (see ***Geometry of the network***) and league tables. For each Bayesian network meta-analysis, the forest plots detail: (i) the treatment effect with 95% credible interval (95% CrI) for each treatment relative to placebo, (ii) the effect measure and samples size associated with each treatment, (iii) probability of each treatment being the highest ranking in the network, and (iv) treatment ranking within the network. The probability of a treatment being the highest ranking within a specific network was determined using the surface under the cumulative ranking curve (SUCRA) score, where 100 denotes the most effective or safe treatment and 0 the least effective or safe.[120 128] A league table is a matrix that presents the treatment effect with 95% CrI for any pair of interventions.[120 128]

Assessment of heterogeneity

In the context of a network meta-analysis, statistical heterogeneity is used to determine and quantify if RCTs that compare the same treatments within a network report similar treatment effects.[122 133] Cochrane's Q-statistic was used to derive the conventional I^2 values to characterise statistical heterogeneity within the Bayesian network meta-analysis for both continuous and dichotomous outcomes.[122 128 133] In situations where an I^2 was not provided by the 'BUGSnet' package it was calculated following the method described in Higgins et al. 2003 (see the ***Imputation methods for dealing with missing values*** section for formula).[134]

Assessment of inconsistency

Inconsistency (also referred to as incoherence) was assessed at both the global and local levels. Within this HTA report, inconsistency refers to the disagreement between the direct and indirect estimable relative effects.[118 135 136] Inconsistency at the global level was assessed by reviewing the fit of consistency and inconsistency models using leverage plots, as well as comparing the deviance

information criterion (DIC) score for both consistency and inconsistency models (the lower the DIC score the better the fit).[122] A difference in DIC scores of 0 to 5 between models was considered minimal, a difference of 5 to 10 was substantial, and finally a difference that was greater than 10 was significant and eliminated the validity of the results of the model with the higher DIC.[137] The presence of local inconsistency was evaluated by a plot that compared the posterior mean difference of each data point produced by the consistency and inconsistency models.[122] In situations where networks do not have closed loops, a DIC score could not be calculated.[138] This HTA report details global and local inconsistency in ***Appendix D***.

The assessment of global inconsistency was performed via DIC scores and leverage plots. However, we were unable to generate the DIC scores (and associated leverage plots) due to the absence of closed loops in most of networks. Therefore, these results were not provided in this HTA.

Frequentist statistical inference

The frequentist network meta-analysis was performed in RStudio using the netmeta (Network Meta-Analysis using frequentist Methods) and meta (General Package for Meta-Analysis) packages.[126 127 139-141] The meta package was used to calculate the pairwise treatment effects that informed the network meta-analysis. An exemplar copy of the code used to conduct Frequentist network meta-analysis is available in the HTA Supplement. The network meta-analysis was performed using a random effects model. For the assumptions used in the pairwise meta-analysis, see the section on pairwise meta-analysis below. The referent comparator for each model was placebo, as most of the available direct evidence was reporting treatment effect relative to placebo.[128]

Dichotomous outcomes

For each dichotomous outcome, the total number of events at longest duration of follow-up were extracted and used in the network meta-analysis. Fracture events were analysed as dichotomous outcomes and used to assess the primary effectiveness of the included treatments. Fractures were delineated into vertebral and nonvertebral fractures. Additionally, the safety outcomes of mortality, AEs, SAEs and withdrawals due to AEs were also analysed as dichotomous outcomes.

Continuous outcomes

The network meta-analysis of dichotomous outcomes was performed in R studio using the netmeta and meta packages.[126 127 139-141] The meta package was used to calculate the pairwise treatment effects that informed the network meta-analysis. The network meta-analysis was performed using a random effects model. For the assumptions used in the pairwise meta-analysis see the section on ***Pairwise meta-***

analysis methods below. The referent comparator for each model was placebo, as most of the available direct evidence was reporting treatment effect relative to placebo.[128]

Mean difference was used to analyse the primary effectiveness data of HRQoL, as well as the surrogate effectiveness measure (i.e. secondary outcomes) of BMD, BTM and fracture risk (FRAX®). To maintain a systematic approach across the two statistical inferences used to inform the network meta-analysis in this HTA report, standardised mean difference was not applied in any of the frequentist network meta-analyses because the SMD is not performed in Bayesian network meta-analyses.[122 125] The mean follow-up period (± 1 SD of the follow-up period) from all included trials was calculated and results at this timepoint were used in the network meta-analysis.

The RCTs that reported the mean percentage change for BMD and/or BTM were extracted for each reported timepoint. In situations where the mean percentage change (T-score, g/cm^2, nmol etc) was not provided in a publication, the measurements at baseline and for all reported timepoints were extracted. The percentage change was then imputed from the extracted baseline and timepoint measurements (see ***Imputation methods for dealing with missing values*** for formula). In trials evaluating BMD across several anatomical locations, measurements taken at FN, LS, TH and trochanter were extracted preferentially. Similarly, in RCTs that evaluated BTM using a variety of markers, CTX, NTX, P1NP and/or B-ALP were extracted preferentially. Individual network meta-analyses were performed for each preferred BMD measurement location as well as for each selected BTM.

Modelling output

The results of the network meta-analysis are presented in forest plots (mentioned above), network diagrams (see ***Geometry of the network***) and league tables. For each frequentist network meta-analysis performed, the forest plots detailed: (i) treatment effect with 95% confidence interval (95% CI) for each treatment relative to placebo, (ii) treatment measure and sample size associated with each treatment, (iii) probability of each treatment being the highest ranking in the network, and (iv) treatment ranking within the network. The probability of a treatment being the highest ranking within a specific network was determined through a P-score, where 1.00 denotes the most effective or safe treatment and 0 the least effective or safe.[121 128] A league table is a matrix that enables treatment effects with 95% CI between any pair of interventions to be presented.[121 128]

Assessment of heterogeneity

In the context of a network meta-analysis, statistical heterogeneity is used to determine and quantify if RCTs that compare the same treatments within a network report similar treatment effects.[133 138 142] The

presence of statistical heterogeneity within a particular network (i.e. within-design and comparison specific/between individual arms) was determined by using Cochran's Q-statistic for heterogeneity (Q^{het}) as defined by Krahn et al. 2013.[133 138 140] I^2 was used to quantify Cochrane's Q^{het} statistic. The tables in ***Appendix D*** present statistical heterogeneity for results for applicable networks included in this HTA report.

In situations where I^2 was not provided, it was calculated following the method described in Higgins et al. 2003 (see ***Imputation methods for dealing with missing values*** for formula).[134]

Assessment of inconsistency

In the frequentist network meta-analysis, inconsistency (also referred to as incoherence) was reviewed at both the local and global level. Inconsistency was defined as any disagreement between the direct and indirect estimable relative effects (i.e. absolute value or ratio of outcome measurements).[128 133 135 136] The global level was reviewed using the Cochrane's Q-statistic for inconsistency (Q^{inc}) as defined by Krahn et al. 2013.[133 138 140] Inconsistency at the local level was assessed by node-splitting.[138 140] Given that the networks do not have closed loops, a Cochrane's Q^{inc} statistic cannot be calculated and is therefore not reported in this HTA.[138] This HTA only reports a summary of the node-splitting conducted to evaluate local inconsistency (see footnote of the league tables in ***Appendix C***). However, the plots are not available in this HTA report.

Pairwise meta-analysis methods

In situations where there was insufficient available data to conduct a network meta-analysis, a pairwise meta-analysis was conducted if there were two or more RCTs comparing denosumab to one of the included comparators (***Table 4***).

Dichotomous outcomes

Dichotomous outcomes were meta-analysed using meta packages.[126 127 139 141] The meta-analysis was performed using random-effects models. The Mantel-Haenszel method was used to estimate primary study weights. Results were reported as RR with 95% CI. For each dichotomous outcome, the total number of events at longest duration of follow-up were extracted and used in the meta-analysis. Fracture events were analysed as dichotomous outcomes and used to assess the primary effectiveness of the included treatments. Fractures were delineated into vertebral and nonvertebral fractures. Additionally, the safety outcomes of mortality, AEs, SAEs and withdrawals due to AEs were also analysed as dichotomous outcomes.

The pairwise meta-analyses of dichotomous outcomes, which were conducted to assess the presence of AEs upon denosumab discontinuation, differed slightly in method. For instance, the total number of events at baseline and at any timepoint after the loss of denosumab effect (approximately six months) were extracted and used in the analyses, instead of end-of-treatment regimen timepoint.

Continuous outcomes

Continuous outcomes were meta-analysed using meta packages in R.[126 127 139 141] The meta-analysis was performed using random-effects models, with restricted maximum likelihood (REML) being used to estimate between-study variance. Continuous outcomes were reported as MD. When extracted, continuous data were accompanied by SD and/or 95% CI.

Assessment of heterogeneity

Meta-analysis results were illustrated using forest plots, because they provide a visual representation of the reported effect sizes and uncertainty across included studies. Heterogeneity was also assessed statistically. The statistical methods used to measure heterogeneity in meta-analyses of continuous and dichotomous outcomes were Tau^2 and I^2. The significance of I^2 depended on the strength of the evidence for heterogeneity (i.e. Tau^2) as well as direction and size of the measured effect. It was interpreted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)*.[128] An I^2 of 0–40% is low (i.e. may not be important); 30–60% is moderate, 50–90% is substantial and 75–100% is considerable heterogeneity.[128]

Synthesis and presentation of single-arm trials

The synthesis of single-arm trials was conducted to investigate if AEs occurred upon discontinuation (i.e. rebound effect) of denosumab. The synthesis of single-arm trials was illustrated using the meta package [126 127 139 141] because it allows for a visual representation of the reported effect sizes relative to baseline values.

Dichotomous outcomes

Single-arm trials that reported dichotomous fracture outcomes were synthesised using the meta package.[126 127 139 141] Results were reported as RR with 95% CI. The total number of events at baseline and at any timepoint after the loss of denosumab effect (approximately six months) were extracted and used in the analyses. Fractures were delineated into vertebral and nonvertebral fractures and used to assess the primary effectiveness of the included treatments.

Continuous outcomes

Single-arm trials that reported continuous surrogate outcomes of BMD and/or BTM were synthesised using the meta package.[126 127 139 141] The BMD or BTM measurements (T-score, g/cm^2, nmol etc) at baseline and any timepoint after the loss of denosumab effect (approximately six months) were extracted and used in the various analyses. Unlike the pairwise meta-analysis of AEs that occurred

after denosumab discontinuation on BMD and BTM, data were not extracted as, or converted to percentage change from baseline. This is because the rebound effect could only be identified in single-arm trials if the measured variable dropped below baseline level.

In trials evaluating BMD across several anatomical locations, measurements taken at FN, LS, TH and trochanter were extracted preferentially. Similarly, in RCTs that evaluated BTM using a variety of markers, CTX, NTX, P1NP and/or B-ALP were extracted preferentially. Individual network meta-analyses were performed for each preferred BMD measurement location as well as for each selected BTM.

Assessment of heterogeneity

Heterogeneity was not assessed because single-arm meta-analysis was not conducted.

Imputation methods for dealing with missing values

Missing SDs were obtained from available means, sample sizes, standard errors and 95% CIs using formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)*.[128] The formula used is detailed below.

$$SD = \sqrt{N}\ x\ (upper\ limit - lower\ limit)/3.92$$

In situations where data were not available to calculate SD, it was imputed using the 'impute_SD' function in the *R* (version 1.4) package 'metagear', following the imputation methods described by Braken et al. 1992.[126 127 143 144]

Where continuous values needed to be combined, formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)* were used.[128] The formulae used are detailed below.

$$Sample\ size = N_1 + N_2$$

$$Mean = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

$$SD = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2\ 2M_2 M_2)}{N_1 + N_2 - 1}}$$

Percentage change was calculated using the formula below.[145]

$$Percentage\ change = \frac{new\ value - old\ value}{old\ value} \times 100$$

For studies that reported outcomes graphically, *WebPlotDigitizer* was used to convert graph points into numerical values.[114]

Assessment of publication bias

Publication bias in the network meta-analyses (either Bayesian or frequentist) was assessed using comparison-adjusted funnel plots (***Appendix E***).[146] This method requires a minimum of 10 studies per outcome.[147] In addition, clinical trial registries were searched to identify unpublished studies/outcomes as a means of narratively describing publication bias.

Meta-regressions

Meta-regressions were performed to explore the impact of potential treatment effect modifiers on the results (i.e. patient characteristics between RCTs).[148] The meta-regressions were used to test for any interactions between trial-level covariates and age on the effectiveness and safety of the included interventions/comparators in postmenopausal women with osteoporosis.[148]

The meta-regressions were only conducted on the data extracted from RCTs on postmenopausal women with osteoporosis that reported the average age of trial participants. A minimum number of trials per outcome was not required in order to perform a meta-regression.[149] However, the Cochrane Handbook advises an arbitrary minimum of 10 trials per outcome for a meta-regression to provide meaningful results.[118] In accordance with the original analysis, the meta-regression was performed in RStudio using the 'BUGSnet' package.[122 125-127] The complete and detailed results from the meta-regressions are presented in the HTA Supplement. Meta-regressions were not conducted for the populations evaluated using a Frequentists inference due to limitations in the software package [126 127 139-141]

Sensitivity analyses

In addition to the main analyses and the meta-regressions, five sensitivity analyses were conducted to explore two possible effect modifiers: (1) imprecision, (2) high and moderate risk of bias. Given that the risk of performance bias (i.e. blinding of participant/ personnel) and detection bias (i.e. measurement of outcomes) were mainly low across the included RCTs, the sensitivity analyses focused on exploring the influence of reporting bias (i.e. selective reporting), attrition bias (i.e. missing outcomes) and selection bias (i.e. randomisation) on the pre-determined outcomes in the included populations.

Two of the sensitivity analyses were performed using a Bayesian inference. The first sensitivity analysis explored the effect of imprecision on the four separate populations. This was achieved by conducting Bayesian NMAs on each individual outcome, using the combined data extracted from the RCTs relevant to all populations. The second sensitivity analysis explored RCTs considered to have a high or medium

risk of bias to investigate the impact this may have on the results of various NMAs conducted on postmenopausal women. This was achieved by running separate Bayesian NMAs for each individual outcome using the data extracted from the RCTs on postmenopausal women with osteoporosis that presented a low risk of selection, attrition or reporting bias.

The remaining sensitivity analyses were performed by running NMAs using a Frequentist inference. These analyses explored RCTs at high or medium risk of bias to investigate the impact this may have on the results of the NMAs conducted on women with breast cancer receiving AAIT who have an increased fracture risk, men with osteoporosis who have an increased fracture risk, or men with prostate cancer on HAT who have an increased fracture risk. The influence of selection, attrition or reporting bias was explored by running separate Frequentist NMAs for each individual outcome and population.

The results from the sensitivity analyses are presented in the HTA Supplement.

7.3 Search results

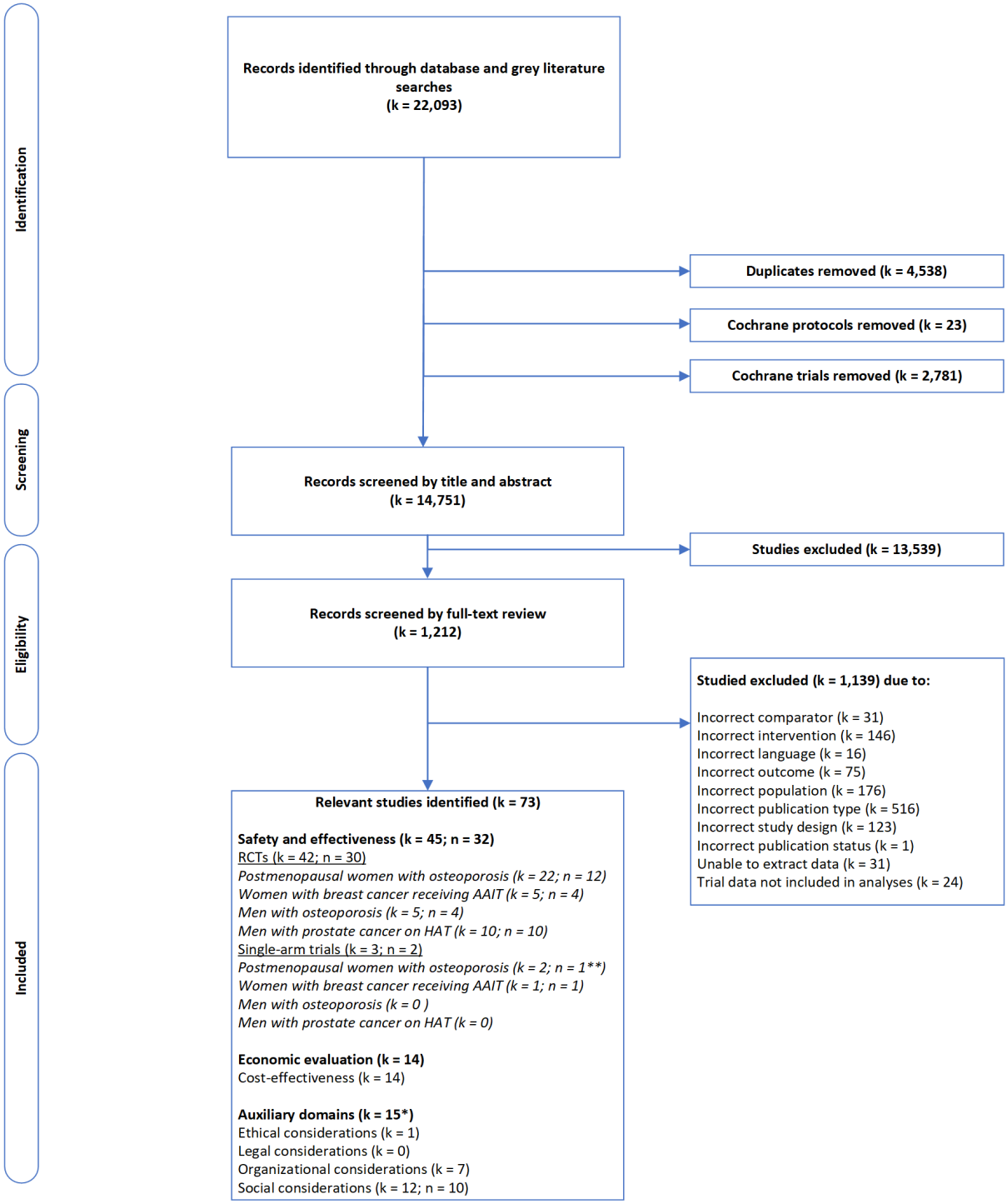
The results of the literature search are summarised in ***Figure 1*** below. The database and grey literature searches identified 22,093 articles. A total of 4,538 duplicate citations were removed and 14,751 items were reviewed by title and abstract. In total, 1,212 articles were reviewed by full text. A complete list of articles excluded at full-text review is available in the HTA Supplement.

A total of 32 trials (k = 45 publications) met the PICO criteria (***Section 5***) for assessing the safety and effectiveness of denosumab against its comparators (i.e. alendronate, ibandronate, risedronate, zoledronate, raloxifene and bazedoxifene).[150-194] The included trials comprised 30 RCTs (k = 42 publications),[150-164 166 167 169-188 190-194] and 2 single-arm trials (k = 3 publications)[165 168 189] (listed in ***Table 6*** and ***Table 7***). One of the included single-arm trials was an extensions of an RCT. The single-arm trials were included to provide evidence to assess the impact of denosumab discontinuation.

In addition, 14 publications assessed the cost-effectiveness of denosumab.[195-208] Twelve publications were associated with social considerations (k = 10),[46 209-219] one with ethical considerations,[189] and 7 with organisational considerations (k = 7).[105 209 215-218 220] The systematic searches did not identify any publications that evaluated legal considerations related to denosumab.

7.3.1 PRISMA flow diagram

Figure 1 PRISMA flow diagram



Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **HAT**: hormone ablation therapy; **PRISMA**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCTs**: randomised control trials.
Notes:
k: number of individual publications.
n: number of RCTs – an RCT can be included in multiple publications.
*Some articles are included in multiple domains
**One trial not counted as it is a single-arm extension of an included RCT

7.4 Evidence base pertaining to efficacy, effectiveness and safety

7.4.1 Study characteristics

7.4.1.1 Randomised control trials

Overall, 30 RCTs were included (k = 42 publications) in the assessment of clinical effectiveness and safety. The characteristics of all included studies are presented below per population.[150-164 166 167 169-188 190-194]

The study characteristics of each trial are reported in ***Table 6*** and characteristics of each RCT (per publication) are reported in ***Appendix B***.

Postmenopausal women with osteoporosis

In total, 12 RCTs (k = 22 publications) were included in the assessment of clinical effectiveness and safety in postmenopausal women with osteoporosis.[150 152 155 158-162 164 171 173 174 179-182 185-188 191 192] Of these 12 RCTs, 10 were multicentre trials,[150 152 155 158-162 164 173 174 179-182 186-188 191 192] one was a single-centre trial,[171] and one trial was unclear.[185] These trials were conducted across North America (n = 7 trials), South America (n = 4 trials), Oceania (n = 5 trials), Europe (n = 8 trials), Asia (n = 5 trials) and South Africa (n = 2 trials). No study was fully conducted in Switzerland; however, two international multicentre trials had centres located in Switzerland [i.e. Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) and HORIZON-Pivotal Fracture Trial (HORIZON-PFT)].

Of the included RCTs, six publications reported an extension phase,[150 159 161 186 187 191] of which three were open-label (OL)[150 159 187] and three remained blinded.[161 186 191] One independent trial was initiated as OL due to the different dosing frequencies of active study drugs without the implementation of a double-dummy technique.[185] Importantly, five publications from two independent trials reported a crossover extension phase;[150 159 161 186 191] however, this information was not utilised unless data were explicitly reported for the rebound effect of denosumab.

In postmenopausal women with osteoporosis, two trials compared denosumab to placebo (k = 5),[150 155 159 160 182] one trial compared denosumab to zoledronate (k = 1),[180] two trials compared raloxifene to placebo (k = 3),[162 164 181] one trial compared bazedoxifene to placebo (k = 1),[173] one trial compared bazedoxifene to raloxifene and placebo (k = 5),[158 161 186 191 192] two trials compared zoledronate to placebo (k = 3),[152 171 174] one trial compared risedronate to placebo (k = 2),[187 188] one trial compared alendronate to ibandronate (k = 1),[179] and one trial compared ibandronate to alendronate and risedronate (k = 1).[185]

As per the inclusion criteria, the dosage of denosumab was fixed (60 mg) across all included studies and administered subcutaneously every six months. As for the active comparators in the included studies (per the inclusion criteria), the dosage of bazedoxifene was 20 mg/day administered orally, the dosage of raloxifene was 60 mg/day administered orally, the dosage of alendronate was 70 mg administered orally once weekly, the dosage of risedronate was 35 mg administered orally once weekly, the dosage of ibandronate was 150 mg administered orally once monthly, and the dosage of zoledronate was 5 mg administered intravenously once per year. It is important to note, other doses of these comparators were also administered in some of the included studies, however these doses were not extracted or analysed as they are not reimbursed in Switzerland.

The median sample size was 534 participants (range 90–7,808), with 34,569 participants included across all 12 independent trials. Participants were typically age 50–90 years, ambulatory, more than 2 years postmenopausal, with a BMD T-score of -2.5 or less. The follow-up duration of included studies ranged from 12–84 months.

For clinical effectiveness, the most frequently studied outcomes included vertebral fracture, nonvertebral fracture and BMD. No studies reported HRQoL or fracture risk (i.e. FRAX®). For safety, the most reported outcomes included mortality, treatment-related AEs and SAEs.

Women with breast cancer receiving AAIT who have an increased fracture risk

In total, four RCTs (k = 5 publications) were included in the assessment of clinical effectiveness and safety in women with breast cancer receiving AAIT who have an increased fracture risk.[163 166 167 169 177] Of these four RCTs, two were multicentre trials[163 166 167] and two were single-centre trials.[169 177] These trials were conducted across North America (n = 2 trials, including USA and Canada), and Europe (n = 2 trials, including Austria, Sweden and Italy). No study was conducted or had centres located in Switzerland.

Of the included RCTs, one publication reported an OL extension phase with the opportunity for crossover,[167]. One RCT was conducted as single-blind (participants),[177] with the remainder of included studies conducted as double-blind.

In women with breast cancer receiving AAIT who have an increased fracture risk, two trials compared denosumab to placebo (k = 3),[163 166 167] one trial compared risedronate to placebo (k = 1)[169] and one trial compared ibandronate to placebo (k = 1).[177]

As per the inclusion criteria, the dosage of denosumab was fixed (60 mg) across all included studies, administered subcutaneously every six months. As for the active comparators in the included studies

(per the inclusion criteria), the dosage of risedronate was 35 mg administered orally once weekly, and the dosage of ibandronate was 150 mg administered orally once monthly.

The median sample size was 211.5 participants (range 87–3,420), with approximately 3,930 participants included across all four trials. Participants were typically age 38–91 years; postmenopausal (natural or surgical); with hormone-receptor-positive breast cancer histologically or cytologically confirmed, undergoing AAIT and completing/completed treatment via radiation, chemotherapy or surgery. The follow-up duration of included studies typically ranged from 12–36 months, with the exception of two trials having a median follow-up duration of 63.3 months[177] and 73 months (range 58–95).[167]

For clinical effectiveness, the most frequently studied outcome was BMD, with few reports of fracture. No studies evaluated HRQoL or fracture risk (i.e. FRAX®). When safety outcomes were evaluated in the included studies, the most commonly reported outcomes were mortality, treatment-related AEs and SAEs. Only one RCT reported withdrawal due to treatment-related AEs.[163] No studies reported AEs upon discontinuation of denosumab (i.e. rebound effect).

Men with osteoporosis who have an increased fracture risk

In total, four multicentre RCTs (k = 5 publications) were included in the assessment of clinical effectiveness and safety in men with osteoporosis.[153 154 176 183 184] These trials were conducted across North America (n = 3 trials), Europe (n = 3 trials), Oceania (n = 3 trials), West Asia (n = 1 trial), Africa (n = 1 trial) and South America (n = 1 trial). No study was fully conducted in Switzerland; however, one international multicentre trial had eight centres located in Switzerland, including Aarau, Baden, Basel, Bern, Geneve, Lausanne, Sion and Zurich.[154]

Of the included RCTs, one reported an OL extension phase during which participants assigned to placebo crossed over to active intervention,[183] the remainder of the included studies were double-blind and placebo-controlled. As previously mentioned, crossover information was not utilised unless data were explicitly reported for the rebound effect of denosumab. One RCT had unequal randomisation (2:1 ratio), with a larger number of participants allocated to the active treatment.[153] The study was a phase-3 trial investigating the efficacy and safety of the study drug in treating a male osteoporotic population.

In men with osteoporosis, one trial compared denosumab to placebo (k = 2),[176 183] one trial compared risedronate to placebo (k = 1),[153] one trial compared zoledronate to placebo (k = 1)[154] and one trial compared zoledronate to alendronate (k = 1).[184]

As per the inclusion criteria, the dosage of denosumab was fixed (60 mg) across all included studies, administered subcutaneously every six months. As for the active comparators in the included studies

(per the inclusion criteria), the dosage of alendronate was 70 mg administered orally once weekly, the dosage of risedronate was 35 mg administered orally once weekly, and the dosage of zoledronate was 5 mg administered intravenously once per year.

The median sample size was 293 participants (range 242–1,199), with approximately 2,027 participants included across all four trials. Participants were typically age 50–85 years, ambulatory, with primary or secondary osteoporosis (i.e. hypogonadism) and low BMD or history of osteoporotic fracture. The follow-up duration of included studies ranged from 12–24 months.

For clinical effectiveness, the most frequently studied outcomes were vertebral and nonvertebral fracture and BMD. No studies reported HRQoL or fracture risk (i.e. FRAX®). For safety, the most commonly reported outcomes included mortality, treatment-related AEs, SAEs and withdrawal due to AEs. No studies reported AEs upon discontinuation of denosumab (i.e. rebound effect).

Men with prostate cancer on HAT who have an increased fracture risk

In total, 10 RCTs (k = 10 publications) were included in the assessment of clinical effectiveness and safety in men with prostate cancer on HAT who have an increased fracture risk.[151 156 157 170 172 175 178 190 193 194] Of these 10 RCTs, seven were multicentre trials[151 157 175 178 190 193 194] and three were single-centre trials.[156 170 172] These trials were conducted across North America (n = 9 trials, including USA, Canada and Mexico), Europe (n = 1 trial, including Finland, Czech Republic and Poland), and Australia (n = 1 trial). One RCT detailed to be conducted in North America and Europe, only partially listed study-centre locations.[194] No study was fully conducted in Switzerland and it is unclear if the RCT with study centres across Europe had any centres located in Switzerland.

Of the included RCTs, all were double-blind, none were conducted as OL and none reported an extension phase or crossover.

In men with prostate cancer on HAT who have an increased fracture risk, one trial compared denosumab to placebo (k = 1),[194] six trials compared zoledronate to placebo (k = 6),[151 156 172 178 190 193] two trials compared alendronate to placebo (k = 2)[170 175] and one trial compared risedronate to placebo (k = 1).[157]

As per the inclusion criteria, the dosage of denosumab was fixed (60 mg) across all included studies, administered subcutaneously every six months. As for the active comparators in the included studies (per the inclusion criteria), the dosage of alendronate was 70 mg administered orally once weekly, and the dosage of risedronate was 35 mg administered orally once weekly. The dose and intervals of administration of zoledronate differed across included studies: in four studies the dosage of zoledronate was 4 mg administered intravenously every three months for the duration of the study,[151 172 190 193] one

study administered 4 mg of zoledronate intravenously only on day 1 of the study (12-month follow-up),[178] and one study administered a single 5 mg dose of zoledronate intravenously at study entry (24-month follow-up).[156]

The median sample size was 109 participants (range 44–1,468), with approximately 2,533 participants included across all 10 trials. Participants were typically age 44–97 years; with histologically confirmed prostate cancer and undertaking HAT/androgen deprivation therapy (ADT) including orchiectomy, on or initiating gonadotropin-releasing hormone (GnRH) agonist therapy or luteinising hormone-releasing hormone (LHRH) therapy, with or without an antiandrogen. The follow-up duration of included studies ranged from 12–36 months.

For clinical effectiveness, the most frequently studied outcome was BMD, with few reports of fracture. No studies reported HRQoL or fracture risk (i.e. FRAX®). For safety, the most commonly reported outcomes included mortality, treatment-related AEs, SAEs and withdrawal due to AEs. No studies reported AEs upon discontinuation of denosumab (i.e. rebound effect).

Table 6 Characteristics of included RCTs and RCT extensions assessing clinical effectiveness and safety

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
Postmenopausal women with osteoporosis							
FREEDOM NCT00089791 155 160 32 countries	RCT, double blind, multicentre (214 sites) 36mo	Postmenopausal women, T-score <-2.5 at LS or TH	DEN (60 mg/6mo) n = 3,902	PL n = 3,906	Overall FREEDOM population: 72.3±5.2	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (LS, TH) *Safety:* Mortality, AEs, SAEs, AEs upon discontinuation of DEN	Amgen Inc.
FREEDOM Extension NCT00523341 150 159 32 countries	OL extension study with crossover from placebo (214 centres) 84mo (total)* *Only data to 36mo extracted. Crossover data was not utilised.	Postmenopausal women, T-score <-2.5 at LS or TH	DEN (60 mg/6mo) n = 3,004 up to 5 years	NA	FREEDOM Extension-Long-term DEN: 74.9±5.0 Crossover DEN: 74.8±5.1	*Safety:* Withdrawal due to AEs, AEs upon discontinuation of DEN	Amgen Inc.
Nakamura et al. 2012[182] NR Japan	RCT, double blind, multicentre (NR) 12mo	Postmenopausal women, T-score -2.5 to -4.0 at LS, or -2.5 to -3.5 at FN or TH	DEN (14 mg/6mo)[a] n = 53 DEN (60 mg/6mo)[a] n = 54 DEN (100 g/6mo)[a] n = 50	PL n = 55	DEN (14 mg): 65.9±7.1 DEN (60 mg): 65.1±6.3 DEN (100 mg): 64.6±7.1 PL: 64.6±7.0	*Effectiveness:* Vertebral fracture, BMD (TH) *Safety:* AEs, SAEs	Amgen Inc.

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
Miller et al. 2016[180] NCT01732770 7 countries	RCT, double blind, double dummy, multicentre (37 sites) 12mo	Postmenopausal women, ≥2y bisphosphonate therapy prior to screening if T-score ≤-2.5 at LS, TH, FN	DEN (60 mg/6mo) n = 321	ZOL (IV 5 mg/ once yearly) n = 322	DEN: 65.1±7.6 ZOL: 69.5±7.7	*Effectiveness:* BMD (FN, TH) *Safety:* Withdrawal due to AEs, AEs, SAEs	Amgen Inc.
Morii et al. 2003[181] NR Japan	RCT, double blind, multicentre (26 sites) 12mo	Postmenopausal women, ≥2y PM, T-score <-2.5 at LS	RLX (oral 60 mg/d) n = 92 RLX (oral 120 mg/d)[b] n = 95	PL n = 97	RLX (60 mg): 65.2±6.2 RLX (120 mg): 64.7±6.2 PL: 64.3±6.5	*Effectiveness:* Vertebral and nonvertebral fracture *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Eli Lilly and Company and Chugai Pharmaceutical Company
MORE[162 164] 25 countries	RCT, double blind, multicentre (180 sites) 48mo	Postmenopausal women, ≥2y PM, Group 1: T-score <-2.5 at LS or FN Group 2: Low BMD with ≥1 moderate or severe vertebral fractures, or ≥2 moderate fractures regardless of BMD	RLX (oral 60 mg/d) n = 2,557 RLX (oral 120 mg/d)[c] n = 2,752	PL n = 2,576	Overall MORE population: 67	*Effectiveness:* Vertebral fracture, BMD (FN, LS) *Safety:* Mortality	Eli Lilly and Company
NCT00205777[158 192] 28 countries	RCT, double blind, multicentre (206 sites) 36mo	Postmenopausal women, ≥2y PM, T-score -2.5 to -4.0 at LS or FN, or prevalent vertebral facture and T-score not below -4.0 at LS or FN	BAZ (oral 20 mg/d) n = 1,886 BAZ (oral 40 mg/d)[d] n = 1,872	RLX (oral 60 mg/day) n = 1,849 PL n = 1,885	BAZ 20 mg: 66.5±6.5 BAZ 40 mg: 66.2±6.8 RLX 60 mg: 66.4±6.7 PL: 66.5±6.8	*Effectiveness:* Nonvertebral fracture, BMD (LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Pfizer Inc.

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
NCT00205777 Extension I[161 191] and Extension II[186] 28 countries	RCT, double blind, multicentre (206 sites), extension study Extension I: 60mo Extension II: 84mo	Postmenopausal women, ≥2y PM, T-score -2.5 to -4.0 at LS or FN, or prevalent vertebral facture and T-score not below -4.0 at LS or FN	BAZ (oral 20 mg/d) → BAZ (oral 20 mg/d) n = 1,047 BAZ (oral 40 mg/day) → BAZ (oral 20 mg/d)[e] n = 1,041	RLX (60 mg/day) → treatment arm discontinued after 3y n = 1,070 PL n = 1,058	Extension I- BAZ 20 mg: 65.9±6.3 BAZ 40/20 mg: 65.7±6.4 PL: 65.9±6.5 Extension II: BAZ 20 mg and 40/20 mg combined: 65.7±6.2 PL: 65.7±6.1	*Effectiveness:* Vertebral fracture *Safety:* Mortality	Pfizer Inc.
Itabashi et al. 2011[173] NCT00238745 Japan	RCT, double blind, multicentre (17 sites) 24mo	Postmenopausal women, intact uterus, ≥2y PM, no prevalent vertebral fracture and T-score <-2.5 or prevalent vertebral fracture and T-score <-1.7 (approximately)	BAZ (oral 20 mg/day) n = 143 BAZ (oral 40 mg/d)[d] n = 140	PL n = 142	BAZ 20 mg: 63.0±6.4 BAZ 40 mg: 63.2±6.3 PL: 64.1±6.6	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Pfizer Inc.
Miller et al. 2008[179] MOTION MM17385 NR	RCT, double blind, double dummy, non-inferiority, multicentre (65 sites) 12mo	Postmenopausal women, ≥5y PM, ambulatory, T-score <-2.5 to ≥-5.0 at LS	IBN (oral 150 mg/once monthly) n = 887	ALN (oral 70 mg/once weekly) n = 873	IBN: 65.6 ALN: 65.6	*Effectiveness:* BMD (FN) *Safety:* AEs, SAEs	F. Hoffmann-La Roche Ltd.

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
TRIO[185] NCT00666627 UK	RCT, OL, multicentre (NR) 24mo	Postmenopausal women, ≥5y PM, ambulatory, T-score ≤-2.5 at LS or PF or T-score ≤-1.0 at LS or PF and a previous fracture from a fall at standing height	IBN (oral 150 mg/ once monthly) n = 57	ALN (oral 70 mg/once weekly) n = 57 RIS (oral 35 mg/ once weekly) n = 58	IBN: 66.9±7.2 ALN: 67.8±7.8 RIS: 66.8±6.7	*Effectiveness:* BMD (FN, LS) *Safety:* AEs, SAEs	Warner Chilcott
Greenspan et al. 2015[171] ZEST NCT00558012 USA	RCT, OL, single-centre 24mo	Frail women with osteoporosis residing in nursing homes or assisted-living facilities, with a history of vertebral or hip fracture or T-score <-2.0 at LS, TH or radius	ZOL (IV 5 mg/once yearly) n = 89	PL n = 92	ZOL: 85.4±0.6 PL: 85.5±0.5	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Mortality, AEs, SAEs	Numerous, see ***Appendix B***
Palomba et al. 2005[188] NR Palomba et al. 2008[187] Extension (NR) Italy	RCT, double blind, multicentre (2 sites) Core trial: 12mo Extension: 36mo	Postmenopausal women, IBD in remission(≥6mo), ambulatory, T-score ≤-2.5 at posterior-anterior LS	RIS (oral 35 mg/once weekly) n = 75	PL n = 45	RIS: 52.3±3.2 PL: 51.4±3.0	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS) *Safety:* AEs	NA
HORIZON-PFT NCT00049829[152 174] 27 countries	RCT, double blind, multicentre (240 sites) 36mo	Postmenopausal women, T-score <-2.5 at FN with or without vertebral fracture, or T-score <-1.5 with radiologic evidence of ≥2 mild vertebral fractures or 1 moderate vertebral fracture	ZOL (IV 5 mg/once yearly) n = 3,889	PL n = 3,876	ZOL:73.1±5.34 PL: 73.0±5.40	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Novartis Pharma NIHR, the Medical Research Council
Women with breast cancer receiving AAIT who have an increased fracture risk							

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
Ellis et al. 2008[163] NCT00089661 USA, Canada	RCT, double blind, multicentre (53 sites) 24mo	Early-stage breast cancer, hormone-receptor-positive, undergoing AAIT, low bone mass or FN T-score of -1.0 to -2.5	DEN (60 mg/6mo) n = 125	PL n = 127	DEN: 59.2±8.9 PL: 59.7±9.7	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH, Trochanteric) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Amgen Inc.
ABCSG-18[166 167] NCT00556374 Austria, Sweden	RCT, double blind/OL phase, multicentre (58 sites) Core trial: 36mo OL phase:73mo (median duration of follow-up)[f]	Postmenopausal women with breast cancer, receptor-positive, receiving AAIT	DEN (60 mg/6mo) n = 1,711	PL n = 1,709	Total ABCSG-18 population: median 64 (58-70)	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Mortality, AEs, SAEs	Amgen Inc.
NCT00118508[169] USA	RCT, double blind, single-centre 12mo	Newly postmenopausal women (≤8y) with breast cancer, treated with chemotherapy with or without tamoxifen or AAIT	RIS (oral 35 mg/once weekly) n = 43	PL n = 44	RIS: 50.1±5.1 PL: 49±5.9	*Effectiveness:* BMD (LS, TH, Trochanteric)	Numerous, see ***Appendix B***
Livi et al. 2019[177] BONADIUV NCT02616744 Italy	RCT, single blind, single-centre 63.3mo (median follow-up)[g]	Postmenopausal women with early breast cancer, hormone-receptor-positive, receiving AAIT	IBN (oral 150 mg/ once monthly) n = 89	PL n = 82	IBN: median 60.5 (54.3-67.0) PL: median 59.6 (53.9-68.0)	*Effectiveness:* BMD (LS, TH) *Safety:* SAEs	NA
Men with osteoporosis who have an increased fracture risk							

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
ADAMO[176 183] NCT00980174 7 countries	RCT, double blind/OL phase (with crossover), multicentre (27 sites) ADAMO: 12mo OL phase: 24mo	Men with osteoporosis, T-score between ≤-2.0 and ≥-3.5 at LS or FN, or had a previous MOF and T-score between ≤-1.0 and ≥-3.5 at LS or FN and had ≥2 vertebral fractures, 1 femur and 1 forearm evaluated by DXA	ADAMO: DEN (60 mg/6mo) n = 121 ADAMO OL phase: DEN → DEN (continued intervention long-term) n = 111 ADAMO OL phase: PL → DEN (crossover) n = 117	ADAMO: PL n = 121	ADAMO-DEN: 64.9±9.8 PL: 65.0±9.1 ADAMO OL phase-Long-term DEN: 65.0±10.2 Crossover: DEN: 65.1±9.2	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH, Trochanteric), *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Amgen Inc.
Boonen et al. 2009[153] NR 11 countries	RCT, double blind, multicentre (25 sites) 24mo	Men with osteoporosis, T-score ≤-2.5 at LS and ≤-1 at FN or T-score ≤-1 at LS and ≤-2 at FN	RIS (oral 35 mg/ once weekly) n = 191	PL n = 93	RIS: 60±11 PL: 62±11	*Effectiveness:* BMD (FN, LS, TH, Trochanteric) *Safety:* Mortality, AEs, SAEs	Alliance for Better Bone Health (Proctor and Gamble)
Boonen et al. 2012[154] NCT00439647 23 countries	RCT, double blind, multicentre (NR) 24mo	Men with primary osteoporosis or osteoporosis from low testosterone levels, T-score ≤-1.5 at TH or FN, and 1-3 prevalent vertebral fractures. If no fracture, T-score of ≤-2.5 at TH, FN, LS	ZOL (IV 5 mg/ once yearly) n = 588	PL n = 611	ZOL: median 66 (50-85) PL: median 66 (50-85)	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Novartis Pharma

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
Orwoll et al. 2010[184] NR Australia, USA and Canada	RCT, double blind, double dummy, non-inferiority, multicentre (30 sites) 24mo	Men with primary or secondary osteoporosis associated with hypogonadism, T-score of -2.0 at FN and -1.0 at LS, or -1.0 at FN and a prior low trauma vertebral or nonvertebral fracture, or a confirmed radiographic vertebral fracture	ZOL (IV 5 mg/ once yearly) n = 154	ALN (oral 70 mg/once weekly) n = 148	ZOL: 64.5±9.90 ALN: 63.5±10.98	*Effectiveness:* Vertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Novartis Pharma
Men with prostate cancer on HAT who have an increased fracture risk							
NCT00089674[194] Canada, USA, Finland, Czech Republic	RCT, double blind, multicentre (156 sites) 36mo	Men with prostate cancer on HAT, ≥70yo or if <70yo with history of osteoporotic fracture or T-score <-1.0 at LS, TH or FN, had either received bilateral orchiectomy or are on ADT for at least next 12mo	DEN (60 mg/6mo) n = 734	PL n = 734	DEN: 75.3±7.0 PL: 75.5±7.1	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Amgen Inc.
Michaelson et al. 2007[178] NR USA	RCT, double blind, multicentre (2 sites) 12mo	Men with prostate adenocarcinoma, receiving GnRH agonists, T-score ≥-2.5 at LS or FN	ZOL (IV 4 mg/ once yearly) n = 22	PL n = 22	ZOL: 65±8 PL: 66±11	*Effectiveness:* BMD (FN, LS, TH)	Novartis Pharma
Choo et al. 2013[157] NR USA	RCT, double blind, multicentre (2 sites) 24mo	Men with prostate adenocarcinoma to be treated with external beam RT plus 2-3y of ADT using LHRH analogues." T-score >-2.5 at LS	RIS (oral 35 mg/ once weekly) n = 52	PL n = 52	RIS: 67.5 PL: 66.8	*Effectiveness:* BMD (FN, LS) *Safety:* SAEs	Aventis Pharma, Procter and Gamble

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
Greenspan et al. 2007b[170] NCT00048841 USA	RCT, double blind, single-centre 12mo	Men with prostate cancer receiving ADT	ALN (oral 70 mg/once weekly) n = 56	PL n = 56	ALN: 70.8±7.9 PL: 72.2±8.8	*Effectiveness:* Nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Mortality, AEs, SAEs	NIH/National Institute of Diabetes and Digestive and Kidney Diseases, NIH/National Center for Research Resources
Israeli et al. 2007[172] NR USA	RCT, double blind, single-centre 12mo	Men with prostate cancer within 1y of starting ADT, received orchiectomy, T- score of ≥-2 at LS and TH	ZOL (IV 4 mg/ 3mo) n = 112	PL n = 110	ZOL: median 74 (44-88) PL: median 73 (47-89)	*Effectiveness:* Nonvertebral fracture, BMD (LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Novartis Pharma
Bhoopalam et al. 2009[151] NR USA	RCT, double blind, multicentre (11 sites) 12mo	Men with prostate cancer, on or initiating ADT (LHRH agonist with or without antiandrogen or bilateral orchiectomy), T-score of ≥-2 at LS and TH	ZOL (IV 4 mg/ 3mo) n = 48	PL n = 45	ZOL: Stratum 1-69.1±10.7 Stratum 2-71.2±6.8 PL: Stratum 1-68.4±6.0 Stratum 2-73.7±.2	*Effectiveness:* BMD (LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs	Novartis Pharma
Cheung et al. 2020[156] NCT01006395 Australia	RCT, double blind, single-centre 24mo	Men with prostate cancer prior to commencing GnRH agonists therapy, ADT intended for at least 2y	ZOL (IV 5 mg/ single dose) n = 39	PL n = 37	ZOL: median 68.8 (63.1-73.2) PL: median 67.5 (65.2-74.3)	*Effectiveness:* Nonvertebral fracture, BMD (LS, TH) *Safety:* Withdrawal due to AEs, AEs, SAEs	NHMRC

Study Trial Country †	Study design Duration	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ± SD	Outcome(s)	Funding
Klotz et al. 2013[175] NR Canada	RCT, double blind, multicentre (30 sites) 12mo	Men with prostate cancer, >1yr of ADT indicated (treatment with an antiandrogen for up to 30d prior to initiation of LHRH was permitted)	ALN (oral 70 mg/ once weekly) n = 84	PL n = 102	ALN: 73.5±8.1 PL: 73.7±8.6	*Effectiveness:* Nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, SAEs	Abbot Laboratories Canada
Ryan et al. 2006[190] NR USA	RCT, double blind, multicentre (19 sites) 12mo	Men with prostate adenocarcinoma planning or initiated ADT in the previous 12mo, T-score >-2.5 at FN, TH or LS	ZOL (IV 4 mg/3mo) n = 61	PL n = 61	ZOL: median 73 (67-80) PL: 71 (64-77)	*Effectiveness:* Nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, SAEs	Novartis Pharma
Smith et al. 2003[193] NR USA	RCT, double blind, double dummy, multicentre (16 sites) 12mo	Men with prostate cancer, initiating ADT with a GnRH agonist with or without an antiandrogen	ZOL (4 mg/3mo) n = 55	PL n = 51	ZOL: 71.1±8.6 PL: 70.2±9.3	*Effectiveness:* Vertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, SAEs	Novartis Pharma

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **ADT**: androgen deprivation therapy; **AEs**: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **BL**: baseline; **BMD**: bone mineral density; **DEN**: denosumab; **DXA**: dual-energy x-ray absorptiometry; **FN**: femoral neck; **GnRH**: gonadotropin-releasing hormone; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **Inc**.: incorporated; **IV**: intravenous; **LHRH**: luteinising hormone-releasing hormone; **LS**: lumbar spine; **mo**: month/s; **PF**: proximal femur; **PL**: placebo; **PM**: postmenopausal; **RCT**: randomised controlled trial; **RLX**: raloxifene; **RIS**: risedronate; **SAEs**: serious adverse events; **TH**: total hip; **mg**: milligrams; **MOF**: major osteoporotic fracture; **NA**: not applicable; **ng/dL**: nanograms per decilitre; **NR**: not reported; **UK**: United Kingdom; **USA**: United States of America, **w**: week/s; **y**: year/s; **yo**: years old; **ZOL**: zoledronate.
Notes:
† Full details of the countries are available in ***Appendix B***.
[a] DEN 60 mg/6mo data extracted and analysed. DEN 14 mg/6mo and 100 mg/6mo excluded as this is not a reimbursed dosage of denosumab in Switzerland.
[b] Raloxifene 60 mg and 120 mg included in Morii et al. 2003,[181] Only 60 mg dosage (i.e. dosage of interest) reported in this table.
[c] RLX oral 120 mg/day data in all MORE trial publications were not extracted or analysed, as this is not a reimbursed dosage of raloxifene in Switzerland.
[d] BAZ oral 40 mg/day data were not extracted or analysed, as this is not a reimbursed dosage of bazedoxifene in Switzerland.
[e] Crossover data for BAZ (oral 40 mg/day) to BAZ (oral 20 mg/day) was not extracted or analysed, as no drug washout was undertaken between dosage periods and this may bias results.
[f] Data from the outcome presented at median timepoint of 73 months in Gnant 2019[167] were not utilised, only relevant safety data presented at 36 months were extracted from this publication.
[g] Data from the outcome presented at median timepoint of 63.3 months in Livi 2019[177] were not utilised, only relevant effectiveness/safety data presented to 24 months were extracted from this publication.

7.4.1.2 Non-randomised trials

Searches did not identify any non-randomised trials assessing AEs upon discontinuation of denosumab (i.e. rebound effect) to be included in the safety evaluation.

7.4.1.3 Single-arm trials

Study characteristics of the included single-arm trials are outlined in ***Table 7***. In total, three single-arm trials that assessed AEs upon discontinuation of denosumab were included in the safety evaluation.[165] [168] [189] In brief, two of the single-arm studies were conducted in postmenopausal women with osteoporosis[165] [189] and one was conducted in women with breast cancer receiving AAIT who have an increased fracture risk.[168] All three studies were single-centre; two (k = 2) were performed in Switzerland[168] [189] and one was performed in Italy (k = 1).[165] A total of 39 participants were evaluated during these studies, with a follow-up duration of approximately 12–24 months post-discontinuation of denosumab and participants evaluated at 18–132 months after receiving their first treatment with denosumab.

Table 7 Characteristics of included single-arm trials assessing AEs upon discontinuation of denosumab

Study Country	Study design	Population	Intervention Sample size (n) Mean age±SD	Duration	Outcome(s)	Funding
Popp et al. 2018[189] Switzerland	Retrospective analysis, single-arm, single-centre	Postmenopausal women; Swiss completers of both the FREEDOM and FREEDOM Extension who agreed to 1y off-treatment follow-up	DEN (60 mg/6mo) n = 9 78.9±1.9 y	12mo (post-discontinuation) 132mo (after first treatment)	*Safety:* AEs upon discontinuation of DEN	Amgen Inc.
Fassio et al. 2019[165] Italy	Prospective, single-arm, single-centre	Postmenopausal women with osteoporosis, without history of vertebral fracture, discontinued treatment due to achieving T-score >-2.5 at LS	DEN (dose not reported, administered every 6mo) n = 15 76.8±5.7 y	12mo (post-discontinuation) 96mo (after first treatment)	*Safety:* AEs upon discontinuation of DEN	Amgen Inc. and Merck Group
Gonzalez-Rodriguez et al. 2020[168] Switzerland	Case series, retrospective, single-centre	Early breast cancer, receiving AAIT	DEN (60 mg/6mo) n = 15 62.3±7.0 y	24.4mo (mean follow-up) 18–84mo (after first treatment)	*Safety:* AEs upon discontinuation of DEN	NA

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **AEs**: adverse events; **DEN**: denosumab; **LS**: lumbar spine; **mo**: months; **NA**: not applicable; **SD**: standard deviation; **y**: year/s.

7.4.2 Risk of bias

7.4.2.1 Randomised control trials

The quality of RCTs was evaluated using the Cochrane Risk of Bias 2.0 (RoB2).[221] RoB was assessed on a per outcome basis for all clinical effectiveness and safety outcomes. Fracture and safety outcomes, and BMD and BTM outcomes were then combined for the domains of missing outcome data (domain 3), measurement of the outcome (domain 4), and selective reporting (domain 5). The RoB graph and the RoB summary are reported in ***Figure 2*** and ***Table 8,*** respectively.

Randomisation process

For clinical effectiveness and safety outcomes, most studies provide adequate details of randomisation, typically consisting of computer-generated randomisation schedules or permuted block designs. Few studies reported concealment strategies; rather they stated that participants and study personnel were unaware of treatment allocation. Baseline differences between intervention groups were usually balanced.

Blinding of participants/personnel

The reporting of blinding was typically mixed. Some studies provided adequate detail on how blinding was ensured, this included the administration of identical interventional products and preparation of study prescriptions by an unrelated research pharmacy service. Other studies provided a limited description of blinding, only stating that the participants and those delivering the intervention were blinded but not how this blinding was ensured. Therefore, for outcomes involving judgement, such as the severity of AEs and relationship with the interventional product, awareness of the intervention may have introduced bias.

Missing outcome data

The majority of studies utilised intent-to-treat or modified intent-to-treat analyses, with few studies using per protocol or undefined analysis methods. Most studies that used a modified intent-to-treat analysis required participants to have received at least one to two doses of the interventional product and at least one post-baseline measurement for the outcome of interest. RCTs were classified as being at high RoB when missing data were ≥10% across treatment arms.

Missing outcome data was a critical bias concern. Missing outcome data was typically related to withdrawn consent, AEs, death or loss to follow-up. Common methods to account for missing outcome data included last-observation-carried-forward and multiple imputation. Very few studies performed

sensitivity analyses to evaluate the impact of missing data, therefore attrition within the included studies may have introduced bias.

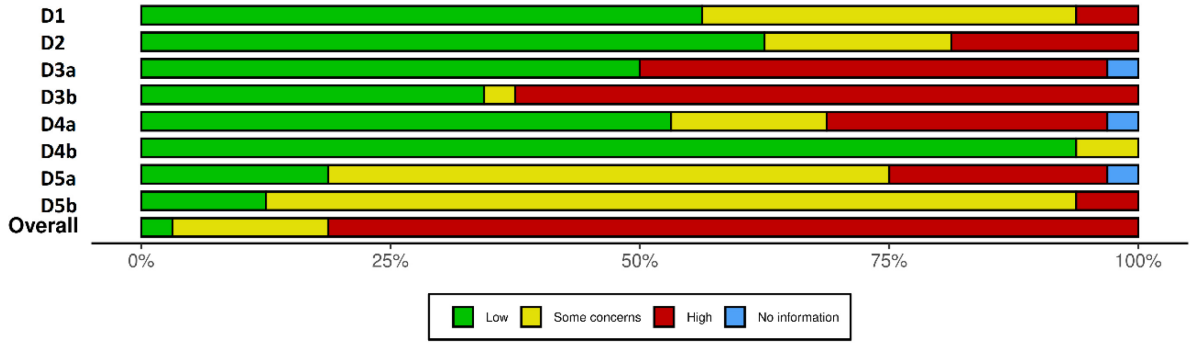
Measurement of the outcome

For clinical effectiveness, most outcomes were objectively measured (e.g. BMD and BTM) thus less likely to be biased. Across the majority of the studies reporting clinical effectiveness outcomes, the methods of measuring the outcomes were generally appropriate, with the exception of a few studies collecting fracture data via self-reporting without providing evidence of confirmatory scans being conducted to ensure the accuracy of such information. On the other hand, safety outcomes such as AEs are subjectively measured and more likely to be biased. Most studies provided little detail on how AE data were collected, measured and analysed, therefore it is likely that ascertainment of the outcome differed between intervention groups and the outcome may have been biased by knowledge of the intervention received.

Selective reporting

The majority of studies did not have a published protocol, therefore it was difficult to assess whether all outcomes and assessment timepoints were defined *a priori*. However, all studies were registered with a clinical trial database, so some primary effectiveness outcomes (usually fracture) and safety outcomes were able to be confirmed through published results. Across all outcomes, publication bias was typically of some concern due to lack of available information to confirm pre-specified outcomes.

Figure 2 Risk of bias graph for RCTs assessing clinical effectiveness and safety outcomes combined (n = 30 RCTs)



Abbreviations:
BMD: bone mineral density; **BTM**: bone turnover marker; **RCTs**: randomised controlled trials.
Notes:
D1: Randomisation process
D2: Blinding of participants/personnel
D3a: Missing outcome data (fracture/safety)
D3b: Missing outcome data (BMD/BTM)
D4a: Measurement of the outcome (fracture/safety)
D4b: Measurement of the outcome (BMD/BTM)
D5a: Selective reporting (fracture/safety)
D5b: Selective reporting (BMD/BTM)

Table 8 Risk of bias summary for clinical effectiveness and safety outcomes in the RCTs

Study	Randomisation process	Blinding of participants/ personnel	Missing outcome data (fracture/safety)[c]	Missing outcome data (BMD/BTM)[d]	Measurement of the outcome (fracture/safety)[c]	Measurement of the outcome (BMD/BTM)[d]	Selective reporting (fracture/safety)[c]	Selective reporting (BMD/BTM)[d]	Overall
FREEDOM[150 155 159 160]	-	+	X	X	+	+	+	-	X
Nakamura et al. 2012[182]	-	+	X	X	+	+	+	+	X
Miller et al. 2016[180]	-	-	+	X	+	+	-	-	X
Morii et al. 2003[181]	+	+	+	+	+	+	-	-	-
MORE[162 164]	-	+	X	X	+	+	-	-	X
NCT00205777[158 161 186 191 192]	+	-	X	X	+	+	-	-	X
Itabashi et al. 2011[179]	-	+	X	X	+	+	X	-	X
Miller et al. 2008[179]	-	+	+	+	X	-	-	-	X
TRIO[185]	+	X	+	+	X	+	-	-	X
Greenspan et al. 2015[171] ZEST	+	+	+	+	+	+	+	+	+
Palomba et al. 2005[188]	+	+	X	X	-	+	-	-	X
*Palomba et al. 2008[187]	+	X	X	X	-	+	-	-	X
HORIZON-PFT[152 174]	+	+	+	X	+	+	-	-	X
Ellis et al. 2008[163]	+	+	+	+	-	-	-	-	-
ABCSG-18[166 167]	+	+	X	X	+	+	+	+	X
Greenspan et al. 2007a[169] NCT00118508	+	+	?	+	?	+	?	-	-
Livi et al. 2019[177]	+	X	X	X	X	+	X	-	X
ADAMO Orwoll et al. 2012[183]	+	+	+	+	+	+	-	-	-
*ADAMO Langdahl et al. 2015[176]	+	X	+	X	X	+	-	-	X
Boonen et al. 2009[153]	-	-	+	+	+	+	-	-	-
[a]Boonen et al. 2012[154]	X	X	+	X	+	+	+	+	X
Orwoll et al. 2010[184]	-	+	X	X	+	+	X	X	X
NCT00089674[194]	-	+	X	X	+	+	-	-	X
Michaelson et al. 2007[178]	+	X	X	X	X	+	-	-	X
[b]Choo et al. 2013[157]	+	+	+	-	+	+	X	-	X
Greenspan et al. 2007b[170]	+	+	X	+	X	+	-	-	X
Israeli et al. 2007[172]	-	-	+	X	+	+	X	-	X
Bhoopalam et al. 2009[151]	-	-	+	+	X	+	+	X	X

Study	Randomisation process	Blinding of participants/ personnel	Missing outcome data (fracture/safety)[c]	Missing outcome data (BMD/BTM)[d]	Measurement of the outcome (fracture/safety)[c]	Measurement of the outcome (BMD/BTM)[d]	Selective reporting (fracture/safety)[c]	Selective reporting (BMD/BTM)[d]	Overall
Cheung et al. 2020[156]	+	+	+	+	X	+	-	-	X
Klotz et al. 2013[175]	X	-	X	X	X	+	-	-	X
Ryan et al. 2006[190]	-	+	+	X	-	+	X	-	X
Smith et al. 2003[193]	+	+	X	X	-	+	X	-	X

Abbreviations:
BMD: bone mineral density; **BTM**: bone turnover markers; **RCT**: randomised controlled trial.
Notes:
+ = low risk; **x** = high risk; **-** = some concerns; **?** = no information.
* This publication is an open-label extension phase of a core trial; therefore risk of bias was assessed separately to the core trial as it would have differing levels of bias due to unblinding.
[a] Boonen et al. 2012[154] was assessed to have varying levels of bias across outcomes for the randomisation process domain and deviation from intended interventions domain, therefore the higher risk of bias score was assigned for this domain.
[b] Choo et al. 2013[157] was assessed to have varying levels of bias across outcomes for the deviation from intended interventions domain, therefore the higher risk of bias score was assigned for this domain.
[c] Where varying risk of bias scores were assigned across the combined outcomes of safety and fracture, the higher risk of bias score was assigned for this domain.
[d] Where varying risk of bias scores were assigned across the combined outcomes of BMD and BTM, the higher risk of bias score was assigned for this domain.

7.4.2.2 Non-randomised trials

Searches did not identify any non-randomised trials assessing AEs upon discontinuation of denosumab (i.e. rebound effect) for inclusion in the safety evaluation. Therefore, the assessment of quality of evidence was not performed using Cochrane Risk of Bias in Nonrandomised Studies (ROBINS-I).[222]

7.4.2.3 Single-arm trials

The quality of single-arm studies for the safety evaluation of AEs upon discontinuation of denosumab (i.e. rebound effect) was appraised using the IHE quality appraisal checklist.[116] Three single-arm studies assessing discontinuation were included in the safety analysis.[165 168 189] For further details pertaining to this evaluation, see ***Table 9***. An overall score was allocated to each study by summing the total number of 'yes' answers for the 18 applicable signalling questions and allocating a final percentage. A score of ≤50% was considered a high level of bias, 51–≤75% considered a moderate level of bias, and 76–100% considered a low level of bias. Overall, the studies were considered to have a moderate[168 189] to low[165] level of bias.

Study design

All studies were conducted in a single centre,[165 168 189] and none of the studies indicated whether patients were recruited consecutively.[165 168 189] One study was prospective;[165] two studies were retrospective.[168 189]

Study population

All studies provided sufficient detail of their study populations, including detailed patient characteristics, and clearly stated the eligibility criteria for inclusion and exclusion.[165 168 189] To assess whether patients entered the study at a similar point in the disease, clear criteria on patients' BMD T-score and fracture history at entry were determined as a prerequisite to assess this domain. Through assessing BMD T-score and fracture history at study entry, two studies were deemed as including patients at a similar point in the disease;[165 189] one study did not include patients at a similar point in the disease.[168]

Intervention and co-intervention

For the domain of intervention, two studies clearly described their intervention of interest;[168 189] one study did not clearly describe its intervention of interest (i.e. no information on 60 mg or 120 mg denosumab dosage).[165] In studies investigating antiresorptive drugs, vitamin D and/or calcium were common co-interventions. Two studies described all co-interventions;[165 168] one study did not include any co-intervention.[189]

Outcome measure

All studies presented a low RoB when assessing whether outcome measures were established *a priori,* measured using appropriate objective methods, and measures made before and after the intervention.[165 168 189] It was unclear if outcome assessors were blinded to the intervention across all studies,[165 168 189] and this could induce detection bias by overestimating or underestimating the size of the effect when investigating AEs upon discontinuation of denosumab (i.e. rebound effect).[128]

Results and conclusions

All studies presented a low/moderate risk of bias for the results and conclusion domain.[165 168 189] In all studies, follow-up was deemed long enough for important outcomes to occur, all conclusions supported the results, and losses to follow were deemed not applicable.[165 168 189] Two studies adequately reported estimates of random variability for all outcomes;[165 168] one study only partially reported these estimates.[189] Additionally, as AEs upon discontinuation of denosumab (i.e. rebound effect) was the

primary outcome of the included studies, the AE signalling question of this domain was seemed not applicable for all included studies.

Competing interest and sources of support

Two studies adequately reported competing interests and sources of support;[165 168] one study reported competing interests but did not report if sources of support were received for the study.[189]

Table 9 Quality of single-arm studies for the safety evaluation of AEs upon discontinuation of denosumab (IHE Quality Appraisal Checklist for Case Series Studies)

	Popp 2018[189]	Fassio 2019[165]	Gonzalez-Rodriguez 2020[168]
Study objective			
1. Objective clearly stated	Y	Y	Y
Study design			
2. Prospective	N	Y	N
3. Multicentre	N	N	N
4. Consecutive recruitment	U	U	U
Study population			
5. Were patient characteristics included?	Y	Y	Y
6. Eligibility criteria clearly stated?	Y	Y	Y
7. Did patient enter the study at a similar point in the disease?	Y	Y	N
Intervention and co-intervention			
8. Was the intervention of interest clearly described?	Y	N	Y
9. Were additional interventions clearly described?	NA	Y	Y
Outcome measure			
10. Were relevant outcome measures established a priori?	Y	Y	Y
11. Were outcome assessors blinded to the intervention?	U	U	U
12. Were the outcomes measured using appropriate objective methods?	Y	Y	Y
13. Were the relevant outcome measures made before and after the intervention?	Y	Y	Y
Statistical analysis			
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y
Results and conclusions			
15. Was follow-up long enough for important events and outcomes to occur?	Y	Y	Y
16. Were losses to follow-up reported?	NA	NA	NA
17. Did study provide estimates of random variability in the data analysis of relevant outcomes?	P[&]	Y	Y
18. Were the AEs reported?	NA	NA	NA
19. Were the conclusions supported by results?	Y	Y	Y
Competing interest and sources of support			
20. Were both competing interests and sources of support for the study reported?	P*	Y	Y
Overall score			
	11/18 (61.11%)	**14/18 (77.78%)**	**13/18 (72.22%)**

Abbreviations:
AEs: adverse events; **IHE**: Institute for Health Economics; **N**: no; **NA**: not applicable; **P***: partial (either competing interest or source of funding reported but not both); **P[&]**: partial (not presented for all timepoints in tables/figures); **U**: unclear; **Y**: yes.
Notes:
Overall scores allocated by totalling the number of yes answers for the 18 applicable questions, with a corresponding percentage. Score of ≤50% = high level of bias, 51–≤75% = moderate level of bias, 76–100% = low level of bias.

7.4.3 Applicability of evidence to Switzerland

Applicability refers to the generalisability of the included clinical trials to the Swiss context. This involves comparing patient demographics and clinical characteristics of the RCTs to what occurs in Swiss practice. An overview of available information on demographics and clinical characteristics of the four populations of interest associated with denosumab and the other relevant comparators in Switzerland is shown in ***Table 10***.

7.4.3.1 Postmenopausal women with osteoporosis

Of the included trials, eight had centres in Europe, seven had centres in North America, five each had centres in Oceania and Asia, four had centres in South America, and two had centres in South Africa. No study was fully conducted in Switzerland; however, two trials had centres located in Switzerland (i.e. FREEDOM [number of centres not reported] and HORIZON-PFT [8 centres]). Of the trials conducted in Europe, the most commonly reported study locations included Belgium, Poland, Denmark, Spain, France, UK, Germany, Italy and Hungary. These countries are likely more applicable to the Swiss context owing to similarities in population, clinical practice (i.e. following European Medicines Agency guidelines)[107] and healthcare systems.

The majority of the trial populations were similar to the population of Swiss postmenopausal women with osteoporosis, with respect to ethnicity/race, age of women with osteoporosis, age at menopause, and BMD T-score (<-2.5) and/or fracture status. For example, participants were mainly Caucasian, age 65–75, with onset of menopause around the age of 50. Three trials were conducted in Japan in predominately Asian postmenopausal women with osteoporosis.[173 181 182] These specific trials are less representative of the Swiss population, as absolute values of BMD in Japanese women are apparently smaller than are those of Caucasian women, and a Japanese woman's T-score typically was applied rather than the WHO T-score obtained from Caucasian women.[182 223]

The included studies were generally consistent with Swiss practice. The dose, administration method and brands (when specified) of denosumab, alendronate, ibandronate, risedronate, zoledronate, bazedoxifene and raloxifene were the same as those listed on the Spezialitätenliste. Patients were generally assessed at academic hospitals, although it was not reported if patients were assessed by a general practitioner, endocrinologist, rheumatologist or oncologist.

7.4.3.2 Women with breast cancer receiving AAIT who have an increased fracture risk

Of the included trials, two had centres in North America, including USA and Canada, and two had study centres in Europe. No study was conducted or had centres located in Switzerland. Of the trials conducted in Europe, study locations included Austria, Sweden and Italy—countries likely more applicable to the Swiss context owing to similarities in population and healthcare systems.

The majority of the trial populations were similar to the population of Swiss women with breast cancer receiving AAIT, with respect to ethnicity/race, age, cancer and treatment status, and BMD T-score. For example, participants were predominately Caucasian, age above 50 years with hormone-receptor-positive breast cancer being treated with AAIT, with a BMD T-score >-2.0. Reflective of the Swiss population, the majority of women were more likely to have osteopenia rather than osteoporosis.

The included studies were generally consistent with Swiss practice. The dose, administration method, and brands (when specified) of denosumab, ibandronate and risedronate were the same as those listed on the Spezialitätenliste. However, it is important to note that the BMD T-score of women with breast cancer in the included trials may not make them eligible to receive certain treatments within the Swiss context, due to the BMD T-score limitations placed on each drug for reimbursement. Patients were generally assessed at academic hospitals, although it was not reported if patients were assessed by a general practitioner, endocrinologist, rheumatologist or oncologist.

7.4.3.3 Men with osteoporosis who have an increased fracture risk

Of the included trials, three had study centres in North America, three trials each had centres in Europe and Oceania, and one trial each had a centre in West Asia, Africa and South America. No study was fully conducted in Switzerland; however, one trial had eight centres located in Switzerland, including Aarau, Baden, Basel, Bern, Geneve, Lausanne, Sion and Zurich.[154] Of the remaining trials conducted in Europe, the most commonly reported study locations included Belgium, Denmark, France, Poland, Sweden, UK, Czech Republic and Hungary. These countries are likely more applicable to the Swiss context owing to similarities in population and healthcare systems.

The majority of the trial populations were similar to the population of Swiss men with osteoporosis, with respect to ethnicity/race and age. For example, participants were mainly Caucasian and age 60 years and above. Little is known about the BMD T-score of men with osteoporosis in Switzerland, therefore it is uncertain whether osteoporosis status in the included trials is comparable.

The included studies were typically consistent with Swiss practice. The dose, administration method, and brand (when specified) of denosumab, risedronate, alendronate and zoledronate were the same as those listed on the Spezialitätenliste. Patients were generally assessed at academic hospitals;

however, it was not reported if patients were assessed by a general practitioner, endocrinologist, rheumatologist or oncologist.

7.4.3.4 Men with prostate cancer on HAT who have an increased fracture risk

Of the included trials, nine had study centres in North America and one trial each had study centres in Europe and Australia. No study was reported to have centres located in Switzerland. The one trial conducted in Europe, had study centres located in Finland, Czech Republic and Poland. These countries are likely more applicable to the Swiss context owing to similarities in population and healthcare systems. However, the majority of trials were conducted in North America, making the comparability uncertain.

The trial population shared some similarities to the population of Swiss men with prostate cancer with respect to ethnicity/race, age, and cancer and treatment status. For example, the majority of participants were Caucasian, aged between 65 to 75 years, with nonmetastatic prostate cancer and receiving HAT. Little is known about the BMD T-score of men with prostate cancer in Switzerland, therefore it is uncertain whether osteoporosis/fracture risk status in the included trials is comparable.

The included studies were typically consistent with Swiss practice. The dose, administration method and brand (when specified) of denosumab, alendronate, risedronate and zoledronate were the same as those listed on the Spezialitätenliste. One study only provided participants a single 5 mg IV dose of zoledronate over two years,[156] when the typical dosing interval is once-yearly, thus these findings are likely not comparable to the Swiss context. Additionally, it is important to note that the BMD T-score of men with prostate cancer in the included trials may make them ineligible to receive certain treatments within the Swiss context, due to the BMD T-score limitations placed on each drug for reimbursement. Patients were generally assessed at academic hospitals; however, it was not reported if patients were assessed by a general practitioner, endocrinologist, rheumatologist or oncologist.

Table 10 Swiss demographics and clinical characteristics of the populations of interest associated with denosumab and other comparators

Parameter	Characteristics
Demographics	<u>General</u> • Average age of permanent residents (Swiss and foreigners, 2019):[224] 42.5 years <u>Postmenopausal women</u> • Mean age of women in Switzerland (Swiss and foreigners, 2019):[224] 41.3 years • Median age of menopause in Swiss women (12mo amenorrhea):[225] 53.2 years (25th percentile: 50.28 years) • Mean age of women with osteoporosis:[226] 75.2+/-3.1 years (1997–1999) (restricted to -2.5 T-score) • Ten-year probability (%) of osteoporotic fracture (with T-score of -2.5) in those without any CRFs:[227] 14.0% • Ten-year probability (%) of osteoporotic fracture (with T-score of -2.5) in those with previous fragility fracture:[227] 22.0% • Fracture rate (incidence per 1,000) in women (>50 years) attributable to osteoporosis in 2020: **Hip**: 2.30 per 1,000 **Vertebral**: 5.98 per 1,000 **Distal forearm**: 1.23 per 1,000 • Prior hip fracture (2010):[228] **50–54**: 0.0% **65–69**: 1.0% **85+**: 15.8% • Prior vertebral fracture (2010):[228] **50–54**: 0.2% **65–69**: 2.3% **85+**: 14.0% <u>Women with breast cancer</u> • Patients >50 years at time of diagnosis:[229] 78.3% (census data 1990–2013) • Swiss citizens (versus non-Swiss):[229] 85.0% • Cancer grade:[230] **Grade 1**: Luminal-A-like (32%) Luminal-B-Like (14%) HER2 enriched (1%), Triple negative (4%) **Grade 2**: Luminal-A-like (68%) Luminal-B-Like (42%) HER2 enriched (29%), Triple negative (23%) **Grade 3**: Luminal-A-like (0%) Luminal-B-Like (36%) HER2 enriched (64%), Triple negative (68%) **Grade X**: Luminal-A-like (0%) Luminal-B-Like (7%) HER2 enriched (6%), Triple negative (5%). • Histology:[230] **Ductal histology**: Luminal-A-like (78%) Luminal-B-Like (79%) HER2 enriched (92%), Triple negative (84%) **Lobular histology**: Luminal-A-like (15%) Luminal-B-Like (13%) HER2 enriched (1%), Triple negative (5%) **Other histology**: Luminal-A-like (7%) Luminal-B-Like (8%) HER2 enriched (7%), Triple negative (12%) • Comorbidities (Charlson Comorbidity Index) based on cancer type:[230] **Score 0–1**: Luminal-A-like (92%) Luminal-B-Like (91%) HER2 enriched (94%), Triple negative (95%) **Score 2+**: Luminal-A-like (8%) Luminal-B-Like (9%) HER2 enriched (6%), Triple negative (5%) <u>Women on AAIT with breast cancer</u> • White ethnicity:[231] 99.65% • Bone fracture in the last 10 years:[231] 5.94% • Prior hysterectomy:[231] 34.27%

	• Previous neo/adjuvant chemotherapy:[231] 26.92% • LS T-score:[231] -1.15 (-3.00 to 3.60) • TH T-score:[231] -0.6 (-3.00 to 1.20) <u>Men</u> • Mean age of men in Switzerland (Swiss and foreigners, 2019):[224] 40.3 years • Prior hip fracture (2010):[228] **50–54**: 0.1% **65–69**: 1.0% **85+**: 8.5% • Prior vertebral fracture:[228] **50–54**: 0.2% **65–69**: 2.2% **85+**: 6.0% • Ten-year probability (%) of osteoporotic fracture (with T-score of -2.5) in those without any CRFs:[227] 11.0% • Ten-year probability (%) of osteoporotic fracture (with T-score of -2.5) in those with previous fragility fracture:[227] 18.0% • Fracture rate (incidence per 1,000) in men (>50yrs) attributable to osteoporosis in 2020:[232] **Hip**: 0.73 per 1,000 **Vertebral**: 2.29 per 1,000 **Distal forearm**: 0.15 per 1,000 <u>Men with prostate cancer</u> • Mean age (of included Swiss patients who were 50+):[233] 63.9 (1992–2012 data) • Swiss citizens:[233] 86.5% (2012) • Individuals with prostate cancer in Zurich undergoing ADT:[234] 9.1% • Comorbidities in individuals underdoing ADT:[234] **Score 0**: 9.1%, **Score 1**: 10.7% **Score 2**: 7.2% • Comorbidities in men with prostate cancer (Charlson Comorbidity Index):[234] **Score 0**: 68.0% **Score 1**: 18.4% **Score 2**: 13.6% • Cancer stage:[234] **T1**: 27.4% **T2**: 51.1%, **T3**: 17.5% **T4**: 4.0%
Intervention	Denosumab (Prolia®) or denosumab (60 mg) (see ***Table 2***)
Comparator	• All bisphosphonates available in Switzerland (see ***Table 3***) o Alendronate: 70 mg tablet once weekly o Ibandronate: 150 mg tablet once monthly, 3 mg/3 mL infusion trimonthly o Risedronate: 35 mg tablet once weekly o Zoledronate: 4 mg/5 mL or 4 mg/100 mL (i.e. post-dilution) infusion monthly/trimonthly/annually, 5 mg/100 mL infusion annually • All SERMs available in Switzerland (see ***Table 3***) o Bazedoxifene: 20 mg tablet once daily o Raloxifene: 60 mg tablet once daily
Clinical characteristics	<u>Limited to:</u>[56] **Denosumab** Prolia®: Treatment of osteoporosis in postmenopausal women (reduction of **more than 2.5 SDs** in

	osteodensitometry or fracture). Concomitant treatment in women with breast cancer receiving AAIT and in men with prostate cancer on HAT if there is an increased risk of fractures. After completing AAIT or HAT, treatment with Prolia should also be stopped. Treatment to increase BMD in men with osteoporosis and an increased risk of fractures. **Alendronate** D3-Mepha®: Documented osteoporosis (reduction of **more than 2.5 SDs** in osteodensitometry or in the case of a fracture). Mepha® 70, Helvepharm®, Sandoz®: None **Ibandronate** Bondronat®: Treatment of patients with bone metastases in breast cancer. Bonviva®, Bonviva® IV, Helvepharm®, Mepha®, Mepha® IV, Sandoz®, Sandoz® IV, Spirig HC®, Spirig HC® IV: Documented osteoporosis (reduction of **more than 2.5 SDs** in osteodensitometry or in the case of a fracture). **Risedronate** Actonel®: Documented osteoporosis with a densitometrically recorded T-value, measured on the pelvis or LS, of **at least -2 SDs** of the osteoporosis or in the case of a fracture. Paget's disease of the bones. **Zoledronate** Osteo Sandoz® and Aclasta®: Documented osteoporosis in postmenopausal women and men and for the treatment of glucocorticoid-induced osteoporosis (in all cases with a reduction of **more than 2.5 SDs** or with a fracture) and in Paget's disease. Onco Labatec®, Accord® Onco, Fresenius® Onco, Teva® Onco, Onco Sandoz® and Zometa®: None **Bazedoxifene** Conbriza®: Treatment and prevention (with a densitometrically recorded T-value of **at least -1 SD**) of osteoporosis or fractures.[a] **Raloxifene** Evista®: Treatment and prevention (with a densitometrically recorded T-value of **at least -1 SD**) of osteoporosis or fractures.
Settings	Primary care setting or hospital General practitioner, endocrinologist, rheumatologist, oncologist

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **ADT**: androgen deprivation therapy; **BMD**: bone mineral density; **CRF**: clinical risk factor; **HAT**: hormone ablation therapy; **LS**: lumbar spine; **mg**: milligrams; **mL**: millilitres; **mo**: months; **SD**: standard deviation; **SERMs**: selective oestrogen receptor modulator; **TH**: total hip.
Notes:
[a] During the production of this report Conbriza® was removed from the Spezialitätenliste.

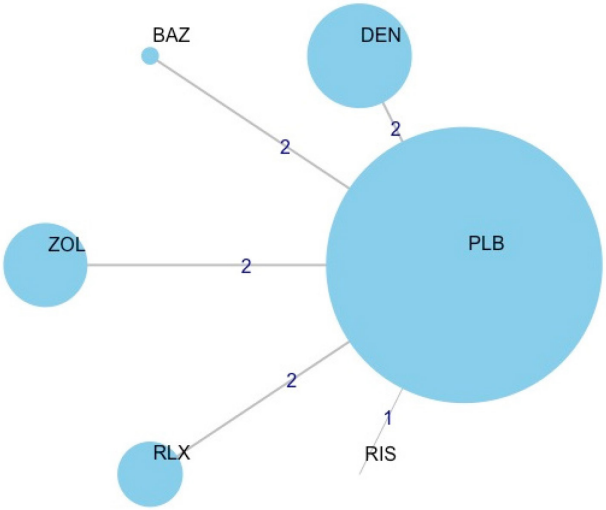
7.4.4 Findings, efficacy and effectiveness

7.4.4.1 Vertebral fractures

Postmenopausal women with osteoporosis

Vertebral fracture data in postmenopausal women with osteoporosis were available from nine two-arm RCTs, which compared six treatments (k = 10 publications; ***Figure 3***).[160 164 171 173 174 181 182 186-188] The included RCTs had a combined sample size of 19,710.[160 164 171 173 174 181 182 186-188]

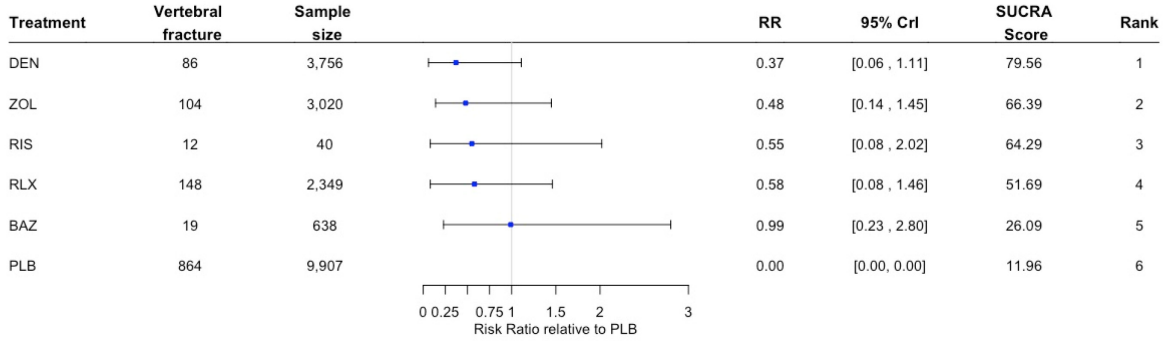
Figure 3 Network diagram for vertebral fractures in postmenopausal women with osteoporosis



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

The treatment effects of intervention in postmenopausal women with osteoporosis relative to placebo after 12 to 84 months are available in ***Figure 4***. None of the included treatments were statistically significant compared to placebo. Of these treatments, denosumab ranked as the most effective treatment at preventing vertebral fractures in postmenopausal women; bazedoxifene was the least effective active treatment.

Figure 4 Forest plot indicating the RR of vertebral fractures (relative to placebo) in postmenopausal women with osteoporosis after 12 to 84 months of treatment



Abbreviations:
BAZ: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability; can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a value of 0% suggests that the included treatment is the least effective treatment in the network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

All pairwise comparisons are available in ***Table 67*** (***Appendix C***). None of the pairwise comparisons were statistically significant. The network did not show significant evidence of statistical heterogeneity or local inconsistency (***Figure 99*** and ***Table 99, Appendix D***). Global inconsistency could not be calculated as the network was not closed-looped.

The results from the meta-regression indicated that denosumab (SUCRA: 68.55) and raloxifene (SUCRA: 63.66) were more effective at preventing vertebral fractures in younger postmenopausal women (approximately 50 to 70 years of age) than older postmenopausal women (approximately over 70 years of age). However, bazedoxifene (SUCRA: 47.07) and zoledronate (SUCRA: 50.31) were only moderately more effective at preventing vertebral fractures in younger postmenopausal women. Additionally, the analysis findings are diminished by a limited number of trials included (n = 9). Consequently, the results should be interpreted with caution. The complete results of the meta-regression are available in the HTA Supplement.

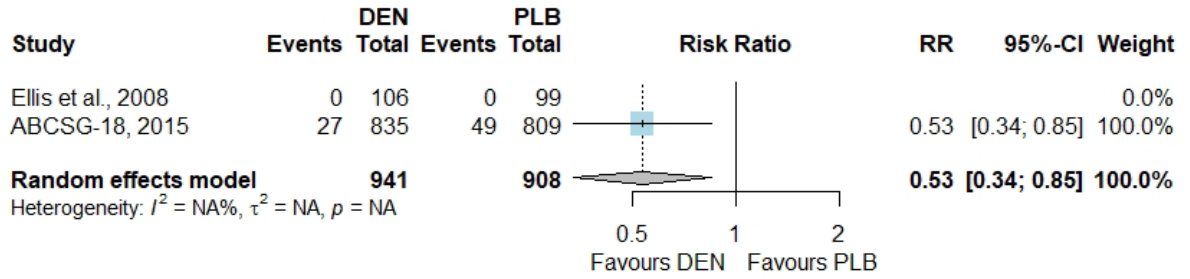
The sensitivity analysis indicated that the results differed from the combined population analysis, suggesting the results are likely impacted by imprecision; compared to placebo, denosumab significantly decreased the risk of vertebral fractures in a combined population by 69% (RR: 0.31; CrI: 0.10, 0.57). Furthermore, the sensitivity analysis indicated that results were not impacted by reporting bias. The impact of attrition bias and selection bias could not be determined as none of the RCTs that

explored the effect of denosumab on vertebral fractures in postmenopausal women presented a low risk of bias in either category. The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

Vertebral fracture data in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from two placebo-controlled RCTs.[163] [166] The total sample size was 1,849.[163] [166] A pairwise meta-analysis was conducted to compare denosumab to placebo (**Figure 5**).

Figure 5 Forest plot indicating the RR of vertebral fractures in women with breast cancer receiving AAIT who have an increased fracture risk after 24 to 36 months of treatment



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **CI**: confidence interval; **DEN**: denosumab; **NA**: not applicable; **PLB**: placebo; **RR**: risk ratio.

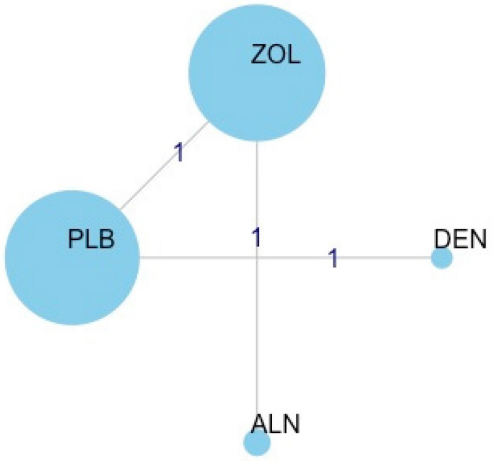
Overall, there was a statistically significant difference suggesting that denosumab can decrease the chance of vertebral fracture in women with breast cancer receiving AAIT at the end of the treatment regimen. Since the results of the Ellis et al. 2008 trial were not estimable,[163] the ABCSG-18 trial was weighted at 100.0% in the pairwise meta-analysis.[166] Therefore, it can be inferred that after 24 months of denosumab treatment a patient's incidence of fractures could decrease by 47%. Given that only a single trial had estimable results, heterogeneity and inconsistency for the pairwise meta-analysis could not be calculated.

The sensitivity analysis indicated that the results were not impacted by imprecision, selection bias, or reporting bias. The impact of attrition bias could not be determined as the results of the single RCT included in the sensitivity analysis were not estimable. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with osteoporosis who have an increased fracture risk

Vertebral fracture data on men with osteoporosis who have an increased fracture risk were extracted from three two-arm RCTs, which compared four treatments (***Figure 6***).[154 183 184] The total sample size of the network was 1,741.[154 183 184]

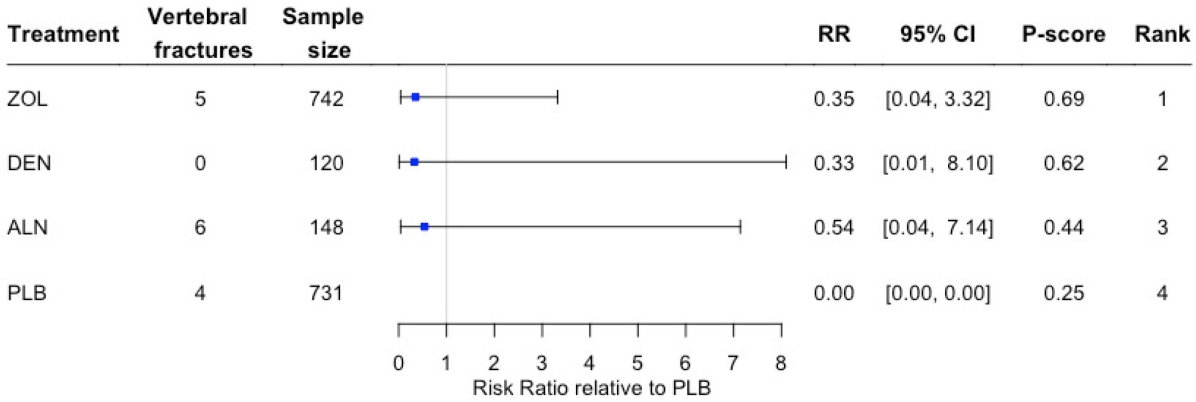
Figure 6 Network diagram for vertebral fractures in men with osteoporosis who have an increased fracture risk



Abbreviations:
ALN: alendronate; **DEN**: denosumab; **PLB**: placebo; **ZOL**: zoledronate.

The treatment effects in men with osteoporosis who have an increased fracture risk relative to placebo are detailed in ***Figure 7***. After a regimen of 12 to 24 months, none of the treatment effects were statistically significant when compared to placebo. Zoledronate was ranked as the most effective treatment at preventing vertebral fracture; alendronate was the least effective active treatment. Denosumab was ranked as the second most effective treatment.

Figure 7 Forest plot indicating the RR of vertebral fractures (relative to placebo) in men with osteoporosis who have increased fracture risk after 12 to 24 months of treatment



Abbreviations:
ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 68*** (***Appendix C*****).** None of the pairwise comparisons were statistically significant.

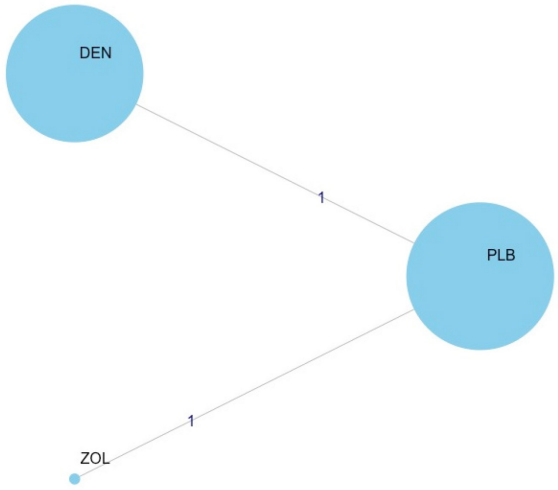
Statistical heterogeneity and global inconsistency could not be assessed. However, there appeared to be no local inconsistency between the direct and indirect comparisons.

The sensitivity analysis indicated that the results were impacted by imprecision. In an analysis of the total combined population, denosumab (compared to placebo) decreased the risk of vertebral fractures by 69% (RR: 0.31; CrI: 0.10, 0.57). Moreover, the sensitivity analysis indicated that the results were not impacted by selection bias or attrition bias. The impact of reporting bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on vertebral fractures in men with osteoporosis were categorised as presenting a low risk of bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

Vertebral fracture data in men with prostate cancer on HAT who have an increased fracture risk were extracted from two separate two-arm RCTs, which compared three treatments (***Figure 8***).[193 194] The total sample size of the network was 1,458.[193 194]

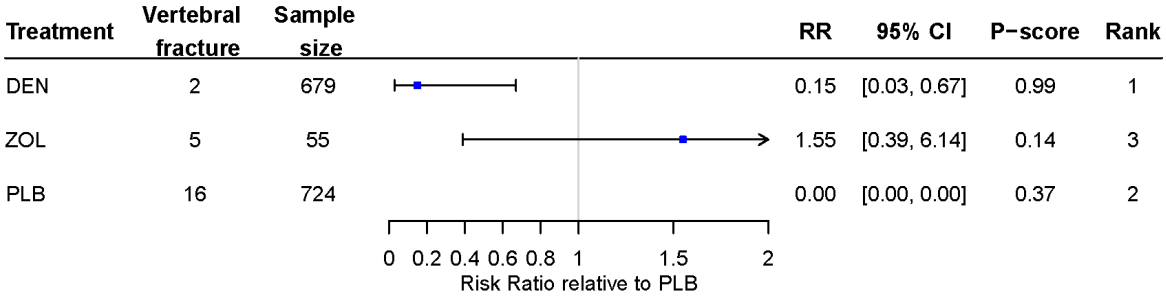
Figure 8 Network diagram for vertebral fractures in men with prostate cancer on HAT



Abbreviations:
DEN: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.

Treatment effects relative to placebo at 12 months in men with prostate cancer on HAT that have an increased fracture risk are detailed in ***Figure 9***. Statistically significant results at 12 months suggest that at the end of a treatment regimen, denosumab can decrease the risk of vertebral fractures by up to 85% in men with prostate cancer on HAT, relative to placebo. Additionally, denosumab was ranked as the most effective treatment at preventing vertebral fractures at 12 months in the treatment regimen; zoledronate was the least effective active treatment.

Figure 9 Forest plot indicating the RR of vertebral fractures (relative to placebo) in men with prostate cancer on HAT at 12 months



Abbreviations:
CI: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 69*** (***Appendix C***). Pairwise comparisons between denosumab and zoledronate were statistically significant, in favour of denosumab.

Statistical heterogeneity and global inconsistency could not be assessed. However, there appeared to be no local inconsistency between the direct and indirect comparisons.

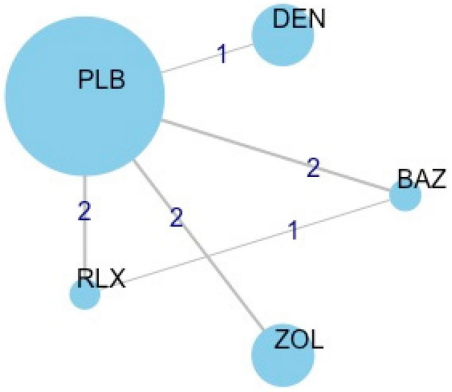
The sensitivity analysis indicated that the denosumab results were not impacted by imprecision. However, the sensitivity analysis could not estimate the impact of reporting bias, selection bias, or attrition bias as none of the RCTs that reported the effect of denosumab on vertebral fractures in men with prostate cancer on HAT presented a low risk of bias in the corresponding categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

7.4.4.2 Nonvertebral Fractures

Postmenopausal women with osteoporosis

Nonvertebral fracture data in postmenopausal women with osteoporosis were available from six two-arm RCTs and one three-arm RCT, which compared six treatments (***Figure 10***).[152 160 171 173 181 187 192] The included RCTs had a combined sample size of 21,873.[152 160 171 173 181 187 192]

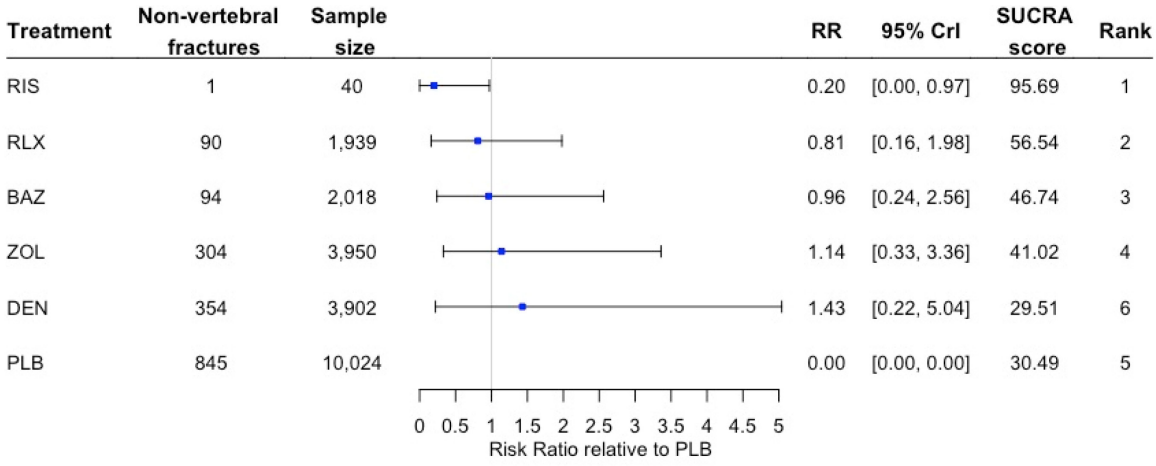
Figure 10 Network diagram for nonvertebral fractures in postmenopausal women with osteoporosis



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

The treatment effects relative to placebo after 12 to 36 months of treatment in postmenopausal women with osteoporosis, are available in ***Figure 11***. This network meta-analysis produced one statistically significant result, which suggested that, compared to placebo, risedronate can decrease the number of nonvertebral fractures experienced by postmenopausal women. Risedronate was ranked as the most effective treatment at preventing nonvertebral fractures in postmenopausal women; denosumab ranked as the least effective active treatment.

Figure 11 Forest plot indicating the RR of nonvertebral fractures (relative to placebo) in postmenopausal women with osteoporosis after 12 to 36 months



Abbreviations:
BAZ: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

All pairwise comparisons are available in ***Table 70*** (***Appendix C***). The pairwise comparison between risedronate and placebo was statistically significant.

The network showed a low to moderate level of statistical heterogeneity (***Table 101, Appendix D***). However, there was no significant evidence of local inconsistency (***Figure 100, Appendix D***) or global inconsistency (***Table 100, Appendix D***).

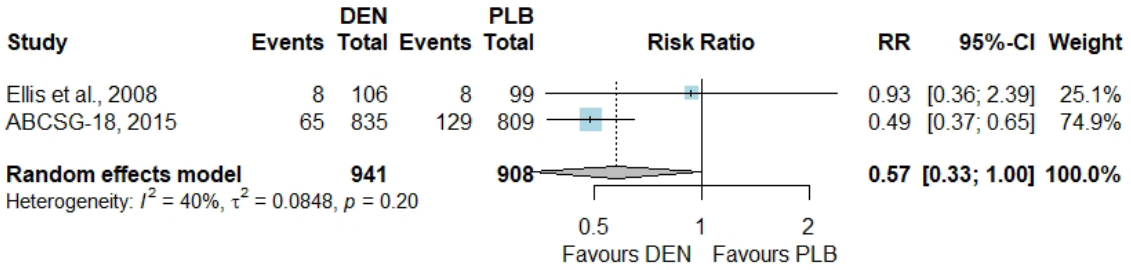
The results of the meta-regression suggested that denosumab (SUCRA: 46.83) was minimally more effective at preventing nonvertebral fracture in older postmenopausal women (approximately over 75 years of age) than younger postmenopausal women (approximately over 50 to 75 years of age). Contrastingly, raloxifene (SUCRA: 63.54) was more effective in younger postmenopausal women. Risedronate (SUCRA: 56.38) and zoledronate (SUCRA: 55.5) were only moderately more effective in younger postmenopausal women. These findings are diminished by a limited number of trials included (n = 6), and should be interpreted with caution. The complete results of the meta-regression are available in the HTA Supplement.

The sensitivity analysis indicated that the results were likely impacted by imprecision. The results indicated that denosumab (compared to placebo) may significantly decrease the risk of nonvertebral fractures in a combined population by 33% (RR: 0.67; CrI: 0.44, 0.95). In addition, the sensitivity analysis indicated that reporting bias did not impact the results. The impact of attrition bias and selection bias on the results could not be determined as none of the RCTs that reported the effect of denosumab on nonvertebral fractures in postmenopausal women presented a low risk of bias in either category. The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

Nonvertebral fracture data in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from two placebo-controlled RCTs.[163 166] The total sample size was 1,849.[163 166] A pairwise meta-analysis was conducted to compare denosumab to placebo (***Figure 12***).

Figure 12 Forest plot indicating the RR of nonvertebral fracture in women with breast cancer receiving AAIT who have an increased fracture risk after 24 to 36 months



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio.

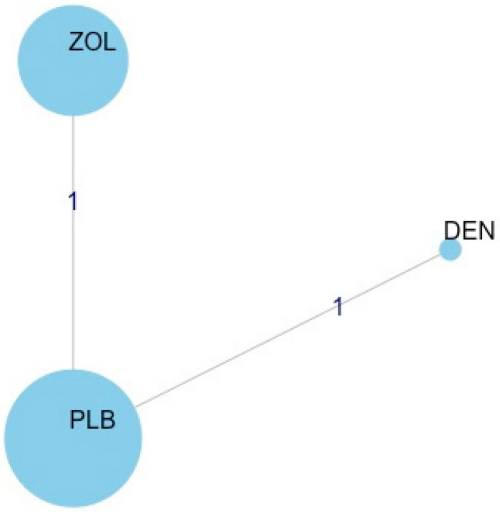
Overall, there was no statistically significant difference between denosumab and placebo at the end of the 24 to 36-month treatment regimen. There were low to moderate levels of heterogeneity and inconsistency in the analysis.

The sensitivity analysis indicated that the results were impacted by both imprecision and reporting bias. The analysis indicated that denosumab could significantly decrease the risk of nonvertebral fractures (compared to placebo) in a combined population by 33% (RR: 0.67; CrI: 0.44, 0.95). The sensitivity analysis also indicated that the results were not likely impacted by attrition bias or selection bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with osteoporosis who have an increased fracture risk

Nonvertebral fracture data for men with osteoporosis who have an increased fracture risk were extracted from two two-arm RCTs, which compared three treatments (***Figure 13***).[154 183] The total sample size of the network was 1,439.[154 183]

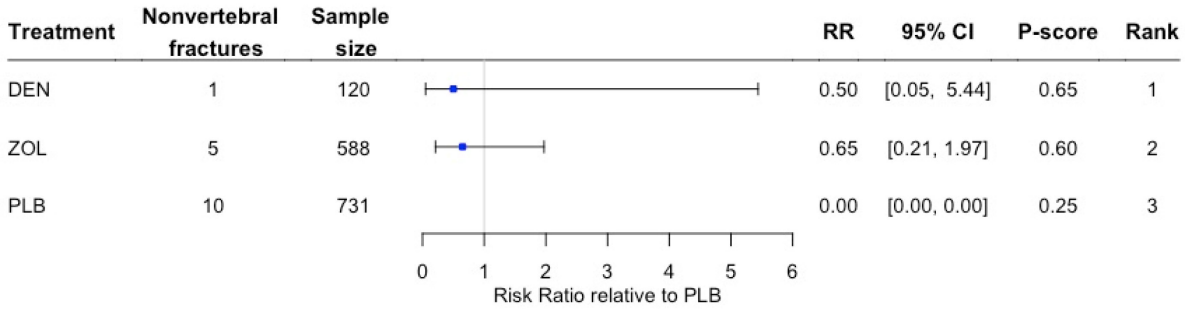
Figure 13 Network diagram for nonvertebral fractures in men with osteoporosis who have an increased fracture risk



Abbreviations:
DEN: denosumab; **PLB**: placebo; **ZOL**: zoledronate.

The treatment effects in men with an increased fracture risk relative to placebo are detailed in ***Figure 14***. None of the treatments were statistically significant compared to placebo after 12 to 24 months. Denosumab was ranked as the most effective treatment at preventing nonvertebral fracture, with zoledronate as the least effective active treatment.

Figure 14 Forest plot indicating the RR of nonvertebral fracture (relative to placebo) in men with osteoporosis who have an increased fracture risk after 12 to 24 months



Abbreviations:
CI: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 71*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

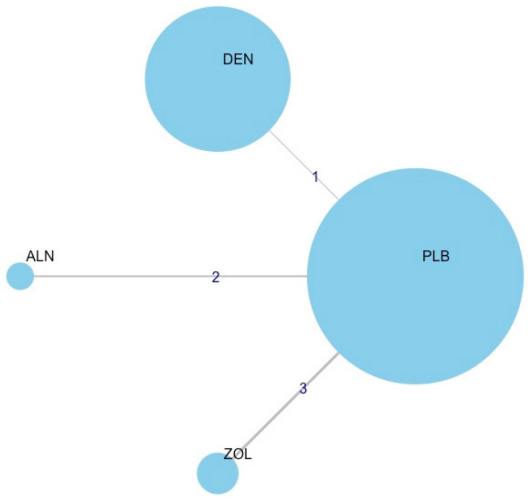
Statistical heterogeneity could not be assessed. There did not appear to be any local inconsistency between the direct and indirect comparisons (***Table 71***, ***Appendix C***).

The sensitivity analysis indicated that the results were likely impacted by imprecision. The results suggested that, compared to placebo, denosumab may significantly decrease the risk of nonvertebral fractures in a combined population by 33% (RR: 0.67; CrI: 0.44, 0.95). Additionally, the sensitivity analysis indicated that the results were likely not impacted by attrition bias or selection bias. The impact of reporting bias could not be determined as none of the RCTs that reported the effect of denosumab on nonvertebral fractures in men with osteoporosis presented a low risk of bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

Nonvertebral fracture data for men with prostate cancer on HAT who have an increased fracture risk were extracted from six two-arm RCTs, which compared four treatments (***Figure 15***).[156 170 172 175 190 194] The total sample size of the network was 2,182.[156 170 172 175 190 194]

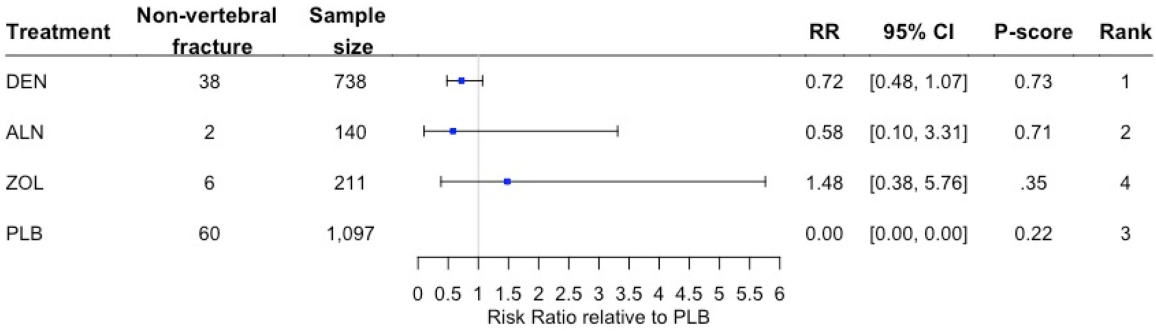
Figure 15 Network diagram for nonvertebral fractures in men with prostate cancer on HAT



Abbreviations:
ALN: alendronate; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.

The treatment effects relative to placebo after a treatment regimen that ranged from 12 to 36 months in men with prostate cancer on HAT who have an increased fracture risk, are detailed in ***Figure 16***. None of the treatments were statistically significant compared to placebo. Denosumab ranked as the most effective treatment at preventing nonvertebral fracture, with zoledronate the least effective active treatment.

Figure 16 Forest plot indicating the RR of nonvertebral fracture (relative to placebo) in men with prostate cancer on HAT after 12 to 36 months



Abbreviations:
ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available (***Table 72, Appendix C***). None of the pairwise comparisons were statistically significant.

The total statistical heterogeneity in the network was low (***Table 102, Appendix D***). Similarly, the heterogeneity between individual arms (i.e. placebo vs zoledronate and placebo vs alendronate) was low. There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 72, Appendix C***).

The sensitivity analysis indicated that the results were likely impacted by imprecision. The results indicated that denosumab could significantly decrease the risk of nonvertebral fractures (compared to placebo) in a combined population by 33% (RR: 0.67; CrI: 0.44, 0.95). The sensitivity analysis could not quantify the impact of reporting bias, selection bias, or attrition bias on the main analysis as none of the RCTs that reported the effect of denosumab on nonvertebral fractures in men with prostate cancer on HAT presented a low risk of bias in the corresponding categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

7.4.4.3 Health-related quality of life (HRQoL)

Postmenopausal women with osteoporosis

There was no available RCT evidence that met the PICO criteria for denosumab investigating HRQoL in postmenopausal women with osteoporosis (***Section 5***).

Women with breast cancer receiving AAIT who have an increased fracture risk

There was no available RCT evidence that met the PICO criteria for denosumab investigating HRQoL in women with breast cancer receiving AAIT who have an increased fracture risk (***Section 5***).

Men with osteoporosis who have an increased fracture risk

There was no available RCT evidence that met the PICO criteria for denosumab investigating HRQoL in men with osteoporosis who have an increased fracture risk (***Section 5***).

Men with prostate cancer on HAT who have an increased fracture risk

There was no available RCT evidence that met the PICO criteria for denosumab investigating HRQoL in men with prostate cancer on HAT who have an increased fracture risk (***Section 5***).

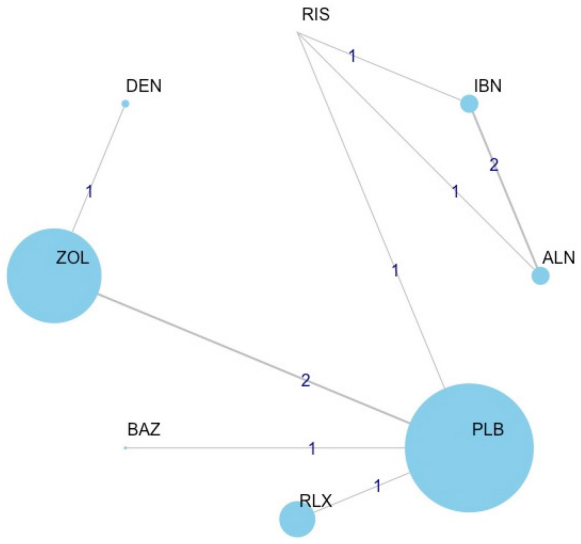
7.4.4.4 Bone mineral density (BMD)

Femoral neck (FN)

Postmenopausal women with osteoporosis

FN BMD data in postmenopausal women with osteoporosis were available from seven two-arm RCTs and one three-arm RCT, which compared eight treatments (***Figure 17***).[152 164 171 173 179 180 185 187] The included RCTs had a combined sample size of 12,128.[152 164 171 173 179 180 185 187]

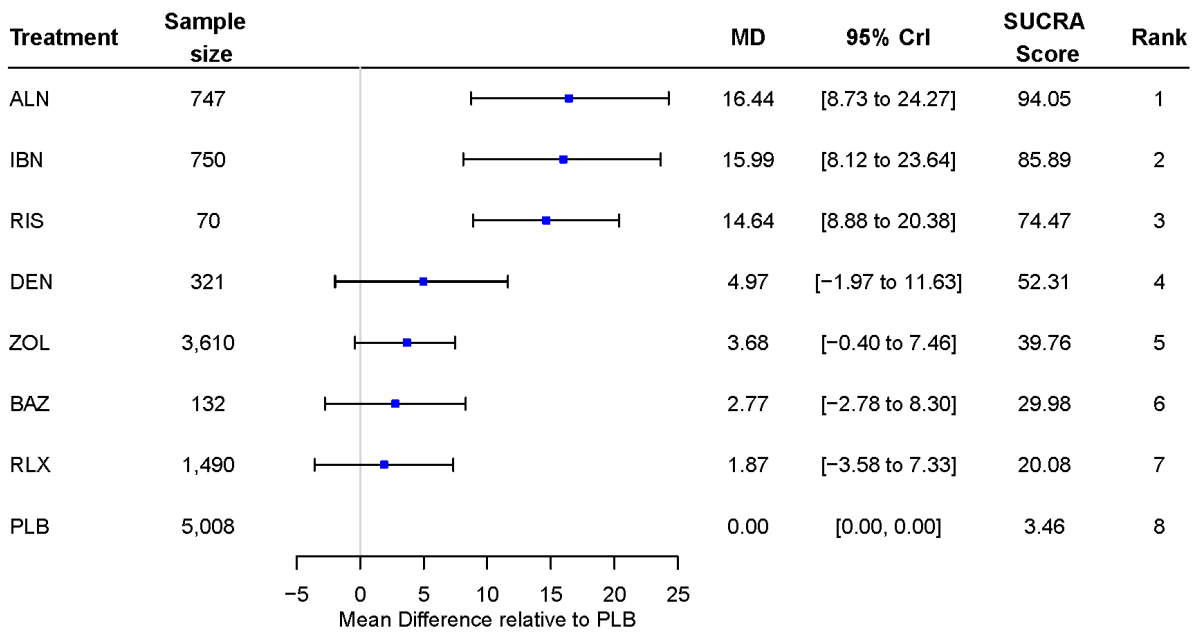
Figure 17 Network diagram for FN BMD in postmenopausal women with osteoporosis



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **FN**: femoral neck; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

The treatment effects relative to placebo in postmenopausal women with osteoporosis are reported in ***Figure 18***. Alendronate, ibandronate and risedronate were associated with statistically significant increases in FN BMD compared to placebo. Of these treatments, alendronate was ranked as the most effective treatment for increasing FN BMD in postmenopausal women; raloxifene was the least effective active treatment. Denosumab was ranked as the fourth most effective treatment.

Figure 18 Forest plot indicating the mean percentage difference in FN BMD (relative to placebo) in postmenopausal women with osteoporosis at 19 (± 1 SD) months



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **CrI**: credible interval; **DEN**: denosumab; **FN**: femoral neck; **IBN**: ibandronate; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.
All pairwise comparisons are available in ***Table 73*** (***Appendix C***). It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

Overall, there was low total heterogeneity within the network (***Table 104, Appendix D***). There was moderate heterogeneity in the network arm that compared ibandronate and alendronate. In contrast, the arm which compared placebo and zoledronate had low heterogeneity. There was no evidence of

local inconsistency (***Figure 101, Appendix D***) or global inconsistency (***Table 103, Appendix D***) in the network.

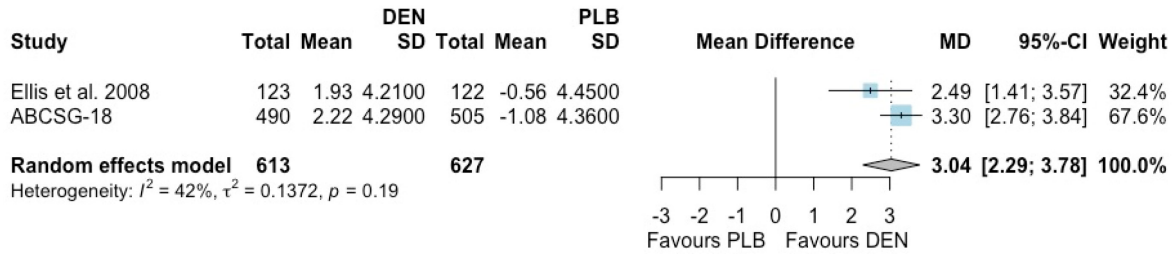
The meta-regression indicated that denosumab (SUCRA: 49.80) and raloxifene (SUCRA: 41.22) were more effective at increasing FN BMD in younger postmenopausal women (approximately 50 to 60 years of age) than in older postmenopausal women (approximately over 70 years of age). However, alendronate (SUCRA: 66.61) was more effective in older postmenopausal women (approximately 65 to 80 years of age) than in younger postmenopausal women; these findings are affected by a limited number of trials included (n = 8), and should be interpreted with caution. The complete results of the meta-regression are available in the HTA Supplement.

The sensitivity analysis indicated that the results were likely impacted by imprecision. The analysis indicated that compared to placebo, denosumab (MD: 3.03; CrI: 0.15, 5.88) and zoledronate (MD: 3.00, CrI: 0.61, 5.34) significantly increased FN BMD in a combined population. The impact of reporting bias, selection bias, or attrition bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on FN BMD in postmenopausal women were classified as presenting a low risk of bias in the respective categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

FN BMD data in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from two placebo-controlled RCTs.[163] [166] The total sample size was 1,240.[163] [166] A pairwise meta-analysis was conducted to compare denosumab to placebo (***Figure 19***).

Figure 19 Forest plot indicating the mean percentage difference in FN BMD (relative to placebo) in women with breast cancer receiving AAIT who have an increased fracture risk at 12 months



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **FN**: femoral neck; **MD**: mean difference; **PLB**: placebo; **SD**: standard deviation.

There was a statistically significant difference between denosumab and placebo, suggesting that a 12-month regimen of denosumab in women with breast cancer receiving AAIT could result in an average

improvement of 3.04% in BMD at the FN, compared to placebo. Determining if the statistically significant result translates to clinical significance is difficult, due to the absence of a verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

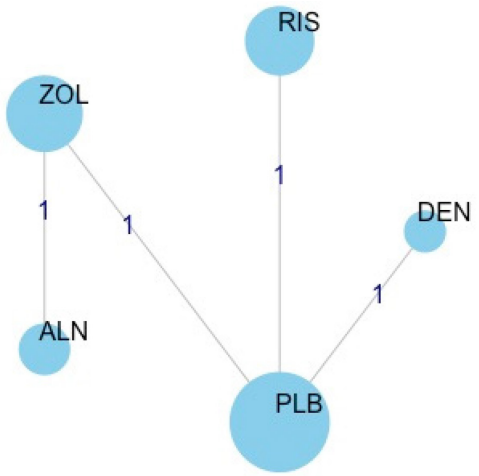
The analysis has a moderate level of heterogeneity and inconsistency.

The sensitivity analysis indicated that the results were not impacted by imprecision, attrition bias, selection bias, or reporting bias.

Men with osteoporosis who have an increased fracture risk

FN BMD data on men with osteoporosis who have an increased fracture risk were extracted from four two-arm RCTs, which compared five treatments (***Figure 20***).[153 154 176 184] The total sample size of the network was 896.[153 154 176 184]

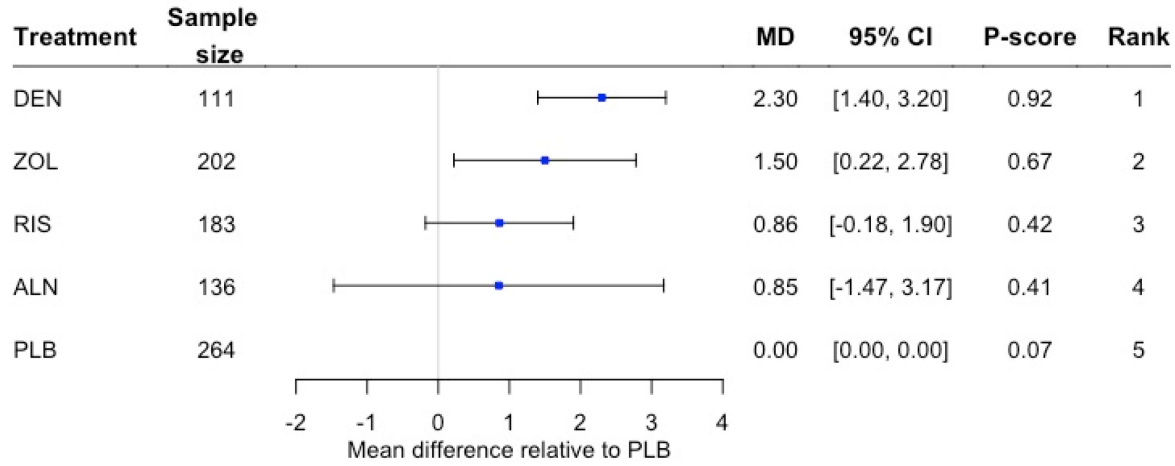
Figure 20 Network diagram for FN BMD in men with osteoporosis who have an increased fracture risk



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **DEN**: denosumab; **FN**: femoral neck; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with an increased fracture risk are detailed in ***Figure 21***. The analysis indicated that after 12 months of treatment with denosumab, the BMD of a male patient with osteoporosis could improve by 2.30%, compared to placebo. Denosumab and zoledronate were statistically significant compared to placebo. Denosumab was ranked as the most effective treatment in the network at increasing FN BMD; alendronate was the least effective active treatment.

Figure 21 Forest plot indicating the mean percentage difference in FN BMD (relative to placebo) in men with osteoporosis who have an increased fracture risk at 12 months



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **FN**: femoral neck; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available (***Table 74***, ***Appendix C***). It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

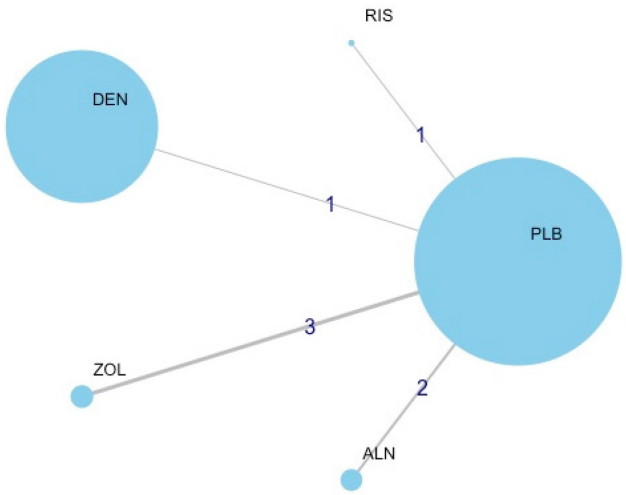
Statistical heterogeneity could not be assessed. There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 74***, ***Appendix C***).

The sensitivity analysis indicated that the results were likely impacted by imprecision. The analysis indicated that in a combined population, alendronate (compared to placebo), significantly increased FN BMD by 4% (MD: 4.04; CrI: 0.64, 7.50). However, the sensitivity analysis also indicated that when compared to placebo, ibandronate (MD: 4.36; CrI: -0.76, 9.55) does not significantly change FN BMD in a combined population. The sensitivity analysis also indicated that the results were not impacted by selection bias. The impact of reporting bias or attrition bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on FN BMD in men with osteoporosis presented a low risk of bias in either category. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

FN BMD data for men with prostate cancer on HAT who have an increased fracture risk were extracted from seven two-arm RCTs, which compared five treatments (***Figure 22***).[157 170 175 178 190 193 194] The total sample size of the network was 1,889.[157 170 175 178 190 193 194]

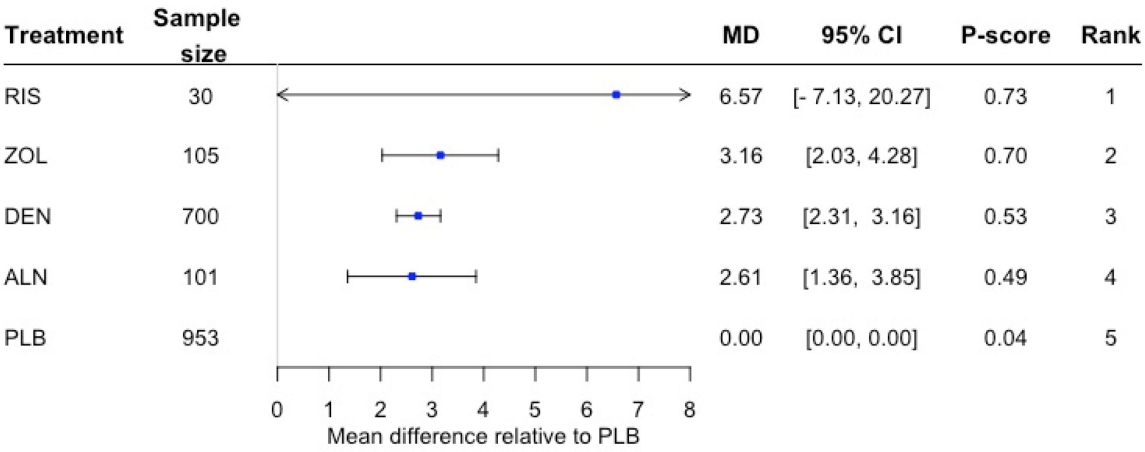
Figure 22 Network diagram for FN BMD in men with prostate cancer on HAT



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **DEN**: denosumab; **FN**: femoral neck; **HAT**: hormone ablation therapy; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with prostate cancer on HAT who have an increased fracture risk, are detailed in ***Figure 23***. The results suggest that after 12 months of treatment with denosumab, BMD measured at the FN may improve by 2.73%, compared to placebo. Additionally, zoledronate, denosumab and alendronate were statistically significant compared to placebo. Risedronate ranked as the most effective treatment at increasing FN BMD; alendronate was the least effective active treatment. Denosumab ranked as the third most effective treatment.

Figure 23 Forest plot indicating the mean percentage difference in FN BMD (relative to placebo) in men with prostate cancer on HAT at 12 months



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **FN**: femoral neck; **HAT**: hormone ablation therapy; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available (***Table 75***, ***Appendix C***). It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

There was low total within-design heterogeneity in the network (***Table 105, Appendix D***). The heterogeneity between individual arms (i.e. placebo vs zoledronate and placebo vs alendronate) was also low. There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 75, Appendix C***).

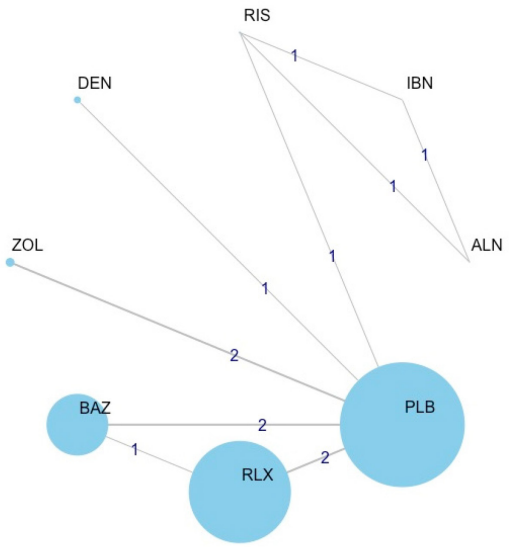
The sensitivity analysis indicated that the results were likely impacted by imprecision. The results indicated that risedronate (compared to placebo) increased FN BMD by 5.47% (MD: 5.47; CrI: 1.83, 9.33) in a combined population. The sensitivity analysis could not quantify the impact of reporting bias, selection bias, or attrition bias on the main analysis as none of the RCTs that reported the effect of denosumab on FN BMD in men with prostate cancer presented a low risk of bias in the corresponding categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

Lumbar spine (LS)

Postmenopausal women with osteoporosis

LS BMD data in postmenopausal women with osteoporosis were available from six two-arm RCTs and two three-arm RCTs, which compared eight treatments (***Figure 24***).[152 160 164 171 173 185 187 192] The included RCTs had a combined sample size of 10,092.[152 160 164 171 173 185 187 192]

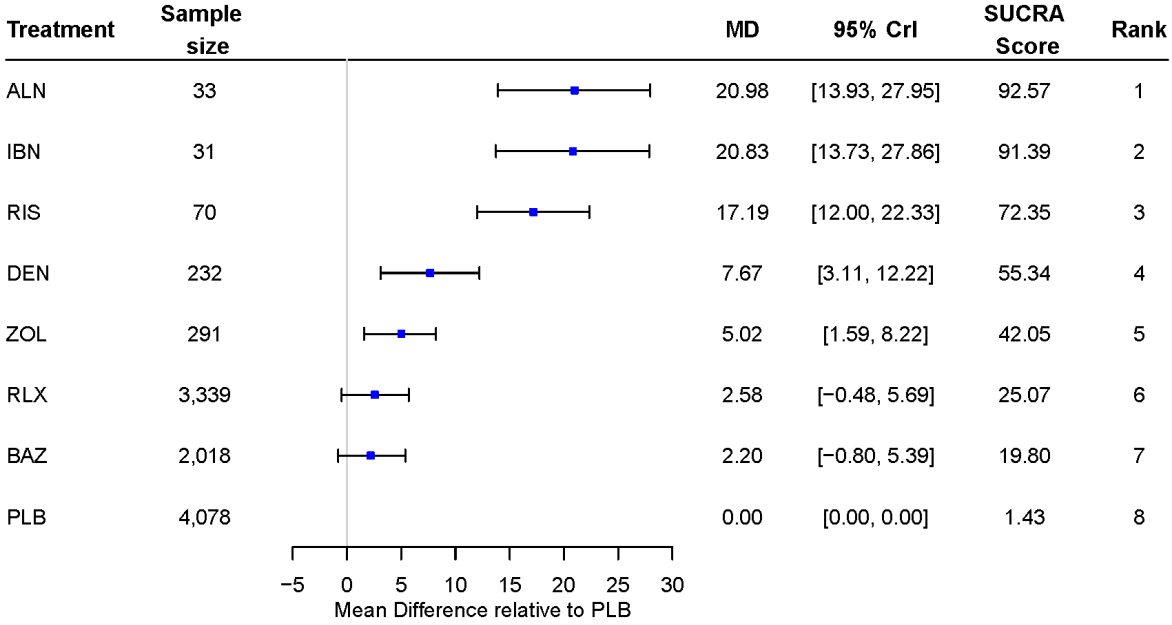
Figure 24 Network diagram for LS BMD in postmenopausal women with osteoporosis



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **IBN**: ibandronate; **LS**: lumbar spine; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

The treatment effects relative to placebo in postmenopausal women with osteoporosis, are available in ***Figure 25***. The findings indicate that after an average of 20 (± 1 SD) months of treatment, denosumab can improve BMD at the LS of a postmenopausal women by 7.67%, compared to placebo. Alendronate, ibandronate, risedronate, denosumab and zoledronate were statistically significant compared to placebo. Of these treatments, alendronate ranked as the most effective at increasing LS BMD in postmenopausal women and bazedoxifene was the least effective active treatment.

Figure 25 Forest plot indicating the mean percentage difference in LS BMD (relative to placebo) in postmenopausal women with osteoporosis 20 (± 1 SD) months



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **CrI**: credible interval; **DEN**: denosumab; **IBN**: ibandronate; **LS**: lumbar spine; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

All pairwise comparisons are available (***Table 76***, ***Appendix C***). The pairwise comparisons presented a statistically significant increase in BMD at the LS in favour of denosumab relative to alendronate, ibandronate and risedronate. It is difficult to determine if any of the statistically significant results are also clinically significant as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

The entire network showed substantial to considerable total heterogeneity (***Table 107***, ***Appendix D***). The network arm comparing placebo to bazedoxifene had considerable heterogeneity; the arm that compared placebo to zoledronate displayed substantial heterogeneity; the arm that compared placebo to denosumab presented low heterogeneity. There was no evidence of local inconsistency (***Figure 102, Appendix D***) or global inconsistency (***Table 106, Appendix D***) in the network.

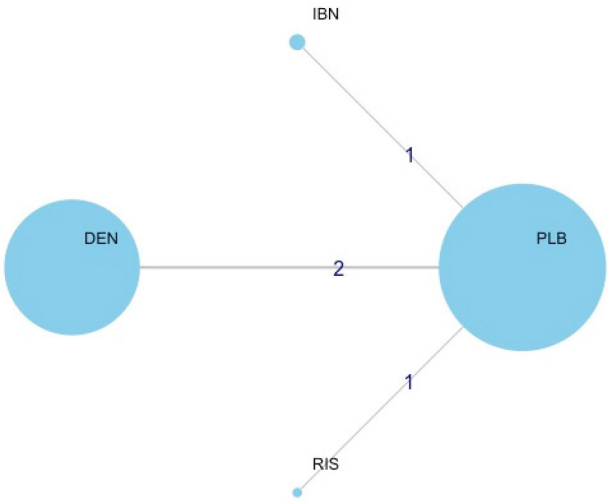
The meta-regression indicated that denosumab (SUCRA: 45.24) was more effective at increasing LS BMD in older postmenopausal women (approximately over 70 years of age) than in younger postmenopausal women (approximately 50 to 70 years of age). However, risedronate (SUCRA: 58.52) was most effective in younger postmenopausal women (approximately 50 to 60 years of age) and least effective in older postmenopausal women. These findings are diminished by a limited number of trials included (n = 8), and should be interpreted with caution. The complete results of the meta-regression are available in the HTA Supplement.

The sensitivity analysis indicated that the results were not impacted by imprecision. The impact of reporting bias, selection bias, or attrition bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on LS BMD in postmenopausal women presented a low risk of bias in the respective categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

LS BMD data in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from four two-arm RCTs, which compared four treatments (***Figure 26***).[163 166 169 177] The total sample size of the network was 1,462.[163 166 169 177]

Figure 26 Network diagram for LS BMD in women with breast cancer receiving AAIT who have an increased fracture risk

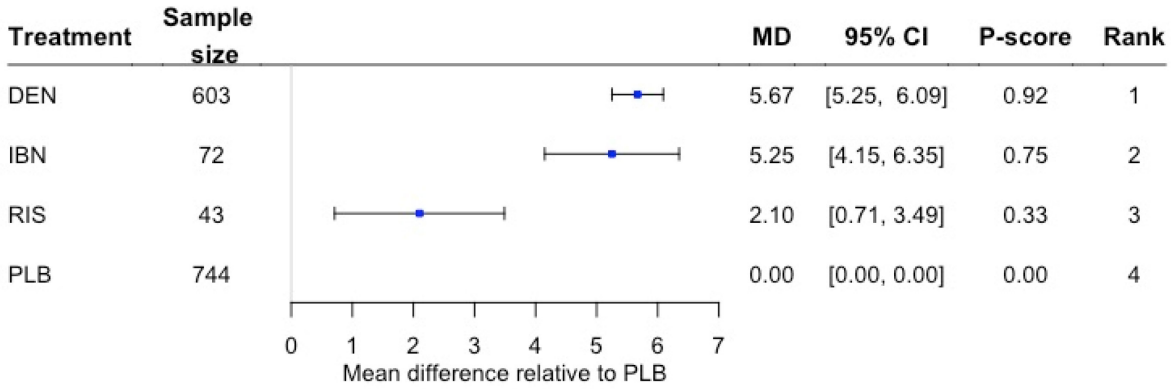


Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **LS**: lumbar spine; **MD**: mean difference; **PLB**: placebo.

The treatment effects in women with breast cancer receiving AAIT who have an increased fracture risk relative to placebo are detailed in ***Figure 27***. The analysis suggested that after 12 months of treatment

with denosumab, the BMD at LS in women with breast cancer receiving AAIT could improve by 5.67%, compared to placebo. All treatments were statistically significant compared to placebo. Denosumab was ranked as the most effective treatment at increasing BMD at the LS. Risedronate was the least effective active treatment.

Figure 27 Forest plot indicating the mean percentage difference in LS BMD (relative to placebo) in women with breast cancer receiving AAIT who have an increased fracture risk at 12 months



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **LS**: lumbar spine; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available (***Table 77***, ***Appendix C***). A pairwise comparison between risedronate and denosumab suggested a statistically significant improvement in BMD at LS in favour of denosumab. It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

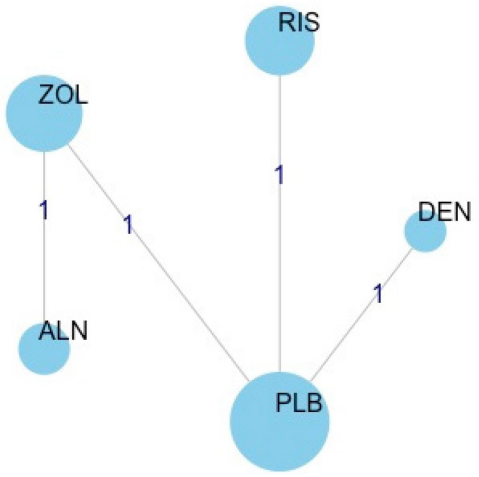
The total within-design heterogeneity in the network was low. The heterogeneity between individual arms (i.e. placebo vs denosumab) was also low (***Table 108, Appendix D***). There was no evidence of local inconsistency in the network (***Table 77, Appendix C***).

The sensitivity analysis indicated that the results were not impacted by imprecision, attrition bias, selection bias, or reporting bias.

Men with osteoporosis who have an increased fracture risk

LS BMD data in men with osteoporosis who have an increased fracture risk were extracted from four two-arm RCTs, which compared five treatments (***Figure 28***).[153 154 176 184] The total sample size of the network was 894.[153 154 176 184]

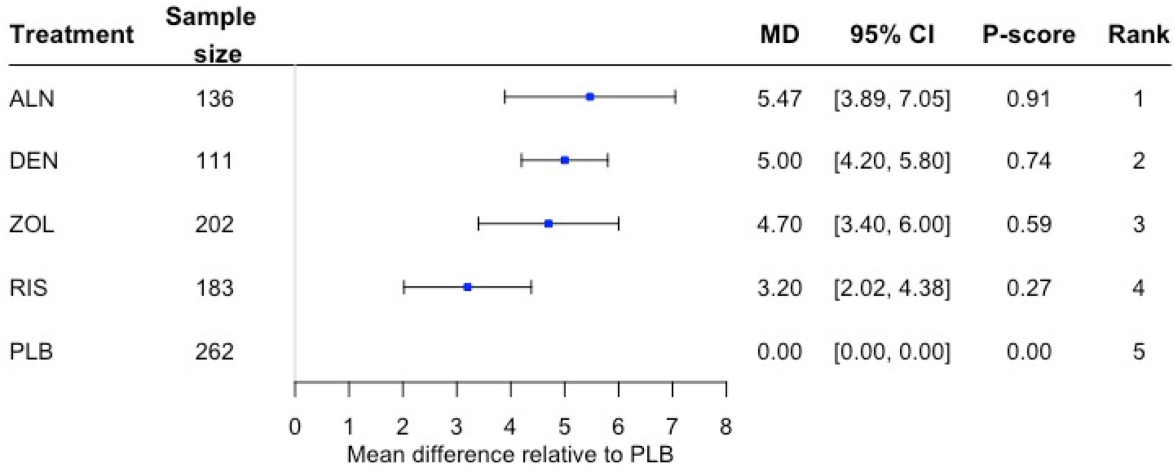
Figure 28 Network diagram for LS BMD in men with osteoporosis who have an increased fracture risk



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **DEN**: denosumab; **LS**: lumbar spine; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with an increased fracture risk are detailed in ***Figure 29***. After 12 months of denosumab treatment, BMD measured at LS in men with osteoporosis improved by 5.00% relative to placebo. All treatments were statistically significant compared to placebo. Alendronate was ranked as the most effective treatment at increasing LS BMD, with risedronate as the least effective active treatment. Denosumab was ranked as the second most effective treatment.

Figure 29 Forest plot indicating the mean percentage difference in LS BMD (relative to placebo) in men with osteoporosis who have an increased fracture risk at 12 months



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **LS**: lumbar spine; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 78***, ***Appendix C***. Statistically significant increases in BMD measured at LS after 12 months of treatment favoured denosumab, relative to risedronate. It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

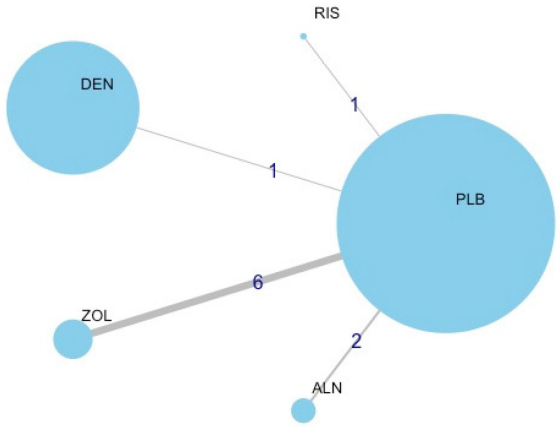
Statistical heterogeneity could not be assessed. In addition, no local inconsistency between the direct and indirect comparisons was detected.

The sensitivity analysis indicated that the results were not impacted by imprecision or selection bias. The impact of reporting bias or attrition bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on LS BMD in men with osteoporosis presented a low risk of bias in either category. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

LS BMD data for men with prostate cancer on HAT who have an increased fracture risk were extracted from ten two-arm RCTs, which compared five treatments (***Figure 30***).[151 156 157 170 172 175 178 190 193 194] The total sample size of the network was 2,315.[151 156 157 170 172 175 178 190 193 194]

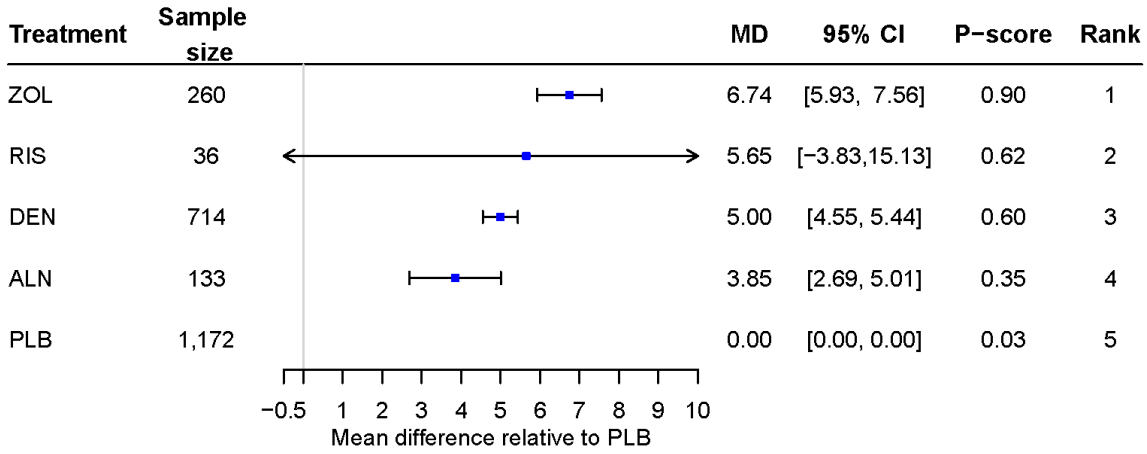
Figure 30 Network diagram for LS BMD in men with prostate cancer on HAT



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **DEN**: denosumab; **HAT**: hormone ablation therapy; **LS**: lumbar spine; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with prostate cancer on HAT who have an increased fracture risk, are detailed in ***Figure 31***. At 12 months of treatment, denosumab can improve BMD measured at LS in men with prostate cancer on HAT by 5.00%. Alendronate, denosumab and zoledronate were statistically significant compared to placebo. Zoledronate was ranked as the most effective treatment at increasing LS BMD, with alendronate the least effective active treatment. Denosumab was ranked as the third most effective treatment at increasing LS BMD.

Figure 31 Forest plot indicating the mean percentage difference in LS BMD (relative to placebo) in men with prostate cancer on HAT at 12 months



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **LS**: lumbar spine; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 79***, ***Appendix C***. It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

The total within-design heterogeneity in the network was low. The heterogeneity between individual arms (i.e. placebo vs alendronate and placebo vs zoledronate) was also low (***Table 109***, ***Appendix D***). There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 79, Appendix C***).

A funnel plot assessing publication bias in the NMA of LS BMD in men with prostate cancer on HAT who have an increased fracture risk is presented in ***Figure 108*** (***Appendix E***), showing no statistical evidence of asymmetry.

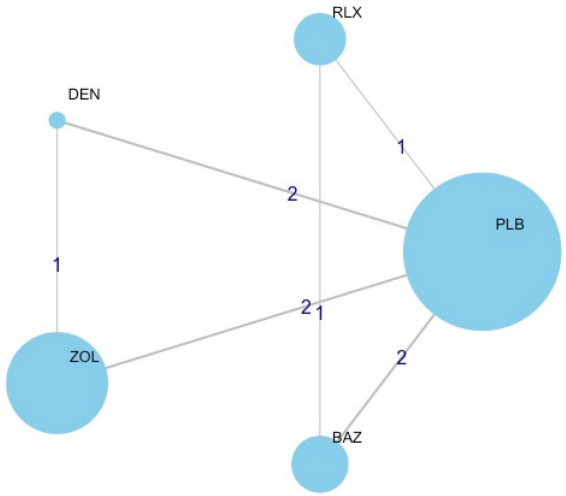
The sensitivity analysis indicated that the results were likely impacted by imprecision. The results indicated that risedronate (compared to placebo) increased LS BMD by 5.6% (MD: 5.60; CrI: 2.73, 8.66) in a combined population. The sensitivity analysis could not quantify the impact of reporting bias, selection bias, or attrition bias on the main analysis as none of the RCTs that reported the effect of denosumab on LS BMD in men with prostate cancer on HAT in the respective categories presented a low risk of bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Total hip (TH)

Postmenopausal women with osteoporosis

TH BMD data in postmenopausal women with osteoporosis were available from six two-arm RCTs and one three-arm RCT, which compared five treatments (***Figure 32***).[152 160 171 173 180 182 192] The included RCTs had a combined sample size of 13,666.[152 160 171 173 180 182 192]

Figure 32 Network diagram for TH BMD in postmenopausal women with osteoporosis

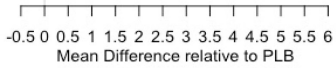


Abbreviations:
BAZ: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **TH**: total hip; **ZOL**: zoledronate.

The treatment effects relative to placebo in postmenopausal women with osteoporosis are available in ***Figure 33***. After 19 (± 1 SD) months, denosumab can increase BMD measured at TH by 4.55%. Both denosumab and zoledronate were statistically significant compared to placebo. Denosumab was ranked as the most effective treatment at increasing TH BMD in postmenopausal women and bazedoxifene was the least effective active treatment.

Figure 33 Forest plot indicating the mean percentage difference in TH BMD (relative to placebo) in postmenopausal women with osteoporosis at 19 (± 1 SD) months

Treatment	Sample size	MD	95% CrI	SUCRA Score	Rank
DEN	607	4.55	[3.08, 6.05]	89.01	1
ZOL	3,604	4.31	[2.60, 5.67]	83.70	2
RLX	1,849	1.87	[-0.20, 4.05]	44.32	3
BAZ	2,018	1.48	[-0.08, 3.25]	31.46	4
PLB	5,588	0.00	[0.00, 0.00]	1.52	5



Abbreviations:
BAZ: bazedoxifene; **BMD**: bone mineral density; **CrI**: credible interval; **DEN**: denosumab; **MD**: mean difference; **PLB**: placebo; **RLX**: raloxifene; **SD**: standard deviation; **SUCRA**: surface under the cumulative ranking curve; **TH**: total hip; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

All pairwise comparisons are available (***Table 80***, ***Appendix C***). It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

There was moderate total heterogeneity within the network (***Table 111, Appendix D***). Two individual network arms that compared placebo to denosumab and placebo to bazedoxifene, presented moderate to substantial heterogeneity. The network arm comparing placebo and zoledronate showed low heterogeneity. There was no evidence of local inconsistency (***Figure 103, Appendix D***) or global inconsistency (***Table 110, Appendix D***).

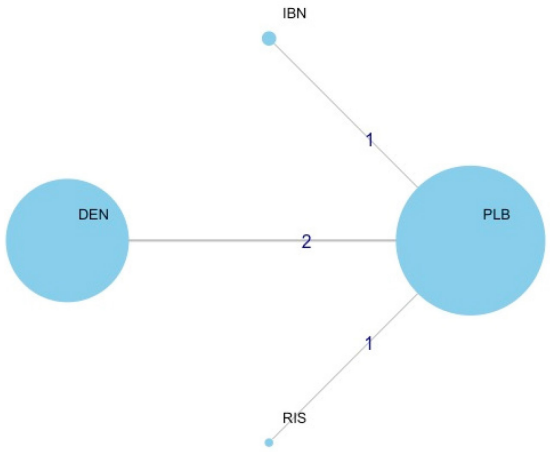
The meta-regression indicated that denosumab (SUCRA: 41.74) was more effective at increasing TH BMD in older postmenopausal women (approximately over 70 years of age) than younger postmenopausal women (approximately 65 to 70 years of age). However, bazedoxifene (SUCRA: 57.48) was less effective in older postmenopausal women than younger postmenopausal women. These findings are diminished by a limited number of trials included (n = 7), and should be interpreted with caution. The complete results of the meta-regression are available in the HTA Supplement.

The sensitivity analysis indicated that the combined population was less precise than the postmenopausal women analysis. The analysis results indicated that compared to placebo, zoledronate (MD: 1.21, CrI: -3.64, 6.05) may not significantly impact TH BMD in a combined population. In addition, the sensitivity analysis also indicated that the results were not impacted by reporting bias. The impact of selection bias or attrition bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on TH BMD in postmenopausal women presented a low risk of bias in the relevant categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

TH BMD data in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from four two-arm RCTs, which compared four treatments (***Figure 34***).[163 166 169 177] The total sample size of the network was 1,468.[163 166 169 177]

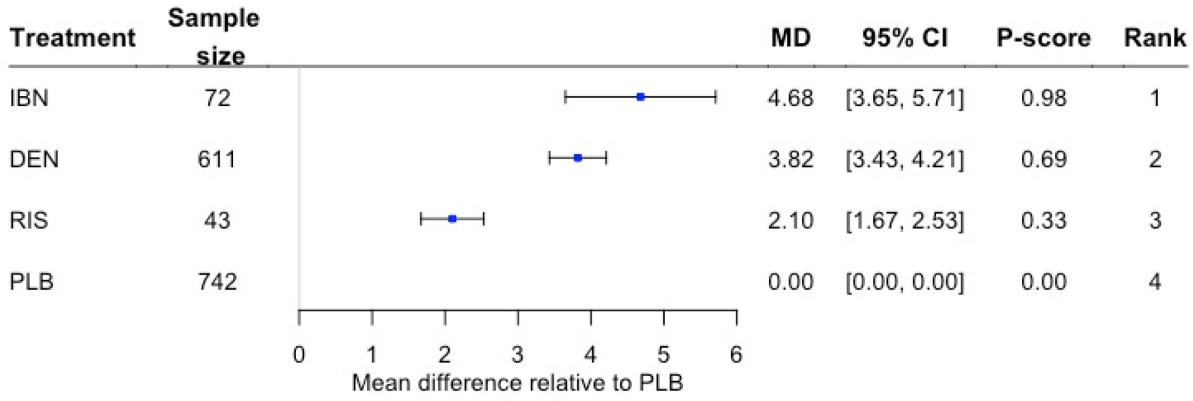
Figure 34 Network diagram for TH BMD in women with breast cancer receiving AAIT who have an increased fracture risk



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **TH**: total hip.

The treatment effects relative to placebo in women with breast cancer receiving AAIT who have an increased fracture risk, are detailed in ***Figure 35***. The results indicate that for women with breast cancer receiving AAIT who underwent 12 months of treatment, denosumab can improve TH BMD by 3.82%. All treatments were statistically significant compared to placebo. Ibandronate was ranked as the most effective treatment at increasing TH BMD, with risedronate the least effective active treatment. Denosumab was ranked as the second most effective treatment in this population.

Figure 35 Forest plot indicating the mean percentage difference in TH BMD (relative to placebo) in women with breast cancer receiving AAIT who have an increased fracture risk at 12 months



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **TH**: total hip.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available (***Table 81***, ***Appendix C***). The pairwise comparison between denosumab and risedronate was statistically significant, in favour of denosumab. It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

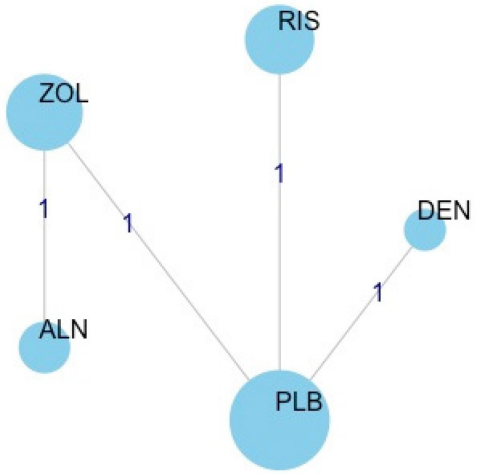
The total within-design heterogeneity in the network was low (***Table 112, Appendix D***). The heterogeneity between individual arms (i.e. placebo vs denosumab) was also low (***Table 112, Appendix D***). Similarly, there was no evidence of local inconsistency between the direct and indirect comparisons (***Table 81, Appendix C***).

The sensitivity analysis indicated that the combined population was less precise than the women with breast cancer analysis. The results indicated that ibandronate (MD: 1.88, CrI: -6.47, 9.99) and risedronate (MD: 0.96; CrI: -4.46, 6.44) do not improve TH BMD in a combined population, when compared to placebo. Nevertheless, the sensitivity analysis indicated that the results were not impacted by attrition bias, selection bias, or reporting bias.

Men with osteoporosis who have an increased fracture risk

TH BMD data in men with osteoporosis who have an increased fracture risk were extracted from four two-arm RCTs, which compared five treatments (***Figure 36***).[153 154 176 184] The total sample size of the network was 896.[153 154 176 184]

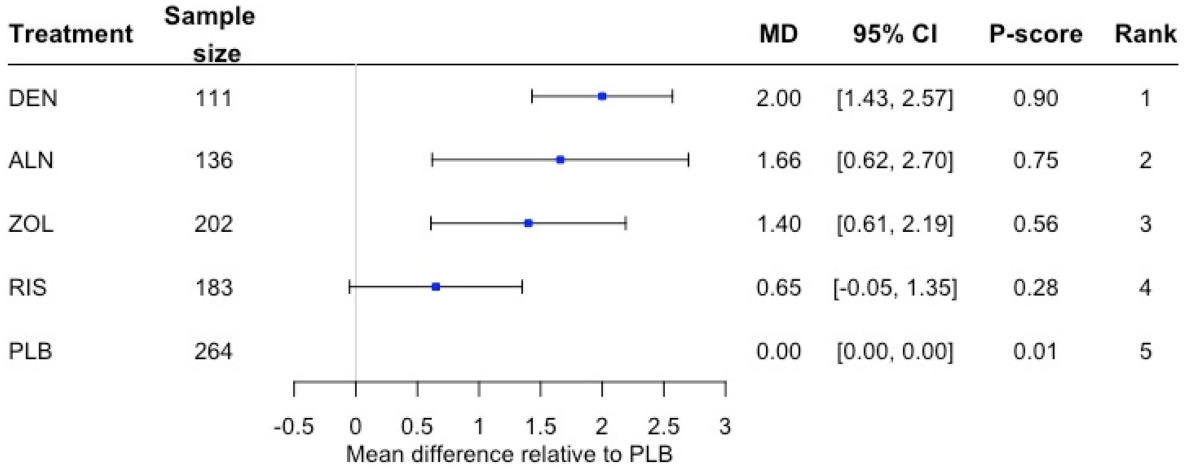
Figure 36 Network diagram for TH BMD in men with osteoporosis who have an increased fracture risk



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **TH**: total hip; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with an increased fracture risk, are detailed in ***Figure 37***. After a 12-month treatment regimen, denosumab could improve BMD measured at TH by 2.00%. All active treatments, besides risedronate, were statistically significant compared to placebo. Denosumab ranked as the most effective treatment at increasing TH BMD, with risedronate the least effective active treatment.

Figure 37 Forest plot indicating the mean percentage difference in TH BMD (relative to placebo) in men with osteoporosis who have an increased fracture risk at 12 months



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **TH**: total hip; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 82***, ***Appendix C***. All active treatments, besides risedronate, were statistically significant relative to placebo. Pairwise comparisons that compared denosumab with risedronate were statistically significant in favour of denosumab. It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

Statistical heterogeneity could not be assessed. Furthermore, no local inconsistency between the direct and indirect comparisons was detected (***Table 82***, ***Appendix C***).

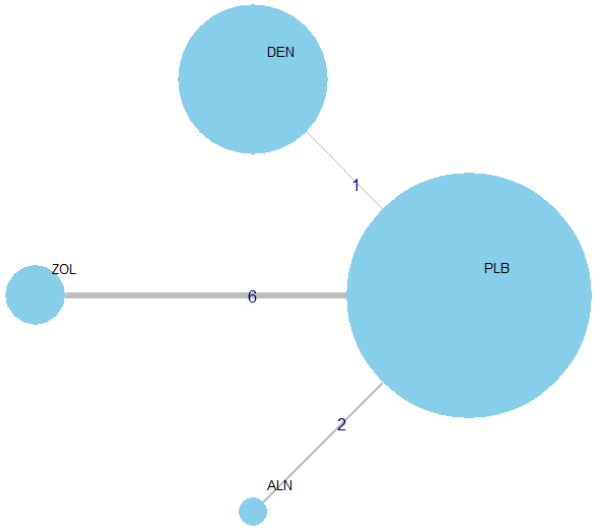
The sensitivity analysis indicated that the combined population was less precise than the analysis in men. The analysis indicated that alendronate (MD: 1.22; CrI: -1.69, 4.10), ibandronate (MD: 1.68; CrI: -6.47, 9.99), denosumab (MD: 3.39, CrI: -0.10, 6.84) and zoledronate (MD: 1.22; CrI: -3.64, 6.05) had no significant impact on TH BMD in a combined population, when compared to placebo. Nonetheless, the sensitivity analysis indicated that the results were not impacted by selection bias. The impact of reporting bias or attrition bias could not be evaluated, as none of the RCTs that reported the effect of

denosumab on TH BMD in men with osteoporosis presented a low risk of bias in either category. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

TH BMD data for men with prostate cancer on HAT who have an increased fracture risk were extracted from nine two-arm RCTs, which compared four treatments (***Figure 38***).[151 156 170 172 175 178 190 193 194] The total sample size of the network was 2,249.[151 156 170 172 175 178 190 193 194]

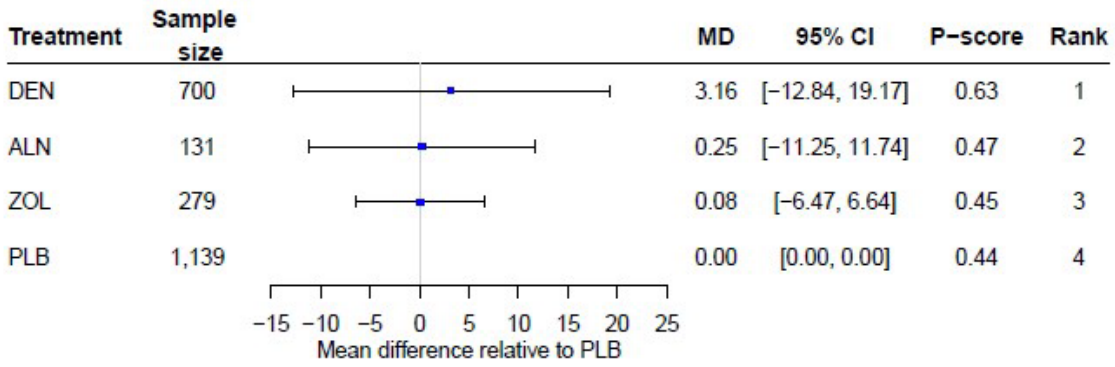
Figure 38 Network diagram for TH BMD in men with prostate cancer on HAT



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **TH**: total hip; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with prostate cancer on HAT who have an increased fracture risk after 12 months of treatment are detailed in ***Figure 39***. None of the treatments were statistically significant compared to placebo. Denosumab was ranked as the most effective treatment at increasing TH BMD; zoledronate was the least effective active treatment.

Figure 39 Forest plot indicating the mean percentage difference in TH BMD (relative to placebo) in men with prostate cancer on HAT at 12 months



Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **HAT**: hormone ablation therapy; **MD**: mean difference; **PLB**: placebo; **TH**: total hip; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available (***Table 83***, ***Appendix C***). None of the pairwise comparisons were statistically significant.

The network showed considerable total statistical heterogeneity (***Table 113, Appendix D***). The network arm comparing placebo with zoledronate presented a considerable amount of heterogeneity; the majority of the network heterogeneity can be attributed to this arm of the network. Contrastingly, the comparison between placebo and alendronate contributed a low level of heterogeneity to the network. There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 83, Appendix C***).

The sensitivity analysis indicated that the combined population was no less precise than the analysis in men with prostate cancer. The sensitivity analysis could not quantify the impact of reporting bias, selection bias, or attrition bias on the main analysis as none of the RCTs that reported the effect of denosumab on TH BMD in men with prostate cancer on HAT presented a low risk of bias in the corresponding categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

Trochanter

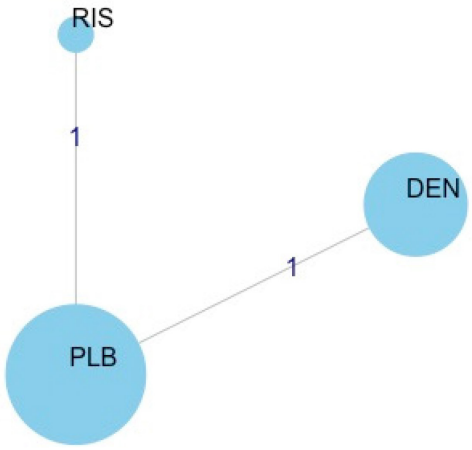
Postmenopausal women with osteoporosis

There was no available RCT evidence that met the PICO criteria on how denosumab could affect BMD measured at the trochanter in postmenopausal women with osteoporosis (***Section 5***).

Women with breast cancer receiving AAIT who have an increased fracture risk

Trochanteric BMD data in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from two two-arm RCTs, which compared three treatments (***Figure 40***).[163 169] The total sample size of the network was 332.[163 169]

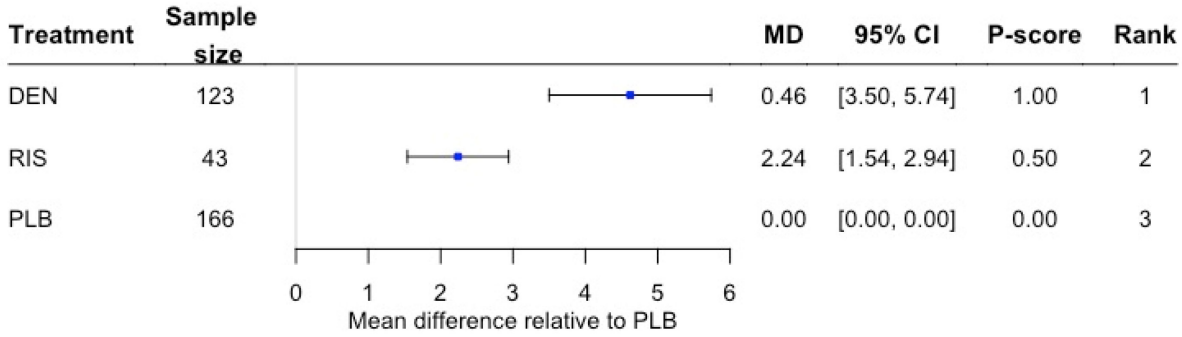
Figure 40 Network diagram for trochanter BMD in women with breast cancer receiving AAIT who have an increased fracture risk



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate.

The treatment effects relative to placebo in women with breast cancer receiving AAIT who have an increased fracture risk, are detailed in ***Figure 41***. In women with breast cancer receiving AAIT, denosumab can improve BMD measured at the trochanter by 0.46% after 12 months of treatment. All treatments were statistically significant compared to placebo. Denosumab was ranked as the most effective treatment at increasing trochanteric BMD, with risedronate as the least effective active treatment.

Figure 41 Forest plot indicating the mean percentage difference in trochanter BMD (relative to placebo) in women with breast cancer receiving AAIT who have an increased fracture risk at 12 months



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 84*** (***Appendix C***). The pairwise comparison between denosumab and risedronate was statistically significant in favour of denosumab. It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

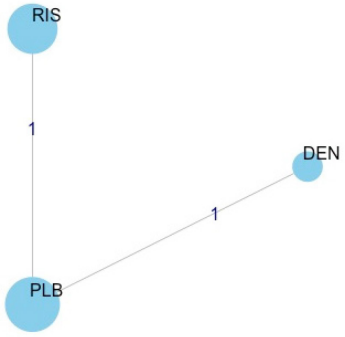
Statistical heterogeneity could not be assessed. There was no evidence of local inconsistency between the direct and indirect comparisons in ***Table 84*** (***Appendix C***).

The sensitivity analysis indicated the results were not different to the combined population, and were not impacted by selection bias and attrition bias. The impact of reporting bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on TH BMD in women with breast cancer receiving AAIT presented a low risk of bias in either category. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with osteoporosis who have an increased fracture risk

Trochanteric BMD data in men with osteoporosis who have an increased fracture risk were extracted from two two-arm RCTs, which compared three treatments (***Figure 42***).[153 176] The total sample size of the network was 494.[153 176]

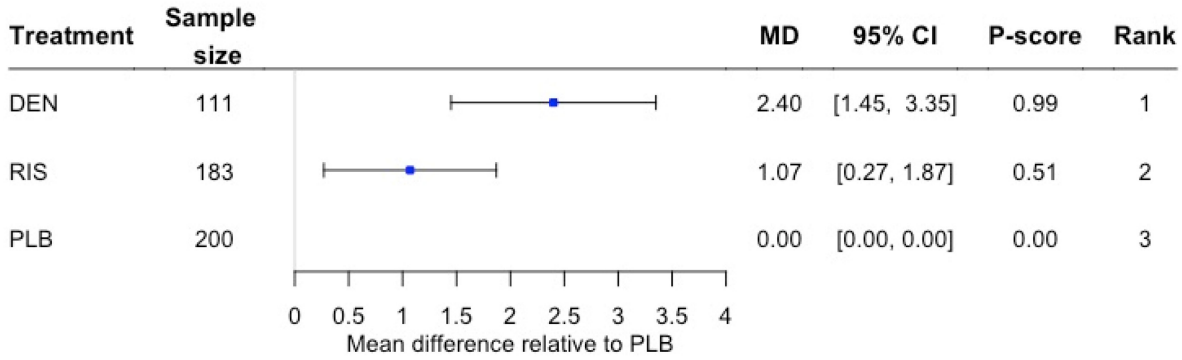
Figure 42 Network diagram for trochanter BMD in men with osteoporosis who have an increased fracture risk



Abbreviations:
BMD: bone mineral density; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate.

The treatment effects relative to placebo in men with an increased fracture risk, are detailed in ***Figure 43***. After 12 months of treatment, denosumab can improve trochanteric BMD in men with osteoporosis by 2.40%. Additionally, both treatments were statistically significant when compared to placebo. Denosumab was ranked as the most effective treatment at increasing trochanteric BMD, with risedronate as the least effective active treatment.

Figure 43 Forest plot indicating the mean percentage difference in trochanter BMD (relative to placebo) in men with osteoporosis who have an increased fracture risk at 12 months



Abbreviations:
BMD: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 85***, ***Appendix C***). The pairwise comparison between denosumab and risedronate was also statistically significant, in

favour of denosumab. It is difficult to determine if any of the statistically significant results are also clinically significant, as there is no verified scale that associates an increase in BMD with a decrease in the risk of vertebral or nonvertebral fractures.[107-109]

Statistical heterogeneity comparisons could not be assessed. Moreover, local inconsistency between the direct and indirect comparisons was not detected (***Table 85***, ***Appendix C***).

The sensitivity analysis indicated that the result was not different to the combined population.The impact of reporting bias and attrition bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on trochanteric BMD in men with osteoporosis presented a low risk of bias in either category. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

The available RCTs that measured BMD at the trochanter in men with prostate cancer on HAT did not include denosumab data,[178] [193] thus did not meet the PICO criteria (***Section 5***).

7.4.4.5 Bone turnover markers (BTM)

Postmenopausal women with osteoporosis

The available RCT evidence that met the PICO criteria (***Section 5***) on BTM in postmenopausal women with osteoporosis was too heterogeneous to combine.

Women with breast cancer receiving AAIT who have an increased fracture risk

The available RCT evidence that met the PICO criteria (***Section 5***) on BTM in women with breast cancer receiving AAIT who have an increased fracture risk was too heterogeneous to combine.

Men with osteoporosis who have an increased fracture risk

The available RCT evidence that met the PICO criteria (***Section 5***) on BTM in men with osteoporosis who have an increased fracture risk was too heterogeneous to combine.

Men with prostate cancer on HAT who have an increased fracture risk

The available RCT evidence that met the PICO criteria (***Section 5***) on BTM in men with prostate cancer on HAT who have an increased fracture risk was too heterogeneous to combine.

7.4.4.6 Fracture risk (FRAX®)

Postmenopausal women with osteoporosis

There was no available RCT evidence that met the PICO criteria (***Section 5***) for denosumab investigating FRAX® in postmenopausal women with osteoporosis.

Women with breast cancer receiving AAIT who have an increased fracture risk

There was no available RCT evidence that met the PICO criteria (***Section 5***) for denosumab investigating FRAX® in women with breast cancer receiving AAIT who have an increased fracture risk.

Men with osteoporosis who have an increased fracture risk

There was no available RCT evidence that met the PICO criteria (***Section 5***) for denosumab investigating FRAX® in men with osteoporosis who have an increased fracture risk.

Men with prostate cancer on HAT who have an increased fracture risk

There was no available RCT evidence that met the PICO criteria (***Section 5***) for denosumab investigating FRAX® in men with prostate cancer on HAT who have an increased fracture risk.

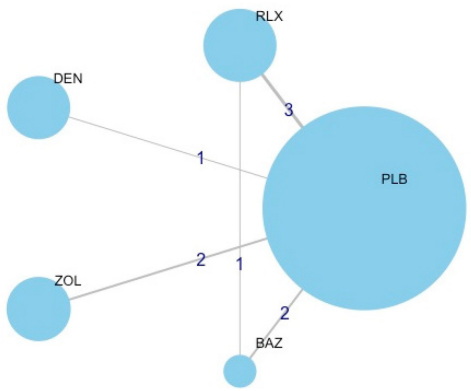
7.4.5 Findings, safety

7.4.5.1 Mortality

Postmenopausal women with osteoporosis

Mortality data in postmenopausal women with osteoporosis were available from six two-arm RCTs and one three-arm RCT, which compared five treatments (k = 9 publications; ***Figure 44***).[152 158 160-162 171 173 181 191] The included RCTs had a combined sample size of 26,882.[152 158 160-162 171 173 181 191]

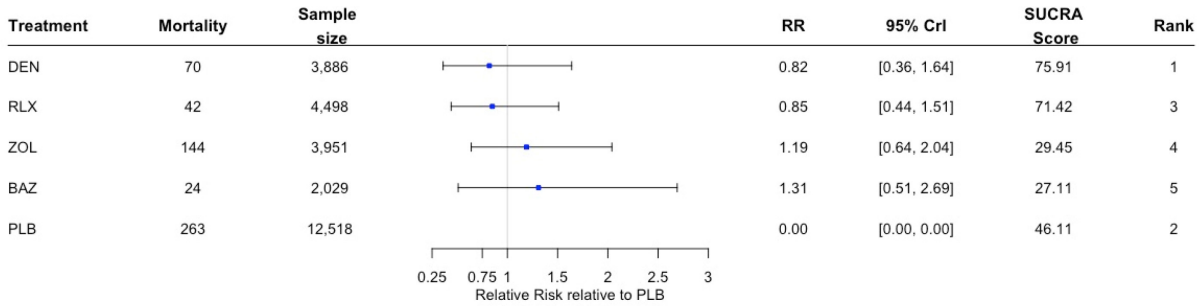
Figure 44 Network diagram for mortality in postmenopausal women with osteoporosis



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **ZOL**: zoledronate.

The treatment effects relative to placebo in postmenopausal women with osteoporosis after a treatment regimen ranging from 12 to 60 months are available in ***Figure 45***. None of the included treatments were statistically significant compared to placebo. Of these treatments, denosumab was associated with the lowest mortality in postmenopausal women and bazedoxifene was associated with the highest mortality.

Figure 45 Forest plot indicating the RR of mortality (relative to placebo) in postmenopausal women with osteoporosis after 12 to 60 months of treatment



Abbreviations:
BAZ: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **RR**: risk ratio; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

All pairwise comparisons are available in ***Table 86*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

Overall, the network presented moderate evidence of statistical heterogeneity (***Table 114, Appendix D***). There was substantial heterogeneity in the network arm which compared raloxifene to placebo. There was no evidence of local inconsistency in the network (***Figure 104***). Global inconsistency could not be calculated as the network was not closed-looped.

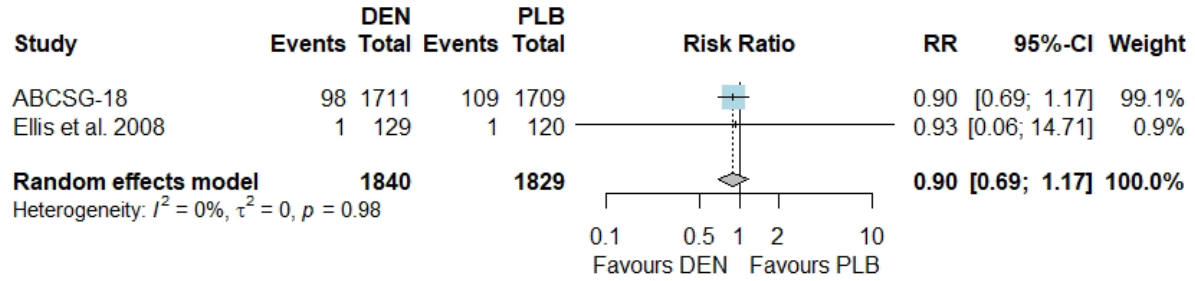
The results of the meta-regression suggested that denosumab (SUCRA: 53.14), raloxifene (SUCRA: 57.08), and bazedoxifene (SUCRA: 63.13) were associated with lower mortality in younger postmenopausal women (approximately over 75 years of age) than older postmenopausal women (approximately over 70 to 85 years of age). Additionally, the analysis findings are diminished by a limited number of trials included (n = 7). Therefore, the results should be interpreted with caution. The complete results of the meta-regression are available in the HTA Supplement.

The sensitivity analysis indicated that the results were not different to the combined population, and were not impacted by reporting bias. The impact of attrition bias and selection bias on the results could not be determined as none of the RCTs that reported on the relationship between mortality and denosumab in postmenopausal women presented a low risk of bias in either category. The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

Mortality data for women with breast cancer receiving AAIT who have an increased fracture risk were extracted from two placebo-controlled RCTs.[163 167] The total sample size was 3,669.[163 167] A pairwise meta-analysis was conducted to compare denosumab to placebo (***Figure 46***).

Figure 46 Forest plot indicating the RR of mortality (relative to placebo) in women with breast cancer receiving AAIT who have an increased fracture risk after 24 to 36 months of treatment



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio.

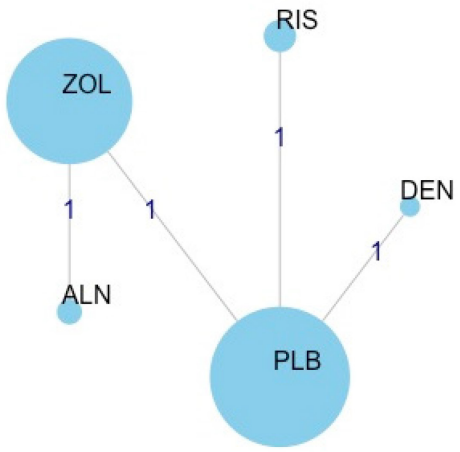
Overall, there was no statistically significant difference between denosumab and placebo after 24 and 36 months of treatment. The analysis indicated low levels of heterogeneity and inconsistency.

The sensitivity analysis indicated that the results were not impacted by selection bias, attrition bias, or reporting bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with osteoporosis who have an increased fracture risk

Mortality data for men with osteoporosis who have an increased fracture risk were extracted from four two-arm RCTs, which compared five treatments (***Figure 47***).[153 154 176 184] The total sample size of the network was 2,024.[153 154 176 184]

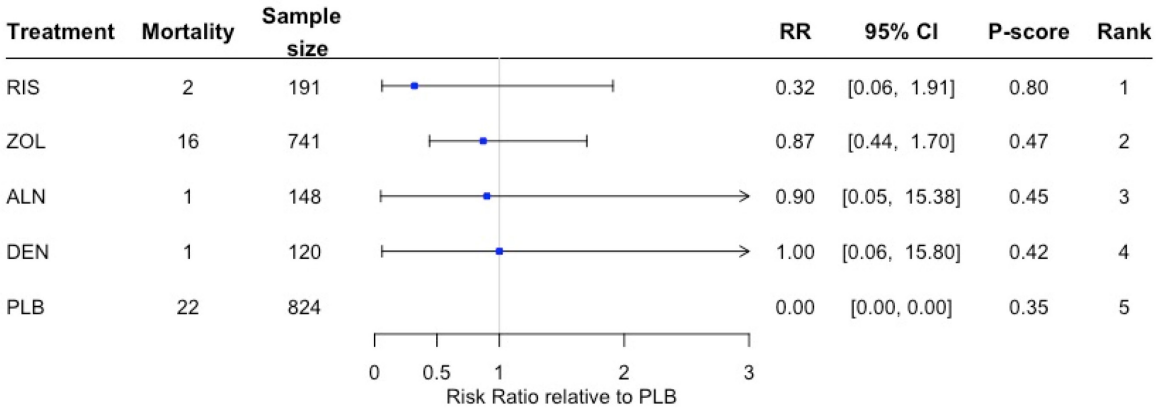
Figure 47 Network diagram for mortality in men with osteoporosis who have an increased fracture risk



Abbreviations:
ALN: alendronate; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with an increased fracture risk after 12 to 24 months of treatment are detailed in ***Figure 48***. None of the treatments were statistically significant compared to placebo. Risedronate was associated with the lowest mortality, with denosumab associated with the highest mortality of all active treatments.

Figure 48 Forest plot indicating the RR of mortality (relative to placebo) in men with osteoporosis who have an increased fracture risk after 12 and 24 months of treatment



Abbreviations:
ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RR**: risk ratio; **ZOL**: zoledronate
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available (***Table 87, Appendix C***). None of the pairwise comparisons were statistically significant.

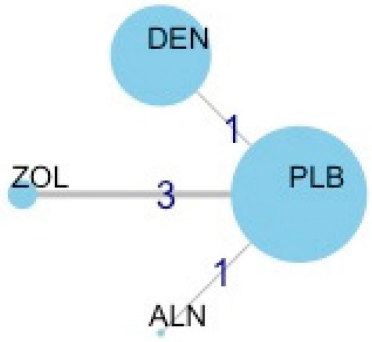
Statistical heterogeneity could not be assessed. In addition, local inconsistency between the direct and indirect comparisons was not detected (***Table 87, Appendix C***).

The sensitivity analysis indicated that the results were not different to the combined population, and were not impacted by attrition bias, or selection bias. The impact of reporting bias on the results could not be determined as none of the RCTs that reported on the relationship between mortality and denosumab in men with osteoporosis presented a low risk of bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

Mortality data in men with prostate cancer on HAT who have an increased fracture risk were extracted from five two-arm RCTs, which compared four treatments (***Figure 49***).[151 170 172 193 194] The total sample size of the network was 2,063.[151 170 172 193 194]

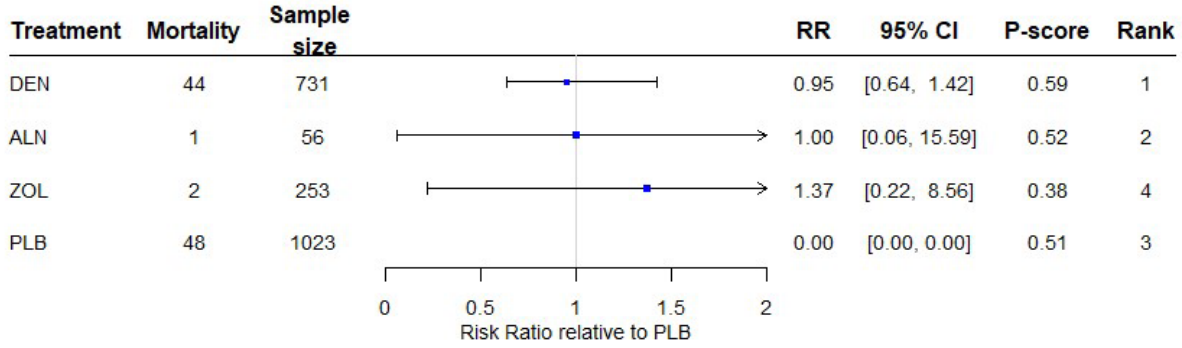
Figure 49 Network diagram for mortality in men with prostate cancer on HAT who have an increased fracture risk



Abbreviations:
ALN: alendronate; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with prostate cancer on HAT who have an increased fracture risk after 12 to 36 months of treatment, are detailed in ***Figure 50***. None of the treatments were statistically significant compared to placebo. Denosumab was associated with the lowest mortality, with zoledronate associated with the highest mortality. All pairwise comparisons from both indirect and direct evidence are available in ***Table 88*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

Figure 50 Forest plot indicating the RR of mortality (relative to placebo) in men with prostate cancer on HAT who have an increased fracture risk after 12 to 36 months of treatment



Abbreviations:
ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **RR**: risk ratio; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

There were low levels of statistical heterogeneity in the network (***Table 115, Appendix D***). Similarly, the network arm that compared placebo to zoledronate showed a low level of heterogeneity. There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 88, Appendix C***).

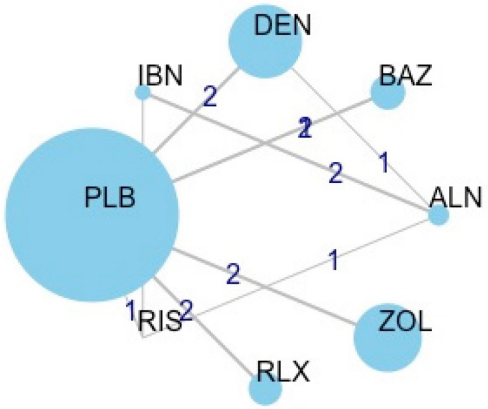
The sensitivity analysis indicated that the results did not differ from the combined analysis significantly. The sensitivity analysis could not determine the impact of reporting bias, selection bias, or attrition bias on the main analysis as none of the RCTs that reported on the association between mortality and denosumab in men with prostate cancer on HAT presented a low risk of bias in the corresponding categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

7.4.5.2 Treatment-related adverse events (AEs)

Postmenopausal women with osteoporosis

Treatment-related AE data in postmenopausal women with osteoporosis were available from nine two-arm RCTs and two three-arm RCT, which compared eight treatments (***Figure 51***).[152 158 160 171 173 179-182 185 187] The included RCTs had a combined sample size of 24,481.[152 158 160 171 173 179-182 185 187]

Figure 51 Network diagram for treatment-related AEs in postmenopausal women with osteoporosis

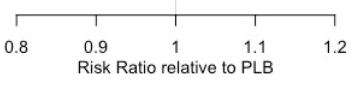


Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

The treatment effects relative to placebo in postmenopausal women with osteoporosis, are available in ***Figure 52***. None of the included treatments were statistically significant compared to placebo. Denosumab was associated with the second lowest risk of treatment-related AEs in postmenopausal women; zoledronate was associated with the highest risk of treatment-related AEs.

Figure 52 Forest plot indicating the RR of treatment-related AEs (relative to placebo) in postmenopausal women with osteoporosis after 12 to 36 months of treatment

Treatment	Adverse events	Sample size	RR	95% CrI	SUCRA Score	Rank
RIS	64	96	0.97	[0.80, 1.16]	65.33	1
DEN	3,851	4,260	0.99	[0.93, 1.05]	59.70	2
RLX	1,809	1,941	1.00	[0.94, 1.08]	49.23	4
BAZ	1,941	2,029	1.01	[.96, 1.07]	48.76	5
ALN	886	1,236	1.00	[0.87, 1.16]	48.55	6
IBN	711	931	1.00	[0.85, 1.17]	46.94	7
ZOL	3,775	3,951	1.02	[0.96, 1.08]	28.54	8
PLB	9,345	10,037	0.00	[0.00, 0.00]	52.94	3



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the

network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

All pairwise comparisons are available in ***Table 89*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

The network did not show any significant evidence of statistical heterogeneity. Similarly, there was minimal local inconsistency (***Figure 105, Appendix D***). Global inconsistency was detected in the network (***Table 116, Appendix D***).

A funnel plot assessing publication bias in the NMA of treatment-related AEs in postmenopausal women with osteoporosis is presented in ***Figure 109, Appendix E***.

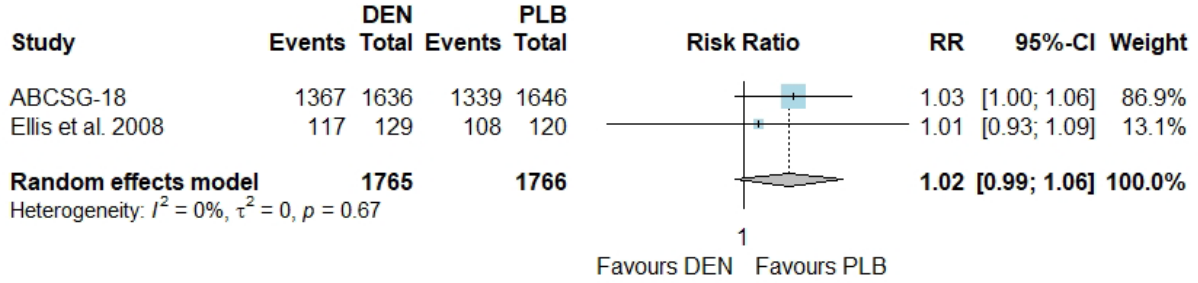
The meta-regression indicated that denosumab (SUCRA: 60.20) was associated with a lower risk of treatment-related AEs in older postmenopausal women (approximately over 70 years of age) than younger postmenopausal women (approximately 50 to 70 years of age). The complete results of the meta-regression are available in the HTA Supplement.

The sensitivity analysis indicated that the results were not significantly different to the combined population, and were not impacted by reporting bias. The impact of selection bias could not be evaluated, as none of the RCTs that reported the effect of denosumab on treatment-related AEs in postmenopausal women presented a low risk of bias. Similarly, the impact of attrition bias could not be assessed as none of the RCTs included the pre-determined referent comparator (i.e. placebo). The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

Treatment-related AE data in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from two placebo-controlled RCTs (***Figure 53***).[163 167] The total sample size was 3,531.[163 167] A pairwise meta-analysis was conducted to compare denosumab to placebo.

Figure 53 **Forest plot indicating the RR of treatment-related AEs (relative to placebo) in women with breast cancer receiving AAIT who have an increased fracture risk after 24 to 36 months of treatment**



Abbreviations:
AEs: adverse events; **AAIT**: adjuvant aromatase inhibitors therapy; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio.

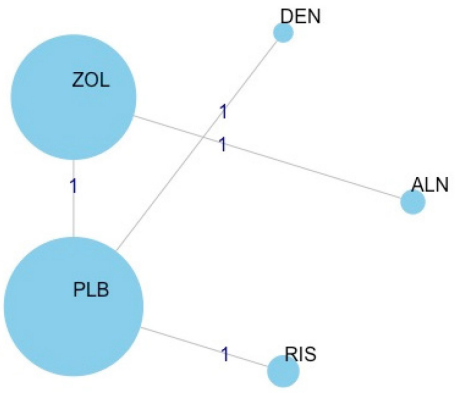
Overall, there was no statistically significant difference between denosumab and placebo after 24 to 36 months of treatment. The analysis had low levels of heterogeneity and inconsistency.

The sensitivity analysis indicated that the results did not differ significantly from the combined analysis, reporting bias, selection bias, or attrition bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with osteoporosis who have an increased fracture risk

Treatment-related AE data in men with osteoporosis who have an increased fracture risk were extracted from four two-arm RCTs, which compared five treatments (***Figure 54***).[153 154 176 184] The total sample size of the network was 2,024.[153 154 176 184]

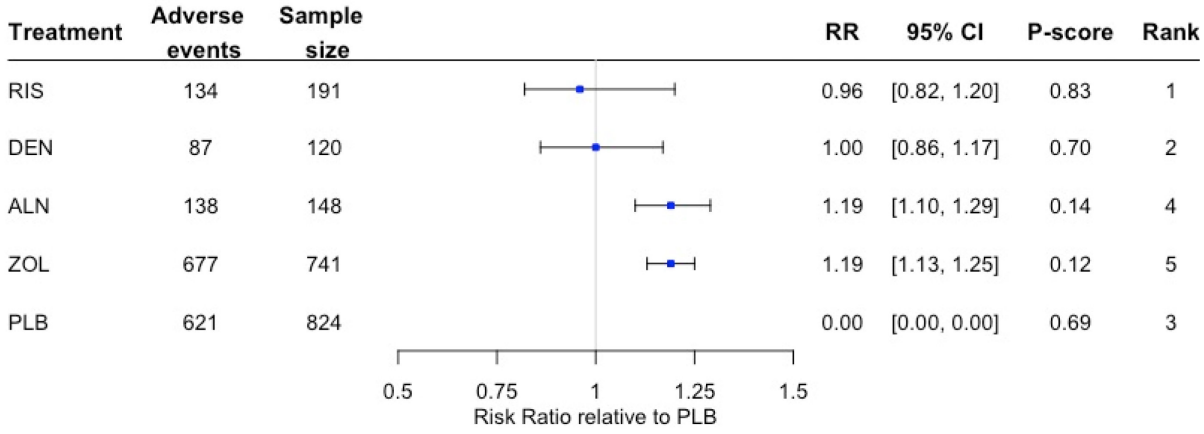
Figure 54 **Network diagram for treatment-related AEs in men with osteoporosis who have an increased fracture risk**



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with an increased fracture risk, are detailed in ***Figure 55***. The analysis associated a statistically significant increase in the risk of treatment-related AEs after 12 to 24 months of treatment with alendronate and zoledronate. Risedronate was associated with the lowest risk of treatment-related AEs; zoledronate was associated with the highest risk of treatment-related AEs. Denosumab was associated with the second-lowest risk of associated AEs.

Figure 55 Forest plot indicating the RR of treatment-related AEs (relative to placebo) in men with osteoporosis who have an increased fracture risk after 12 to 24 months of treatment



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 90*** (***Appendix C***).

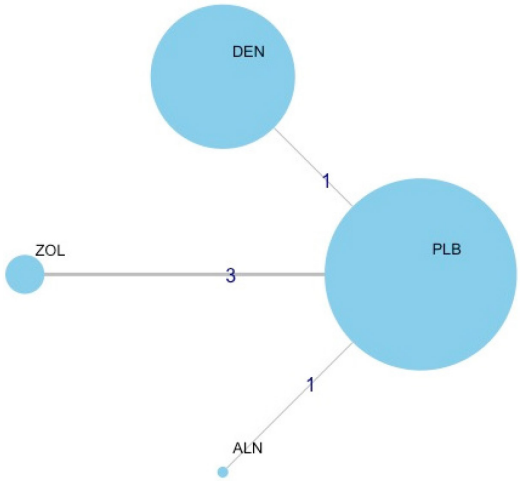
Statistical heterogeneity could not be assessed. Moreover, there was no evidence of local inconsistency between the direct and indirect comparisons (***Table 90, Appendix C***).

The sensitivity analysis indicated that the results were different to the combined population. The analysis indicated that when compared to placebo, alendronate (MD: 1.02; CrI: 0.92, 1.13) may not cause a significant increase in treatment-related AEs in a combined population. The sensitivity analysis indicated that the results were not impacted by attrition bias or selection bias. The sensitivity analysis could not determine the impact of reporting bias on the main analysis as none of the RCTs that reported the effect of denosumab on treatment-related AEs in men with osteoporosis presented a low risk of bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

Treatment-related AEs in men with prostate cancer on HAT who have an increased fracture risk was extracted from five two-arm RCTs, which compared four treatments (***Figure 56***).[151 156 170 172 194] The total sample size of the network was 1,957.[151 156 170 172 194]

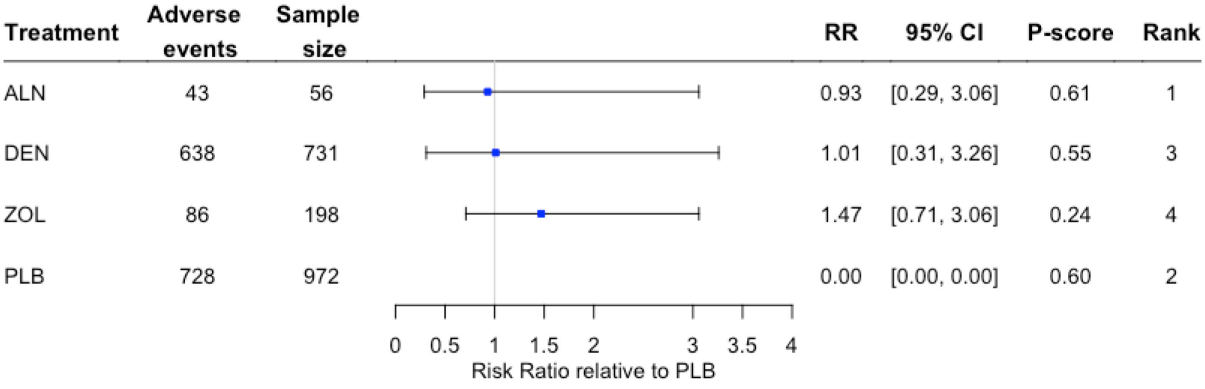
Figure 56 Network diagram for treatment-related AEs in men with prostate cancer on HAT who have an increased fracture risk



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with prostate cancer on HAT who have an increased fracture risk after individual treatment regimens ranging from 12 to 36 months, are detailed in ***Figure 57***. None of the treatments were statistically significant compared to placebo. Alendronate was associated with the lowest risk of treatment-related AEs; zoledronate was associated with the highest risk of treatment-related AEs.

Figure 57 Forest plot indicating the RR of treatment-related AEs (relative to placebo) in men with prostate cancer on HAT who have an increased fracture risk after 12 to 36 months of treatment



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **RR**: risk ratio; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 91*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

There was moderate to considerable statistical heterogeneity in the total network (***Table 118, Appendix D)***. The network arm that compared placebo to zoledronate showed a moderate to considerable level of heterogeneity. There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 91, Appendix C***).

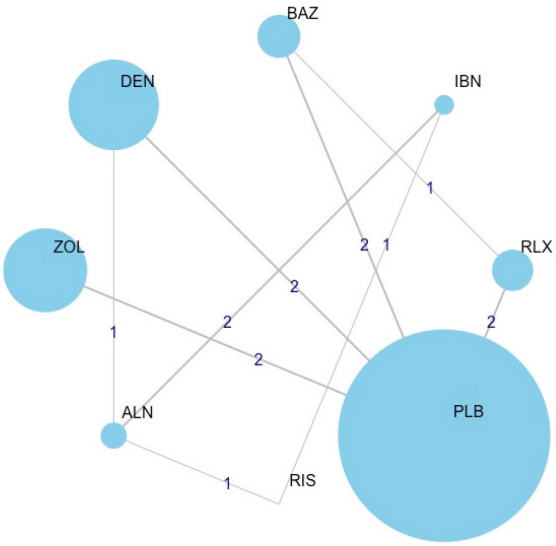
The sensitivity analysis indicated that the results may have been impacted by imprecision. The analysis indicated that when compared to placebo, zoledronate (MD: 1.08; CrI: 1.01, 1.18) may significantly increase the risk of treatment-related AEs in a combined population. The sensitivity analysis could not evaluate the impact of reporting bias, selection bias, or attrition bias on the main analysis as none of the RCTs that reported the effect of denosumab on treatment-related AEs in men with prostate cancer on HAT presented a low risk of bias in the corresponding categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

7.4.5.3 Serious adverse events (SAEs)

Postmenopausal women with osteoporosis

SAE data in postmenopausal women with osteoporosis were available from eight two-arm RCTs and two three-arm RCTs, which compared eight treatments (***Figure 58***).[152 158 160 171 173 179-182 185] The included RCTs had a combined sample size of 24,400.[152 158 160 171 173 179-182 185]

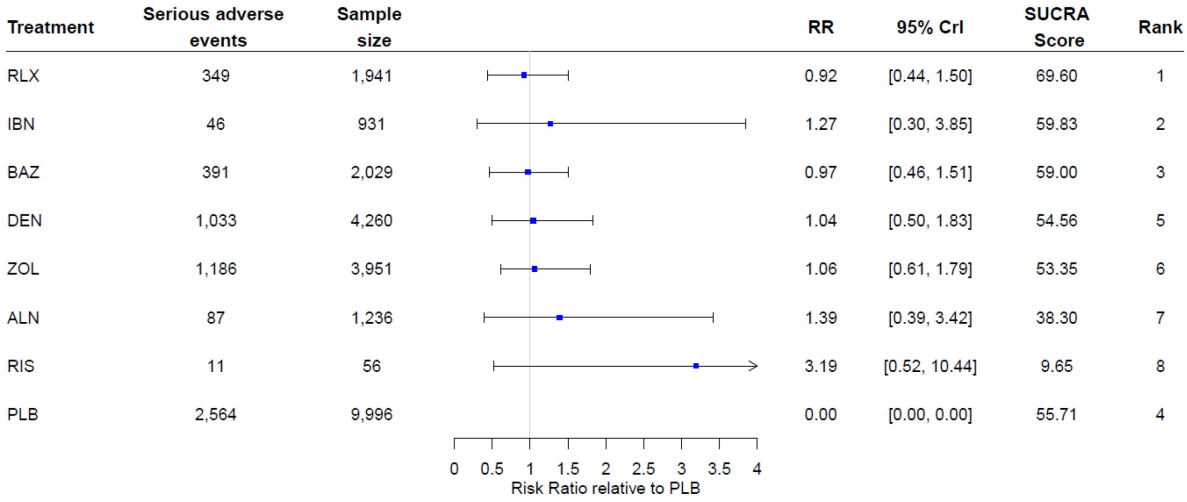
Figure 58 Network diagram for SAEs in postmenopausal women with osteoporosis



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SAEs**: serious adverse events; **ZOL**: zoledronate.

The treatment effects relative to placebo in postmenopausal women with osteoporosis after 12 to 36 months of treatment are available in ***Figure 59***. None of the included treatments were statistically significant compared to placebo. Raloxifene was associated with the lowest risk of SAEs in postmenopausal women; risedronate was associated with the highest risk of SAEs. Denosumab was associated with the fifth-lowest risk of SAEs.

Figure 59 Forest plot indicating the RR of SAEs (relative to placebo) in postmenopausal women with osteoporosis after 12 to 36 months of treatment



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SAEs**: serious adverse events; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

All comparisons are available in ***Table 92*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

In total, the network did not show any significant evidence of statistical heterogeneity (***Table 120, Appendix D***). Low to moderate levels of heterogeneity were detected in the individual network arms that compared placebo to bazedoxifene, and placebo to zoledronate. There was no evidence of local inconsistency (***Figure 106, Appendix D***) or global inconsistency (***Table 119, Appendix D***) in the network.

A funnel plot assessing publication bias in the NMA of SAEs in postmenopausal women with osteoporosis is presented in ***Figure 110, Appendix E***, showing no statistical evidence of asymmetry.

The meta-regression indicated that denosumab (SUCRA: 50.96) was associated with higher risk of SAEs in older postmenopausal women (approximately over 75 years of age) than younger postmenopausal women (approximately 60 to 70 years of age). Similarly, ibandronate (SUCRA: 60.54) was associated with higher risk of SAEs in older postmenopausal women (approximately over 60 years

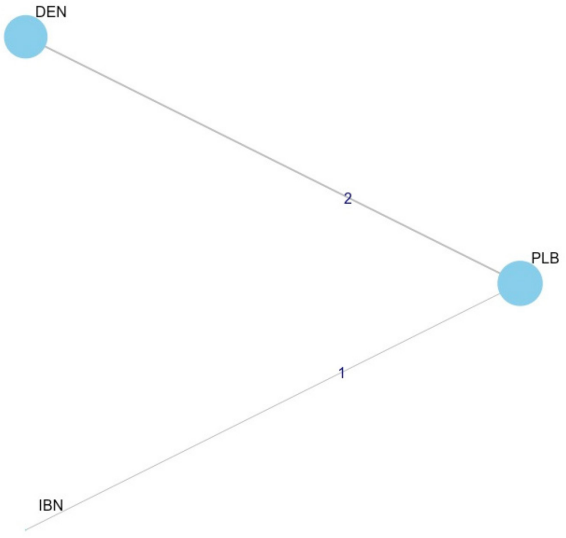
of age). Whereas, alendronate (SUCRA: 43.76) was associated with minimally less risk of SAEs in older postmenopausal women (approximately over 70 years of age) than younger postmenopausal women. The complete results of the meta-regression are available in the HTA Supplement.

The sensitivity analysis indicated that the results were not different from the combined population, and were not affected by reporting bias. The sensitivity analysis could not calculate the impact of selection bias on the main analysis as none of the RCTs that reported the effect of denosumab on SAEs in postmenopausal women in the respective categories presented a low risk of bias. Similarly, the impact of attrition bias could not be quantified as none of the RCTs included the pre-determined referent comparator (i.e. placebo). The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

SAE data in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from three two-arm RCTs, which compared three treatments (***Figure 60***).[163 167 177] The total sample size of the network was 3,675.[163 167 177]

Figure 60 Network diagram for SAEs in women with breast cancer receiving AAIT who have an increased fracture risk

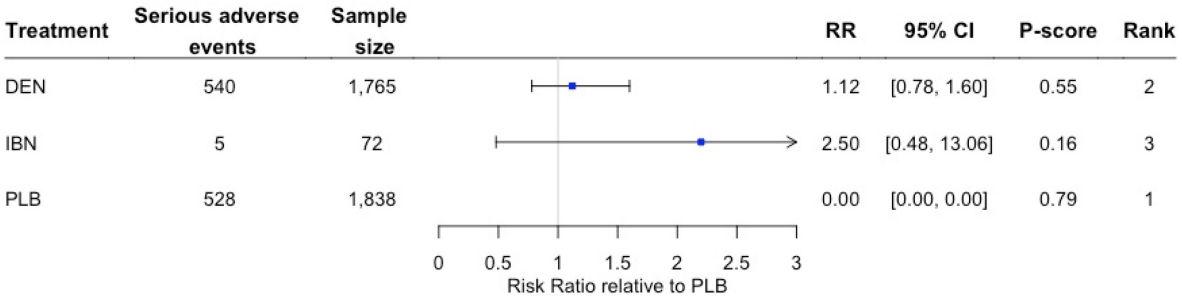


Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **SAEs**: serious adverse events.

The treatment effects relative to placebo in women with breast cancer receiving AAIT who have an increased fracture risk after individual treatment regimens that ranged from 24 to 36 months, are detailed in ***Figure 61***. No treatments were statistically significant compared to placebo. Placebo was

associated with the lowest risk, denosumab with the second lowest risk and ibandronate with the highest risk of SAEs.

Figure 61 Forest plot indicating the RR of SAEs (relative to placebo) in women with breast cancer receiving AAIT who have an increased fracture risk after 24 to 36 months of treatment



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **CI**: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RR**: risk ratio; **SAEs**: serious adverse events.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 93*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

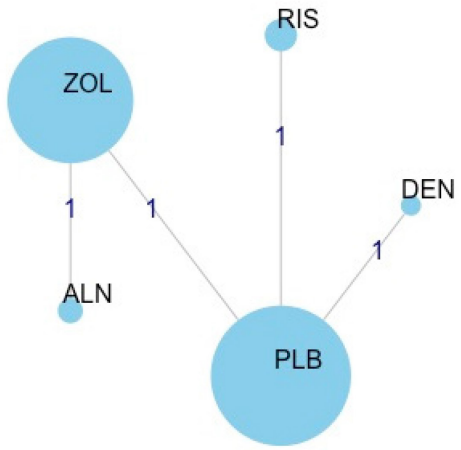
Overall, the network showed low to moderate levels of total within-design heterogeneity (***Table 121, Appendix D***). The network arm that compared placebo to denosumab showed low to moderate level of heterogeneity, though there was no evidence of local inconsistency between the direct and indirect comparisons (***Table 93, Appendix C***).

The sensitivity analysis indicated that the results were not different from the combined population, and were not affected by attrition bias, reporting bias, or selection bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with osteoporosis who have an increased fracture risk

SAE data in men with osteoporosis who have an increased fracture risk were extracted from four two-arm RCTs, which compared five treatments (***Figure 62***).[153 154 176 184] The total sample size of the network was 2,024.[153 154 176 184]

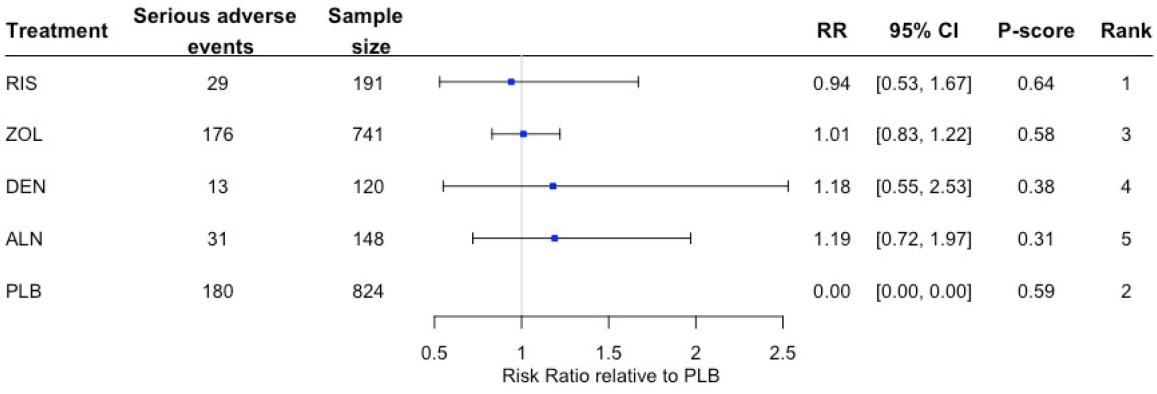
Figure 62 Network diagram for SAEs in men with osteoporosis who have an increased fracture risk



Abbreviations:
ALN: alendronate; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **SAEs**: serious adverse events; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with an increased fracture risk after a treatment period ranging from 12 to 24 months are detailed in **Figure 63**. None of the treatments were statistically significant compared to placebo. Risedronate was associated with the lowest risk and alendronate with the highest risk of SAEs. Denosumab was associated with the fourth lowest risk of SAEs.

Figure 63 Forest plot indicating the RR of SAEs (relative to placebo) in men with osteoporosis who have an increased fracture risk after 12 to 24 months of treatment



Abbreviations:
ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RR**: risk ratio; **SAEs**: serious adverse events; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 94*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

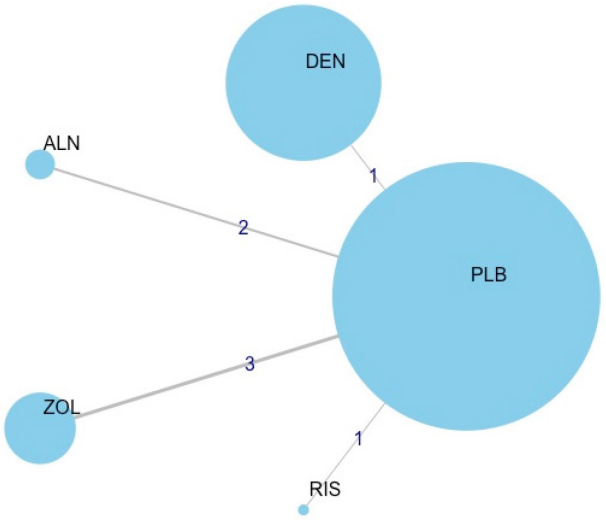
Statistical heterogeneity could not be assessed. Additionally, there was no evidence of local inconsistency between the direct and indirect comparisons (***Table 94, Appendix C***).

The sensitivity analysis indicated that the results were not different to the combined analysis, and were not affected by selection bias or attrition bias. The analysis could not evaluate the impact of reporting bias on the main analysis as none of the RCTs that reported on the association between SAEs and denosumab in men with osteoporosis presented a low risk of bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

SAE data in men with prostate cancer on HAT who have an increased fracture risk were extracted from eight two-arm RCTs, which compared five treatments (***Figure 64***).[156 157 170 172 175 190 193 194] The total sample size of the network was 2,380.[156 157 170 172 175 190 193 194]

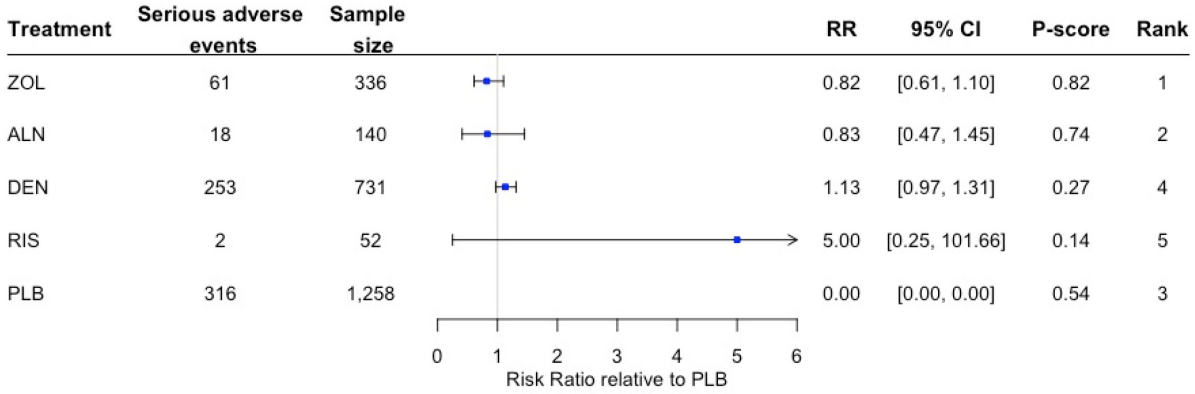
Figure 64 Network diagram for SAEs in men with prostate cancer on HAT who have an increased fracture risk



Abbreviations:
ALN: alendronate; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **SAEs**: serious adverse events; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with prostate cancer on HAT who have an increased fracture risk after a treatment period ranging from 12 to 36 months, are detailed in ***Figure 65***. None of the treatments were statistically significant compared to placebo. Zoledronate was associated with the lowest risk and risedronate with the highest risk of SAEs. Denosumab was associated with the fourth lowest risk of SAEs.

Figure 65 Forest plot indicating the RR of SAEs (relative to placebo) in men with prostate cancer on HAT who have an increased fracture risk after 12 to 36 months of treatment



Abbreviations:
ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **RR**: risk ratio; **PLB**: placebo; **SAEs**: serious adverse events; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 95*** (***Appendix C***). None of the pairwise comparisons were statistically significant.

The total within-design heterogeneity in the network was low (***Table 122, Appendix D***). Similarly, the network arms comparing placebo to alendronate, and placebo to zoledronate showed low levels of heterogeneity. There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 95, Appendix C***).

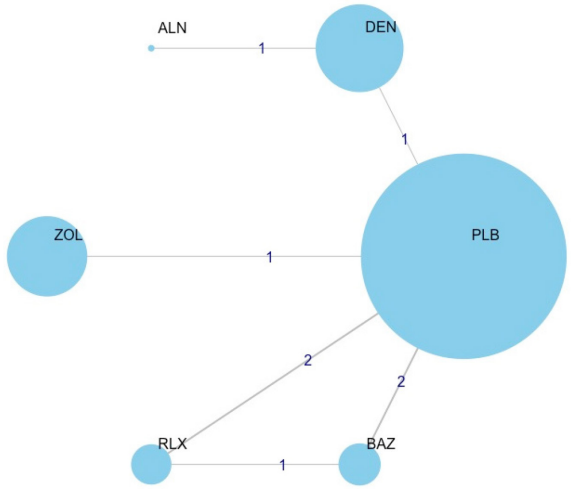
The sensitivity analysis indicated that the results were not different from the combined analysis. The sensitivity analysis could not evaluate the impact of reporting bias, selection bias, or attrition bias on the main analysis as none of the RCTs that reported the effect of denosumab on SAEs in men with prostate cancer on HAT presented a low risk of bias in the corresponding categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

7.4.5.4 Study withdrawal due to treatment-related adverse events (AEs)

Postmenopausal women with osteoporosis

Data for withdrawal due to treatment-related AEs in postmenopausal women with osteoporosis were available from five two-arm RCTs and one three-arm RCT, which compared six treatments (***Figure 66***).[150 152 158 173 180 181] The included RCTs had a combined sample size of 22,254.[150 152 158 173 180 181]

Figure 66 Network diagram for study withdrawal due to treatment-related AEs in postmenopausal women with osteoporosis

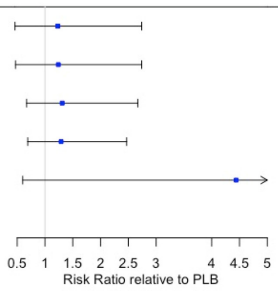


Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **ZOL**: zoledronate.

The treatment effects relative to placebo in postmenopausal women with osteoporosis after individual treatment periods ranging from 12 to 36 months are available in ***Figure 67***. None of the included treatments showed a statistically significant difference compared to placebo. Among the active treatments, zoledronate was associated with the lowest risk (ranked second overall behind placebo) and alendronate was associated with the highest risk of withdrawal due to treatment-related AEs. Denosumab was associated with the third lowest risk of withdrawal due to treatment-related AEs.

Figure 67 Forest plot indicating the RR of study withdrawal due to treatment-related AEs (relative to placebo) in postmenopausal women with osteoporosis after 12 to 36 months of treatment

Treatment	Withdrawal due to adverse events	Sample size	RR	95% CrI	SUCRA Score	Rank
ZOL	80	3,862	1.23	[0.46, 2.74]	57.46	2
DEN	97	4,222	1.24	[0.47, 2.74]	57.19	3
RLX	280	1,941	1.31	[0.67, 2.67]	48.45	4
BAZ	299	2,029	1.29	[0.69, 2.47]	48.44	5
ALN	9	320	4.44	[00.60, 16.89]	11.17	6
PLB	420	9,880	0.00	[0.00, 0.00]	77.28	1



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **RR**: risk ratio; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Credible interval (CrI): interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
Surface under the cumulative ranking curve (SUCRA): The probability that a specific treatment is among the most

effective options (i.e. “best”) in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[120]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

All pairwise comparisons are available in ***Table 96*** (***Appendix C***). None of the pairwise comparisons showed a statistically significant difference.

The network showed low levels of statistical heterogeneity (***Table* 124, *Appendix D***). In addition, there was no evidence of local inconsistency (***Figure 107*, *Appendix D***) or global inconsistency (***Table* 123, *Appendix D***) between the direct and indirect comparisons in the network.

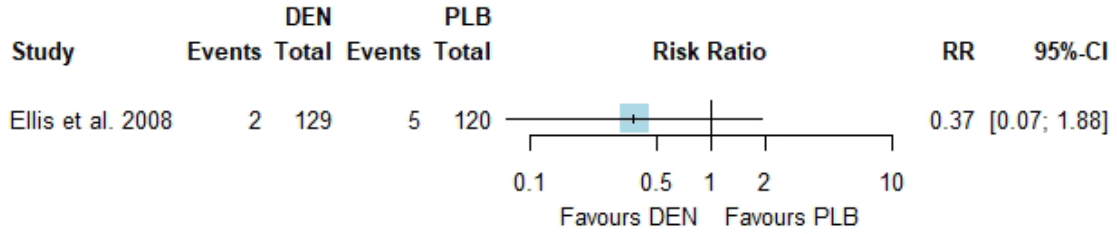
The meta-regression indicated that denosumab (SUCRA: 48.49) was associated with a lower risk of withdrawal due to treatment-related AEs in younger postmenopausal women (approximately between 65 and 67.5 years of age) than older postmenopausal women (approximately over 70 years of age). Likewise, raloxifene (SUCRA: 42.47) was associated with a lower risk of withdrawal due to treatment-related AEs in older postmenopausal women than younger postmenopausal women. Bazedoxifene (SUCRA: 49.89) was associated with a lower risk of withdrawal due to treatment-related AEs in younger postmenopausal women. In addition, the analysis findings are diminished by a limited number of trials included (n = 6). Consequently, the results should be interpreted with caution. The complete results of the meta-regression are available in the HTA Supplement.

The sensitivity analysis results indicated that the results were not different from the combined analysis, and were not impacted by reporting bias. Given that none of population specific trials included risedronate, the combined sensitivity analysis results was not considered. The impact of selection bias could not be evaluated, as none of the RCTs that reported the association between denosumab and withdrawal due to treatment-related AEs in postmenopausal women presented a low risk of bias. Likewise, the impact of attrition bias could not be assessed as none of the RCTs included the pre-determined referent comparator (i.e. placebo). The complete results of the sensitivity analysis are available in the HTA Supplement.

Women with breast cancer receiving AAIT who have an increased fracture risk

Data for withdrawal due to treatment-related AEs in women with breast cancer receiving AAIT who have an increased fracture risk were extracted from one placebo-controlled RCT.[163] The total sample size was 249.[163] Results were synthesised to compare denosumab to placebo (***Figure 68***).

Figure 68 Forest plot indicating the RR of study withdrawal due to treatment-related AEs (relative to placebo) in women with breast cancer receiving AAIT who have an increased fracture risk at 24 months



Abbreviations:
AEs: adverse events; **AAIT**: adjuvant aromatase inhibitors therapy; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio.

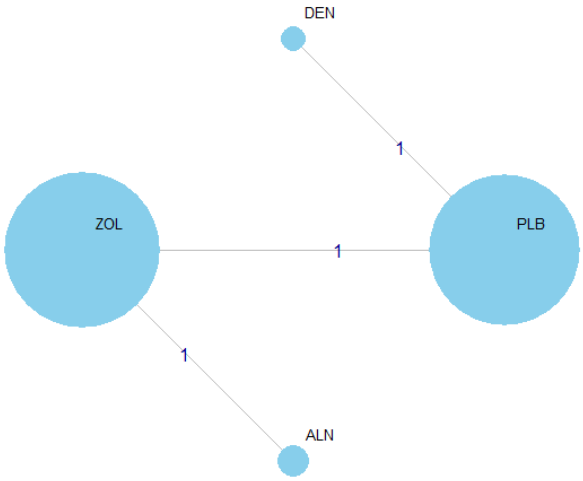
Overall, there was no statistically significant difference between denosumab and placebo for withdrawal due to treatment-related AEs after 24 months of treatment.

The sensitivity analysis indicated that the results were not different from the combined analysis. Reporting bias, selection bias, and attrition bias could not be evaluated as there was only one study in this analysis. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with osteoporosis who have an increased fracture risk

Data for withdrawal due to treatment-related AEs in men with osteoporosis who have an increased fracture risk were extracted from three two-arm RCTs, which compared four treatments (***Figure 69***).[154 176 184] The total sample size of the network was 1,740.[154 176 184]

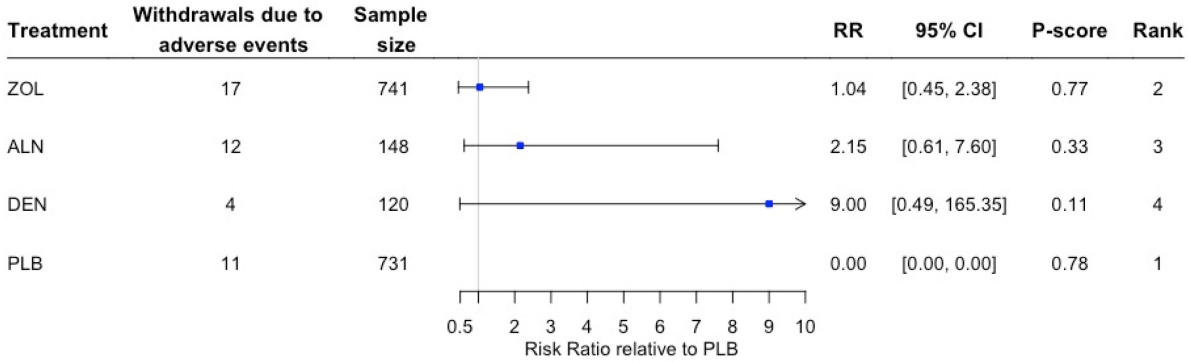
Figure 69 Network diagram for study withdrawal due to treatment-related AEs in men with osteoporosis who have an increased fracture risk



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **DEN**: denosumab; **PLB**: placebo; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with an increased fracture risk after individual treatment periods ranging between 12 and 24 months are detailed in ***Figure 70***. None of the treatments showed a statistically significant difference compared to placebo. Among the active treatments, zoledronate was associated with the lowest risk and denosumab with the highest risk of withdrawal due to treatment-related AEs.

Figure 70 Forest plot indicating the RR for study withdrawal due to treatment-related AEs (relative to placebo) in men with osteoporosis who have an increased fracture risk after 12 to 24 months of treatment



Abbreviations:
AEs: adverse events; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.

This forest plot is the result of a network meta-analysis performed using a frequentist inference.

All pairwise comparisons from both indirect and direct evidence are available in ***Table 97*** (***Appendix C***). None of the pairwise comparisons showed a statistically significant difference.

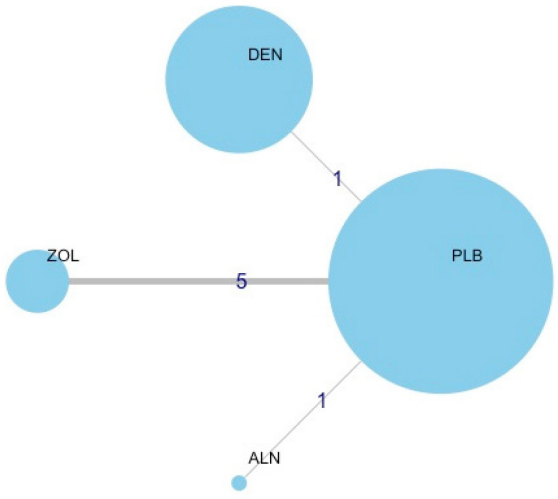
Statistical heterogeneity and inconsistency between the direct and indirect comparisons could not be assessed.

The sensitivity analysis indicated that the results were not different from the combined analysis, and were not impacted by selection bias, and attrition bias. In addition, the sensitivity analysis could not determine the impact of reporting bias on the main analysis as none of the RCTs that reported the association between denosumab and withdrawal due to treatment-related AEs in men with osteoporosis presented a low risk of bias. The complete results of the sensitivity analysis are available in the HTA Supplement.

Men with prostate cancer on HAT who have an increased fracture risk

Data for withdrawal due to treatment-related AEs in men with prostate cancer on HAT who have an increased fracture risk were extracted from seven two-arm RCTs, which compared four treatments (***Figure 71***).[151 156 172 175 190 193 194] The total sample size of the network was 2,238.[151 156 172 175 190 193 194]

Figure 71 Network diagram for study withdrawal due to treatment-related AEs in men with prostate cancer on HAT who have an increased fracture risk

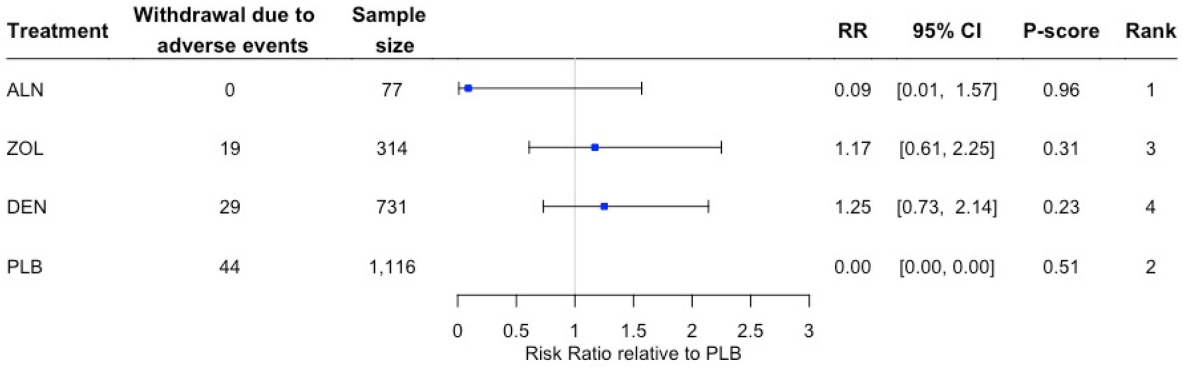


Abbreviations:
AEs: adverse events; **ALN**: alendronate; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.

The treatment effects relative to placebo in men with prostate cancer on HAT who have an increased fracture risk after individual treatment periods ranging from 12 to 36 months, are detailed in ***Figure 72***.

None of the treatments showed a statistically significant difference compared to placebo. Alendronate was associated with the lowest risk and denosumab with the highest risk of withdrawal due to treatment-related AEs.

Figure 72 Forest plot indicating the RR for study withdrawal due to treatment-related AEs (relative to placebo) in men with prostate cancer on HAT who have an increased fracture risk after 12 to 36 months of treatment



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **RR**: risk ratio; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
P-score: extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[121]
Rank: position of treatment hierarchy within the network based on the P-score, with 1 representing the most effective treatment.
This forest plot is the result of a network meta-analysis performed using a frequentist inference

All pairwise comparisons from both indirect and direct evidence are available in ***Table 98*** (***Appendix C***). None of the pairwise comparisons showed a statistically significant difference.

There was low total heterogeneity in the network (***Table 125, Appendix D***). Similarly, the network arm that compared placebo to zoledronate showed low levels of heterogeneity. There was no evidence of local inconsistency between the direct and indirect comparisons (***Table 98, Appendix C***).

The sensitivity analysis indicated that the results were not different from the combined analysis. The sensitivity analysis could not quantify the impact of reporting bias, selection bias, or attrition bias on the main analysis as none of the RCTs that reported the association between denosumab and withdrawal due to treatment-related AEs in men with prostate cancer on HAT presented a low risk of bias in the corresponding categories. The complete results of the sensitivity analysis are available in the HTA Supplement.

7.4.5.5 Adverse events (AEs) upon discontinuation of denosumab (rebound effect)

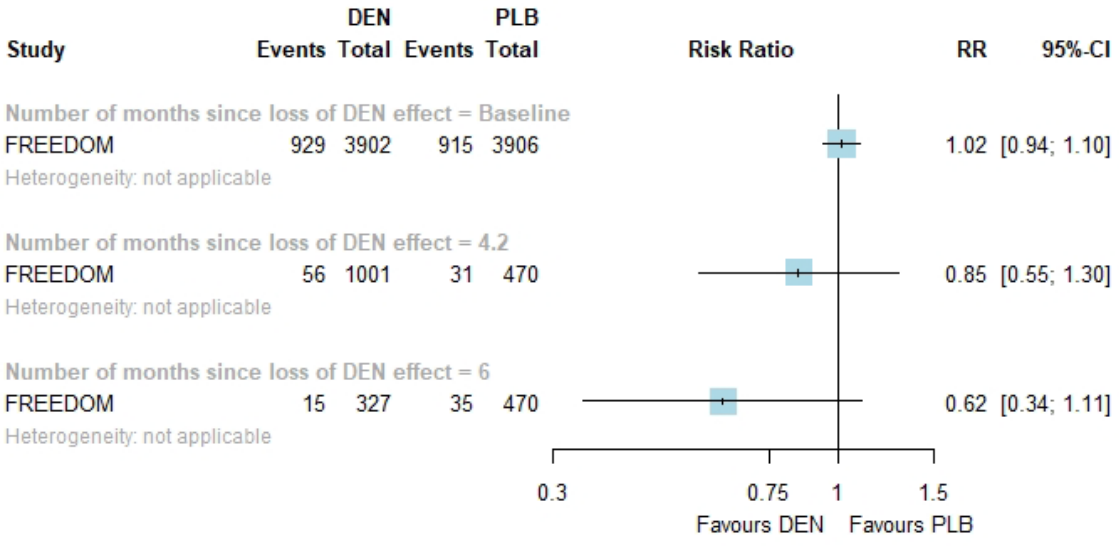
Postmenopausal women with osteoporosis

Vertebral fractures

Vertebral fracture data after denosumab discontinuation in postmenopausal women with osteoporosis were extracted from one RCT[155 159 160] and one single-arm trial.[189] The results of these analyses are presented separately because of the difference in study designs.

In the RCT, the sample size was 7,808 at baseline, 1,471 at 4.2 months after a loss of treatment effect from denosumab, and 797 at 6 months.[155 159 160] It is unclear if these patients represent losses to follow-up of the same sample of patients, or different cohorts from the overall trial population (n = 7,808). The relative vertebral fracture rates between denosumab and placebo at baseline (prior to denosumab initiation) and at 4.2 and 6 months (median) after loss of the denosumab effect are presented in ***Figure 73***. Overall, there was likely no significant change in vertebral fracture rates between denosumab and placebo at 4.2 and 6 months (median) after the loss of the denosumab treatment effect. It is important to note; however, that there were significant losses to follow-up at both timepoints in both treatment arms. As such, the results presented are subject to considerable uncertainty and should be interpreted with caution. Sensitivity analysis was not conducted because there was only one study in this analysis.

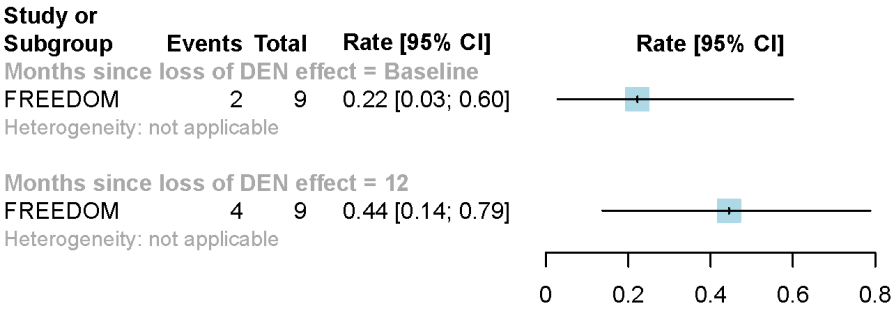
Figure 73 Forest plot indicating the RR of vertebral fractures between placebo and denosumab discontinuation in postmenopausal women with osteoporosis



Abbreviations:
CI: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio.
Notes:
Loss of effect defined as 6 months post-last dose of denosumab. An additional 1-month study visit window was also reported.[155 159]

The single-arm trial included follow-up of nine patients from the FREEDOM trial.[160 189] The results show vertebral fractures at baseline (prior to denosumab initiation) and at 12 months after the loss of denosumab's treatment effect (***Figure 74***). Overall, there was likely no significant difference between vertebral fracture at baseline and at 12 months after the loss of denosumab's treatment effect. However, the results are mitigated by the lack of a comparator as well as the small sample size, and thus should be interpreted with caution. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 74 Forest plot of a single-arm trial indicating the rate of vertebral fractures after denosumab discontinuation in postmenopausal women with osteoporosis

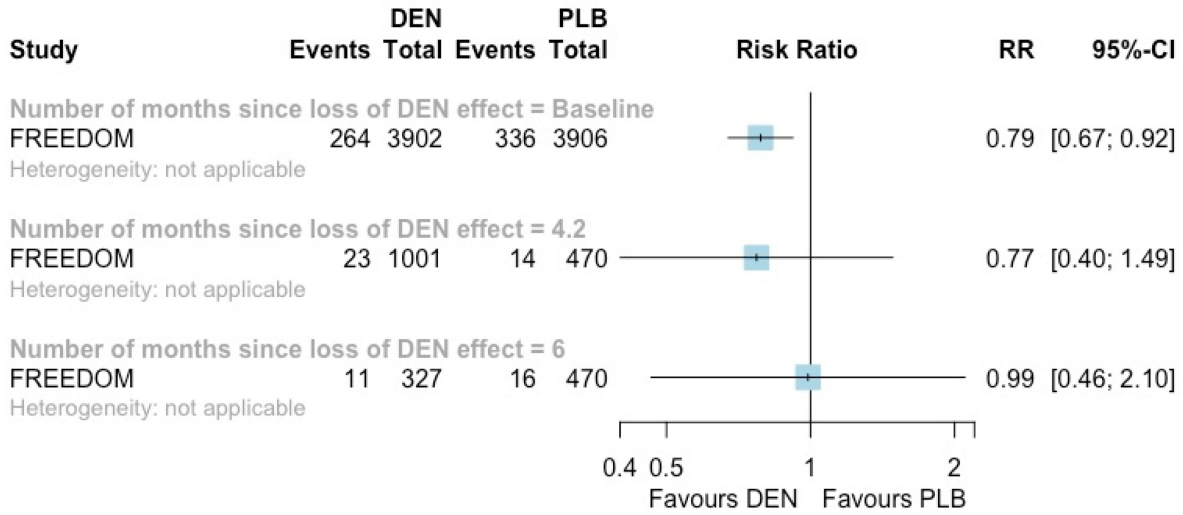


Abbreviations:
CI: confidence interval; **DEN**: denosumab.
Notes:
Loss of effect defined as 6 months post-last dose of denosumab.[189]

Nonvertebral fractures

Nonvertebral fracture data after denosumab discontinuation in postmenopausal women with osteoporosis were extracted from one RCT.[155 159 160] The sample size was 7,808 at baseline, 1,471 at 4.2 months after a loss of treatment effect from denosumab, and 797 at 6 months.[155 159 160] ***Figure 75*** presents the RR of nonvertebral fracture. Overall, there was likely no significant difference in nonvertebral fracture between denosumab and placebo at 4.2 and 6 months (median). It is important to note that there were significant losses to follow-up at both timepoints in both treatment arms and, as such, the results presented are subject to considerable uncertainty and should be interpreted with caution. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 75 Forest plot indicating the RR of nonvertebral fractures between placebo and denosumab discontinuation in postmenopausal women with osteoporosis



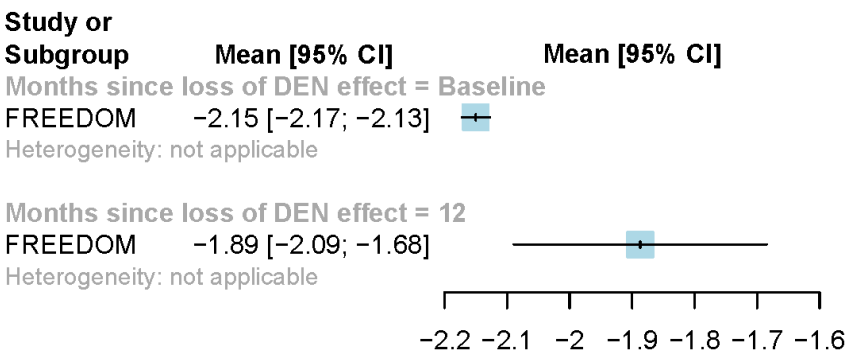
Abbreviations:
CI: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio.
Notes:
Loss of effect defined as 6 months post-last dose of denosumab. An additional 1-month study visit window was also reported.[155 159]

Bone mineral density

Femoral neck (FN)

Change in FN BMD after denosumab discontinuation was extracted from one post-hoc single-arm analysis of the FREEDOM trial, including nine patients, and is plotted against the baseline FN BMD scores reported in the main RCT publication (n = 3,902).[160 189] ***Figure 76*** presents FN BMD at baseline (prior to denosumab initiation) and at 12 months after the loss of denosumab's treatment effect. Due to the large disparity in sample size between the baseline and follow-up scores, no conclusions could be drawn based on these results. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 76 Forest plot of a single-arm trial indicating the change in FN BMD after denosumab discontinuation in postmenopausal women with osteoporosis



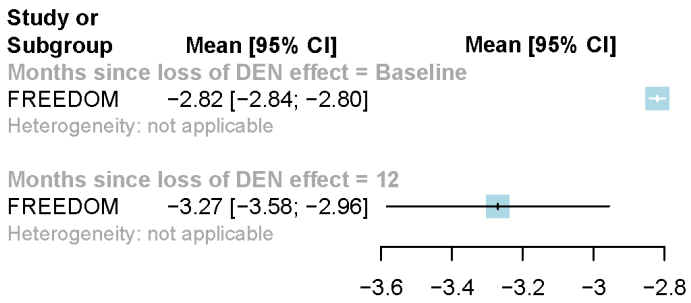
Abbreviations:
BMD: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **FN**: femoral neck.
Notes:
T-score: patient's relative BMD status compared to a young adult of the same sex. Normal bone density range is -1 to 0.5.[11]
This forest plot presents T-scores.
Loss of effect defined as 6 months post-last dose of denosumab.[189]

The impact of imprecision, reporting bias, attrition bias and selection bias could not be determined as only one single-arm trial was included in the analysis. The complete results of the sensitivity analysis are available in the HTA Supplement.

Lumbar spine (LS)

Change in LS BMD was extracted from one post-hoc single-arm analysis of the FREEDOM trial, which included nine patients, and is plotted against the baseline FN BMD scores reported in the main RCT publication (n = 3,902) (***Figure 77***).[160 189] Due to the large disparity in sample size between the baseline and follow-up scores, no conclusions could be drawn based on these results. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 77 Forest plot of a single-arm trial indicating the change in LS BMD after denosumab discontinuation in postmenopausal women with osteoporosis

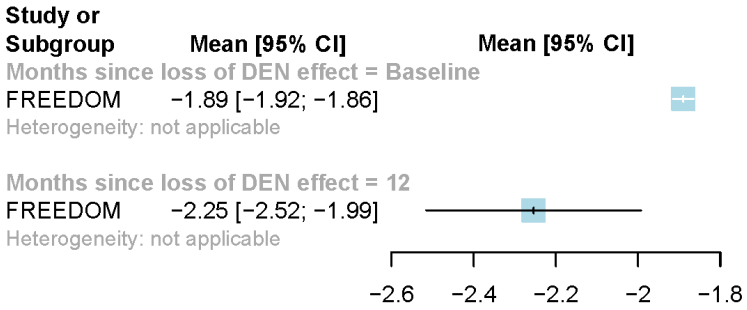


Abbreviations:
BMD: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **LS**: lumbar spine.
Notes:
This forest plot presents T-scores: patient's relative BMD status compared to a young adult of the same sex. Normal bone density range is -1 to 0.5.[11]
Loss of effect defined as 6 months post-last dose of denosumab.[189]

Total hip (TH)

Change in TH BMD after denosumab discontinuation was extracted from one post-hoc single-arm analysis of the FREEDOM trial, including nine patients.[189] To investigate a possible rebound effect, results were synthesised to compare TH BMD at baseline for the entire trial cohort (prior to denosumab initiation)[160] to TH BMD at 12 months after loss of denosumab effect (***Figure 78***). Due to the large disparity in sample size between the baseline and follow-up scores, no conclusions could be drawn based on these results. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 78 Forest plot of a single-arm trial indicating the change in TH BMD after denosumab discontinuation in postmenopausal women with osteoporosis



Abbreviations:
BMD: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **TH**: total hip.
Notes:
This forest plot presents T-scores: patient's relative BMD status compared to a young adult of the same sex. Normal bone density range is -1 to 0.5.[11]
Loss of effect defined as 6 months post-last dose of denosumab.[189]

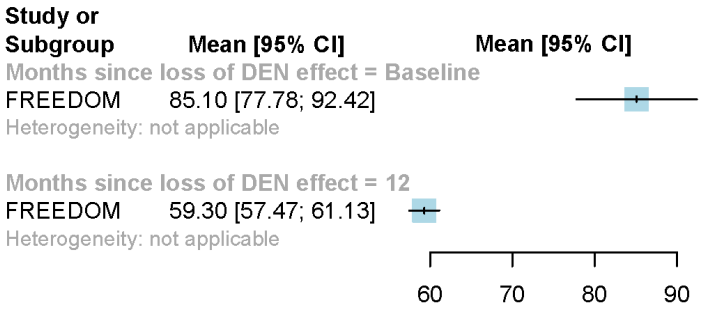
Bone turner markers (BTM)

Bone formation markers

B-ALP

Changes in B-ALP levels after denosumab discontinuation were extracted from a post-hoc single-arm analysis of the FREEDOM trial, including nine patients.[189] To investigate a possible rebound effect, results were synthesised to compare B-ALP at baseline (prior to denosumab initiation) to B-ALP at 12 months after loss of denosumab effect (***Figure 79***). Due to the large disparity in sample size between the baseline and follow-up scores, no conclusions could be drawn based on these results. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 79 **Forest plot of a single-arm trial indicating the change in bone formation markers measured by B-ALP after denosumab discontinuation in postmenopausal women with osteoporosis**



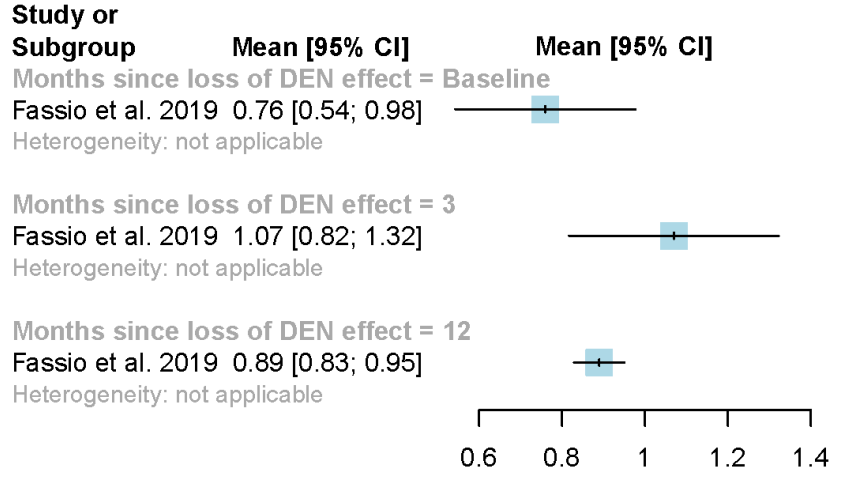
Abbreviations:
B-ALP: bone-specific alkaline phosphatase; **CI**: confidence interval; **DEN**: denosumab.
Notes:
Loss of effect defined as 6 months post-last dose of denosumab.[189]

Bone resorption markers

CTX

Changes in CTX levels after denosumab discontinuation were extracted from one single-arm trial with 15 patients.[165] The results were synthesised to compare CTX at baseline (prior to denosumab initiation) to CTX levels at 3 and 12 months after the loss of denosumab's treatment effect (***Figure 80***). Overall, there was likely no significant difference between CTX levels at baseline and CTX levels at either 3 or 12 months after loss of denosumab effect. However, the results are mitigated by the lack of a comparator as well as the small sample size. Therefore, the results should be interpreted with caution. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 80 **Forest plot of a single-arm trial indicating the change in bone resorption markers measured by CTX after denosumab discontinuation in postmenopausal women with osteoporosis**



Abbreviations:
CI: confidence interval; **CTX**: C-terminal telopeptide of type 1 collagen; **DEN**: denosumab.
Notes:
Loss of effect defined as 6 months post-last dose of denosumab.[165]

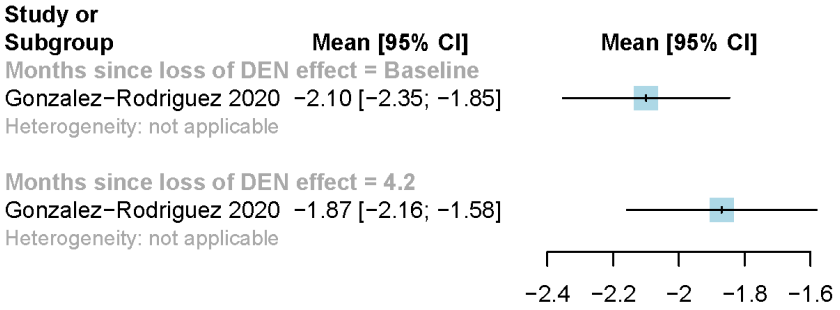
Women with breast cancer receiving AAIT who have an increased fracture risk

Bone mineral density (BMD)

Femoral neck (FN)

Change in FN BMD after denosumab was extracted from one single-arm trial with 15 patients.[168] The results were synthesised to compare FN BMD at baseline (prior to denosumab initiation) to FN BMD at 4.2 months (mean) after the loss of denosumab's treatment effect (***Figure 81***). Overall, there was likely no significant difference between FN BMD at baseline and after 4.2 months (mean). Results show that after denosumab's loss of effect, FN BMD could have remained increased—with a BMD T-score of -1.58—or decreased below baseline to -2.16. Thus, the findings are inconclusive. Additionally, the analysis findings are diminished by the lack of a comparator and the small sample size. Therefore, the results should be interpreted with caution. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 81 Forest plot of a single-arm trial indicating the change in FN BMD after denosumab discontinuation in women with breast cancer receiving AAIT who have an increased fracture risk



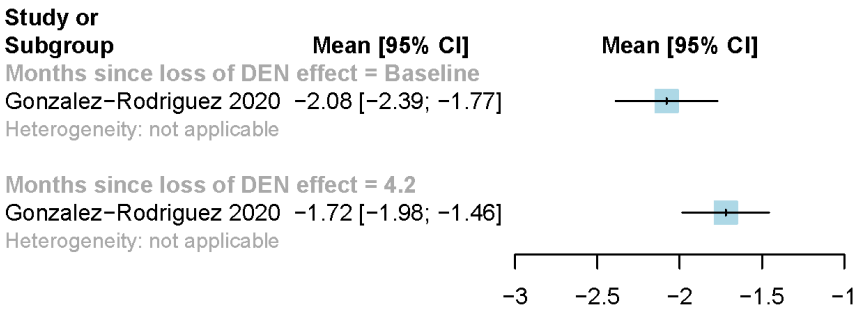
Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **FN**: femoral neck.
Notes:
T-score: patient's relative BMD status compared to a young adult of the same sex. Normal bone density range is -1 to 0.5.[11] This forest plot presents T-scores.
Loss of effect defined as 6 months post-last dose of denosumab.[168]

Lumbar spine (LS)

Change in LS BMD was extracted from one single-arm trial involving 15 patients.[168] The results were synthesised to compare LS BMD at baseline (prior to denosumab initiation) to LS BMD at 4.2 months (mean) after the loss of denosumab's treatment effect (***Figure 82***). Overall, there was likely no

statistically significant difference between LS BMD at baseline and after 4.2 months (mean) since the loss of denosumab's effect. These results are mitigated by the lack of a comparator and the small sample size, and should be interpreted with caution. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 82 Forest plot of a single-arm trial indicating the change in LS BMD after denosumab discontinuation in women with breast cancer receiving AAIT who have an increased fracture risk

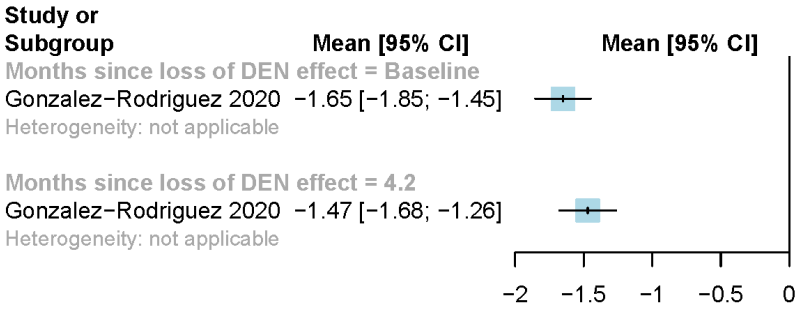


Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **LS**: lumbar spine.
Notes:
T-score: patient's relative BMD status compared to a young adult of the same sex. Normal bone density range is -1 to 0.5.[11] This forest plot presents T-scores.
Loss of effect defined as 6 months post-last dose of denosumab.[168]

Total hip (TH)

Change in TH BMD was extracted from one single-arm trial involving 15 patients.[168] The results were synthesised to compare TH BMD at baseline (prior to denosumab initiation) to TH BMD at 4.2 months (mean) after the loss of denosumab's effect to investigate possible rebound (***Figure 83***). Overall, there was likely no statistically significant difference between TH BMD at baseline and at 4.2 months (mean) after the loss of denosumab's effect. The analysis results are lessened by the lack of a comparator as well as the small sample size, therefore they should be interpreted with caution. Sensitivity analysis was not conducted because there was only one study in this analysis.

Figure 83 Forest plot of a single-arm trial indicating the change in BMD measured at TH after denosumab discontinuation in women with breast cancer receiving AAIT who have an increased fracture risk



Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **TH**: total hip.
Notes:
T-score: patient's relative BMD status compared to a young adult of the same sex. Normal bone density range is -1 to 0.5.[11]
This forest plot presents T-scores.
Loss of effect defined as 6 months post-last dose of denosumab.[168]

Men with osteoporosis who have an increased fracture risk

No evidence was available for AEs upon discontinuation of denosumab, that is, the rebound effect in men with osteoporosis who have an increased fracture risk.

Men with prostate cancer on HAT who have an increased fracture risk

No evidence was available for AEs upon discontinuation of denosumab, that is, the rebound effect in men with prostate cancer on HAT who have an increased fracture risk.

7.4.6 Findings for compliance

There was no available evidence that met the PICO criteria on compliance to denosumab (***Section 5***). Additional evidence relating to compliance for osteoporosis from a wider population of patients is discussed in ***Section 9.3.2*** (social issues).

7.4.7 GRADE summary of findings

The following tables (***Table 11*** to ***Table 14***) summarise the overall strength of evidence supporting the key findings related to the safety and efficacy of the drugs under investigation. The results presented in the summary of findings tables are network estimates, except where noted. The treatment rankings presented include placebo (the common comparator), as per the forest plots reported in ***Section 7.4.4***, which means that some treatment rankings skip numbers; the missing number in the rank order is the placebo's rank. Finally, the total number of patients includes all patients in the network, whereas the

number of reported RCTs refer to direct evidence comparing the intervention to placebo. Where zero RCTs is reported, this means the evidence reported in the GRADE table is from indirect evidence only.

As per the GRADE approach, only key outcomes are reported in the summary of findings tables for each comparison.[236] These outcomes are reflected in the PICO criteria in ***Section 5***. For measures of BMD, FN has been selected to represent all outcomes for BMD as it is used in the calculation of fracture risk using the FRAX® tool.[15] The absolute BMD effects for placebo were reported variably across the included studies (e.g. studies reported T scores, g/cm^2 or neither). As such, it was impossible to standardise the unit of measurement across all populations. Quality of life outcomes are not reported in the tables, as none of the included studies measured this outcome. In addition, discontinuation effects are not reported in the tables, as the available data were not robust enough to inform meaningful conclusions.

The certainty of evidence supporting an outcome, as scored according to the GRADE approach, is defined into the following categories:[236]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Table 11 GRADE summary of findings table for postmenopausal women with osteoporosis

Patient or population: postmenopausal women with osteoporosis
Intervention: denosumab, bisphosphonates or SERMs
Comparison: placebo

	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	Surface under the cumulative ranking curve score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Vertebral fracture (follow-up period: 12 to 84 months), network graph presented in *Figure 4*						
Denosumab	87 per 1,000	**32 per 1,000** (5 to 97)	**RR 0.37** (0.06 to 1.11)	13,663 (2 RCTs)	79.56 (1)	⊕⊕◯◯ LOW [a,b]
Zoledronate	87 per 1,000	**42 per 1,000** (12 to 126)	**RR 0.48** (0.14 to 1.45)	12,927 (2 RCTs)	66.36 (2)	⊕⊕⊕◯ MODERATE [a,b]
Risedronate	87 per 1,000	**48 per 1,000** (7 to 176)	**RR 0.55** (0.08 to 2.02)	9,947 (1 RCT)	64.29 (3)	⊕◯◯◯ VERY LOW [a,b,c]
Raloxifene	87 per 1,000	**51 per 1,000** (7 to 127)	**RR 0.58** (0.08 to 1.46)	12,256 (2 RCTs)	51.69 (4)	⊕⊕◯◯ LOW [a,b]
Bazedoxifene	87 per 1,000	**86 per 1,000** (20 to 244)	**RR 0.99** (0.23 to 2.80)	10,545 (2 RCTs)	26.09 (5)	⊕⊕◯◯ LOW [a,b]
Nonvertebral fracture (follow-up period: 12 to 36 months), network graph presented in *Figure 11*						
Risedronate	84 per 1,000	**17 per 1,000** (0 to 82)	**RR 0.20** (0.00 to 0.97)	10,064 (1 RCT)	95.69 (1)	⊕◯◯◯ VERY LOW [a,c,d]
Raloxifene	84 per 1,000	**68 per 1,000** (13 to 167)	**RR 0.81** (0.16 to 1.98)	11,963 (2 RCTs)	56.54 (2)	⊕⊕◯◯ LOW [a,b]
Bazedoxifene	84 per 1,000	**81 per 1,000** (20 to 216)	**RR 0.96** (0.24 to 2.56)	12,042 (2 RCTs)	46.74 (3)	⊕⊕◯◯ LOW [a,b]
Zoledronate	84 per 1,000	**96 per 1,000** (28 to 283)	**RR 1.14** (0.33 to 3.36)	13,974 (2 RCTs)	41.02 (4)	⊕⊕⊕◯ MODERATE [b]
Denosumab	84 per 1,000	**121 per 1,000** (19 to 425)	**RR 1.43** (0.22 to 5.04)	13,926 (1 RCT)	29.51 (6)	⊕⊕◯◯ LOW [a,b]
FN BMD (follow-up period: 19 ± 1SD months), network graph presented in *Figure 18*						
Alendronate	Mean **0.58** g/cm^2	MD **16.44% higher** (8.73 higher to 24.27 higher)	-	5,755 (0 RCTs)	94.05 (1)	⊕⊕⊕⊕ HIGH

	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	Surface under the cumulative ranking curve score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Ibandronate	Mean **0.58** g/cm²	MD **15.99% higher** (8.12 higher to 23.64 higher)	-	5,758 (0 RCTs)	85.89 (2)	⊕⊕⊕⊕ HIGH
Risedronate	Mean **0.58** g/cm²	MD **14.64% higher** (8.88 higher to 20.38 higher)	-	5,078 (1 RCT)	74.47 (3)	⊕◯◯◯ VERY LOW a,b,c
Denosumab	Mean **0.58** g/cm²	MD **4.97% higher** (1.97 lower to 11.63 higher)	-	5,329 (0 RCTs)	52.31 (4)	⊕◯◯◯ VERY LOW a,b,c
Zoledronate	Mean **0.58** g/cm²	MD **3.68% higher** (0.4 lower to 7.46 higher)	-	8,618 (2 RCTs)	39.76 (5)	⊕⊕⊕◯ MODERATE a
Bazedoxifene	Mean **0.58** g/cm²	MD **2.77% higher** (2.78 lower to 8.3 higher)	-	5,140 (1 RCT)	29.98 (6)	⊕◯◯◯ VERY LOW a,b,c
Raloxifene	Mean **0.58** g/cm²	MD **1.87% higher** (3.58 lower to 7.33 higher)	-	6,498 (1 RCT)	20.08 (7)	⊕⊕⊕◯ MODERATE a
Mortality (follow-up period: 12 to 60 months), network graph presented in *Figure 45*						
Denosumab	21 per 1,000	**17 per 1,000** (8 to 34)	**RR 0.82** (0.36 to 1.64)	16,404 (1 RCT)	75.91 (1)	⊕⊕◯◯ LOW a,b
Raloxifene	21 per 1,000	**18 per 1,000** (9 to 32)	**RR 0.85** (0.44 to 1.51)	17,016 (3 RCTs)	71.42 (3)	⊕⊕◯◯ LOW a,b
Zoledronate	21 per 1,000	**25 per 1,000** (13 to 43)	**RR 1.19** (0.64 to 2.04)	16,469 (2 RCTs)	29.45 (4)	⊕⊕⊕◯ MODERATE b
Bazedoxifene	21 per 1,000	**28 per 1,000** (11 to 57)	**RR 1.31** (0.51 to 2.69)	14,547 (2 RCTs)	27.11 (5)	⊕⊕◯◯ LOW a,b
Total AEs (follow-up period: 12 to 36 months), network graph presented in *Figure 52*						
Risedronate	931 per 1,000	**903 per 1,000** (745 to 1,000)	**RR 0.97** (0.80 to 1.16)	10,133 (1 RCT)	65.33 (1)	⊕◯◯◯ VERY LOW a,c,d

	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	Surface under the cumulative ranking curve score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Denosumab	931 per 1,000	**922 per 1,000** (866 to 978)	**RR 0.99** (0.93 to 1.05)	14,297 (2 RCTs)	59.70 (2)	⨁⨁⨁◯ MODERATE [a]
Raloxifene	931 per 1,000	**931 per 1,000** (875 to 1,000)	**RR 1.00** (0.94 to 1.08)	11,978 (2 RCTs)	49.23 (4)	⨁⨁⨁◯ MODERATE [a]
Bazedoxifene	931 per 1,000	**940 per 1,000** (894 to 996)	**RR 1.01** (0.96 to 1.07)	12,066 (2 RCTs)	48.76 (5)	⨁⨁⨁◯ MODERATE [a]
Alendronate	931 per 1,000	**931 per 1,000** (810 to 1,000)	**RR 1.00** (0.87 to 1.16)	11,273 (0 RCTs)	48.55 (6)	⨁⨁◯◯ LOW [a,b]
Ibandronate	931 per 1,000	**931 per 1,000** (791 to 1,000)	**RR 1.00** (0.85 to 1.17)	10,968 (0 RCTs)	46.94 (7)	⨁⨁◯◯ LOW [a,b]
Zoledronate	931 per 1,000	**950 per 1,000** (894 to 1,000)	**RR 1.02** (0.96 to 1.08)	13,988 (2 RCTs)	28.54 (8)	⨁⨁⨁⨁ HIGH
SAEs (follow-up period: 12 to 36 months), network graph presented in *Figure 59*						
Raloxifene	257 per 1,000	**236 per 1,000** (113 to 385)	**RR 0.92** (0.44 to 1.50)	11,937 (2 RCTs)	69.60 (1)	⨁⨁◯◯ LOW [a,b]
Ibandronate	257 per 1,000	**326 per 1,000** (77 to 988)	**RR 1.27** (0.30 to 3.85)	10,927 (0 RCTs)	59.83 (2)	⨁⨁◯◯ LOW [a,b]
Bazedoxifene	257 per 1,000	**249 per 1,000** (118 to 387)	**RR 0.97** (0.46 to 1.51)	12,025 (2 RCTs)	59.00 (3)	⨁⨁◯◯ LOW [a,b]
Denosumab	257 per 1,000	**267 per 1,000** (128 to 469)	**RR 1.04** (0.50 to 1.83)	14,256 (2 RCTs)	54.56 (5)	⨁⨁◯◯ LOW [a,b]
Zoledronate	257 per 1,000	**272 per 1,000** (156 to 459)	**RR 1.06** (0.61 to 1.79)	13,947 (2 RCTs)	53.35 (6)	⨁⨁⨁◯ MODERATE [b]
Alendronate	257 per 1,000	**357 per 1,000** (100 to 877)	**RR 1.39** (0.39 to 3.42)	11,232 (0 RCTs)	38.30 (7)	⨁⨁◯◯ LOW [a,b]
Risedronate	257 per 1,000	**818 per 1,000** (133 to 1,000)	**RR 3.19** (0.52 to 10.44)	10,052 (0 RCTs)	9.65 (8)	⨁◯◯◯ VERY LOW [a,d]

Abbreviations:
AEs: adverse events; **BMD**: bone mineral density; **CI**: confidence interval; **FN**: femoral neck; **g/cm²**: grams per square centimetre; **RR**: risk ratio; **RCT**: randomised controlled trial; **MD**: mean difference; **SAEs**: serious adverse events.
Notes:
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[a] Certainty of evidence downgraded due to serious risk of bias.
[b] Certainty of evidence downgraded due to serious imprecision.
[c] Certainty of evidence downgraded due to serious indirectness.
[d] Certainty of evidence downgraded twice due to very serious imprecision.

Table 12 GRADE summary of findings table for women with breast cancer receiving AAIT

Patient or population: women with breast cancer receiving AAIT
Intervention: denosumab or bisphosphonates
Comparison: placebo

Outcome Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	P score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Vertebral fracture (follow-up period: 24 to 36 months), network graph presented in *Figure 5*						
Denosumab	54 per 1,000	**29 per 1,000** (18 to 46)	**RR 0.53** (0.34 to 0.85)	1,849 (2 RCTs)	NA	⊕⊕⊕◯ MODERATE [a]
Nonvertebral facture (follow-up period: 24 to 36 months), network graph presented in *Figure 12*						
Denosumab	151 per 1,000	**86 per 1,000** (50 to 151)	**RR 0.57** (0.33 to 1.00)	1,849 (2 RCTs)	NA	⊕⊕⊕◯ MODERATE [a]
FN BMD (follow-up period: 12 months), network graph presented in *Figure 19*						
Denosumab	NR	MD **3.04% higher** (2.29 higher to 3.78 higher)	-	1,240 (2 RCTs)	NA	⊕⊕⊕◯ MODERATE [a]
Mortality (follow-up period: 24 to 36 months), network graph presented in *Figure 46*						
Denosumab	60 per 1,000	**54 per 1,000** (41 to 70)	**RR 0.90** (0.69 to 1.17)	3,669 (2 RCTs)	NA	⊕⊕◯◯ LOW [a,b]
Total AEs (follow-up period: 24 to 36 months), network graph presented in *Figure 53*						
Denosumab	819 per 1,000	**836 per 1,000** (811 to 869)	**RR 1.02** (0.99 to 1.06)	3,531 (2 RCTs)	NA	⊕⊕⊕◯ MODERATE [a]
SAEs (follow-up period: 24 to 36 months), network graph presented in *Figure 61*						
Denosumab	287 per 1,000	**322 per 1,000** (224 to 460)	**RR 1.12** (0.78 to 1.60)	3,603 (2 RCTs)	0.55 (2)	⊕⊕◯◯ LOW [a,b]

Outcome Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	P score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Ibandronate	287 per 1,000	**718 per 1,000** (138 to 1,000)	**RR 2.50** (0.48 to 13.06)	1,910 (1 RCT)	0.16 (3)	⨁◯◯◯ VERY LOW [a,c]

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy, **AEs**: adverse events; **BMD**: bone mineral density; **CI**: confidence interval; **FN**: femoral neck; **RCT**: randomised controlled trial; **RR**: risk ratio; **MD**: mean difference; **NA**: not applicable. **NR**: not reported; **SAEs**: serious adverse events.
Notes:
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
**Results from a pairwise meta-analysis compared to placebo.
[a] Certainty of evidence downgraded due to serious risk of bias.
[b] Certainty of evidence downgraded due to serious imprecision.
[C] Certainty of evidence downgraded twice due to very serious imprecision.

Table 13 GRADE summary of findings table for men with osteoporosis who have an increased fracture risk

Patient or population: men with osteoporosis and an increased fracture risk
Intervention: denosumab, bisphosphonates or SERMs
Comparison: placebo

Outcome Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	P score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Vertebral fracture (follow-up period: 12 to 24 months), network graph presented in *Figure 7*						
Zoledronate	5 per 1,000	**2 per 1,000** (0 to 18)	**RR 0.35** (0.04 to 3.32)	1,473 (1 RCT)	0.69 (1)	⨁⨁◯◯ LOW [a,b]
Denosumab	5 per 1,000	**2 per 1,000** (0 to 44)	**RR 0.33** (0.01 to 8.10)	851 (1 RCT)	0.62 (2)	⨁⨁⨁◯ MODERATE [a]
Alendronate	5 per 1,000	**3 per 1,000** (0 to 39)	**RR 0.54** (0.04 to 7.14)	879 (0 RCTs)	0.44 (3)	⨁⨁◯◯ LOW [a,b]
Nonvertebral fracture (follow-up period: 12 to 24 months), network graph presented in *Figure 14*						
Denosumab	14 per 1,000	**7 per 1,000** (1 to 74)	**RR 0.50** (0.05 to 5.44)	851 (1 RCT)	0.65 (1)	⨁⨁◯◯ LOW [d]
Zoledronate	14 per 1,000	**9 per 1,000** (3 to 27)	**RR 0.65** (0.21 to 1.97)	1,319 (1 RCT)	0.60 (2)	⨁⨁◯◯ LOW [a,b]
FN BMD (follow-up period: 12 months), network graph presented in *Figure 21*						

Outcome Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	P score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Denosumab	Mean T score -2.19	Mean **2.3% higher** (1.4 higher to 3.2 higher)	-	375 (1 RCT)	0.92 (1)	⊕⊕⊕◯ MODERATE [a]
Zoledronate	Mean T score -2.19	Mean **1.5% higher** (0.22 higher to 2.78 higher)	-	466 (1 RCT)	0.67 (2)	⊕⊕◯◯ LOW [a,b]
Risedronate	Mean T score -2.19	Mean **0.86% higher** (0.18 higher to 1.9 higher)	-	447 (1 RCT)	0.41 (3)	⊕⊕⊕◯ MODERATE [a]
Alendronate	Mean T score -2.19	Mean **0.85% higher** (1.47 lower to 3.17 higher)	-	400 (0 RCTs)	0.42 (4)	⊕⊕◯◯ LOW [a,b]
Mortality (follow-up period: 12 to 24 months), network graph presented in *Figure 48*						
Risedronate	27 per 1,000	**9 per 1,000** (2 to 51)	**RR 0.32** (0.05 to 1.91)	1,015 (1 RCT)	0.80 (1)	⊕⊕⊕◯ MODERATE [a]
Zoledronate	27 per 1,000	**23 per 1,000** (12 to 45)	**RR 0.86** (0.44 to 1.70)	1,565 (1 RCT)	0.47 (2)	⊕⊕◯◯ LOW [a,b]
Alendronate	27 per 1,000	**24 per 1,000** (1 to 411)	**RR 0.90** (0.05 to 15.38)	972 (0 RCTs)	0.45 (3)	⊕◯◯◯ VERY LOW [a,d]
Denosumab	27 per 1,000	**27 per 1,000** (2 to 422)	**RR 1.00** (0.06 to 15.80)	944 (1 RCT)	0.42 (4)	⊕⊕◯◯ [d] LOW
Total AEs (follow-up period: 12 to 24 months), network graph presented in *Figure 55*						
Risedronate	789 per 1,000	**757 per 1,000** (647 to 947)	**RR 0.96** (0.82 to 1.20)	1,015 (1 RCT)	0.83 (1)	⊕⊕⊕◯ MODERATE [a]
Denosumab	789 per 1,000	**789 per 1,000** (678 to 923)	**RR 1.00** (0.86 to 1.17)	944 (1 RCT)	0.70 (2)	⊕⊕◯◯ LOW [a,b]
Alendronate	789 per 1,000	**939 per 1,000** (868 to 1,000)	**RR 1.19** (1.10 to 1.29)	972 (0 RCTs)	0.14 (4)	⊕⊕⊕◯ MODERATE [b]
Zoledronate	789 per 1,000	**939 per 1,000** (891 to 986)	**RR 1.19** (1.13 to 1.25)	1,565 (1 RCT)	0.12 (5)	⊕⊕◯◯ LOW [a,b]
SAEs (follow-up period: 12 to 24 months), network graph presented in *Figure 63*						

Outcome Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	P score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Risedronate	218 per 1,000	**205 per 1,000** (116 to 365)	**RR 0.94** (0.53 to 1.67)	1,087 (1 RCT)	0.60 (1)	⊕⊕⊕◯ MODERATE [b]
Zoledronate	218 per 1,000	**221 per 1,000** (181 to 267)	**RR 1.01** (0.83 to 1.22)	1,637 (1 RCT)	0.54 (3)	⊕⊕⊕◯ MODERATE [b]
Denosumab	218 per 1,000	**258 per 1,000** (120 to 553)	**RR 1.18** (0.55 to 2.53)	1,016 (1 RCT)	0.36 (4)	⊕⊕⊕◯ MODERATE [a]
Alendronate	218 per 1,000	**260 per 1,000** (157 to 430)	**RR 1.19** (0.72 to 1.97)	1,044 (0 RCTs)	0.31 (5)	⊕⊕◯◯ LOW [a,b]

Abbreviations:
AEs: adverse events; **BMD**: bone mineral density; **CI**: confidence interval; **FN**: femoral neck; **RCT**: randomised controlled trial; **RR**: risk ratio; **MD**: mean difference; **SAEs**: serious adverse events.
Notes:
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[a] Certainty of evidence downgraded due to serious risk of bias.
[b] Certainty of evidence downgraded due to serious imprecision.
[c] Certainty of evidence downgraded due to serious indirectness.
[d] Certainty of evidence downgraded due to very serious imprecision.

Table 14 GRADE summary of findings table for men with prostate cancer on HAT

Patient or population: men with prostate cancer on HAT
Intervention: denosumab or bisphosphonates
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	P score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Vertebral fracture (follow-up period: 12 months), network graph presented in *Figure 9*						
Denosumab	22 per 1,000	**3 per 1,000** (1 to 15)	**RR 0.15** (0.03 to 0.67)	1,403 (1 RCT)	0.99 (1)	⊕⊕⊕◯ MODERATE [a]
Zoledronate	22 per 1,000	**34 per 1,000** (9 to 136)	**RR 1.55** (0.39 to 6.14)	779 (1 RCT)	0.14 (2)	⊕◯◯◯ VERY LOW [a,d]
Nonvertebral fracture (follow-up period: 12 to 36 months), network graph presented in *Figure 16*						
Denosumab	55 per 1,000	**39 per 1,000** (26 to 59)	**RR 0.72** (0.48 to 1.07)	1,835 (1 RCT)	0.73 (1)	⊕⊕◯◯ LOW [a,b]
Alendronate	55 per 1,000	**32 per 1,000** (5 to 181)	**RR 0.58** (0.10 to 3.31)	1,237 (2 RCTs)	0.71 (2)	⊕⊕◯◯ LOW [a,b]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	P score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Zoledronate	55 per 1,000	**81 per 1,000** (21 to 315)	**RR 1.48** (0.38 to 5.76)	1,308 (3 RCTs)	0.35 (4)	⊕◯◯◯ VERY LOW [a,b,c]
FN BMD (follow-up period: 12 months), network graph presented in *Figure 23*						
Risedronate	Mean T score **-1.44**	MD **6.57% higher** (7.13 lower to 20.27 higher)	-	983 (1 RCT)	0.73 (1)	⊕⊕◯◯ LOW [d]
Zoledronate	Mean T score **-1.44**	MD **3.16% higher** (2.03 higher to 4.28 higher)	-	1,058 (3 RCTs)	0.70 (2)	⊕◯◯◯ VERY LOW [a,b,c]
Denosumab	Mean T score **-1.44**	MD **2.73% higher** (2.31 higher to 3.16 higher)	-	1,653 (1 RCT)	0.53 (3)	⊕⊕⊕◯ MODERATE [a]
Alendronate	Mean T score **-1.44**	MD **2.61% higher** (1.36 higher to 3.85 higher)	-	1,054 (2 RCTs)	0.49 (4)	⊕⊕◯◯ LOW [a,b]
Mortality (follow-up period: 12 to 36 months), network graph presented in *Figure 50*						
Denosumab	47 per 1,000	**45 per 1,000** (30 to 67)	**RR 0.95** (0.64 to 1.42)	1,754 (1 RCT)	0.59 (1)	⊕⊕◯◯ LOW [a,b]
Alendronate	47 per 1,000	**47 per 1,000** (3 to 731)	**RR 1.00** (0.06 to 15.59	1,079 (1 RCT)	0.52 (2)	⊕◯◯◯ VERY LOW [a,d]
Zoledronate	47 per 1,000	**64 per 1,000** (10 to 402)	**RR 1.37** (0.22 to 8.56)	1,276 (3 RCTs)	0.38 (4)	⊕◯◯◯ VERY LOW [a,d]
Total AEs (follow-up period: 12 to 36 months), network graph presented in *Figure 57*						
Alendronate	749 per 1,000	**697 per 1,000** (217 to 1,000)	**RR 0.93** (0.29 to 3.06)	1,028 (1 RCT)	0.61 (1)	⊕⊕◯◯ LOW [a,b]
Denosumab	749 per 1,000	**756 per 1,000** (232 to 1,000)	**RR 1.01** (0.31 to 3.26)	1,703 (1 RCT)	0.55 (2)	⊕⊕◯◯ LOW [a,b]
Zoledronate	749 per 1,000	**1,000 per 1,000** (532 to 1,000)	**RR 1.47** (0.71 to 3.06)	1,170 (3 RCTs)	0.24 (4)	⊕◯◯◯ VERY LOW [a,b,e]
SAEs (follow-up period: 12 to 36 months), network graph presented in *Figure 65*						
Zoledronate	251 per 1,000	**206 per 1,000** (153 to 276)	**RR 0.82** (0.61 to 1.10)	1,594 (3 RCTs)	0.82 (1)	⊕⊕◯◯ LOW [a,b]
Alendronate	251 per 1,000	**208 per 1,000** (118 to 364)	**RR 0.83** (0.47 to 1.45)	1,398 (2 RCTs)	0.74 (2)	⊕⊕◯◯ LOW [a,b]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants in the network (studies from direct evidence)	P score (rank)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Intervention				
Denosumab	251 per 1,000	**284 per 1,000** (244 to 329)	**RR 1.13** (0.97 to 1.31)	1,989 (1 RCT)	0.27 (4)	⊕⊕◯◯ LOW [a,b]
Risedronate	251 per 1,000	**1,000 per 1,000** (63 to 1,000)	**RR 5.00** (0.25 to 101.66)	1,310 (1 RCT)	0.14 (5)	⊕◯◯◯ VERY LOW [a,d]

Abbreviations:
AEs: adverse events; **BMD**: bone mineral density; **CI**: confidence interval; **FN**: femoral neck; **HAT**: hormone ablation therapy; **RCT**: randomised controlled trial; **RR**: risk ratio; **MD**: mean difference; **SAEs**: serious adverse events.
Notes:
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[a] Certainty of evidence downgraded due to serious risk of bias.
[b] Certainty of evidence downgraded due to serious imprecision.
[c] Certainty of evidence downgraded due to serious indirectness.
[d] Certainty of evidence downgraded twice due to very serious imprecision.
[e] Certainty of evidence downgraded due to serious inconsistency.

8 Costs, cost-effectiveness and budget impact

8.1 Summary statement costs, cost-effectiveness and budget impact

A discrete event simulation (DES) model was developed to explore the cost-effectiveness of denosumab in postmenopausal women with osteoporosis as an exemplar case. Postmenopausal osteoporosis was chosen as an exemplar case as it represents the largest population in which denosumab is used in Switzerland and it has the most robust data supporting its safety and efficacy.

Time-to-fracture distributions for hip, clinical vertebral and non-hip nonvertebral (NHNV; i.e. forearm, humeral) fractures, derived from Swiss-specific FRAX® probabilities of MOF in women of postmenopausal age at various risk levels (moderate, high and very high) formed the backbone of the economic model. Reductions in the risk of vertebral and nonvertebral fracture due to treatment were informed by the network meta-analysis, while real-world adherence data were obtained from the literature. Cost-effectiveness was assessed via cost-effectiveness frontier analysis. Additionally, pairwise comparisons between denosumab and each comparator were made.

In women starting therapy at age 70 years with a high fracture risk (i.e. base case cohort), IV ibandronate was the most cost-effective option at a hypothetical WTP threshold of CHF100,000. Scenario analysis found zoledronate was the most cost-effective option in women starting therapy at age 60 (except for women at very high risk of fracture, for whom IV ibandronate was cost-effective), and IV ibandronate remained the most cost-effective option in women of any fracture risk starting therapy at age 70 or 80 years.

In women aged 70 years at high fracture risk, denosumab had incremental cost-effectiveness ratios (ICERs) of CHF15,927, CHF23,135, CHF86,776, CHF107,460, CHF166,451 and CHF615,149 when compared with no treatment, bazedoxifene, raloxifene, zoledronate, oral bisphosphonates and IV ibandronate, respectively. The higher intervention costs, smaller reduction in the risk of hip fracture and shorter duration of residual benefit associated with denosumab contributed to the high ICER values seen in pairwise comparisons with oral bisphosphonates and IV ibandronate, despite improved patient persistence with denosumab.

The budget impact analysis explored the potential costs of denosumab over the period 2021 to 2024. In the base case, it was assumed that use of denosumab would continue to decline by 1.6% per annum (p.a.), which reflects the average annual decline in use over the period 2018 to 2020. Under this assumption, the payer cost of denosumab was estimated to be CHF26.6 million in 2024, representing a decrease of CHF1.6 million compared to 2020 (CHF28.2 million). While the utilisation of denosumab has declined in recent years, uptake of bisphosphonates has increased, suggesting a substitution may

be occurring in practice. Crude analyses indicated the potential for cost savings through the natural substitution of denosumab with bisphosphonates (CHF0.36 million in 2021, increasing to CHF1.43 million in 2024).

8.2 Methodology costs, cost-effectiveness and budget impact

A DES model was developed to quantify the cost-effectiveness of denosumab versus oral bisphosphonates, intravenous (IV) ibandronate, zoledronate, raloxifene, bazedoxifene and no treatment for the management of osteoporosis in postmenopausal women. Postmenopausal osteoporosis was chosen as an exemplar case because it represents the largest population in which denosumab is used in Switzerland and it has the most robust clinical data supporting its safety and efficacy.

Risk of MOF in untreated patients was derived using 10-year probabilities calculated via the Swiss-specific FRAX® calculator.[237] Reductions in the risk of vertebral and nonvertebral fracture due to treatment were informed by the network meta-analysis described in the clinical effectiveness review (***Section 7.4.4***).

The analysis took the perspective of the Swiss payer, so only direct costs were included. QALYs were used as the outcome measure. Cost-effectiveness outcomes were calculated over a lifetime horizon, and both costs and QALYs were discounted at 3% p.a. Sensitivity of results to different model assumptions and input data was explored via deterministic sensitivity analysis (DSA).

In 2019, recommendations for the conduct of economic evaluations in osteoporosis were put forward by a working group convened by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis.[238] As part of these recommendations, a minimum set of criteria that economic evaluations in osteoporosis should, at a minimum, comply, were defined (see ***Table 127*** in ***Appendix G***).[238] These criteria were used to guide the construct of the *de novo* model.

8.2.1 Economic modelling background

8.2.1.1 Review of economic literature

Findings of the literature review have been previously described in the HTA Scoping Report. Only a brief overview of the included studies is given here, with a more detailed review available in the scoping report. An extraction table summarising the results of the included studies is presented in the HTA Supplement.

Eleven (73.3%) of 15 identified economic studies were restricted to postmenopausal women.[196 199 202 205 239-245] Nine of these studies (81.8%) directly utilised population eligibility criteria from the FREEDOM

RCT.[246] Two (13.3%) of the 15 studies considered both men and women over the age of 50, with the aim of determining FRAX®-derived probabilities at which pharmacotherapeutic intervention is cost-effective.[247 248] Finally, two (13.3%) studies were limited to male populations.[205 249]

Twelve of the included economic evaluations (80%) adopted a Markov cohort model, while three studies utilised more flexible and complex modelling techniques (Markov microsimulation model, n = 2; DES model, n = 1)[199 202 239].

There were similarities in Markov cohort studies, with many evaluations adopting a model built for the Swedish postmenopausal osteoporosis population[243] with parameter adjustments to suit the specific country. This Markov cohort model comprised eight states: well, hip fracture, vertebral fracture, wrist fracture, other osteoporotic fracture, post-hip fracture, post-vertebral fracture and an absorbing dead state. The fracture health state of 'other' comprised fractures of the pelvis, ribs, humerus, tibia, fibula, clavicle, scapula, sternum and femur.[243] The included DES model considered six events, comprising hip, vertebral and NHNV fractures; death due to hip fracture; entering a nursing home following hip fracture; and death due to causes other than hip fracture.[202]

Despite ample published models available in the evidence base, it was considered necessary to undertake an independent economic evaluation due to the significant limitations of applying available results to the Swiss context. The structure and assumptions of the *de novo* model were informed by published models; however, treatment efficacy estimates obtained in the network meta-analysis (***Section 7.4.4***), Swiss-specific baseline fracture risk estimates, and Swiss-specific cost data were used. Swiss-specific utility estimates were not available, therefore values from neighbouring countries (Germany, France and Italy)[250] and from the International Cost and Utilities Related to Osteoporosis fractures Study (ICUROS)[251] were utilised.

8.2.1.2 Overview of the economic model

A DES model (summarised in ***Table 15***) was developed to estimate costs and QALYs associated with denosumab, bisphosphonates, SERMs and no treatment, on a per-patient level via microsimulation. The model was developed using TreeAgePro (Version R1.1).[252]

Table 15 Summary of the economic evaluation

Perspective	Swiss payer
Patient population	Post-menopausal women with osteoporosis i.e. post-menopausal women with a BMD T-score of – 2.5 SDs or less, or in the case of fracture
Intervention	Denosumab (Prolia®)
Comparator	No treatment *Bisphosphonates*: Alendronate, Ibandronate, Risedronate, Zoledronate *SERMs*: Bazedoxifene, Raloxifene
Type of economic evaluation	Cost-utility analysis
Source of evidence	Trials, studies, TARMED, Swiss Spezialitätenliste, © COGE GmbH. Tarifpool. © SASIS AG, FRAX® calculation tool
Time horizon	Lifetime (10 years in sensitivity analysis)
Outcomes	QALYs
Methods used to generate results	Microsimulation using a DES model *Events:* hip, clinical vertebral and NHNV fractures; death due to background mortality *Fracture-attributable outcomes:* death due to hip or vertebral fracture; move to nursing home following hip fracture
Discount rate	3% p.a. (0% and 6% p.a. in sensitivity analysis)
Software package used	TreeAge Pro

Abbreviations:
BMD: bone mineral density; **DES**: discrete event simulation; **NHNV**: non-hip nonvertebral; **p.a.**: per annum; **SD**: standard deviation; **SERM**: selective oestrogen receptor modulator; **QALYs**: quality-adjusted life years.
Notes:
Morphometric vertebral fractures were excluded. NHNV includes fractures of the wrist and humerus. Osteoporotic fractures at other sites were not included given FRAX® algorithm was used to determine fracture probability.

Type of economic evaluation

A model-based economic evaluation using a DES structure was conducted. DES is run using patient-level simulation, allowing the effect of individual patient history on future events to be captured. While a state-transition model can be run using microsimulation, a DES model has the advantage of capturing time to clinical events in a more flexible and natural way.[202] In a DES system, patient progression is driven by events that occur rather than by probabilities of transition between health states within a fixed interval of time (i.e. the model cycle). Further discussion around the choice of a DES model is presented in the HTA Supplement.

A lifetime horizon was adopted, given that the prevention of an osteoporotic fracture, in particular of the hip or vertebra, has long-term consequences on costs and outcomes.[238] A scenario restricting the time horizon of the analysis to 10 years was included as a sensitivity analysis. The DES model was run with 200,000 iterations for each scenario.

Events in the DES system

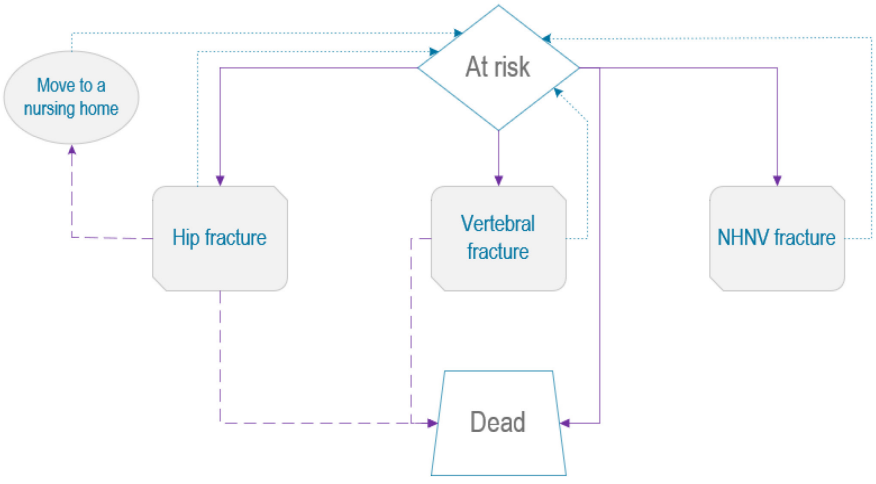
Fragility fractures are the main clinical outcome of osteoporosis and are thus the cornerstone of economic models. The consequences of fracture differ by site, so the site of fracture should be distinguished. In line with recommendations,[238] hip, clinical vertebral and NHNV fractures were included as separate events in the DES system. NHNV fracture events were limited to fractures of the forearm and humerus because FRAX®-based probabilities for MOF were used to derive time-to-fracture distributions. The FRAX® algorithm is limited to fractures of the hip, vertebra (clinical), forearm and humerus. Death due to background mortality was also included as an event within the DES system.

The events included in the DES system are depicted in ***Figure 84***. Patients begun the simulation at risk of an incident hip, vertebral or NHNV fracture or death due to background mortality. The occurrence of each of these events was driven by time-to-event data.

Fracture-attributable deaths and fracture-attributable nursing home admissions were assigned a probability of occurrence upon fracture. Excess mortality after fracture was computed from RRs of death after fracture reported for a Swedish population (see ***Section 8.3.2.3***).[253 254] Sensitivity analyses were undertaken to explore the sensitivity of model outcomes to the inclusion of each of these fracture-related events.

After a fracture event, surviving patients remained at risk of future fracture events and of death due to background mortality. The simulation ended upon a patient's death.

Figure 84 Visual depiction of the DES system



Abbreviations:
NHNV: non-hip non-vertebral
Notes:
The solid purple lines indicate events driven by time-to-event data. The dashed purple lines indicate fracture-attributable events which are assigned a probability upon fracture occurrence. Patients remain at risk of future fracture events and of background mortality after a non-fatal incident fracture. For each patient, the simulation is ended when they die.

Dummy events were required to allow age-dependent risk of fracture and QoL estimates to be updated as patients aged. We considered dummy events to be non-clinical events (i.e., not fracture related events nor background mortality), included in the model to allow the updating of certain patient attributes (age-dependent QoL and times-to-fracture) at set time points. These were included at time zero, at the end of treatment, the end of the offset period, and at five-yearly intervals.

In line with a recent osteoporosis DES model, an upper limit was set on the number of fractures that could be experienced—two hip fractures, four vertebral fractures and four NHNV fractures (i.e. one fracture per bone).[255] There were no limits on the sequence of fractures that could be experienced.[255]

Outcome

A cost-utility analysis was performed, employing QALYs as the outcome measure. The QALY is an attractive outcome measure for economic evaluations of anti-osteoporotic therapies, given that it can simultaneously capture the morbidity and mortality effects of fracture events and thus of anti-osteoporotic therapies.[238]

8.2.1.3 Intervention and comparator

The purpose of this evaluation was to estimate the cost-effectiveness of denosumab for the treatment of osteoporosis in postmenopausal women in Switzerland. In Switzerland, denosumab is reimbursed for the treatment of osteoporosis for postmenopausal women with a BMD T-score < –2.5 SDs or in the case of a fracture.[256] It is administered via a subcutaneous route, in 60 mg doses once every 6 months. Comparator anti-osteoporotic pharmacotherapies considered in the evaluation included alendronate, ibandronate, risedronate, zoledronate, raloxifene and bazedoxifene.

The network meta-analysis analyses informing the economic modelling excluded ibandronate and alendronate in the assessment of treatment effect on vertebral and nonvertebral fracture risk. Given this, oral bisphosphonates were grouped together in the DES system. IV ibandronate was considered separately given potential differences in patient adherence to therapy. While bazedoxifene was reimbursed at the time the research protocol was developed, the only preparation listed on the Spezialitätenliste (Conbriza®) has since been de-listed (removed 1 June 2021).[256]

Intervention and comparators included in the DES system are listed in ***Table 16***.

Table 16 Intervention and comparator drugs included in the economic model

Drug	Indication (postmenopausal women)	Dosing and regimen	Intended duration
Intervention			
DEN	T-score < –2.5 SDs or fracture	60 mg subcutaneous injection, every 6 months	5 years (10 in DSA)
Comparator*: *Bisphosphonates			
ALN †	T-score < –2.5 SDs or fracture	70 mg tablet, weekly	5 years
IBN (IV)	T-score < –2.5 SDs or fracture	3 mg IV injection, every 3 months	5 years
IBN (oral)	T-score < –2.5 SDs or fracture	150 mg tablet, monthly	5 years
RIS	T-score < –2 SDs at pelvis or LS or fracture	35 mg tablet, weekly	5 years
ZOL			
Comparator*: *SERMs			
RLX	T-score ≤ –1S D or fracture	20 mg tablet, daily	5 years
BAZ ‡	T-score ≤ –1 SD or fracture	60 mg tablet, daily	5 years

Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **DSA**: deterministic sensitivity analysis; **IBN**: ibandronate; **IV**: intravenous; **LS**: lumbar spine; **mg**: milligrams; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate
Notes:
T-score refers to a measure of BMD, defined as the number of SDs between a patient's BMD and the mean BMD peak value in a cohort of healthy younger individuals.
†: limit not specified for all ALN preparations listed on the Spezialitätenliste
‡: the only preparation of BAZ available on the Spezialitätenliste was de-listed 1 June 2021.

As per guidelines,[238] no treatment was included as a comparator in the DES system. The uptake of anti-fracture medication in the eligible population in Switzerland has been shown to be low,[21] suggesting many postmenopausal women with osteoporosis do not receive treatment.

Treatment duration

The economic evaluations identified in the literature review assumed a treatment duration for denosumab and its comparators of either three (n = 3)[199 239 242] or five (n = 12)[196 202 205 206 208 240 241 243-245 247-249] years.

Within the Swiss context, the SVGO has provided advice on the duration of therapy with anti-resorptive agents.[18 257] For postmenopausal women who have been on bisphosphonate therapy for three years (IV) or five years (oral), reassessment of individual fracture risk is recommended.[18] In women who remain at high risk, switching to either denosumab or teriparatide is recommended, while a drug holiday is recommended for patients at low risk.[18] European guidelines on the treatment of osteoporosis in postmenopausal women suggest that treatment with zoledronate has been found to provide only marginal benefits beyond three years.[31] In the DES model, intended treatment durations of five years

for alendronate, ibandronate and risedronate were assumed, while an intended duration of three years for zoledronate was adopted (***Table 16***). An intended duration of therapy of 3 years for IV ibandronate was explored in sensitivity analysis given it is an IV preparation.

For postmenopausal women who have been treated with SERMs for three to five years and remain at high risk, switching to denosumab or a bisphosphonate is recommended by the SVGO.[18] The intended treatment duration for raloxifene and bazedoxifene was also assumed to be five years in the DES model (***Table 16***).

For postmenopausal women who have been treated with denosumab for at least three to five years and remain at high risk, the SVGO recommends continuation of treatment for up to ten years or combination therapy with teriparatide, in women remaining at very high fracture risk.[18] For women at low risk after three to five years of treatment, discontinuation can be considered, after which sequential therapy with a bisphosphonate (or SERM in cases of bisphosphonate intolerance) is noted as mandatory by the SVGO.[18] In the DES model, an intended treatment duration of five years was assumed for denosumab in the base case, while a duration of ten years was explored in a sensitivity analysis (***Table 16***). A recent HTA from the UK perspective adopted an intended treatment duration of ten years for denosumab (and similarly to our DES system, five years for alendronate, ibandronate, risedronate and raloxifene, and three years for zoledronate).[255] Sequential therapy with a bisphosphonate upon discontinuation of denosumab was not considered because sequential therapies were outside scope of this HTA.

8.2.1.4 Methods used to generate results

The economic evaluation was limited to postmenopausal women with osteoporosis. The FRAX® tool, recommended for use in SVGO guidelines,[257] was used to quantify the baseline risk of fracture in Swiss women of postmenopausal age. The FRAX® tool determines the probability that an individual will sustain at least one fracture of the hip, spine, forearm or humerus (i.e. a MOF) within the next 10 years. Probabilities are estimated according to several CRFs and are presented as ten-year probabilities of MOF and of hip fracture. The FRAX® tool has previously been calibrated for Swiss-specific fracture risk and life expectancy,[227 258 259] and a FRAX® calculation tool specific to the Swiss context is available online.[237]

To use the FRAX® tool to inform time-to-fracture distributions, certain patient profiles had to be established, as described below.

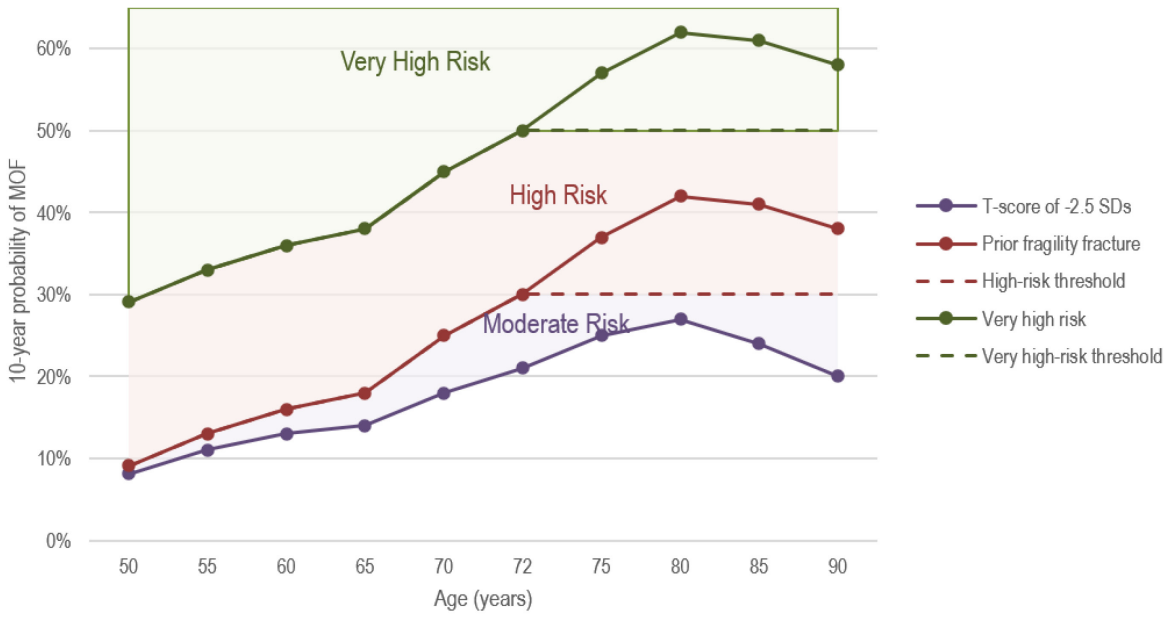
Baseline risk of fracture data

In Switzerland, denosumab is reimbursed for the treatment of osteoporosis in postmenopausal women with a BMD T-score of less than –2.5 SDs, or with a prevalent fracture.[256] In ***Figure 85***, the 10-year age-dependent FRAX®-derived probabilities of MOF for women with *(a)* a T-score of –2.5 SDs and no CRFs, and *(b)* a prior fragility fracture, no other CRFs and no measure of BMD, are shown.

SVGO guidelines define both high- and very high- (or imminent) risk thresholds, which are used to guide treatment recommendations.[22 257] Patients are considered high-risk if their FRAX® 10-year probability of MOF equals that of a woman of the same age with a prevalent fracture.[22 257] In guidelines, this high-risk threshold plateaus from the age of 72 (see ***Figure 85***). Patients are considered at imminent risk if they have suffered a recent (<2 years) clinical vertebral or low-trauma hip fracture, or any recent MOF after the age of 65 years. Patients are considered at very high-risk when their 10-year risk of MOF is ≥20% absolute risk above the intervention threshold at a given age (***Figure 85***).[22]

Patients with a BMD score less than –2.5 SDs, no previous fracture and a 10-year probability below the high-risk threshold are considered at moderate risk.

Figure 85 Sample age-specific FRAX® 10-year probabilities of MOF and associated risk levels



Abbreviations:
FN: femoral neck; **MOF**: major osteoporotic fracture; **SD**: standard deviation; **SVGO**: Schweizerische Vereinigung gegen die Osteoporose (Swiss Association against Osteoporosis).
Notes:
The FRAX® algorithm considers T-score at the FN.
High- and very high-risk threshold as per SVGO guidelines.[22] High-risk threshold set equal to 10-year risk in a woman of the same age with a prevalent fracture up to the age of 72 years, after which the threshold plateaus at a 10-year risk of 30%.
Very high-risk threshold at 20% absolute risk above the high-risk threshold.

The SVGO recommends a potent anti-resorptive therapy (a bisphosphonate or denosumab) for patients considered to be at high risk, with consideration being given to the potential use of teriparatide if there is a vertebral fracture or spine T-score <–3.5 SDs.[22] For patients at imminent or very high risk, first-line therapy with an anabolic agent (e.g. teriparatide) followed by an inhibitor of bone resorption is typically recommended.[22] Zoledronate, or alternatively denosumab, may be considered following a hip fracture.[22] Similarly, European guidelines recommend an oral bisphosphonate or other inhibitor of bone resorption (e.g. denosumab) in high-risk patients, and an anabolic agent followed by an inhibitor of bone resorption in very high-risk patients.[260] For patients believed to be at moderate risk, it is recommended that a SERM is considered, followed by an oral bisphosphonate if BTM remains above the premenopausal threshold.[22]

Taking risk-dependent treatment recommendations into account, the pale red shaded area in ***Figure 85*** captures the most likely 10-year probabilities of MOF among patients treated with denosumab (i.e. patients at high fracture risk).

The cohorts considered in the economic evaluation were defined by FRAX® risk levels rather than by specific clinical indicators (e.g. BMD or fracture history). We mapped the clinical indications for the use of denosumab (T-score of –2.5 SDs or a history of fracture) to FRAX® 10-year probabilities of MOF. These, in the absence of other CRFs, correspond to the moderate or high-risk thresholds, respectively. We also considered women at the very high-risk threshold, which reflects the upper bound for first line intervention with denosumab according to the SVGO guidelines. Above this threshold, first line therapy with an anabolic agent, rather than an anti-resorptive, is recommended. In summary, the DES model has considered patient populations with age-dependent 10-year probabilities along the solid purple, red and green lines in ***Figure 85*** (moderate, high and very high risk, respectively).

Conversion of FRAX® probabilities into fracture rates

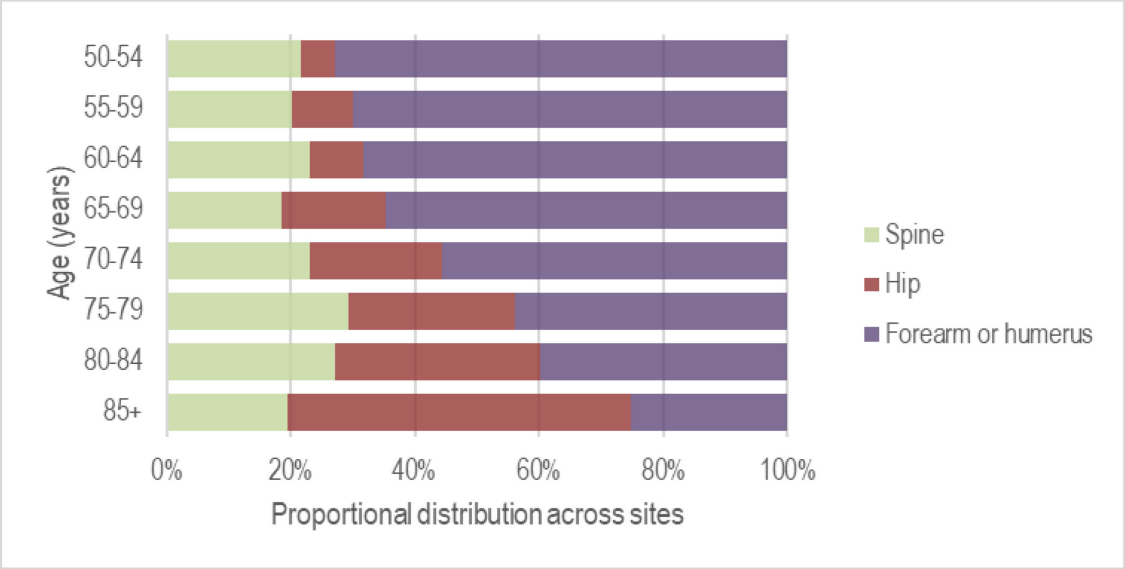
To inform the DES model, age-dependent ten-year probabilities of MOF were extracted from the web interface at five-yearly intervals for each of the three risk levels. The extracted probabilities were then converted to annual rates and further proportionally distributed across vertebral, hip and NHNV fracture locations to align with the events included in the economic model. This approach allowed the baseline 10-year MOF probabilities from the FRAX® tool to be converted to fracture site-specific annual rates across age brackets.

Annual incidences of osteoporotic-related fractures at the hip, spine, distal radius or proximal humerus (hospitalised and non-hospitalised) in Switzerland have previously been determined from national epidemiological data.[258] The proportions of fractures at each site were calculated from these data to inform the age-dependent proportion of MOF risk attributable to each fracture type included in the DES

model (***Figure 86***). In line with the DES model structure, the four fracture locations were simplified to hip and vertebral fractures, plus a combined fracture location where the forearm and humerus fractures were aggregated to represent NHNV fractures.

Notably, the proportion of MOF risk attributable to hip fractures increases with age, while the proportion attributable to forearm or humeral fractures decreases (***Figure 86***).

Figure 86 Age-specific distribution of MOF risk across fractures sites, Switzerland



Use of FRAX® -derived 10-year probabilities of MOF allowed us to model the major incident fractures occurring in our population of interest; however, the overall risk of fragility fracture will be underestimated, given that fractures at other sites (i.e. femur, pelvis, rib, clavicle, scapula, sternum) have not been considered.

The annual event rates were used to simulate time-to-event distributions via survival analysis. In the DES model, patients were assigned times-to-vertebral, -hip, and -NHNV fracture from these distributions. The assigned values were interpreted as either time since treatment initiation/discontinuation, or time since last fracture (depending on when the patient was assigned the time-to-fracture value). Details of the simulation process are provided below.

Time-to-fracture analysis for baseline population

Upon obtaining the fracture event rates from the 10-year FRAX® probabilities, the rates were further converted back to annual probabilities to simulate the survival curve. Prior to this conversion, annual rates against the nine age brackets were linearly interpolated across individual ages to smooth the prediction. A cohort of 1,000 patients was used to simulate the hazard and survival function, where the number of patients at risk reduced over time due to fractures. Hazards were calculated as the patients

experiencing fracture events over the remaining patients at risk. Survival probabilities were then produced iteratively for model fitting using Weibull parametric regression.

This approach was undertaken against the three possible fracture locations (hip, vertebral and NHNV) and the regression parameters for Weibull distribution (i.e. the shape and the scale parameters) were estimated as inputs for the DES system. The simulated data were plotted against the parametric predicted values to examine the model fitting. As all the fitted models exhibited highly significant outcome with goodness of fit over 95%, other parametric forms for other distributions were not produced. Further discussion around the methodology adopted, including details on the choice of Weibull model and an examination of model fit, is presented in the HTA Supplement.

8.3 Evidence table

8.3.1 Utilisation of the clinical effectiveness outcome in DES model

The aim of treatment with anti-osteoporotic therapies is to reduce the risk of fracture. The clinical effectiveness of different drugs for postmenopausal women was investigated by Bayesian network meta-analysis. RRs of fractures compared to placebo were produced as the result of network meta-analysis. The detailed results are reported and discussed in ***Section 7.4.4***. RRs were calculated for both vertebral and nonvertebral fracture, and against five of the seven included drugs (denosumab, risedronate, zoledronate, raloxifene and bazedoxifene). The RRs for two drugs (ibandronate and alendronate) could not be derived due to limitations of the available data. Instead, the RR for risedronate was used as a proxy to reflect the risk reduction from treatment with any oral bisphosphonate or IV ibandronate. Across all drugs, the reduction in risk of nonvertebral fracture was used to reflect the risk reduction for both hip and NHNV fractures.

The network meta-analysis with all drugs included (where possible) generated viable RR values to be used for the DES model. However, almost all the credible intervals were across the neutral line, indicating almost no therapies were significantly better than placebo. The point estimate for the RR for risedronate for nonvertebral fracture (used as a proxy for both oral bisphosphonates and IV ibandronate) was significantly lower than others, with its CrI significantly wider (RR = 0.2; 95% CrI = 0.00–0.97). However, the 95% CrI of all alternatives overlapped, suggesting we cannot be confident that the true effect of risedronate on nonvertebral fracture risk is significantly greater than any other anti-osteoporotic drug, despite this being suggested by the point estimates.

A recent network meta-analysis exploring the comparative effectiveness of drug treatments to prevent fragility fractures, reported hazard ratios (HR) for risedronate of 0.52, 0.73 and 0.66 in the prevention of vertebral, nonvertebral and hip fractures, respectively.[255] This same study reported HRs of 0.47, 0.78

and 0.64 for bisphosphonates (class effect).[255] Notably, point estimates for the effect of risedronate or oral bisphosphonates (class effect) on nonvertebral (HR = 0.73 and 0.78, respectively) or hip fracture risk (HR = 0.66 and 0.64, respectively) were not lower than the estimates for denosumab, zoledronate and/or raloxifene (nonvertebral, HR = 0.73 to 0.99; hip, HR = 0.56 to 0.94). While this network meta-analysis was not restricted to postmenopausal women, most of the included RCTs were conducted in this population, therefore the results most directly apply to those patients. Results suggest the difference in effect between risedronate/oral bisphosphonates and other interventions may not be as large as is implied by our network meta-analysis point estimates.

Further clinical investigation indicated that the low point estimate for risedronate in our network meta-analysis was likely due to low sample sizes and event counts in both the active therapy arms and the placebo arms. This may result in bias against other drugs. Therefore, a sensitivity analysis of the network meta-analysis was undertaken to exclude risedronate for nonvertebral fracture. The complete results of the sensitivity analysis are presented in the HTA Supplement. Updated RRs for denosumab, zoledronate, raloxifene and bazedoxifene were produced and applied to the DES model for the base case evaluation. Given the evidence limitations around alendronate and ibandronate, the exclusion of risedronate left limited clinical effectiveness data to inform the nonvertebral fracture RR input variable for oral bisphosphonates and IV ibandronate. The point estimate for the RR of raloxifene on nonvertebral fractures (i.e. the next lowest point estimate after the exclusion of risedronate) was used as a proxy for both oral bisphosphonates and IV ibandronate, and the impact was tested by sensitivity analyses (described below).

Results from the network meta-analysis informing the economic model are listed in ***Table 17***.

Table 17 RRs used in the economic model

Drug	Vertebral Fracture RR (95% CrI)	Rank	Nonvertebral Fracture RR (95% CrI)	Rank
ALN	NA	–	NA	–
BAZ	0.99 (0.23 to 2.80)	*5*	0.92 (0.32 to 2.04)	*3*
DEN	0.37 (0.06 to 1.11)	*1*	0.92 (0.24 to 2.54)	*2*
IBN	NA	–	NA	–
RIS	0.55 (0.08 to 2.02)	*3*	NA	–
RLX	0.58 (0.08 to 1.46)	*4*	0.80 (0.23 to 1.70)	*1*
ZOL	0.48 (0.14 to 1.45)	*2*	1.04 (0.42 to 2.52)	*4*

Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **IBN**: ibandronate; **NA**: not applicable; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
For nonvertebral fracture, RRs for BAZ, DEN, RLX and ZOL taken from an updated network meta-analysis from which RIS was excluded.

Due to overlapping 95% CrIs, we cannot be confident that one intervention will perform better than any other in terms of fracture risk reduction, unlike what is suggested by the reported point estimates. To explore whether uncertain differences in the point estimates were driving the economic outcomes, sensitivity analyses were conducted in which the efficacies of all therapies in reducing (1) vertebral fracture risk, (2) nonvertebral fracture risk, and (3) both vertebral and non-vertebral fracture risk were assumed equivalent.

8.3.1.1 Time-to-fracture for patients on drug therapies

Time-to-fracture analyses for patients receiving therapies were undertaken using parametric survival analysis, using the same techniques as for FRAX® for the baseline population. Age-specific fracture rates were multiplied by the RR for individual therapies to derive the drug-specific fracture hazard. As a result, three fracture sites and five drugs combined with nine age brackets to produce a total of 135 (135 = 5 × 3 × 9) fracture rates. These annual rates were then modelled to simulate time-to-fracture data and fitted for parametric survival analysis using the Weibull scenario. A total of 15 sets of Weibull parameters (shape and scale) were computed as inputs for the DES model to characterise times-to-fracture for each drug therapy.

Further description of the methodology adopted, and the translational issues encountered is provided in the HTA Supplement.

8.3.1.2 Other considerations for the time-to-fracture event

Each patient, upon entry into the model, was assigned a time-to-fracture for each event in the system (i.e. hip, vertebral and NHNV fractures) by sampling corresponding Weibull distributions. These events would occur sequentially to drive patients through the model. To allow repeat fractures at the same site, upon sustaining a fracture, patients are assigned a new time-to-fracture for the same fracture. This process occurs through a similar sampling mechanism as occurs at model entry, taking into account a patient's current age within the model. This is realised by altering the initial age of the survival analyses against different drugs and fracture sites to obtain alternative parameters for the Weibull distributions. Additionally, each patient was assigned new times-to-fracture upon ending treatment and ending the offset period. This was necessary to ensure that a patient's risk of fracture was reflective of their risk going forward, at the age they were when they ended treatment or the offset period.

Fracture-attributable deaths and fracture-attributable nursing home admissions were assigned a probability of occurrence upon fracture. The maximum number of repeated fractures (i.e. vertebral = 4, NVNH = 4 and hip = 2) were also implemented to reflect the plausible clinical scenarios during resampling.

8.3.2 Additional model inputs

8.3.2.1 Residual effect after treatment

Bisphosphonates

Bisphosphonates are characterised by a residual effect after discontinuation. As per recommendations,[238] the beneficial effect of bisphosphonates was assumed to decline in a linear manner over a period of time equal to treatment duration (up to five years) (***Table 18***).

In a recent HTA,[255] the offset period for zoledronate was assumed to be longer; it being assumed that the beneficial treatment effects falls to zero after ten years from the start of a three-year treatment period (or over a proportional period if treatment was discontinued early). This assumption was, conservatively, borrowed for our model (***Table 18***). A sensitivity analysis in which the offset period for zoledronate was set equal to treatment duration, as done for the other bisphosphonates, was also conducted.

Denosumab

The residual effects of denosumab are limited, with recent studies suggesting rapid decline in BMD and increased risk of multiple vertebral fractures.[99 261].

In a post-hoc analysis of the FREEDOM RCT, Cummings et al. 2018 analysed the risk of new or worsening vertebral fractures in participants who discontinued denosumab during the FREEDOM study or its extension.[159] It was found that among participants who discontinued denosumab, the risk of new and worsening vertebral fracture quickly increased to levels similar to the risk in untreated participants.[159]

As per a recent example,[255] the beneficial effect of denosumab was assumed to disappear by one year after treatment discontinuation (or after a period equal to the treatment duration if the patient was on treatment for less than one year) (***Table 18***). Sensitivity analyses were conducted in which *(1)* the offset period of denosumab was removed completely, and *(2)* the offset period of denosumab was set equal to treatment duration. These analyses were conducted to facilitate an exploration of the impact of the limited residual benefit of denosumab on cost-effectiveness outcomes.

SERMs

As per a recent example,[255] the beneficial effect of raloxifene was assumed to disappear by 1 year post-treatment discontinuation (or after a period equal to the treatment duration if the patient was on treatment for less than one year) (***Table 18***). We also extended this assumption to bazedoxifene (***Table***

18). Sensitivity analyses were conducted in which *(1)* the offset period for raloxifene, and *(2)* the offset period for bazedoxifene, were set equal to treatment duration.

Table 18 Offset periods assumed in the economic evaluation

Drug	Intended duration	Offset period (base case)
DEN	5 years (10 years in DSA)	1 year (or equal to treatment duration if treatment <1 year)
Oral bisphosphonates	5 years	Up to 5 years (equal to treatment duration)
IV IBN	5 years	Up to 5 years (equal to treatment duration)
ZOL	3 years	Up to 7 years (or proportionally equivalent period if duration <3 years)
SERMs	5 years	1 year (or equal to treatment duration if treatment <1 year)

Abbreviations:
DEN: denosumab; **DSA**: deterministic sensitivity analysis; **IBN**: ibandronate; **IV**: intravenous; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate

Additional time-to-fracture distributions were constructed for patients during the offset period. RR reductions were assumed to decline linearly over the offset period. To reflect this, the midpoint between the RR reduction and no effect (i.e. RR = 1), was applied to patients' baseline risk of fractures during the offset period, and time-to-fracture distributions for the offset period were derived.

8.3.2.2 Adherence to therapy

For optimal outcomes from anti-osteoporotic therapy, patients must adhere to intended dosing instructions for the prescribed duration (i.e. comply with and persist with therapy). However, adherence to anti-osteoporotic medication is far from optimal. Poor adherence negatively impacts the anti-fracture benefit, and thereby cost-effectiveness, of anti-osteoporotic medications. Reduced drug effectiveness due to poor compliance/persistence has been found to be a potentially important driver of cost-effectiveness.[262 263] It has been suggested that persistence can improve cost-effectiveness as long as the difference in drug price is not too large.[262]

It is possible that the benefit of improved compliance is, to some extent, captured by RCTs, and a conservative approach to modelling compliance may be appropriate.[262] As per a previous example, poor compliance was not adjusted for in our economic evaluation – it thereby being assumed that compliance would be similar as seen in the RCTs from which the data on efficacy were taken.[243]

Persistence with therapy

A previous osteoporosis economic evaluation in the Swiss context, which assessed the cost-effectiveness of intervention with alendronate versus no treatment, assumed a 50% dropout rate during the first half-year cycle and no dropouts thereafter.[259] However, this study did not consider persistence across other anti-osteoporotic therapies of interest.

Many previous evaluations assessing the cost-effectiveness of denosumab in other European countries have used country-specific real-world medication adherence data for oral bisphosphonates and applied the RR of non-persistence from the Denosumab Adherence Preference Satisfaction (DAPS) study.[199 205 208 243] A Spanish cost-effectiveness study taking this approach used medication adherence data from Sweden, given a lack of country-specific data.[241] Studies including other parenteral administrations (e.g. zoledronate) have assumed the same persistence as denosumab, taking into account the different timepoints of administration.[205 241 247]

The DAPS study—a 2-year randomised cross-over trial comparing patient preference, adherence to and satisfaction with oral alendronate vs denosumab among postmenopausal women—found that at 12 months, 20.2% of patients in the alendronate arm had discontinued therapy compared with 9.5% in the denosumab arm (RR = 0.5; 95% CI 0.27 to 0.93).[46]

No publications describing persistence rates with anti-osteoporotic therapies in Switzerland were identified.

Persistence at 12 months

In a systematic review of retrospective studies estimating treatment persistence with oral bisphosphonates, the pooled rate of persistence at 12 months across Europe was estimated to be 46% [95% CI 43 to 49].[264] Another systematic review provided pooled estimates on persistence with parenteral osteoporosis therapies at 12 months (median: 47.5% for IV ibandronate; 81% for denosumab; 42% for zoledronate); however, these were not specific to Europe.

In Germany, 12-month persistence with oral bisphosphonates of 51% (ibandronate), 44.8% (alendronate) and 35.2% (risedronate) have been reported.[265] When weighted by the size of patient populations for alendronate, oral ibandronate and risedronate in Switzerland (calculated from © COGE GmbH. Tarifpool. © SASIS AG sales data; see ***Figure 97***, ***Section 8.5.4.1***), a 12-month persistence of 0.457—close to the meta-analysis result—is derived. For oral bisphosphonates, this rate was adopted in the base case (***Table 19***). In this same German study,[265] 12-month persistence rates of 56.6% and 65.6% for IV ibandronate and zoledronate, respectively, were also reported and have been used in the base case (***Table 19***). In another German study, 12-month persistence with oral bisphosphonates, IV

ibandronate and zoledronate were reported at 30.1–31.4%, 42.9% and 33.8%, respectively.[105] These estimates were used in a sensitivity analysis.

In Germany, 12-month persistence with denosumab has been reported at 55.9% and 93.0% in two different studies.[105 211] Applying the rate ratio for non-persistence reported in the DAPS study (RR = 0.5)[46] to the non-persistence rate adopted for oral bisphosphonates, the derived 12-month persistence rate for denosumab falls between the two reported values (i.e. 0.729). This rate was used in the base case evaluation (***Table 19***).

In Sweden,12-month persistence with raloxifene of 42.4% has been reported.[266] In this same study, 12-month persistence with alendronate and risedronate were reported at 51.7% and 50.6%,[266 267] respectively, slightly higher than the 45.7% used in the DES. Nonetheless, a 12-month persistence of 42.4% was adopted for both raloxifene and bazedoxifene in the base case; a potentially conservative assumption.

Persistence at 24 months

In the systematic reviews described above,[264 268] mean 24-month persistence with oral bisphosphonates, IV ibandronate, denosumab and zoledronate were reported at 30%, 25%, 45.5% and 35.8%, respectively. None of these values were specific to Europe.

Of the European studies reporting 24-month persistence data for oral bisphosphonates,[264] the weighted average reported persistence was 26.2% (calculated ad hoc here). This value was used in the base case analysis (***Table 19***). Of the European studies reporting 24-month persistence data for IV ibandronate, the average reported value was 31.7%; for zoledronate, it was 35.8% (***Table 19***). 24-month data reported by Hadji et al. 2016 of 16.7–17.5%, 24.8% and 20.9%, respectively, for oral bisphosphonates, IV ibandronate and zoledronate were used in the sensitivity analysis.

In Germany, 24-month persistence with denosumab has been reported at 39.8–75.1%,[105 269] with an average of 57.5% (calculated ad hoc here) (***Table 19***). Differences in estimated persistence rates may be due to alternate endpoint definitions, or the prospective versus retrospective study designs.[105]

In Sweden, 24-month persistence with raloxifene of 26.0% has been reported.[266] The Swedish estimate was again used in the base case (***Table 19***).

Table 19 Non-persistence data used in the economic evaluation

Drug	Regimen	Intended duration	Persistence at 1 year	Persistence at 2 years
DEN	Subcutaneous injection, 6-monthly	5 years (10 years in DSA)	0.729 (0.559; 0.93 in DSA)	0.575 (0.398; 0.751 in DSA)
Oral bisphosphonates	Weekly (ALN; RIS) or monthly (IBN) tablet	5 years	0.457 (0.302 in DSA)	0.262 (0.172 in DSA)
IV IBN	IV injection, every 3 months	5 years	0.566 (0.429 in DSA)	0.317 (0.248 in DSA)
ZOL	IV injection, yearly	3 years	0.656 (0.338 in DSA)	0.358 (0.209 in DSA)
BAZ	Daily tablet	5 years	0.424 (0.302 in DSA)	0.26 (0.172 in DSA)
RLX	Daily tablet	5 years	0.424 (0.302 in DSA)	0.26 ().172 in DSA)

Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **DSA**: deterministic sensitivity analysis; **IBN**: ibandronate; **IV**: intravenous; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

Summary

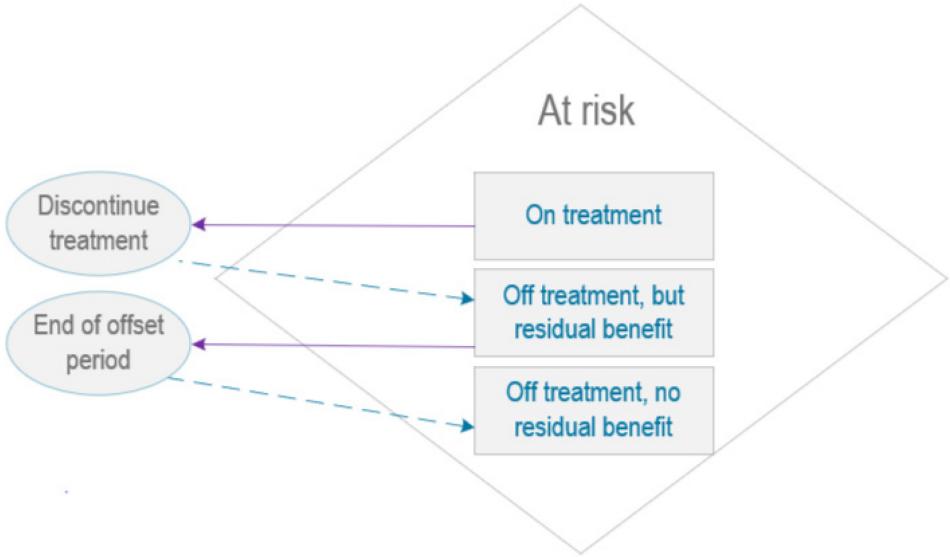
Patients were assumed to be at risk of non-persistence during the first two years of treatment and if persistent at two years, were assumed to remain persistent for the intended five-year period. This differs slightly from a previous model, which assumed patients to be at risk of non-persistence during the first three years of treatment,[243] as German real-world data were limited to two years follow-up. Non-persistence estimates informed TreeAge table distributions, from which each patient who entered the DES system was assigned a duration of therapy for each therapy, based on the non-persistence estimates reported in ***Table 19***.

For example, for denosumab, 72.9% and 57.5% of patients were assumed to remain on treatment at one and two years, respectively (***Table 19***). Each patient had a 27.1% chance of be assigned a duration of therapy value of either 6 months or 1 year (13.6% chance for each), a 15.4% chance of being assigned a value of either 1.5 or 2 years (7.7% chance for each), and a 57.5% chance of being assigned a value of 5 years. Denosumab is administered as a 6-monthly dose, therefore duration of therapy values were assigned at 6-monthly intervals. For bisphosphonates and SERMs, 3-monthly intervals were used, except for zoledronate for which a yearly-interval was used given it is administered as a once-yearly injection.

A patient remained on therapy until the simulation clock reached the patient's assigned time-on-therapy. At this point, the patient's attributes were updated to reflect that they had discontinued therapy and entered an offset period. The patient was re-assigned age-dependent time-to-fractures based on

distributions derived using RRs reflective of a treatment's residual benefit (see ***Section 8.3.2.1***). A patient's attributes were again updated when they moved from the offset period to the off-treatment period, and age-dependent times-to-fracture from baseline distributions (i.e., without any RRs applied) re-assigned. As noted in ***Section 8.3.1.2***, the re-assignment of time-to-fractures at these time points was needed to ensure that a patient's risk of fracture was reflective of their risk going forward, at the age they were when they ended the treatment or offset period. Dummy events were required to allow these updates to occur (visual representation provided in ***Figure 87***). The assumed durations of residual benefit for each drug were discussed previously, in ***Section 8.3.2.1***.

Figure 87 Visual depiction of dummy events included to capture changes in fracture risk upon treatment discontinuation



Notes:
Purple arrows indicate the occurrence of a dummy event – i.e., the discontinuation of therapy or the end of the offset period. Upon the occurrence of each dummy event, patients are reassigned time to fracture distributions representative of their fracture risk based on their current age and treatment status.

Several sensitivity analyses were performed on non-persistence estimates. The first assigned values reported by Hadji et al. 2016 for all interventions (these were not applied in the base case, given they were consistently lower than pooled estimates).[105] The second and third maintained base case assumptions for all interventions except denosumab, for which alternative persistence data for Germany was used.[105 211 269] In one scenario this translated into improved persistence with denosumab relative to base case assumptions; in the other, this translated into worsened persistence with denosumab. Finally, a scenario assuming full persistence for all therapies was conducted.

8.3.2.3 Mortality

Background mortality

The Swiss lifetable for 2019 published by the WHO provided the input data to inform background mortality in the DES system.[270] The reported age-specific rates informed a TreeAge distribution from which every patient who entered the system was assigned an age at death (conditional sampling above start age). Time to background mortality was constantly updated until the entity's age reached the assigned age at death.

Excess mortality after a fracture event

Each patient who sustained a hip or clinical vertebral fracture was exposed to an increased risk of mortality in the year of the fracture event. This was included in the DES system as a probability of death due to fracture. The probabilities used in the model are outlined in ***Table 128*** (***Appendix H***).

The method taken to compute excess mortality after hip and clinical vertebral fracture was informed by previous publications in which fracture-attributable deaths across 27 European countries, and later, Switzerland, were estimated.[21 254] Documented RRs of death after fracture for Sweden were applied to age- and country-specific mortality rates.[253 254] In contrast to the aforementioned publications,[21 254] death due to NHNV fractures was not considered because guidelines currently recommend the inclusion of excess mortality after hip and clinical vertebral fractures only in economic evaluations.[238]

It must be considered that only 25–30% of observed excess mortality after fracture events may be directly attributable to the fracture itself.[238] As per the aforementioned publications, [21 254] it was assumed that 30% of the excess mortality was attributable to the fracture itself, and that excess mortality was only present during the first year.

While the aforementioned publications modelled fracture-attributable deaths to occur 140 days after the fracture event,[21 254] we assumed that all death related to hip and vertebral fractures occurred exactly three months (approximately 90 days) after the fracture events, as per a previous DES osteoporosis model.[255 271] In our DES model, three months' worth of QALYs—accrued at the age-specific utility adjusted by the post-hip or post-vertebral fracture utility multiplier—was assigned as a final payoff to those dying from a fracture.

8.3.2.4 Nursing home admission after hip fracture

Hip fractures are associated with increased admission to long-term care facilities, which carry long-term fracture-attributable costs and should be included in economic models.[238] As per recommendations,[238] patients were at risk of admission to a nursing home facility following a hip fracture event.

The risk of nursing home admission was included as a probability following a hip fracture event; the age-dependent probabilities being informed by a recent evaluation in the UK context (see ***Table 128***, ***Appendix H***).[255] As per previous examples,[208 243] patients who were admitted to a nursing home were assumed to remain there permanently.

The inclusion of nursing home care costs was considered appropriate given a previous economic evaluation of anti-osteoporotic pharmacotherapy which, similarly to our model, adopted a Swiss healthcare system perspective and included the cost of nursing home care.[259] Nonetheless, a scenario analysis in which the chance of nursing home admission was removed from the model was undertaken to explore the overall sensitivity of cost-effectiveness outcomes to this inclusion.

The cost of nursing home care was included to capture the long-term disability costs associated with fragility fractures. Background risk of nursing home admission has not been considered within the DES system. The cost of nursing home care directly attributable to fragility fractures may be slightly overestimated; if background risk was considered, some patients may have already moved to a nursing home for other reasons prior to fracture. QoL and risk of fracture may differ between patients living at home versus those in an aged care facility; however, the DES system assumed that patient utilities and fracture risks are not dependent on residential status. This was a purely pragmatic decision but one thought to have minimal impact, given the risk of nursing home admission is small.

8.3.2.5 Adverse events (AEs)

Recommendations suggest side effects be included in sensitivity analyses;[238] however, the network meta-analysis performed as part of the clinical effectiveness review found no statistically significant differences in AE or SAE rates across interventions or between any intervention and placebo (***Section 7.4.5***). Previous economic evaluations have, in general, found treatment-related adverse events to have only a small impact on cost-effectiveness outcomes (discussed in detail in ***Section 12.4***). As such, the direct impact of AEs on cost and QoL has not been considered. However, having incorporated estimates of non-persistence into the model, some negative impact of AEs on treatment efficacy may have been captured indirectly.

8.3.3 Utility measures

With regard to utilities, guidelines for the conduct of economic evaluations in osteoporosis suggest the use of age-specific population norms and the application of disutility multipliers following fracture events by fracture site and time since fracture (first and subsequent years).[238]

8.3.3.1 EQ-5D population norms

National EQ-5D population utility norms for Switzerland were not identified. Instead, gender- and age-specific EQ-5D-3L index population norms for three (France, Germany and Italy) of five neighbouring countries valued using country-specific time trade-off value sets,[250] were used (see ***Table 129***, ***Appendix H***). Guidelines recommend the use of data from neighbouring countries if national data is not available.[238] Preference-based valuation sets, such as those derived from time trade-off data, are preferable in economic studies.[254 272]

8.3.3.2 Disutility multipliers due to fracture

Disutility multipliers were sourced indirectly from ICUROS.[251 273] ICUROS is a multinational observational study in which participant QoL was measured using EQ-5D-3L and translated into health state utility values using a value-set based on population preferences in the UK (derived using the time trade-off method).[251] Guidelines recommend use of national ICUROS data if available or overall ICUROS data in the absence of national data.[238] A recent economic framework in the context of fracture prevention in osteoporosis provided the disutility multiplier values needed for the DES model—for the first and subsequent years after hip, vertebral and NHNV fractures—sourced from the ICUROS.[273] The utility multipliers used in the model are outlined in ***Table 130*** (***Appendix H***).

8.3.4 Cost inputs

8.3.4.1 Medication costs

Medication costs were calculated on an annual basis, with patients incurring medication costs for a period equal to the time spent on therapy. Annual medication costs were derived using Spezialitätenliste prices for medications, along with TARMED prices for the associated services provided as part of drug administration or treatment monitoring. Medication costs inputs used in the model are outlined in ***Table Table*** 131 (***Appendix H***).

SVGO guidelines note therapy monitoring usually involves repeat measurements of bone mineral content levels (after two years of treatment) or levels of bone formation and absorption markers (three to six months after the start of therapy).[257] In line with a previous Swiss study,[21] monitoring costs were calculated by assuming all patients made an annual physician visit and received a DXA scan every two years to monitor treatment effect.

Parenteral injections were assumed to be given by a specialist (e.g. rheumatologist or endocrinologist), with zoledronate additionally assumed to require a short stay in an outpatient or day clinic.[255] Previous evaluations have applied the cost of two nurse visits per year to reflect the cost of denosumab administration.[205 208 243] For denosumab administration costs, the TARMED position for “injection by a

non-medical personnel" (00.0750) was used in a sensitivity analysis to account for potential variations in practice.

8.3.4.2 Fracture-related costs

Acute fracture-related costs comprised hospital, rehabilitation and ambulatory care costs. Long-term disability costs were included for patients requiring long-term nursing home care after a hip fracture. Fracture-related costs used in the model are outlined in ***Table 132*** (***Appendix H***).

Swiss-specific, acute, fracture-related costs were estimated for hip, vertebral and forearm fracture events. This costing approach was informed by previous Swiss osteoporosis models and other studies.[21 28 259 274] For NHNV (i.e. forearm or humeral) fracture events, the average cost of vertebral and forearm fractures was used as a proxy. In previous burden of disease studies across Switzerland and other European countries,[21 254] the cost of fractures at sites other than the hip, spine or forearm have been equated to the cost of fracture at one of these sites; the cost for a humeral fracture having been equated to the cost of a vertebral fracture.[21 254]

Hospital care was assumed to be required for 100%, 33% and 53% of patients after hip, vertebral and NHNV fractures, respectively.[259 274] Hospital costs were estimated by multiplying Swiss length of stay (LOS) data by the daily cost of acute care (CHF2,303)[275] LOS used in previous evaluations was derived using hospital data from the year 2000;[259 276] however, LOS in acute care has dropped over time, so LOS data were adjusted to account for this.[275]

Similarly, rehabilitation costs after hip fracture were estimated by multiplying Swiss LOS data by the daily cost of care in a rehabilitation facility for patients requiring rehabilitation care (CHF816).[275] In the base case it was assumed that 76% of patients would require rehabilitation after a hip fracture, 44% after a vertebral fracture and 11% after a forearm fracture.[28] Again, LOS in a rehabilitation facility was adjusted to account for the decreasing LOS over time.[259 275 277]

Reported ambulatory costs following hip, vertebral and forearm fractures in Switzerland for the year 2000 (CHF6,442, CHF2,250, and CHF1,750, respectively) were projected to 2020 costs.[259 274 278]

The annual cost of nursing home care was calculated by multiplying the daily cost of nursing home care (CHF307)[275] by 365, except for the first year after fracture, for which nursing home costs were applied for a period of nine months.[28]

8.3.5 Limitations of the economic model structure

8.3.5.1 Treatment sequencing

Post-hoc analysis of the FREEDOM RCT and its extension has shown that vertebral fracture risk quickly returns to pre-treatment levels upon discontinuation of denosumab therapy, suggesting patients who receive two or more doses and then discontinue denosumab should transition rapidly to another antiresorptive therapy, especially those with a history of vertebral fracture.[159] European and Swiss guidelines now recommend treatment with a bisphosphonate upon discontinuation of denosumab.[18 31] In our DES system, which sought to make a direct comparison between denosumab and alternative interventions, sequential therapies upon treatment discontinuation were not considered. This is an oversimplification of what would occur in practice.

8.3.5.2 Imminent risk

Evidence suggests the risk of subsequent osteoporotic fracture is highest immediately after the index fracture (termed imminent risk) and wanes progressively with time.[279 280] In our DES system, a patient's fracture risk was set at either a moderate, high or very-high level (as described in ***Section 8.2.1.4***). The model allowed for fracture risk to be altered during the treatment and offset periods, and for aged-based increases to occur at 5-yearly intervals to capture treatment- and age-related impacts on fracture risk. However, patients' categorisation as either moderate, high, or very high risk was not altered during the simulation process, and thus, increases in fracture risk immediately after a fracture event were omitted. Again, this is an oversimplification of reality. Underestimating a patient's risk of fracture immediately after an incident fracture may result in an underestimation of the full benefit of fracture prevention. Analyses based upon a novel economic framework (published JAN- 2021) found model outcomes for a sequential therapy (bone forming agent following by antiresorptive) versus antiresorptive therapy comparison to be sensitive to the inclusion of imminent fracture, with the deactivation of the imminent fracture risk algorithm being associated with lower incremental QALYs and higher incremental costs.[273]

8.3.6 Willingness-to-pay threshold

An explicit willingness-to-pay (WTP) threshold does not exist in Switzerland. Where an ICER could be calculated (i.e. when the intervention was not dominated or extendedly dominated), a hypothetical WTP threshold of CHF100,000 was considered.

8.3.7 Sensitivity analysis

Base case results were obtained for women with a start age of 70 years and a risk of MOF equivalent to that of a woman of the same age with a prevalent fracture and no other CRFs. Scenario analyses

were undertaken to explore the impact of age and baseline fracture risk on cost-effectiveness outcomes. Start ages of 60 and 80 years, as well as risks of MOF equivalent to those of a woman with a T-score of –2.5SDs or equivalent to the very high-risk threshold (see ***Section 8.2.1.4***), were considered.

Deterministic sensitivity analyses were undertaken to explore the robustness of model outcomes to various structural and parameter-related assumptions, including treatment efficacy point estimates (***Section 8.3.1***), the intended duration of denosumab (***Section 8.2.1.3***), persistence with therapy (***Section 8.3.2.2***), the offset period for various drugs (***Section 8.3.2.1***), and structural assumptions around the time horizon, discount rate, and inclusion of fracture-related deaths and transitions to nursing home care (***Section 8.2.1.2***).

In addition, descriptive and comparative analyses were conducted on the 200,000 individual Monte Carlo patient-level simulation outputs to evaluate the propagation of stochastic (first order) uncertainty. Costs and QALY outcomes were analysed separately to investigate differences across the seven treatment options. The methods and results for these analyses are presented in the HTA Supplement. Furthermore, the 200,000 incremental cost-effect pairs from the denosumab versus IV ibandronate comparison were plotted on the cost-effectiveness plane. This cost-effectiveness plot is presented in the results section below. The decision to focus on the denosumab versus IV ibandronate comparison was informed by results of the base case analysis.

Finally, a probabilistic sensitivity analysis was undertaken to investigate parameter-level (second order) uncertainty in fracture-related cost and utility variables (distributions listed in ***Table 20***). The probabilistic sensitivity analysis was run using 20,000 first-order trials and 1,000 second-order parameter samples. A CEAC curve was produced to evaluate the probability of each intervention being cost-effective as a function of the WTP threshold.

All sensitivity analyses were performed on the base case cohort of women starting therapy at age 70 years with a risk of MOF equivalent to that of a woman of the same age with a prevalent fragility fracture.

Table 20 List of parameters included in the probabilistic sensitivity analysis

Variable	Parameter value Mean (standard deviation)	Distribution type
Cost of HF event	CHF 56,527.10 (5,652.71)	Gamma
Cost of VF event	CHF 16,456.75 (1,645.68)	Gamma
Cost of NHNV fracture event	CHF 12,131.38 (1,213.14)	Gamma
Utility multiplier (VF; initial)	0.671 (0.0671)	Beta
Utility multiplier (VF; subsequent)	0.841 (0.0841)	Beta
Utility multiplier (HF; initial)	0.545 (0.0545)	Beta
Utility multiplier (HF; subsequent)	0.857 (0.0857)	Beta
Utility multiplier (NHNV fracture; initial)	0.791 (0.0791)	Beta
Utility multiplier (NHNV fracture; subsequent)	0.952 (0.0952)	Beta

Abbreviations:
CHF: Swiss francs; **HF**: hip fracture; **NHNV**: non-hip non-vertebral; **VF**: vertebral fracture

8.4 Results: cost-effectiveness

Cost-effectiveness was determined via cost-effectiveness frontier analysis. For each scenario, mean cost and QALY outcomes for each intervention were calculated. Next, interventions were ranked in order of least to most costly and absolutely dominated alternatives (i.e. interventions more costly and less effective than another) were excluded. ICERs were calculated, comparing each intervention with the next most costly, undominated alternative. Finally, any extendedly dominated interventions (i.e. an alternative dominated by a combination of two others) were removed and ICERs recalculated if necessary. Pairwise comparisons between denosumab and each comparator were also made.

8.4.1 ICER for the base case

Table 21 and ***Figure 88*** show cost and QALY outcomes for each intervention when the DES model is run for the base case scenario (i.e. women age 70 years at the high-risk threshold). IV ibandronate was the most cost-effective option at a hypothetical WTP threshold of CHF100,000, with the only other undominated, more costly alternative (denosumab) having an ICER of CHF615,149 relative to IV ibandronate (***Table 21*** and ***Figure 88***).

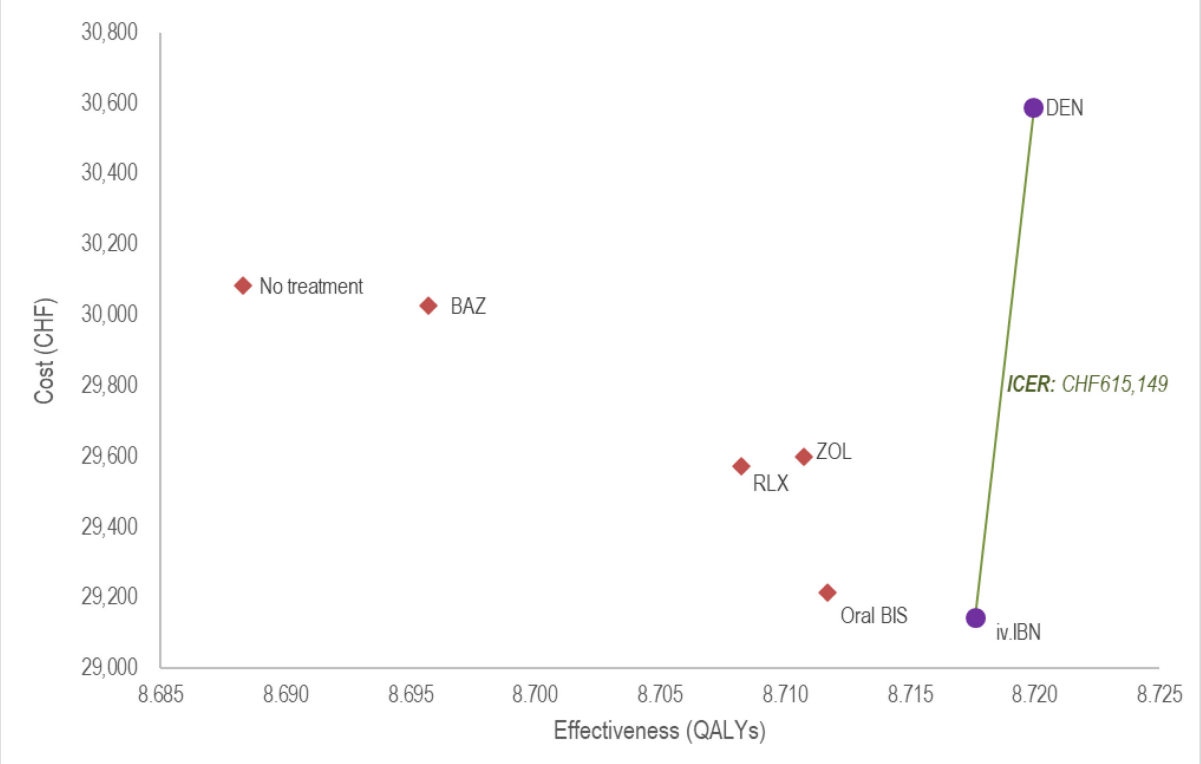
ICERs for the pairwise comparisons of denosumab with no treatment, bazedoxifene, and raloxifene were less than the hypothetical WTP threshold of CHF100,000, while ICERs for the comparisons with oral bisphosphonates and IV ibandronate were above the hypothetical WTP threshold (***Table 21***). The ICER for the pairwise comparison with zoledronate was close to the hypothetical WTP threshold, at CHF107,460 (***Table 21***).

Table 21 ICER results for the base case scenario

Treatment	Cost (CHF)	Effect (QALYs)	ICER (CHF per QALY) Frontier approach	ICER (CHF per QALY) Pairwise comparisons
IV IBN	29,144	8.7176		615,149
Oral BIS	29,214	8.7117	Dominated	166,451
RLX	29,573	8.7082	Dominated	86,776
ZOL	29,601	8.7108	Dominated	107,460
BAZ	30,028	8.6957	Dominated	23,135
No treatment	30,084	8.6883	Dominated	15,927
DEN	30,589	8.7200	615,149	

Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **CHF**: Swiss francs; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous; **QALY**: quality-adjusted life year; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
Interventions have been ranked in order of least to most costly. For the cost-effectiveness frontier analysis, ICERs have been calculated for interventions that are neither dominated nor extendedly dominated.

Figure 88 Cost and effect outcomes, base case scenario



Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **CHF**: Swiss franc; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous; **QALY**: quality-adjusted life year; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
Red diamond represents dominated alternatives. Purple circle reflects undominated alternatives, between which, ICERs are calculated.

8.4.2 ICERs for alternate base case scenarios

8.4.2.1 Scenario analyses on start age and baseline risk level

Details of cost and QALY outcomes for each intervention under each scenario, as well as results of pairwise comparisons between denosumab and each comparator individually, are available in ***Table 133***, ***Table 134*** and ***Table 135*** (***Appendix I***). Summaries of the cost-effectiveness frontier analyses outcomes are provided in ***Table 22***, ***Table 23*** and ***Table 24***.

For therapy starting at age 60 years, zoledronate was the most cost-effective option in women at moderate or high fracture risk at a hypothetical WTP threshold of CHF100,000, with ICERs of CHF47,817 and CHF31,075 relative to the next undominated, lower cost option (***Table 22***). For women at very high risk, IV ibandronate was the most cost-effective option at a hypothetical WTP threshold of CHF100,000, with the only undominated, more costly alternative (denosumab) having an ICER of CHF501,781 relative to IV ibandronate (***Table 22***). In women at moderate fracture risk, denosumab was dominated by IV ibandronate (***Table 22***). In women at high fracture risk, denosumab was undominated; however, its ICER relative to the next undominated, lower cost option (zoledronate) was CHF1.23 million (***Table 22***).

Table 22 Cost-effectiveness frontier analysis results: start age of 60 years at various risk levels

Age: 60 years	Moderate	High	Very high
Undominated (ICERs calculated)	1. No treatment 2. Oral BIS (ICER: 20,890) 3. **ZOL** (ICER: 47,817) 4. IV IBN (ICER: 156,524)	1. No treatment 2. Oral BIS (ICER: 12,514) 3. **ZOL** (ICER: 31,075) 4. DEN (ICER: 1,230,256)	1. **IV IBN** 2. DEN (ICER: 501,781)
Dominated	BAZ, RLX, DEN	BAZ, IV IBN and RLX	BAZ, no treatment, oral BIS, RLX, ZOL
Extendedly dominated	None	None	None

Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
ICERs are Swiss franc per QALY gained. ICERs have been calculated comparing the corresponding intervention with the previous, undominated alternative (e.g. for the moderate risk column, ICERs presented are for RLX vs no treatment and DEN vs RLX).
Interventions in bold are the most cost-effective option at a hypothetical willingness-to-pay threshold of approximately CHF100,000.

For women starting therapy at age 70 years, IV ibandronate was the most cost-effective option at all risk levels at a hypothetical WTP threshold of CHF100,000 (***Table 23***). Denosumab was undominated at all risk levels, however its ICERs relative to the next undominated, lower cost option (IV ibandronate)

were CHF1.5million, CHF615,149, and CHF438,327 in women age 70 years at moderate, high, and very high risk (***Table 23***).

Table 23 Cost-effectiveness frontier analysis results: start age of 70 years at various risk levels

Age: 70 years	Moderate	High (base case scenario)	Very high
Undominated (ICERs calculated)	1. Oral BIS 2. **IV IBN** (ICER: 82,710) 3. DEN (ICER: 1,499,549)	**1. IV IBN** 2. DEN (ICER: 615,149)	**1. IV IBN** 2. DEN (ICER: 438,327)
Dominated	No treatment, RLX, BAZ, ZOL	Oral BIS, BAZ, ZOL, RLX, No treatment	No treatment, BAZ, ZOL
Extendedly dominated	None	IV IBN	Oral BIS, IV IBN

Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
ICERs are Swiss franc per QALY gained. ICERs have been calculated comparing the corresponding intervention with the previous, undominated alternative (e.g. for the moderate risk column, ICERs presented are for IV IBN vs oral BIS and DEN vs IV IBN).
Interventions in bold are the most cost-effective option at a hypothetical willingness-to-pay threshold of approximately CHF100,000.

For women starting therapy at age 80 years, IV ibandronate was the most cost-effective option at all risk levels at a hypothetical WTP threshold of CHF100,000 (***Table 24***). Denosumab was undominated in all scenarios; however, it had ICERs relative to the next undominated, lower cost option (IV ibandronate) of CHF1.15 million, CHF1.62 million, and CHF1.05 million at each risk level, respectively (***Table 24***).

Table 24 Cost-effectiveness frontier analysis results: start age of 80 years at various risk levels

Age: 80 years	Moderate	High	Very high
Undominated (ICERs calculated)	1. Oral BIS 2. **IV IBN** (ICER: 93,418) 3. DEN (ICER: 1,149,246)	1. Oral BIS 2. **IV IBN** (ICER: 41,188) 3. DEN (ICER: 1,616,479)	**1. IV IBN** 2. DEN (1,051,800)
Dominated	No treatment, RLX, BAZ, ZOL	No treatment, RLX, BAZ, ZOL	No treatment, RLX, BAZ, ZOL, oral BIS
Extendedly dominated	None	None	None

Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
ICERs are Swiss franc per QALY gained. ICERs have been calculated comparing the corresponding intervention with the previous, undominated alternative (e.g. for the moderate risk column, ICERs presented are for IV IBN vs oral BIS and DEN vs IV IBN).
Interventions in bold are the most cost-effective option at a hypothetical willingness-to-pay threshold of approximately CHF100,000.

8.4.3 Sensitivity analysis on base case

8.4.3.1 Deterministic sensitivity analyses

To better inform decision-makers about alternate drivers of cost-effectiveness, deterministic sensitivity analyses were run on the base case scenario (i.e. start age of 70 years and a high baseline risk of fracture) to test the sensitivity of the model to certain structural or parameter-related assumptions (***Table 25***). All ICERs reported in ***Table 25*** are calculated in relation to the previous lowest cost, undominated alternative, consistent with a cost-effectiveness frontier analysis approach. Pairwise comparisons for each scenario are available in ***Table 136*** (***Appendix I***)

Under almost all scenarios, IV ibandronate remained the most cost-effective option at a hypothetical WTP threshold of CHF100,000. There were a few scenarios in which this was not the case. Oral bisphosphonates were the most cost-effective option under the assumption of full persistence for all drugs (ICER for IV ibandronate vs. oral bisphosphonates of CHF353,654; ***Table 25***), suggesting improved persistence with IV preparations may be an important contributor to the favourable cost-effectiveness outcome for IV ibandronate over oral preparations (i.e. IV ibandronate dominant over oral bisphosphonates in the base case; ***Table 21***). It is unlikely to observe full persistence to all drugs in practice; however, this scenario provides insight into the impact of non-persistence on cost-effectiveness outcomes.

Zoledronate was the most cost-effective option when the RRs for the effects of all treatments on both vertebral and nonvertebral fracture risk were set equal, and when the RRs for only nonvertebral fracture risk (but not vertebral fracture risk) were set equal (***Table 25***). These findings are explained by zoledronate's poor point estimate for nonvertebral fracture risk reduction (RR = 1.04), which has reduced the cost-effectiveness of zoledronate in the base case. These scenarios are particularly relevant given the 95% CRIs for all interventions overlap, suggesting there is considerable uncertainty around whether one treatment is truly superior over the others (see ***Section 8.3.1***).

Denosumab was never the most cost-effective option, however it did approach being the most cost-effective option when its intended duration of therapy was increased to 10 years, and when its offset period was set equal to treatment duration (ICERs of CHF136,026 and CHF146,777 relative to the next undominated, less costly alternative [IV ibandronate], respectively; ***Table 25***). Assumed persistence was not altered under the scenario in which the intended treatment duration was extended to 10 years, thus 57.5% of patients were persistent with denosumab for 10 years – an optimistic assumption. Furthermore, current evidence suggests the treatment effect of denosumab rapidly disappears upon discontinuation (***Section 8.3.2.1***) thus it is unrealistic that the offset period for denosumab would equal

treatment duration. Nonetheless, this scenario demonstrates the impact of the poorer residual benefit associated with denosumab on cost-effectiveness outcomes.

Table 25 Sensitivity analysis on the base case scenario: start age 70 years and high-risk

Scenario	Result
Treatment efficacy estimates	
RR of all interventions equal	ZOL became the most cost-effective option. All other alternatives were dominated by ZOL.
RRs for vertebral fractures set equal across all interventions	IV IBN remained the most cost-effective option. All other alternatives were dominated by IV IBN.
RRs for non-vertebral fractures set equal across all interventions	ZOL became the most cost-effective option. ICER DEN vs. ZOL of CHF1.39 million. All other alternatives dominated by ZOL.
Duration offset period	
No offset period for DEN	IV IBN remained the most cost-effective option. All other alternatives were dominated by IV IBN.
Offset period for DEN equal to treatment duration	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF146,777. All other alternatives dominated by IV IBN.
Offset period for RLX equal to treatment duration (i.e., increased)	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF615,149. All other alternatives dominated by IV IBN.
Offset period for ZOL equal to treatment duration (i.e., reduced)	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF615,149. All other alternatives dominated by IV IBN.
Offset period for BAZ equal to treatment duration (i.e., increased)	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF615,149. All other alternatives dominated by IV IBN.
No offset period for any intervention	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF233,337. ICER IV IBN vs. oral BIS of CHF60,807. All other alternatives dominated by oral BIS and IV IBN.
Non-persistence inputs	
Improved persistence for DEN	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF233,427. All other alternatives dominated by IV IBN.
Worsened persistence with DEN	IV IBN remained the most cost-effective option. All other alternatives were dominated by IV IBN.
All non-persistence rates from Hadji et al (2016)	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF1.87million. ICER IV IBN vs. oral BIS of CHF8,094. All other alternatives dominated by oral BIS and IV IBN.
Full persistence	Oral BIS became the most cost-effective option. ICER IV IBN vs. oral BIS of CHF353,654. All other alternatives dominated by oral BIS and IV IBN.
Duration therapy	
10 years for DEN	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF136,026. All other alternatives dominated by IV IBN.

Scenario	Result
3 years for IV IBN	IV IBN remained the most cost-effective option. ICER DEN vs. oral BIS of CHF166,451. ICER oral BIS vs. IV IBN of CHF144,533. IV IBN the lowest cost option. All other alternatives dominated by IV IBN and/or oral BIS.
Cost Inputs	
Reduced cost of DEN administration	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF534,084. All other alternatives dominated by IV IBN.
Alternate source of cost for fracture events	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF596,939. All other alternatives dominated by IV IBN.
Time Horizon	
10-year time horizon	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF668,667. ICER IV IBN vs. oral BIS of CHF60,371. All other alternatives dominated by oral BIS and IV IBN.
Discount Rate	
0%	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF545,916. All other alternatives dominated by IV IBN.
6%	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF678,506. ICER IV IBN vs. oral BIS of CHF6,490. All other alternatives dominated by oral BIS and IV IBN.
Fracture-related outcomes	
No risk of death after VF	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF1.08 million. All other alternatives dominated by IV IBN.
No risk of death after HF	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF496,497. All other alternatives dominated by IV IBN.
No risk of nursing home admission after HF	IV IBN remained the most cost-effective option. ICER DEN vs. IV IBN of CHF589,773. ICER IV IBN vs. oral BIS of CHF44,749. ICER oral BIS vs. no treatment of CHF2,905. RLX, BAZ and ZOL dominated.

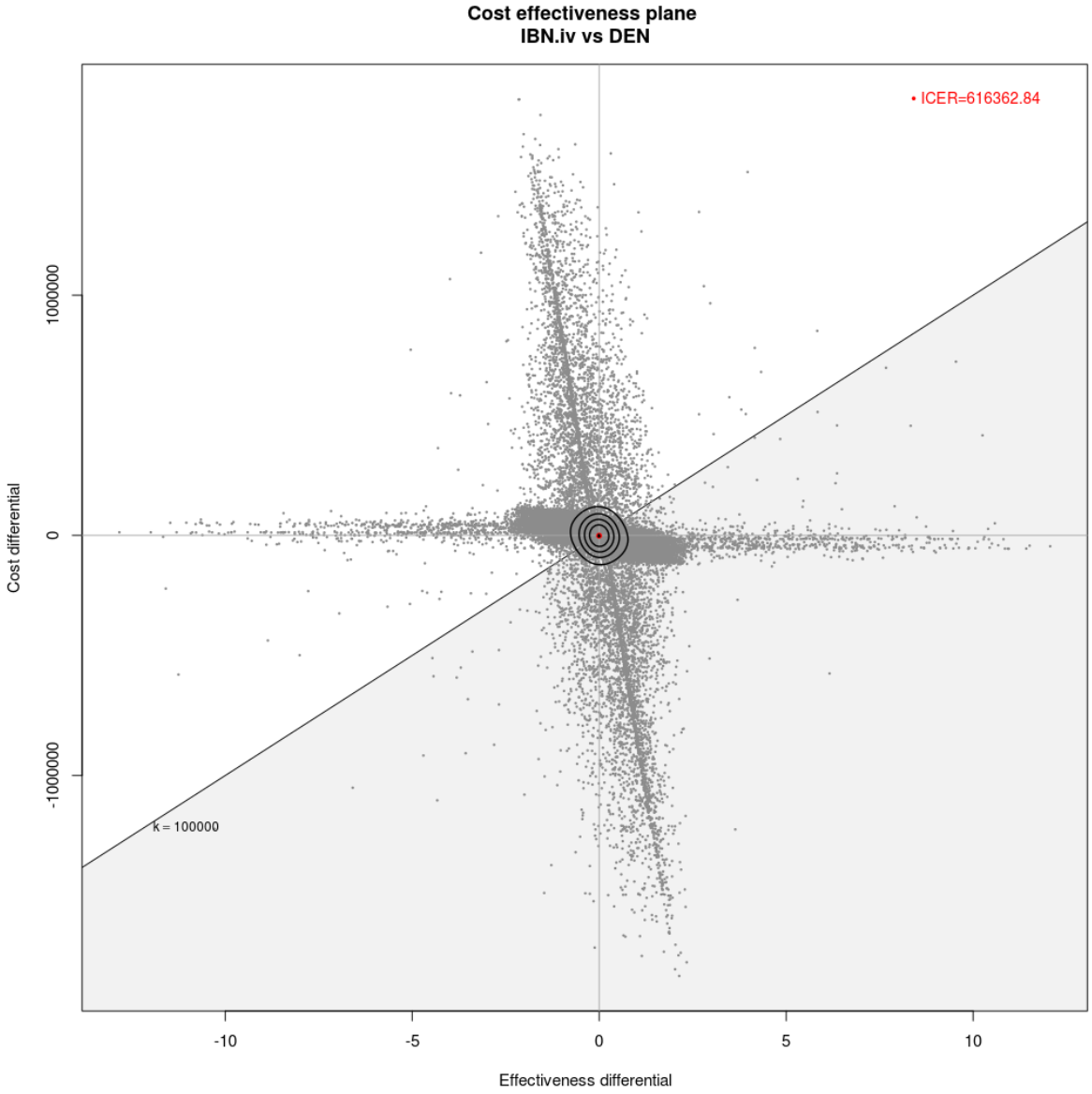
Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **CHF**: Swiss franc; **CRI**: credible interval; **DEN**: denosumab; **IBN**: ibandronate; **IV**: intravenous; **ICER**: incremental cost-effectiveness ratio; **RLX**: raloxifene; **RR**: risk ratio; **WTP**: willingness to pay; **ZOL**: zoledronate.
Notes:
All reported ICERs have been calculated in relation to the previous lowest cost, undominated alternative, consistent with a cost-effectiveness frontier analysis approach.

8.4.3.2 First-order uncertainty

In the base case, IV ibandronate was shown to be the most cost-effective treatment option at a hypothetical WTP threshold of CHF100,000 (see ***Table 21*** and ***Figure 88***). Denosumab was the only treatment option that was not dominated by IV ibandronate. The cost-effectiveness plane below (***Figure 89***) shows the 200,000 Monte Carlo patient-level incremental cost-effect pairs for the pairwise

comparison between denosumab and IV ibandronate. The contours on the cost-effectiveness plot outline each quintile (***Figure 88***). It can be observed that results were significantly impacted by extreme values from the simulation. Also, the shape of the ICER cloud appears to be relatively symmetrical around the origin. This reflects the result of the comparison to be highly uncertain.

Figure 89 Cost-effectiveness plane for the comparison between denosumab and IV ibandronate



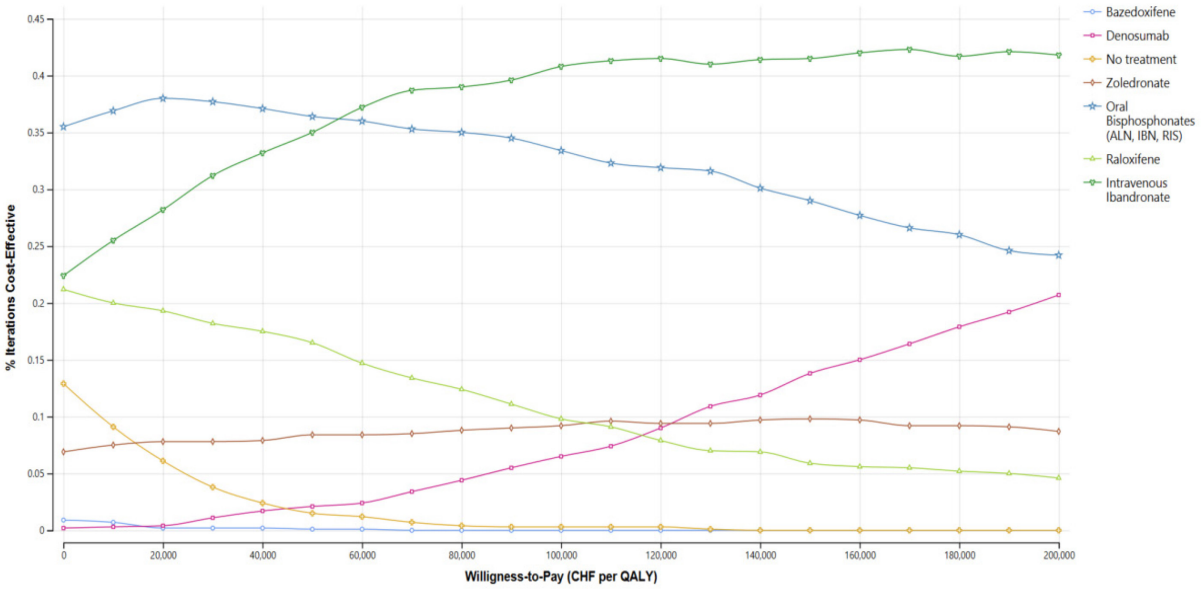
Abbreviations:
DEN: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous
Notes:
The scatter plot above was produced directly from the 200,000 patient-level simulation results. The ICER point estimate in the plot is the mean of the entire simulation dataset, therefore is slightly different to what was presented in the base case from the TreeAge output. The discrepancy was likely caused by TreeAge internal optimisation procedures where the simulation results are handled. Nonetheless, this discrepancy was not significant to lead to any variation in conclusion.

8.4.3.3 Probabilistic sensitivity analysis

Figure 90 displays the cost-effectiveness acceptability curve (CEAC), which shows the probability of each intervention being cost-effective as a function of the WTP threshold.

The CEAC curve suggests that at the hypothetical WTP threshold of CHF100,000, IV ibandronate has the greatest probability of being the most cost-effective option (40.8%), followed by oral bisphosphonates (33.4%). Denosumab has only a 6.5% probability of being the most cost-effective option. The probability of denosumab being the most cost-effective option was shown to increase with an increasing WTP; denosumab had a 20.7% chance of being the most cost-effective option at a WTP of CHF200,000. Nevertheless, IV ibandronate was the intervention with the highest chance of being the most cost-effective option at any WTP above approximately CHF55,000 (***Figure 90***). At a WTP less than approximately CHF55,000, oral bisphosphonates had the highest probability (***Figure 90***).

Figure 90 Cost-effectiveness acceptability curve for the probabilistic sensitivity analysis run for fracture-related cost and utility variables



Abbreviations:
ALN: alendronate; **CHF**: Swiss francs; **IBN**: ibandronate; **QALY**: quality-adjusted life year; **RIS**: risedronate

8.5 Financial implications

The budgetary impact of denosumab over the period 2021 to 2024 was explored under the assumption of no policy change. Trends in utilisation in recent years were used to predict what may be observed under such an assumption. In addition, the market share of denosumab relative to the bisphosphonates and SERMs reimbursed in Switzerland was explored, and a comparison made between trends in use of denosumab and those of these alternate anti-resorptive drug classes.

8.5.1 Assumptions for budgetary impact analysis

8.5.1.1 Number of patients currently treated with denosumab

Denosumab (Prolia®) sales data (CHF and packs sold) over the period 2014 to 2020 was sourced from © COGE GmbH. Tarifpool. © SASIS AG.

The number of patients was estimated by dividing the annual number of packs sold by the number of packs required per patient per annum, adjusted for suboptimal adherence. Adherence to anti-osteoporotic therapies is known to be poor—if suboptimal adherence was not corrected for in the estimation of patient numbers from sales data, the patient number could be underestimated.[26]

Previous studies seeking to estimate the uptake of anti-osteoporotic therapies across a number of European countries, including Switzerland, have used an adjustment factor informed by the Swedish Prescribed Drug Register.[21 26 254] Specifically, from an analysis of filled prescriptions from the Swedish register it was estimated that for all patients, their prescriptions would cover 73% of the total observed time. The same adjustment factor was used to estimate the potential size of the Swiss population currently using denosumab; it was assumed that patients are, on average, covered for 73% of the year.

The calculated number of patients across the period 2016 to 2020 is shown in ***Table 26***.

Table 26 Estimated number of patients using denosumab, 2016 to 2020

		2016	2017	2018	2019	2020	Calc.
A	Packs sold	87,318	103,674	96,659	96,432	93,622	COGE© data
B	Estimated patient number (base)	59,807	71,010	66,205	66,049	64,126	A ÷ 1.46

Notes:
Denosumab sales data limited to Prolia® (Xgeva® excluded).
Denosumab is intended to be injected twice per year. If fully adherent, each patient would receive two packs per annum.
Assuming patients are, on average, covered for 73% of the year, they would each receive 1.46 packs per annum (2 × 0.73).

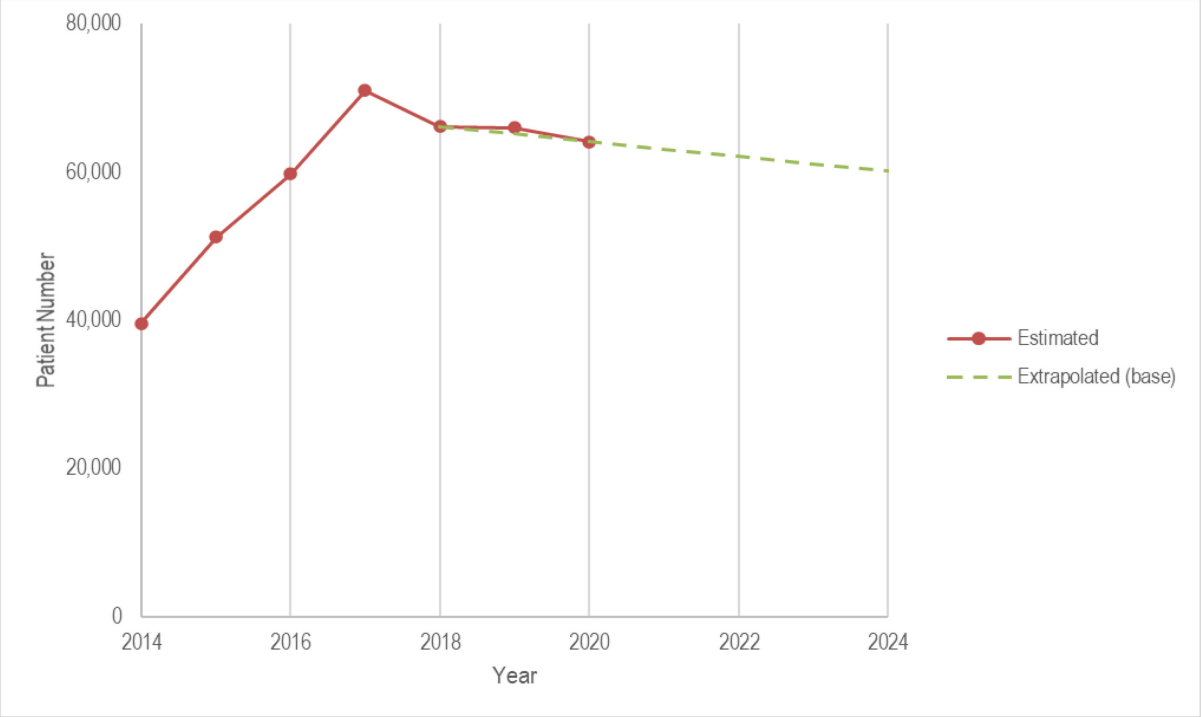
There is uncertainty around the actual patient numbers as only a crude adjustment for non-adherence was made. Exact rates of adherence and discontinuation for denosumab in Switzerland are unknown.

Therefore, sensitivity analyses were conducted using the following assumptions: adherence is improved with denosumab over anti-osteoporotic therapy in general (adjustment factor of 90%); assuming perfect adherence to denosumab (i.e. no adjustment factor) (***Table 27***).

8.5.1.2 Projected number of patients to be treated with denosumab

For the budget impact analysis, it was assumed that the use of denosumab would continue to decline by 1.6% per annum, which reflects the average annual decline in use over the period 2018 to 2020 (***Figure 91***).

Figure 91 Estimated and extrapolated patient numbers 2014 to 2024



Notes:
Base case extrapolation assumes a decline of 1.6% p.a.

Reasons behind the recent decrease in use of denosumab in Switzerland were not investigated thoroughly. While we have assumed that the decreasing trend will continue, this is subject to uncertainty.

To inform a sensitivity analysis, United Nations population projections by age bracket for Switzerland for the years 2020 and 2025 were used to estimate the annual growth rate for the Swiss population age over 50 years (1.42% p.a.).[281] This figure is higher than the current annual growth rate for the Swiss population (0.7% p.a.),[282] as could be expected given the ageing population.

In the sensitivity analysis, the number of patients using denosumab was assumed to rise by 1.42% per annum from 2020 onwards (***Figure 91***; ***Table 27***). Additional sensitivity analyses were conducted, adjusting the assumed base case value (decline of 1.6% p.a.) by ± 20% (***Table 27***).

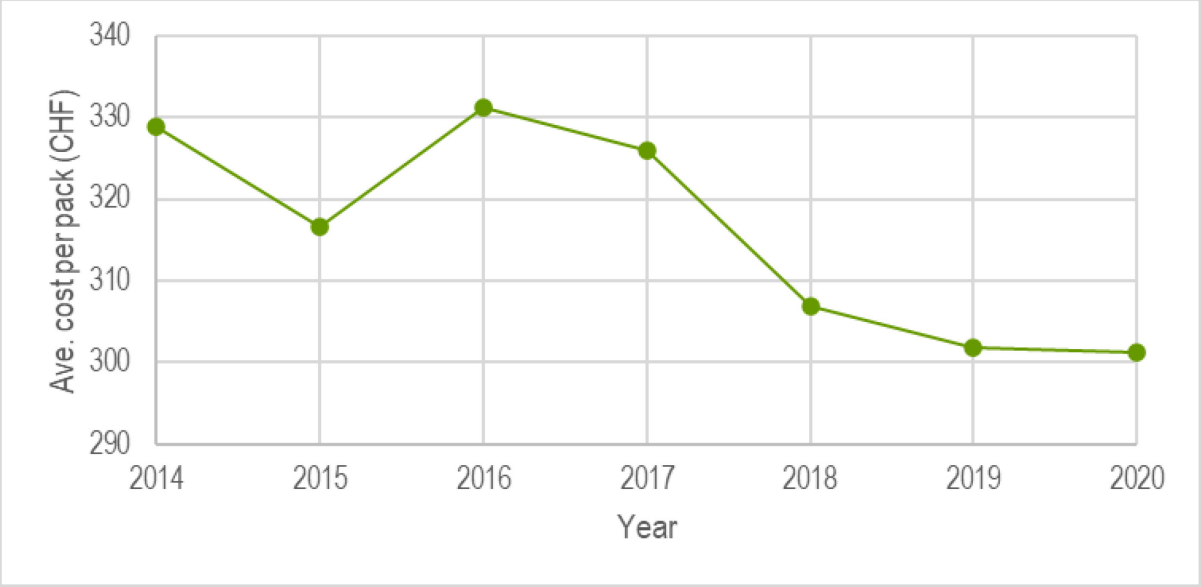
Table 27 Projected number of patients treated with denosumab under varying assumptions

Scenario	2020	2021	2022	2023	2024
Base case	64,125	63,109	62,109	61,126	60,158
Sensitivity analysis: **adjustment factor**					
Adjustment factor of 90%	52,012	51,188	50,378	49,580	48,795
No adjustment factor	46,811	46,070	75,340	44,622	43,915
Sensitivity analysis: **extrapolation approach**					
Growth rate – 20%	64,125	62,906	61,710	60,537	59,387
Growth rate + 20%	64,125	63,312	62,510	61,718	60,936
Growth rate equal to growth in population above age 50 years	64,125	65,034	65,956	66,891	67,840

8.5.1.3 Projected unit cost for denosumab

The average price per pack was estimated by dividing the annual sales volume (CHF) by the number of packs sold. © COGE GmbH. Tarifpool. © SASIS AG sales data indicate that the average price per pack has decreased over time (from CHF328.97 in 2014 to CHF301.32 in 2020); however, the average price was stable at CHF301–302 across the 2019–2020 period (CHF301.74 in 2019, CHF301.32 in 2020) (***Figure 92***).

Figure 92 Average reimbursed price per pack, 2014 to 2020



Abbreviations:
CHF: Swiss franc.

In July 2021, the reimbursed price per denosumab pack was CHF302.45.[256] Given the stability of the price per pack over the last two years, the price per pack was assumed to remain constant at CHF302.45 over the period 2021 to 2024 in the budget impact projections.

8.5.2 Projected budgetary impact of denosumab, 2020 to 2024

The projected sales (packs sold plus value of sales) are shown in ***Table 28***.

Table 28 Projected denosumab sales (CHF), 2020 to 2024

		2020	2021	2022	2023	2024	Calc.
A	Projected patient number	64,125	63,109	62,109	61,126	60,158	***Table 27***
B	Projected packs sold	93,622	92,139	90,680	89,244	87,830	A × 1.46
C	Projected sales (million CHF)	28.2M	27.9M	27.4M	27.0M	26.6M	B × CHF302.45

Abbreviations:
CHF: Swiss franc.
Notes:
Assuming patients are covered for 73% of the year, each patient receives 1.46 (2 × 0.73) packs.
Per © COGE GmbH. Tarifpool. © SASIS AG sales data, 93,622 packs of denosumab were sold in 2020, with total sales volume of CHF28.2 million (at average cost per pack of CHF301.32).
The audience award for Prolia® on the Spezialitäteniste as of August 2021 (CHF302.45) was used over the extrapolation period (2021–2024).

The payer cost of denosumab was estimated to be CHF26.6 million in 2024, representing a decrease of CHF1.6 million compared to 2020 (CHF28.2 million) (***Table 28***).

8.5.2.1 Sensitivity analysis

Some of the key assumptions used in the budget impact analysis are uncertain. The base case analysis assumed the declining trend in denosumab utilisation over the period 2018 to 2020 would continue at the rate of 1.6% per annum; however, it is uncertain if the decline in sales will continue or at what rate. Alternate assumptions were explored in sensitivity analyses altering the direction and/or rate of growth (***Table 29***). An alternate scenario was explored assuming that utilisation would stabilise and grow in line with the population growth rate for the Swiss population age 50 years and over (***Table 29***). Under this assumption, the payer cost was estimated to be CHF30.0 million in 2024—an increase of CHF0.8 million compared to 2020.

Scenarios assuming annual declines in utilisation of 1.3 and 1.9% per annum (i.e. adjustments of ± 20% on the base case value) were also explored (***Table 29***). Sensitivity analyses altering the price per pack of denosumab by ± 10% (CHF272.21–332.70) were also included.

The net payer cost was most sensitive to the direction of extrapolation (increasing or decreasing). The net payer cost was also sensitive to the price per pack of denosumab. While the number of patients accessing denosumab was sensitive to the adjustment factor used when estimating patient numbers from sales data, estimates of the net cost to the payer were not impacted because the adjustment factor was assumed to remain constant over time.

Table 29 Projected denosumab sales – sensitivity analyses

	Scenario						
	Base case						
A	Projected patient number	64,125	63,109	62,109	61,126	60,158	***Table 27***
B	Projected packs sold	93,622	92,139	90,680	89,244	87,830	***Table 28***
C	Projected sales (CHF; millions)	28.2M	27.9M	27.4M	27.0M	26.6M	***Table 28***
	Growth rate: **– 1.9% p.a. (–20%)**						
D	Projected patient number	64,125	62,906	61,710	60,537	59,387	***Table 27***
E	Projected packs sold	93,622	91,842	90,097	88,385	86,705	D × 1.46
F	Projected sales (CHF; millions)	28.2M	27.8M	27.2M	26.7M	26.2M	E × CHF 302.45
	Growth rate: **– 1.3% p.a. (+20%)**						
G	Projected patient number	64,125	63,312	62,510	61,718	60,936	***Table 27***
H	Projected packs sold	93,622	92,436	91,264	90,108	88,966	G × 1.46
I	Projected sales (CHF; millions)	28.2M	28.0M	27.6M	27.3M	26.9M	H × CHF 302.45
	Growth rate: +1.42% p.a. (alternate assumption)						
J	Projected patient number	64,125	65,034	65,956	66,891	67,840	***Table 27***
K	Projected packs sold	93,622	94,949	96,296	97,661	99,046	J × 1.46
L	Projected sales (CHF; millions)	28.2M	28.7M	29.1M	29.5M	30.0M	K × CHF 302.45
	Cost per pack: **±10%**						
M	Projected patient number	64,125	63,109	62,109	61,126	60,158	***Table 27***
N	Projected packs sold	93,622	92,139	90,680	89,244	87,830	***Table 28***
O	Projected sales (million CHF) (-10%)	28.8M	25.1M	24.7M	24.3M	23.9M	N × CHF272.21

	Scenario						
P	Projected sales (CHF; millions) (+10%)	28.2M	30.7M	30.2M	29.7M	29.2M	N × CHF 332.70
	Adjustment factor: **90%**						
Q	Projected patient number	52,012	51,188	50,378	49,580	48,795	***Table 27***
R	Projected packs sold	93,622	92,139	90,680	89,244	87,830	Q × 1.8
S	Projected sales (CHF; millions)	28.2M	27.9M	27.4M	27.0M	26.6M	R × CHF 302.45
	Assume full adherence						
T	Projected patient number	46,811	46,070	45,340	44,622	43,915	***Table 27***
U	Projected packs sold	93,622	92,139	90,680	89,244	87,830	T × 2
V	Projected sales (million CHF)	28.2M	27.9M	27.4M	27.0M	26.6M	U × CHF302.45

Abbreviations:
CHF: Swiss franc.
Notes:
Per © COGE GmbH. Tarifpool. © SASIS AG sales data, 93,622 packs of denosumab were sold in 2020, with total sales volume of CHF28.2 million (at average cost per pack of CHF301.32).
The audience award for Prolia® on the Spezialitätenliste as of August 2021 (CHF302.45) was used over the extrapolation period (2021–2024).

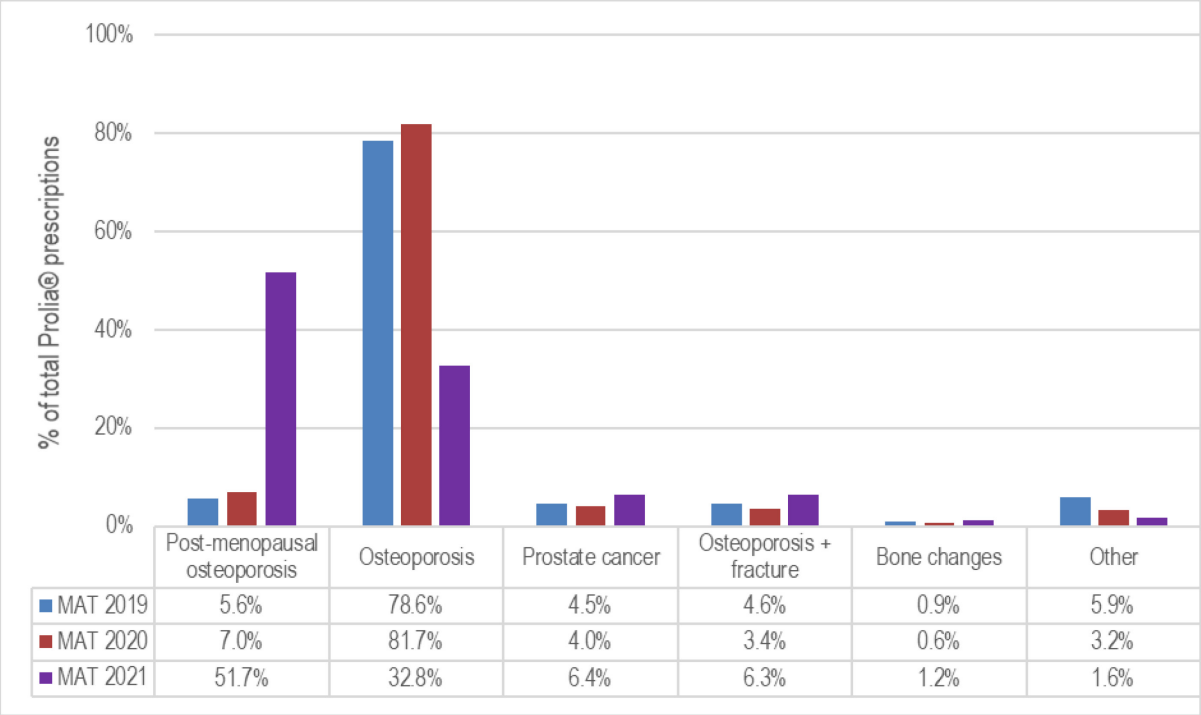
8.5.3 Projected market share of each subpopulation

Data provided by IQVIA were used to estimate the market share of each of the four subpopulations who can access denosumab via the Spezialitätenliste.[283] IQVIA collects data each quarter from 304 doctors across Switzerland, which it then extrapolates to all doctors in Switzerland to provide detailed health-related information on the Swiss population.

8.5.3.1 Indications for prescription of denosumab

IQVIA data suggests that, for denosumab, the most common indication for use in the last 12 months was postmenopausal osteoporosis (***Figure 93***). This differs from the previous two years in which osteoporosis was the leading indication (***Figure 93***). An indication of either postmenopausal osteoporosis, osteoporosis, or osteoporosis with fracture accounts for approximately 90% of all prescriptions over the last three years. The 13 indications comprising the category of 'other' are unknown.

Figure 93 Indications for use of denosumab over three-year period 2018-2021



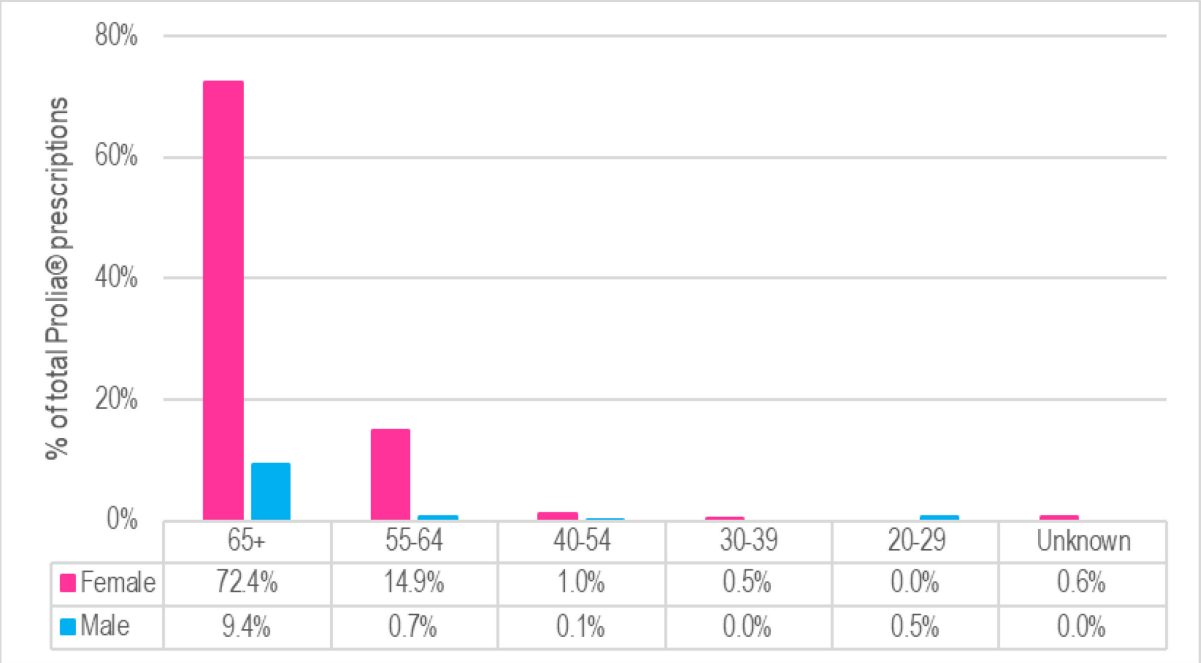
	Post-menopausal osteoporosis	Osteoporosis	Prostate cancer	Osteoporosis + fracture	Bone changes	Other
MAT 2019	5.6%	78.6%	4.5%	4.6%	0.9%	5.9%
MAT 2020	7.0%	81.7%	4.0%	3.4%	0.6%	3.2%
MAT 2021	51.7%	32.8%	6.4%	6.3%	1.2%	1.6%

Abbreviations:
MAT: moving annual total
Notes:
MAT2019 = April 2018–March 2019; MAT2020 = April 2019–March 2020; MAT2021 = April 2020–March 2021.
Data limited to Prolia® (Xgeva® excluded).

Gender and age breakdown

IQVIA data suggests that in the 12-month period April 2020 to March 2021, women age 65 years and over accounted for just over 70% of the population prescribed denosumab (***Figure 94***). Women age 55 years and over accounted for approximately 87.2% (***Figure 94***). Overall, women accounted for 89.3% of the population; men accounted for 10.7% of the population (***Figure 94***).

Figure 94 Age and gender breakdown of denosumab users, April 20 to March 21



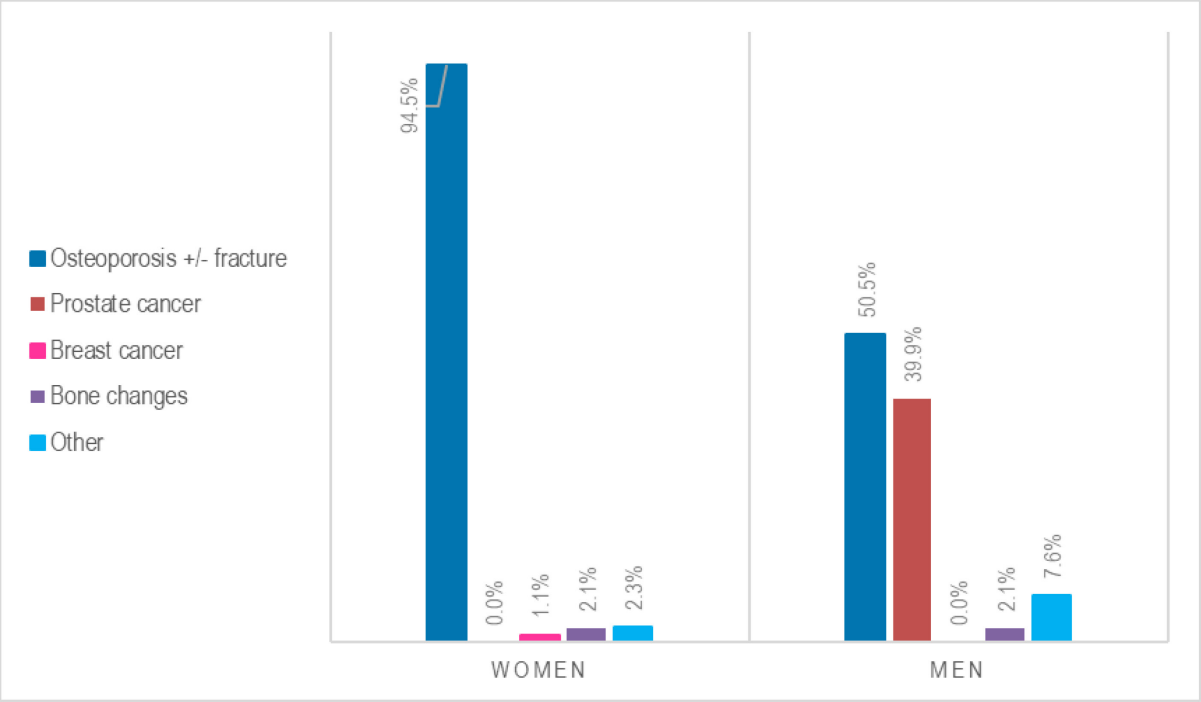
	65+	55-64	40-54	30-39	20-29	Unknown
Female	72.4%	14.9%	1.0%	0.5%	0.0%	0.6%
Male	9.4%	0.7%	0.1%	0.0%	0.5%	0.0%

Notes:
Data limited to Prolia® (Xgeva® excluded).

It was not possible to assess gender-specific indications for denosumab prescriptions; however, gender-specific indications for use of all medications included in our sample could be assessed.

In the period April 2020 to March 2021, osteoporosis (or osteoporosis plus fracture) accounted for approximately 50% of indications in men, while prostate cancer accounted for approximately 40% (***Figure 95***). For women, postmenopausal osteoporosis, osteoporosis or osteoporosis plus fracture accounted for over 90% of prescriptions (***Figure 95***). Breast cancer was the indication for prescriptions in approximately 1.0% of all patients (i.e. total men, women and gender unknown), equating to 1.1% of the female population when assuming all prescriptions with this indication were for women (***Figure 95***).

Figure 95 Gender-specific indications (combined for denosumab and comparators)



Notes:
Data for the period April 2020 to March 2021.

8.5.3.2 Projected patient numbers and budgetary impact across subpopulations

Using proportional estimates from the IQVIA dataset, the numbers of patients in each of the four populations included in this HTA—postmenopausal women with osteoporosis, women with breast cancer receiving AAIT, men with osteoporosis who have an increased fracture risk, and men with prostate cancer on HAT—were estimated (***Table 30***). The category of other in ***Table 30*** captures indications not specific to any of the four populations (e.g. bone changes) or those unknown (i.e. not a top 10 indication in the IQVIA dataset).

Table 30 Projected denosumab patients by indication, 2020 to 2024

		2020	2021	2022	2023	2024	Calc.
A	Projected patient number (overall)	64,125	63,109	62,109	61,126	60,158	***Table 27***
	Gender breakdown						
B	Women	57,276	56,369	55,476	54,597	53,733	A × 89.3%
C	Men	6,849	6,740	6,633	6,528	6,425	A × 10.7%
	Subpopulations						
D	Postmenopausal women with osteoporosis	54,106	53,249	52,405	51,575	50,759	B × 94.5%
E	Women with breast cancer on AAIT	617	607	597	588	578	B × 1.1%
F	Men with osteoporosis	3,455	3,401	3,347	3,294	3,242	C × 50.5%
G	Men with prostate cancer on HAT	2,732	2,689	2,646	2,604	2,563	C × 39.9%
H	Other indications	3,215	3,164	3,114	3,064	3,016	(B × 4.5%) + (C × 9.7%)

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **HAT**: hormone ablation therapy.

Based on the population estimates shown in ***Table 30,*** the projected costs of denosumab use within each of the four subpopulations (under base case assumptions) were estimated (***Table 31***). By far the biggest indication for use of denosumab in Switzerland is as an anti-fracture therapy for postmenopausal women with osteoporosis. It was estimated that in 2024, payer costs for denosumab use in postmenopausal women will be CHF22.4 million, with this indication holding approximately 84.4% of the market share.

Table 31 Projected budgetary impact (CHF) across subpopulations, base case assumptions

		2020	2021	2022	2023	2024
A	Projected budgetary impact (overall)	28.2M	27.9M	27.4M	27.0M	26.6M
	Subpopulations					
B	Postmenopausal women with osteoporosis	23.8M	23.5M	23.1M	22.8M	22.4M
C	Women with breast cancer on AAIT	0.27M	0.27M	0.26M	0.26M	0.26M
D	Men with osteoporosis	1.5M	1.5M	1.5M	1.5M	1.4M
E	Men with prostate cancer on HAT	1.2M	1.2M	1.2M	1.2M	1.1M
F	Other indications	1.4M	1.4M	1.4M	1.4M	1.3M

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **CHF**: Swiss franc; **HAT**: hormone ablation therapy.
Notes:
Per © COGE GmbH. Tarifpool. © SASIS AG sales data, the average cost per pack was CHF301.32 in 2020. The assumed cost per pack for years 2021 to 2024 is CHF302.45.

8.5.3.3 Limitations

The dataset provided by IQVIA is based upon a small sample of doctors (and their patients) across Switzerland and may therefore not paint an entirely accurate picture when extrapolated to the whole of the Swiss population. It is possible that the sample group of doctors prescribes for one indication at a disproportionate rate when compared to all Swiss doctors. Moreover, while prescriptions by gender could be estimated for denosumab, prescriptions by gender *and* indication could only be estimated across all drugs included in our select market (i.e. denosumab, ibandronate, alendronate, zoledronate, raloxifene and risedronate). Nonetheless, with a lack of alternate options, this dataset provided a reasonable means by which to estimate the market share of each of the four subpopulations utilising denosumab.

8.5.4 Overall market share of denosumab

The market share of denosumab versus comparator anti-osteoporotic therapies, based on © COGE GmbH. Tarifpool. © SASIS AG annual sales data (CHF and packs sold), was explored. For the analyses, comparators were grouped into their respective drug class—bisphosphonates or SERMs. Bazedoxifene was included in these analyses, even though the only available product on the Spezialitätenliste, Conbriza® was de-listed in June 2021.

8.5.4.1 Annual sales

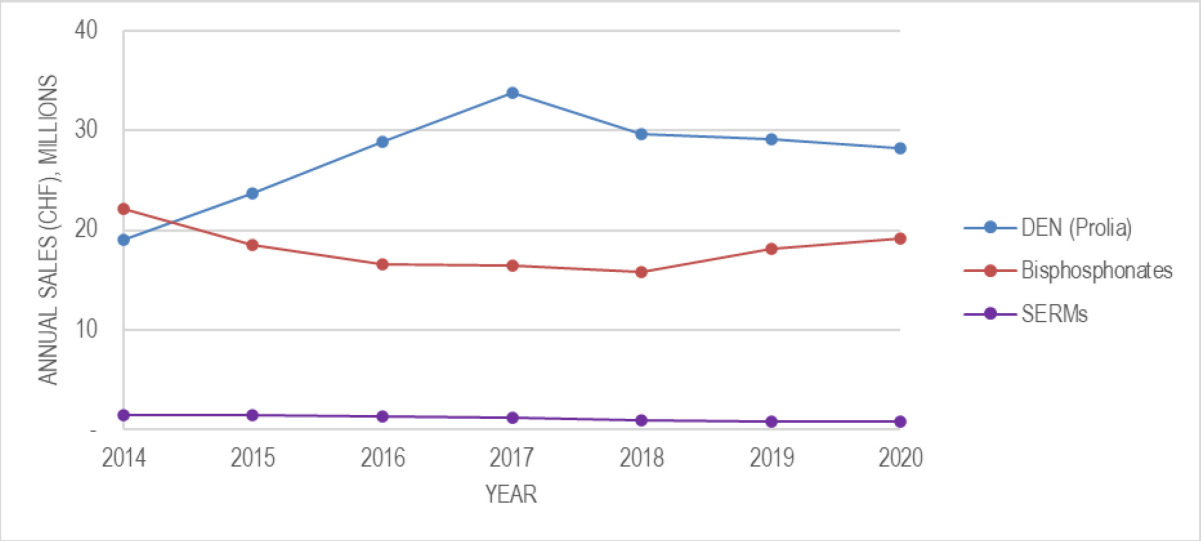
Annual costs of denosumab, bisphosphonates and SERMs sales to the payer over the period 2014 to 2020 are shown in ***Figure 96***.

The annual cost of denosumab increased over the period 2014 to 2017 (CHF19.0–33.8 million), then decreased between 2017 and 2020 (CHF33.8–28.2 million) (***Figure 96***). While the cost per pack of denosumab decreased between 2017 and 2020 (***Figure 92***), so too did the number of packs sold (from 103,674 to 93,622; ***Table 26***), indicating a decrease in the use of denosumab in Switzerland.

In contrast, the annual cost of bisphosphonates decreased over the period 2014 to 2018 (CHF22.2–15.9 million), before increasing between 2018 and 2020 (CHF15.9–19.2 million) (***Figure 96***). When looking at the number of packs sold, ibandronate and risedronate sales have been declining, while alendronate sales increased over the period 2017 to 2020 and zoledronate sales increased over the period 2016 to 2020 (***Figure 97***).

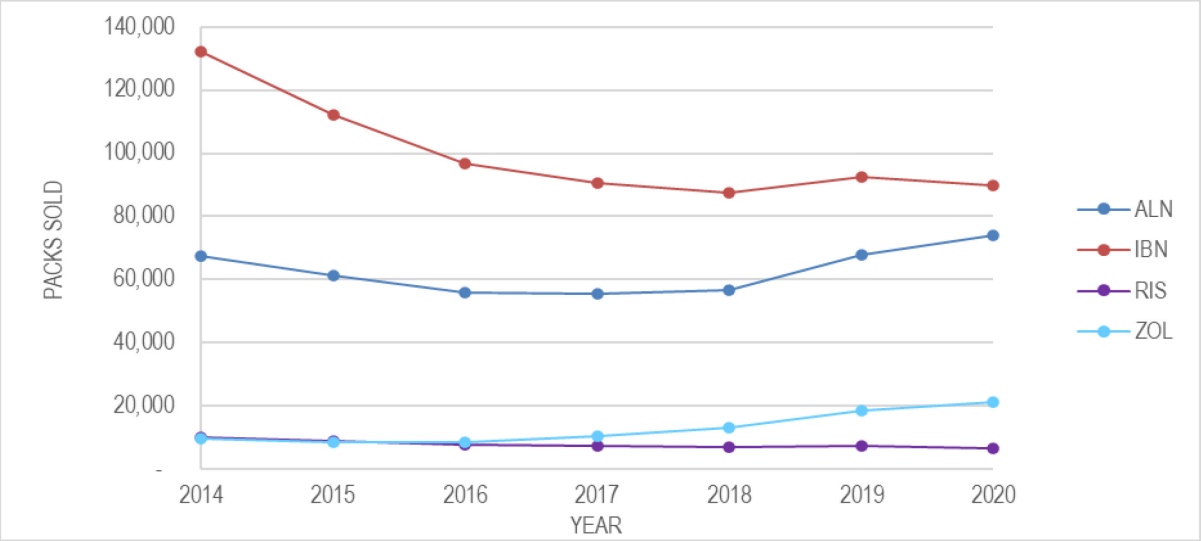
The overall budget impact of antiresorptive osteoporosis medications to the payer in the year 2020 was CHF 48.2 million.

Figure 96 Annual sales (CHF) for denosumab and comparator drug classes, 2014 to 2020



Abbreviations:
CHF: Swiss franc; **DEN**: denosumab; **SERM**: selective oestrogen receptor modulators.

Figure 97 Annual sales (packs sold) for bisphosphonates, 2014 to 2020



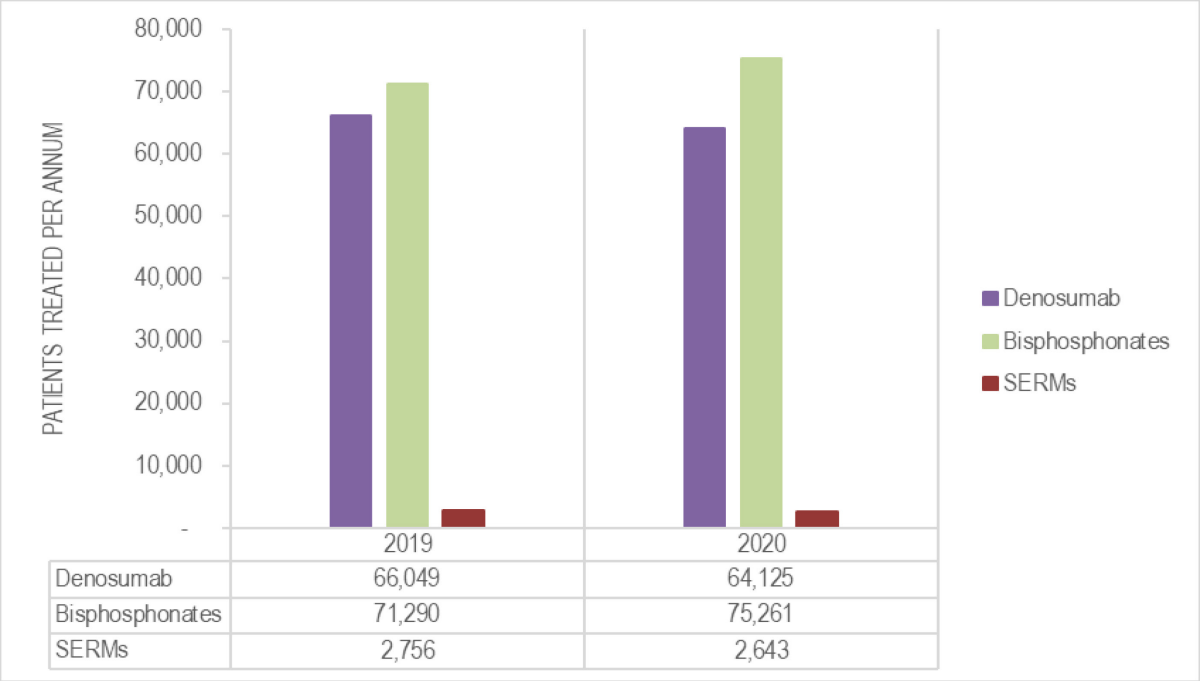
Abbreviations:
ALN: alendronate; **IBN**: ibandronate; **RIS**: risedronate; **ZOL**: zoledronate.

8.5.4.2 Estimated number of patients currently treated

As described above for denosumab, the number of patients using each of the comparator drugs was estimated by dividing the annual number of packs sold by the number of packs required per patient per annum, adjusting for suboptimal adherence to therapy. Patient numbers for the comparators were again grouped into drug classes—bisphosphonates or SERMs.

Assuming the same adjustment factor for all drugs except zoledronate, which is only required once per year (no adjustment factor needed), slightly more patients were estimated to receive treatment with bisphosphonates than with denosumab in both 2019 and 2020 (***Figure 98***). However, denosumab has been shown to improve adherence to therapy over oral bisphosphonates.[46] It is thus possible that the relative difference in the number of patients using denosumab and bisphosphonates is underestimated, given the same adjustment factor was used across all therapies.

Figure 98 Estimated patient numbers, accounting for imperfect adherence to therapy



	2019	2020
Denosumab	66,049	64,125
Bisphosphonates	71,290	75,261
SERMs	2,756	2,643

Abbreviations:
SERM: selective oestrogen receptor modulators.

While the estimated number of patients treated with denosumab decreased between 2019 and 2020, the estimated number of patients treated with a bisphosphonate increased (***Figure 98***), suggesting a substitution may be occurring in practice. This observation provided the incentive to explore the potential budget impacts of a natural / practice-driven substitution.

8.5.5 Potential financial implications of a natural substitution

Patient numbers shown in ***Figure 98*** (***Section 8.5.4.2***) indicate that in 2019 and 2020, respectively, approximately 140,096 and 142,028 Swiss patients were estimated to be treated with anti-resorptive osteoporosis medications. This translates to a growth rate of 1.38% p.a. over the period; close to the projected annual growth rate for the Swiss population age 50 years and over of 1.42% p.a. (***Section 8.5.1.2***).[281]

Whilst the overall utilisation of anti-resorptive therapies has increased at close to the population growth rate, utilisation of denosumab has been declining. This indicates a shift in choice of anti-resorptive therapies away from denosumab. The difference between the number of patients who could be expected to uptake denosumab according to population growth versus the number of patients predicted to use denosumab according to a trends analysis (continuing annual decline of 1.6% p.a.) (***Table 32***) was used to inform the financial impact assessment. Specifically, we assumed the difference between the expected and predicted patient numbers reflects the number of patients who may uptake a bisphosphonate in place of denosumab due to changing clinical practices.

There appears to be the potential for cost savings through the natural substitution of denosumab with bisphosphonates (CHF359,456 in 2021, increasing to CHF1.43 million in 2024; ***Table 32***). These estimates should be interpreted with caution given the wider financial implications attributed to treatment efficacy and safety outcomes (e.g. fracture-related costs) have not been included.

Table 32 Estimated budgetary impact under a natural substitution scenario

		2021	2022	2023	2024	Calc.
	Estimated no. patients making the substitution					
A	Expected patient number (Population growth)	65,034	65,956	66,891	67,840	***Table 27***
B	Projected patient number (Continuing annual decline)	63,109	62,109	61,126	60,158	***Table 27***
C	Difference (Patients making the substitution)	1,925	3,846	5,765	7,682	A - B
	Cost under each scenario					
D	Cost if these patients were treated with denosumab (CHF)	849,958	1.70M	2.55M	3.39M	C * 441.58
E	Cost if these patients were treated with a bisphosphonate (CHF)	490,503	980,192	1.47M	1.96M	C * 254.83
	Budgetary impact of substitution					
F	Cost difference (CHF)	359,456	718,315	1.08M	1.43M	D – E

Abbreviations:
CHF: Swiss franc.
Note:
Projected patient number extrapolation assumes a decline of 1.6% p.a. Expected patient number extrapolation assumes a growth of 1.42% p.a.
Annual cost of denosumab calculated as the assumed price per pack (CHF302.45) times 1.46.
Annual cost of bisphosphonate therapy calculated as the total sales in 2020 (CHF19.2 million) divided by the estimated patient number in 2020 (75,261).

8.5.5.1 Sensitivity Analysis

Some of the key assumptions used in the financial analysis are uncertain.

First, the natural substitution scenario assumes that the declining trend in denosumab utilisation over the period 2018 to 2020 would continue. This assumption is uncertain; however, it provides the rationale to explore a potential natural substitution and can therefore not be altered.

Second, under the assumption of declining use, the exact rate of decline in denosumab utilisation is uncertain. Scenarios assuming annual declines in utilisation of 1.3% and 1.9% p.a. (i.e. adjustments of ± 20% on the base case value) were explored. These analyses had the effect of altering the estimated number of patients potentially substituting denosumab with bisphosphonate therapy.

Further, the adjustment factor used to estimate the number of patients accessing denosumab from sales data is uncertain. Sensitivity analyses were conducted using the following assumptions: adherence is improved with denosumab over anti-osteoporotic therapy in general (adjustment factor of 90%); perfect adherence to denosumab (i.e. no adjustment factor) (see ***Table 27***). These adjustments affected both the estimated number of patients switching to a bisphosphonate and the annual price per patient treated with denosumab.

Lastly, sensitivity analyses altering the annual price per patient treated with bisphosphonate therapy (CHF254.83 in the base case) by ± 20% (CHF203.86–305.80) were considered to account for uncertainties in the choice of bisphosphonate therapy being substituted. This had the effect of altering the price saved per patient switching from denosumab to bisphosphonate therapy from CHF135.78 to CHF237.71 (CHF186.75 in base case).

Overall, these sensitivity analyses suggest there is potential for cost savings through the natural substitution of denosumab with bisphosphonates of between CHF1.04M to CHF1.96M in 2024 (***Table 33***). Base case calculations appear to be most sensitive to the assumed adherence to denosumab used in the calculations, and the difference in cost between denosumab and bisphosphonate therapy.

Again, these results should be interpreted with caution given the wider financial implications attributed to treatment efficacy and safety outcomes (e.g. fracture-related costs) have not been included.

Table 33 Sensitivity analyses on the natural substitution scenario

Scenario	2021	2022	2023	2024
Base case				
Projected number of patients making the substitution	1,925	3,846	5,765	7,682
Project cost savings (CHF)	359,456	718,315	1.08M	1.43M
Adjustment factor: 90% for denosumab				
Projected number of patients making the substitution	1,561	3,120	4,676	6,231
Project cost savings (CHF)	452,106	903,462	1.35M	1.80M
Assume full adherence for denosumab				
Projected number of patients making the substitution	1,405	2,808	4,209	5,608
Project cost savings (CHF)	491,891	982,967	1.47M	1.96M
Growth rate: – 1.9% p.a. (–20%)				
Projected number of patients making the substitution	2,128	4,246	6,354	8,453
Project cost savings (CHF)	397,388	792,857	1.19M	1.58M
Growth rate: – 1.3% p.a. (+20%)				
Projected number of patients making the substitution	1,722	3,446	5,173	6,904
Project cost savings (CHF)	321,523	643,532	966,084	1.29M
Annual cost of bisphosphonate therapy: -CHF203.86 (–20%)				
Projected number of patients making the substitution	1,925	3,846	5,765	7,682
Project cost savings (CHF)	457,556	914,353	1.37M	1.83M
Annual cost of bisphosphonate therapy: CHF305.80 (+20%)				
Projected number of patients making the substitution	1,925	3,846	5,765	7,682
Project cost savings (CHF)	261,355	522,276	782,824	1.04M

Abbreviations:
CHF: Swiss franc.

8.5.6 A note on the uptake of anti-fracture drugs

The budgetary impact analysis has used a market approach to estimate the number of patients being treated with denosumab or comparator drugs. The number of Swiss potentially eligible for treatment was not needed in these calculations.

The uptake of anti-osteoporotic therapies amongst the Swiss population indicated for treatment is low, suggesting there is an unmet need for treatment within the population. A Swiss quality control study

verifying the implementation of therapy in patients who had sustained a fracture and for whom anti-osteoporotic therapy was recommended by a rheumatology specialist, found that at one year after fracture, only 52% of patients with an indication for therapy had actually received anti-osteoporotic drugs.[284] In another study, the treatment gap between women receiving therapy and all women with a FRAX® 10-year probability of fracture equal to the intervention threshold, was estimated at 58%.[21] With improvements in the uptake of therapy, the overall budget impact of antiresorptive osteoporosis medications (not estimated here) may increase.

9 Legal, social and ethical issues

9.1 Summary statement legal, social and ethical issues

The literature searches did not identify any literature related to the legal implications of denosumab use. Regarding social issues, the evidence-base indicated that patients significantly preferred biannual or quarterly subcutaneous denosumab injections over a daily, weekly or monthly bisphosphonate or SERM treatment, resulting in higher levels of adherence. Furthermore, the evidence showed that patients' views on anti-osteoporotic therapy in the form of pharmaceuticals are generally negative, typically a result of patient hesitance, lack of understanding around osteoporosis, and patient health information sources. Patient views and hesitancy towards osteoporotic drug therapy can be overcome with improvements in patient and physician information sources on osteoporosis and how anti-osteoporotic treatments work. Finally, healthcare access and equity concerns may arise when patients are no longer eligible to receive reimbursement for denosumab, resulting in discontinuation. This suggests that reimbursement status is a driver of uptake.

9.2 Methodology: legal, social and ethical issues

Literature identified from systematic and non-systematic searches was used to address legal, social and ethical issues. The search terms and search strings used for the systematic search are outlined in ***Appendix A***. The non-systematic searches involved targeted keyword searches of PubMed and Google using terms such as 'access', 'autonomy', 'benefits', 'burden', 'adherence', 'preference', 'perception', 'osteoporosis' and 'denosumab'. No limitations were placed on study design for inclusion. The non-systematic searches were conducted by a single reviewer. The results of the literature search are summarised using narrative synthesis.

9.3 Results: legal, social and ethical issues

9.3.1 Evidence table

A total of 13 publications were identified and included through the systematic and non-systematic search for legal, social and ethical issues. All 13 publications assessed social or ethical considerations; no publications were identified addressing the legal issues relating to osteoporotic treatments. A PRISMA flow diagram is not provided in this section given that both systematic and non-systematic searches were conducted.

Thirteen publications were included in the assessment of social and ethical issues relating to osteoporotic treatments (***Table 34***). These publications were conducted across Europe (k = 6), including

France, Germany, Austria, Greece, Belgium and Switzerland; North America (k = 5), including USA and Canada; Oceania (k = 2), including Australia; and Asia (k = 1), including Singapore.

Table 34 Characteristics of included studies for social and ethical issues

Study; country	Indication; sample size (n)	Design; duration; setting	Outcomes
Social Issues			
Alami et al. 2016[209] France	Women with postmenopausal osteoporosis confirmed by BMD test and prescribed long-term osteoporotic treatment n = 37	Qualitative study – face-to-face semi-structured interviews and focus groups 4 mo Hospital, doctor's office, home settings	General views, personal experiences, attitudes towards treatment, decision-making processes, outcomes and expectations
Barrionuevo et al. 2019[210] USA	Women with postmenopausal osteoporosis or osteopenia, or women at risk of developing postmenopausal osteoporosis or osteopenia n = 15,348 (26 studies)	Systematic review – surveys, interviews, focus groups NA NA	Values and preferences prior to commencement of or whilst taking anti-osteoporosis treatments
Freemantle et al. 2011[46 213 214] USA, Canada, UK	Ambulatory postmenopausal women, ≥55yo, T-score between -4.0 and -2.0 at LS, TH or FN. DEN (60 mg/6 mo) ALN (oral 70 mg/once weekly) n = 250	RCT, OL, crossover, multicentre 12 mo NA	Treatment adherence, compliance, persistence, preference, beliefs and satisfaction of patients
Hadji et al. 2015[211] Germany, Austria, Greece, Belgium	Postmenopausal women prescribed denosumab (60 mg/6 mo) n = 1,500	Prospective study, non-interventional, multicentre – questionnaire 12 mo Medical care centres	Persistence, adherence, medication coverage ratio
Hiligsmann et al. 2013[212] Australia, Canada, UK, USA	Patients prescribed osteoporotic medications, calcium and vitamin D supplements n = 14,662	Systematic review – interventional studies NA NA	Adherence and persistence
Modi et al. 2014[215] USA	Women and men with osteoporosis NA	Review NA NA	Challenges in the treatment of osteoporosis
Naik-Panvelkar et al. 2020[216] Australia	GPs managing patients with osteoporosis n = 13	Phase 1 – Longitudinal retrospective cohort study Phase 2 – In-depth interview General practice setting	Knowledge, attitudes, organisational factors and perceived patient factors and their management
Rabenda et al. 2010[217] Belgium	Patients prescribed osteoporotic medication NA	Review NA NA	Adherence
Yeam et al. 2018[218] Singapore	Patients prescribed osteoporotic medication NA	Systematic review NA NA	Adherence, persistence and compliance

Study; country	Indication; sample size (n)	Design; duration; setting	Outcomes
Yu et al. 2015[219] USA	Osteoporotic women, ≥55yo, evidence of osteoporosis via health claims history n = 430	Cross-sectional study – mail survey ~26 mo Home setting	Knowledge, beliefs and reason for initiation/non-initiation of osteoporotic treatment
Ethical Issues			
Popp et al. 2018[189] Switzerland	Postmenopausal women with osteoporosis n = 12	Single-arm extension of an RCT 10 years Tertiary hospital	Reasons for discontinuation related to reimbursement status

Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **DEN**: denosumab; **FN**: femoral neck; **LS**: lumbar spine; **mg**: milligram; **mo**: month/s; **OL**: open-label; **RCT**: randomised controlled trial; **TH**: total hip; **USA**: United States of America; **UK**: United Kingdom; **NA**: not applicable; **yo**: year/s old.

9.3.2 Findings: social issues

There is scarce evidence (k = 12 publications) on social issues related to denosumab and the active comparators of bisphosphonates and SERMs in osteoporotic patients.[46 209-219] The social issues highlighted by the publications include, treatment adherence, patient/physician health information sources and beliefs, and access and equity within a healthcare system.[46 209-219]

The evidence-base indicated that patients significantly preferred biannual or quarterly subcutaneous denosumab injections over an oral daily, weekly or monthly bisphosphonate treatment.[46 210-214 217 218] Patients were found to specifically prefer injectable over oral treatments administered at infrequent intervals.[210 212] This patient preference is reflected in Kendler et al. 2011 and Hadji et al. 2015.[211 214] Kendler et al. 2011 found that patients taking the oral bisphosphonate alendronate had a lower adherence (76.6%) over 12 months compared to subcutaneous injections of denosumab (Prolia®) (87.3%) every 6 months.[214] Moreover, Hadji et al. 2015 reported that compliance to subcutaneous denosumab was between 1.0 to 1.5 times higher than for any bisphosphonate.[211] Treatment compliance is explored in more detail in ***Section 8***.

The evidence showed that patient views on anti-osteoporotic therapy in the form of pharmaceuticals is generally negative.[209 215] Reasons for this including patient hesitance, lack of understanding around osteoporosis, and patient health information sources.[209 215 216 219] Many patients are hesitant to begin osteoporotic therapy due to pre-existing medical conditions or gender.[209 215] Men often view osteoporosis as a “female” condition and can be hesitant to undertake treatment for this reason.[215] Some patients misunderstand how osteoporosis and bone fragility are treatable pathologies, not just

part of the “normal aging” process.[209 215 219] These views are generally a result of the media misinforming patients and focusing on the “negatives” of osteoporotic drug therapy (i.e. side effects) instead of the effectiveness and benefits of these pharmaceuticals.[209 215 219] A lack of credible information for patients can be compounded when there is evidence that physicians are uncertain about the benefits of osteoporotic drugs and fail to explain how improvements in bone health are determined after undergoing treatment regimens.[209 215 216 219] Patient views and hesitancy towards osteoporotic drug therapy can be overcome with improvements in patient and physician information sources on osteoporosis and how anti-osteoporotic treatments work.[209 215 216 219]

9.3.3 Findings: ethical issues

Issues related to healthcare access and equity were highlighted in a single-arm extension of the FREEDOM trial conducted in Switzerland.[189] A small sample of Swiss patients reported that once their T-score was above -2.5, they were no longer eligible to receive reimbursement for denosumab. These patients then decided to discontinue denosumab treatment rather than pay out of pocket, suggesting that reimbursement status is a driver of uptake.[189]

10 Organisational issues

10.1 Summary statement organisational issues

The evidence-base indicated that the main organisational issues related to denosumab and its comparators (i.e. bisphosphonates and SERMs) revolve around the health education of patients and medical practitioners (i.e. doctors, nurses, dentists), and patient preferences. If denosumab were to be limited, patients and clinicians would need clear guidance around the most suitable follow-up treatments, and strategies would be needed to increase adherence to alternative treatments.

10.2 Methodology: organisational issues

Literature identified from systematic and non-systematic searches was used to address organisational issues. The search terms and search strings used for the systematic search are outlined in ***Appendix A***. The non-systematic searches involved targeted search of PubMed and Google using terms such as, 'osteoporosis', 'denosumab', 'Prolia' 'postmenopausal', 'breast cancer', 'prostate cancer', 'fracture', 'adjuvant therapy', 'aromatase inhibitor', 'ablation therapy', 'education', 'cost', 'access', 'adherence', 'burden' and 'reimbursement'. No limitations were placed on study design for inclusion. The non-systematic searches were conducted by a single reviewer. The results of the literature search are summarised narratively.

10.3 Results: organisational issues

10.3.1 Evidence table

Seven publications were identified and included through the systematic and non-systematic search for organisational issues relating to denosumab therapy and the consequences of limiting denosumab therapy (***Table 35***). A PRISMA flow diagram was not provided in this section given that both systematic and non-systematic searches were conducted. The included studies were conducted in North America (k = 1), Europe (k = 3), Oceania (k = 1), Asia (k = 1) and Asia/Middle East (k = 1).

Table 35 Characteristics of included studies for organisational issues

Study; country	Indication; sample size	Design; follow-up; setting	Outcomes
Alami et al. 2016[209] France	Physicians involved in the management of osteoporosis, with postmenopausal osteoporotic women among the patients treated n = 18	Qualitative study, face-to-face semi-structured interviews 4 mo Hospital, doctor's office, home settings	Views on osteoporosis, on osteoporosis management (e.g. diagnosis and clinical decision-making), expectations and patient interactions
Fogelman et al. 2016[220] Israel	Primary care physicians involved in the management of osteoporosis n = 363	Cross-sectional study – questionnaire NA Medical conference	Personal knowledge, source of knowledge attainment, and self-evaluation of knowledge on the diagnosis and treatment of osteoporosis
Hadji et al. 2015[105] Germany, Austria, Greece, Belgium	Physicians treating postmenopausal women receiving denosumab (60 mg/6 mo) n = 141	Prospective study, non-interventional, multicentre 12 mo Medical care centres	Reason for prescribing denosumab
Modi et al. 2014[215] USA	Women and men with osteoporosis NA	Review NA NA	Challenges in the treatment of osteoporosis
Naik-Panvelkar et al. 2020[216] Australia	GPs managing patients with osteoporosis n = 13	Phase 1 – Longitudinal retrospective cohort study Phase 2 – In-depth interview General practice setting	Knowledge, attitudes, organisational factors and perceived patient factors and their management
Rabenda et al. 2010[217] Belgium	Patients prescribed osteoporotic medication NA	Review NA NA	Adherence, persistence and compliance
Yeam et al. 2018[218] Singapore	Patients prescribed osteoporotic medication NA	Systematic review NA NA	Knowledge and beliefs, and reason for initiation/non-initiation of osteoporotic treatment

Abbreviations:
mo: month/s; **NA**: not applicable; **mg**: milligrams, **USA**: United States of America; **GPs**: general practitioners.

10.3.2 Findings: organisational issues

Seven studies investigated potential organisational issues relevant to denosumab.[105 209 215-218 220] The main organisational issues related to denosumab and its comparators (i.e. bisphosphonates and SERMs) revolve around the health education of patients and medical practitioners (i.e. doctors, nurses, dentists), and patient preferences.[105 209 215-218 220]

As explained above (***Section 8*** and ***Section 10***), misinformation about osteoporosis and osteoporotic treatments (i.e. denosumab) can contribute to patient hesitancy and decreased medication adherence.[209 211 215] This hesitancy is further compounded with some medical practitioners failing to

provide patients with detailed information about their condition and treatment options.[209 215] However, patient hesitancy can be overcome. Compliance with osteoporotic medication has been shown to improve with patient and practitioner education and with good patient-practitioner communication.[209 215-218 220] This can be achieved with in-practice patient education as well as improved education of non-specialised medical practitioners to provide continuity of care and advice that can simplify, streamline and improve patient care.[209 215-218 220]

Complying with a patient's preference could also streamline services and improve healthcare outcomes.[209 211 215] Patients prefer infrequent and IV treatments such as denosumab (***Section 8*** and ***Section 10***).[209 211 217 218] Adherence decreases in situations where the benefit of a long interval between doses (i.e. biannual) is replaced by a daily, weekly or monthly (i.e. short interval) bisphosphonate or SERM treatment regimen.[209 211 217 218] If osteoporotic patients are to be treated with bisphosphonates or SERMs instead of denosumab, patient education (in-treatment or otherwise) and improved communication between medical practitioners (i.e. doctors, nurses, dentists) is paramount.[215-218]

11 Additional issues

11.1 Clinical practice position statements and guidelines

In total, 17 clinical practice position statements and guidelines were identified through the systematic search and targeted searches (***Table 36***). Fourteen of these were clinical practice guidelines,[18 285-297] and 3 were clinical practice position statements.[18 22 31] The issuing organisations were from Australia, Europe and USA.

There was some disagreement in the guidelines regarding the use of denosumab for the treatment of osteoporosis across the four populations of interest. A clear consensus has not been reached regarding the use of denosumab as a first-line treatment, second-line treatment and/or in patients with contraindications or intolerance to bisphosphonates. Of importance, ten publications recommended the use of a subsequent antiresorptive therapy after discontinuing denosumab treatment,[18 31 286 288 289 292-294 297 298] with seven publications being in postmenopausal women with osteoporosis, one in postmenopausal women and men with osteoporosis, and one in women with breast cancer receiving AAIT.

Table 36 Summary of clinical guidelines and recommendations regarding denosumab

Author; Country	Recommendation	Strength of recommendation[a,b]
Guidelines		
American Association of Clinical Endocrinologists and American College of Endocrinology (AACE) 2020[289] USA	*Postmenopausal women with osteoporosis:* Denosumab recommended as an initial therapy to reduce hip, nonvertebral and vertebral fractures. Denosumab recommended for those unable to use oral therapies as an initial therapy if at a very high risk of fracture. Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended.	 Grade A Grade A Grade A
American College of Physicians (ACP) 2017[295] USA	*Postmenopausal women with osteoporosis:* Denosumab recommended in patients to reduce the risk of hip and vertebral fracture. *Men with osteoporosis:* No recommendation for the use of denosumab.	 Strong (1); Grade A NR
Australian Government, Cancer Australia 2020[285] Australia	*Women with breast cancer receiving AAIT:* Denosumab recommended for patients to manage treatment-induced bone loss.	 NR
Bouvard et al. 2019[286] (AFSOS, GEMO, GRIO, SFRO, SFR, SFSPM) France	*Women with breast cancer receiving AAIT:* Denosumab recommended as a second-line treatment. Not licensed for use in this population. Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended.	 NR NR

Author; Country	Recommendation	Strength of recommendation[a,b]
Briot et al. 2019[287] (Bone Task Force of the French SFR and GRIO) France	*Men with prostate cancer on HAT:* Denosumab recommended to decrease the risk of vertebral fracture if osteoporosis treatment required (not reimbursed in France). Denosumab recommended in patients if contraindication or intolerant to bisphosphonates if osteoporosis treatment required (not reimbursed in France).	Grade A Grade C
Briot et al. 2018[288] (SFR, GRIO, GEMO, AFSOS, AFU, SFRO) France	*Postmenopausal women with osteoporosis:* Denosumab (only reimbursed if used after a bisphosphonate) recommended in patients with severe nonvertebral fracture, vertebral fracture, hip fracture, non-severe fracture and without fracture (with corresponding BMD T-score in each at-risk group). Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended.	NR Grade C
Eastell et al. 2019[298] (European Society of Endocrinology) Europe	*Postmenopausal women with osteoporosis:* Denosumab recommended in patients at high risk of fracture as an alternative initial therapy. Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended.	Strong (1); Level A Level C
Prostate Cancer Guidelines Panel 2021[290] (EAU, EANM, ESTRO, ESUR, ISUP, SIOG) Europe	*Men with prostate cancer on HAT:* Denosumab recommended in patients at risk of fracture or annual bone loss >5% (supportive care).	Strong (1)
Guideline of the Umbrella Organization of the German-Speaking Scientific Osteological Societies (DVO) 2017,[293] 2018[294] Germany, Austria, Switzerland	*Postmenopausal women with osteoporosis:* Denosumab recommended to prevent vertebral, nonvertebral and hip fracture in patients if contraindication or intolerant to bisphosphonates. Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended. *Men with osteoporosis:* Denosumab recommended in patients with osteoporosis. *Men with prostate cancer on HAT:* Denosumab recommended in patients with increased risk of fracture.	Grade A Grace C NR NR
NICE 2019[291] UK	*Men with prostate cancer on HAT:* Denosumab recommended in patients with osteoporosis if bisphosphonates cannot be tolerated or contraindicated.	NR
National Osteoporosis Guideline Group (NOGG) 2017[292] UK	*Postmenopausal women and men with osteoporosis:* Denosumab recommended in patients with osteoporosis if bisphosphonates are not tolerated or contraindicated. Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended.	Grade A Grade C
RACGP and Osteoporosis Australia 2017[296] Australia	*Postmenopausal women with osteoporosis:* Denosumab recommended in patients with osteoporosis at increased fracture risk.	Grade A

Author; Country	Recommendation	Strength of recommendation[a,b]
	Men with osteoporosis: Denosumab should be considered as an alternative treatment to bisphosphonates in patients at increased risk of fracture.	Grade B
SIGN 2021[296] UK	*Postmenopausal women with osteoporosis:* Denosumab recommended to prevent vertebral, nonvertebral and hip fracture in patients when oral bisphosphonates contraindicated or cannot be tolerated.	Strong (1); Grade A
	Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended.	Strong (1); Grade B
Position statements		
Swiss Association against Osteoporosis (SVGO) 2017[18] Switzerland	*Postmenopausal women with osteoporosis:* Denosumab recommended in patients at high risk of fracture following treatment (3–5 years) with a bisphosphonate or SERM.	NR
	Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended.	NR
Swiss Association against Osteoporosis (SVGO) 2020[22] Switzerland	*Postmenopausal women and men with osteoporosis:* Denosumab recommended in patients at high/very high risk of fracture.	NR
The International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis 2019[31] Europe	*Postmenopausal women with osteoporosis:* Denosumab recommended as a second-line treatment and when oral bisphosphonates contraindicated or cannot be tolerated.	Grade A
	Upon discontinuation of denosumab a subsequent antiresorptive therapy is recommended.	NR

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **AFSOS**: Association Francophone pour les Soins Oncologiques de Support; **AFU**: Association Francaise d'Urologie; **EANM**: European Association of Nuclear Medicine; **EAU**: European Association of Urology; **ESTRO**: European Society for Radiotherapy and Oncology; **ESUR**: European Society of Urogenital Radiology; **GEMO**: Groupe Européen d'Etudes des Métastases Osseuses; **GRIO**: Groupe de Recherche et d'Information sur les Ostéoporoses; **HAT**: hormone ablation therapy; **ISUP**: International Society of Urological Pathology; **NICE**: National Institute of Health and Care Excellence; **NR**: not reported; **RACGP**: Royal Australasian College of General Practitioners; **SFRO**: Société Francaise de Radiothérapie Oncologique; **SFR**: Société Francaise de Rhumatologie; **SFSPM**: Société Francaise de Sénologie et de Pathologie Mammaire; **SIOG**: International Society of Geriatric Oncology; **SIGN**: Scottish Intercollegiate Guidelines Network **UK**: United Kingdom; **USA**: United States of America.
Notes:
[a] **Quality of evidence**:
Grade A: Data sourced from randomised clinical trial/s or meta-analyses.
Grade B: Data sourced from well-designed controlled study without randomisation, quasi-experimental study or non-experimental descriptive study.
Grade C: Consensus of opinion/reports of experts or clinical experience of authorities.
[b] **Strength of recommendation**: **Strong (1)**: Benefits outweigh harms; **Conditional (2)**: Benefits balanced with harms

12 Discussion

The objective of this HTA was to evaluate the efficacy/effectiveness, safety, cost, cost-effectiveness and budget impact of denosumab compared to bisphosphonates and SERMs for the treatment of osteoporosis in postmenopausal women, women with breast cancer on AAIT, men with osteoporosis who have an increased fracture risk, and men with prostate cancer on HAT with an increased fracture risk. Legal, social, ethical or organisational issues associated with denosumab therapy were also considered.

12.1 Comparison to previous HTA reports

An existing HTA report by Davis et al. 2020 and two systematic reviews by Beaudoin et al. 2016 and Yanbeiy and Hansen 2019 examined the clinical effectiveness and safety of denosumab relative to placebo or bisphosphonates.[299-301]

12.1.1 Comparison to Davis et al. 2020

The HTA report by Davis et al. 2020 was conducted for the National Institute for Health Research in the UK. It used a network meta-analysis to review the clinical effectiveness, safety and cost-effectiveness of denosumab, raloxifene, romosozumab and teriparatide, relative to placebo, alendronate, risedronate, ibandronate and zoledronate.[300]

The findings of the current HTA report are generally in accordance with those in the review by Davis et al. 2020.[300] Both reviews report the same direction of treatment effect with regards to denosumab (relative to placebo) preventing vertebral fractures and increasing BMD measured at the FN. The reviews report different directions of treatment effect for the effect of denosumab (relative to placebo) on nonvertebral fractures.[300] Davis et al. 2020 reported that denosumab was associated with a non-statistically significant reduction in nonvertebral fractures; the current HTA found that denosumab was also associated with a non-significant reduction in nonvertebral fractures (relative to placebo) for each population except for postmenopausal women, in whom denosumab was associated with a non-significant increase in the risk of nonvertebral fracture.[300] The difference in the postmenopausal women findings was most likely caused by precision issues with the postmenopausal women analysis,[300] i.e. when all populations were combined, denosumab was associated with a significant reduction in nonvertebral fractures.

There were several differences between the two HTA reports,[300] the first being the policy context under which the HTAs were written. The policy context for this HTA necessitated the investigation of four different population groups and included studies from WHO-Mortality-Stratum A countries. In contrast,

the policy context under which the HTA by Davis et al. 2020 was written enabled the inclusion of all adults of any gender at a high risk of fracture, specifically excluding cancer patients.[300] Additionally, the Davis et al. 2020 HTA report measured the occurrence of medical events using HRs,[300] while this HTA report measured the occurrence of medical events as binary outcomes and calculated RRs. A further difference between the two HTA reports was that Davis et al. 2020 did not meta-analyse BMD data measured at the LS, TH or trochanter, whereas this HTA report did.[300] The review by Davis et al. 2020 also evaluated the safety and effectiveness of romosozumab and teriparatide—two pharmaceuticals excluded from this HTA. Lastly, the Davis et al. 2020 report did not review the treatment effects related to AEs that could possibly occur upon denosumab discontinuation.[300]

12.1.2 Comparison to Beaudoin et al. 2016 and Yanbeiy and Hansen 2019

The findings of the current HTA report are generally in accordance with the two systematic reviews conducted by Beaudoin et al. 2016 and Yanbeiy and Hansen 2019.[299 301] This HTA report and the two systematic reviews all report the same direction of treatment effect with regard to the use of denosumab (relative to bisphosphonate), resulting in statistically significant increases in BMD measured at TH.[299 301] Similarly, Yanbeiy and Hansen 2019 and this HTA both report that denosumab (relative to bisphosphonate) can result in statistically significant improvements in LS BMD.[301] With regard to AEs and withdrawals due to AEs, this HTA and that by Beaudoin et al. 2016 both report similar non-statistically significant treatment effects that remain around the line of no effect.[299]

This HTA could not compare fracture outcomes with either of the previously mentioned systematic reviews as the publications do not delineate between vertebral and nonvertebral fractures. Yanbeiy and Hansen 2019 report specific AEs (infection etc) without reporting an aggregate number, therefore the results could not be compared with the findings of this HTA. Neither Beaudoin et al. 2016 nor Yanbeiy and Hansen 2019 reported the AEs that could possibly occur upon denosumab discontinuation.[299 301]

12.1.3 Comparison to existing economic literature

Earlier this year (2021), an updated systematic review of cost-effectiveness analyses of drugs for osteoporosis was published.[263] Of 27 included studies, 8 made comparisons between denosumab and oral alendronate. Five studies demonstrated denosumab to be cost-effective at a WTP threshold of US$100,000 (approximately CHF99,300; SEP-2019),[302] one study showed denosumab to be dominant, and two studies showed that denosumab was not cost-effective.[263] When compared with risedronate and ibandronate, denosumab was shown to be cost-effective (n = 2) or dominant (n = 2).[263] When compared to zoledronate, denosumab was shown to be dominant (n = 2).[263]

Our results did not find denosumab to be cost-effective over oral bisphosphonates at a hypothetical WTP threshold of CHF100,000 at any ages or baseline risk levels tested (***Table 133***, ***Table 134*** and ***Table 135***, ***Appendix I***). Denosumab was shown to be dominant over zoledronate in women age 80 years at high or very-high fracture risk, and cost-effective over zoledronate in women age 80 years at moderate risk or age 70 years at moderate- or very-high risk (***Table 134*** and ***Table 135***, ***Appendix I***). In women age 60 years, zoledronate was cost-effective over denosumab at the hypothetical WTP threshold of CHF100,000 (***Table 133***, ***Appendix I***).

In the clinical review, although none of the treatments were statistically significant compared to placebo, denosumab ranked as the most effective treatment at preventing vertebral fracture in postmenopausal women (***Figure 4, Section 7.4.4.1***). This was reflected in the model outputs, with denosumab being associated with the lowest number of vertebral fractures in women starting therapy at age 70 or 80 years at any risk level (results not shown). Nonetheless, this did not translate to favourable cost-effectiveness outcomes for denosumab, even considering its improved persistence versus comparator drugs. Lower intervention costs, a reduced number of hip fractures, and longer offset periods seen with oral bisphosphonates and IV ibandronate (relative to denosumab) may have contributed to the relative cost ineffectiveness of denosumab despite its positive impact on vertebral fracture outcomes. Sensitivity analyses showed the ICERs for denosumab relative to IV ibandronate and oral bisphosphonates to improve when the cost of denosumab administration was reduced, when the nonvertebral fracture RRs were set equal across all interventions, and when the assumed offset period for denosumab was set equal to treatment duration (***Table 136***; ***Appendix I***).

Recent evidence suggests the risk of new and worsening vertebral fracture quickly returns to levels similar to the risk in untreated patients upon denosumab discontinuation.[159] Accordingly, our model assumed a maximum offset period of 1 year upon denosumab discontinuation, shorter than the offset periods assumed for the bisphosphonates (***Section 8.3.2.1***). In sensitivity analyses, ICERs for denosumab relative to comparator treatments (pairwise comparisons) improved when the assumed offset period for denosumab was increased to equal treatment duration, and worsened when the offset period after discontinuation was removed completely (***Table 136***; ***Appendix I***). For example, the ICER for denosumab relative to oral bisphosphonates was CHF548,512 when the offset period for denosumab was completely removed, CHF166,451 under base case assumptions, and CHF81,895 when the offset period was assumed to equal treatment duration (***Table 136***; ***Appendix I***).

12.2 Limitations in the HTA methods

There are several limitations related to the methodology used to conduct this HTA. The first, is that even though bazedoxifene (Conbriza®) has been removed from the Spezialitätenliste,[56] it is still included in

this HTA report. Bazedoxifene was included because it was delisted during the preparation of this report and there was no opportunity to remove it and rerun all the relevant analyses. Further, the report separated the four included populations in order to best reflect the Swiss policy context; as a result, this limited the statistical precision of the analyses. A sensitivity analysis combining the four populations was conducted, and the results more closely align with the Davis et al. 2020 HTA for key outcomes such as vertebral fracture, NVAF, and FN BMD, showing favourable results for denosumab.[300]

12.3 Limitations in the clinical analysis

There are several key limitations related to the data analysed in this HTA report. First, the meta-analysis (network or pairwise) suffered from imprecision. The extent to which this limitation affected the overall quality of the evidence is reflected in the GRADE tables (***Section 7.4.7***). Second, although statistically significant treatment effects were observed when comparing the treatments of interest to placebo, few outcomes reported statistically significant pairwise comparisons relative to other active interventions. Third, there is a lack of evidence on how the presence or absence of heterogeneity and inconsistency can impact the findings of a network meta-analysis.[133] Therefore, it is unclear if moderate to considerable levels of heterogeneity and/or inconsistency in a network lead to less reliability of the results or the ability for the results to impute comparisons (i.e. generate indirect evidence when direct comparison are unavailable).[133] Finally, there is a lack of consensus on an evidence-based MCID for BMD that relates changes in BMD scores to fracture risk.[107-109] Even though some effectiveness findings in this report show that denosumab (relative to placebo and other comparators) can result in statistically significant increases in the surrogate outcome of BMD (measured at various locations) across the populations, it is difficult to interpret the clinical significance of these findings.

There are several limitations to the method used to conduct the meta-regressions. The key limitation in this HTA is the risk of a false association between the selected outcomes and the covariates (i.e. age).[303 304] The risk of false associations was minimised as the covariates were selected for investigation during the protocol phase of this HTA.[303 304] An additional limitation is that it can be difficult to draw robust conclusions from the results of meta-regression as the relationship identified between the outcomes and the covariate are considered observational—even though the evidence is extracted from RCTs.[304 305] Finally, meta-regressions generally have low statistical power due to minimal trials (i.e. less than ten) that report both the outcomes (in the relative population) and the covariate.[118 303-305]

12.4 Limitations in the economic analysis

There were several limitations and uncertainties in the economic analysis. The economic evaluation was limited to one of four indications for denosumab—postmenopausal osteoporosis—which was

considered as an exemplar case. The outcomes seen for postmenopausal women cannot simply be transferred to the other three indications, meaning no conclusions can be drawn regarding the cost-effectiveness of denosumab in Switzerland for these other three indications. Despite capturing the four major sites of fragility fracture, use of FRAX®-derived 10-year probabilities of fracture meant that not all potential sites of fracture were captured in the model. Moreover, the model considered individual therapies in isolation. In clinical practice; however, sequential therapies may be required to achieve optimal outcomes. For example, European and Swiss guidelines now recommend treatment with a bisphosphonate upon discontinuation of denosumab.[18] [306] Sensitivity analyses showed treatment efficacy inputs to be drivers of cost-effectiveness. However, the network meta-analysis data informing these inputs showed a high degree of uncertainty in the true effect of treatments on vertebral and nonvertebral fracture risk, and did not include all treatments.

A limitation of our DES model is that it did not consider costs and QoL reductions directly attributable to treatment-related side effects. Previous economic evaluations including GI side effects in a sensitivity analysis found these to have only a small impact on the ICER for denosumab, versus either alendronate or risedronate.[208] [243] A recent HTA concluded that rare AEs, including cellulitis and ONJ, are unlikely to be significant drivers of cost-effectiveness.[255] Although, for raloxifene, it was suggested that the AE of venous thromboembolism may be a driver of cost-effectiveness.[255] Cost-effectiveness results for raloxifene may need to be interpreted cautiously.

The budget impact analysis explored the potential costs of denosumab between 2021 and 2024, assuming no policy change, with extrapolation assumptions informed by trends in utilisation over recent years. A decline in the utilisation of denosumab over the period 2017 to 2020 was observed. While base case estimates assumed that this declining trend would continue, it is unclear what has driven the decline and whether the contributing factor(s) will continue to be influential in the future. Finally, there is uncertainty around the actual patient numbers presented, as only a crude adjustment for non-adherence was made. Exact rates of adherence and discontinuation for denosumab in Switzerland are unknown.

12.5 Strengths in the HTA methods

The methodology used to conduct this HTA report was rigorous and comprehensive. The overall methodology follows best practices outline by PRISMA and GRADE.[236] [307] Multiple bibliographic databases (***Table 37*** to ***Table 41***, ***Appendix A***) were systematically and comprehensively searched for the highest available level of evidence with context-specific comparisons relevant to the Swiss policy context. A network meta-analysis was conducted, which enabled treatments to be ranked and treatment effect measures to be generated in situations where no direct comparative data were available. For

example, the network meta-analysis permitted treatment effect measures between denosumab and SERMs (i.e. raloxifene and bazedoxifene) to be imputed, as direct RCT evidence was unavailable for any of the outcomes in the target populations. The final strength of this HTA is the exemplar economic evaluation of denosumab in postmenopausal women with osteoporosis in Switzerland. A de novo cost-effectiveness model was constructed, which could be built upon Swiss-specific estimates of fracture risk and, where possible, incorporate assumptions informed by SVGO guidelines.

12.6 Evidence gaps

The evidence gaps in this HTA report reflect the limited available evidence applicable to the Swiss policy context. The most significant gap in evidence relates to AEs that occur upon discontinuation of denosumab (i.e. “rebound effect”). This HTA was unable to draw evidence-based conclusions about whether a rebound effect occurs in postmenopausal women or women with breast cancer receiving AAIT, as only scarce and low-quality evidence was available. Furthermore, there was no evidence on the rebound effect in men with osteoporosis or men with prostate cancer on HAT. Limited information also extended to the lack of evidence applicable to the Swiss policy context on how a treatment regimen of denosumab affects HRQoL, FRAX® and compliance in the four populations.

12.7 Ongoing clinical trials

The search of clinical trial registries identified six relevant ongoing clinical trials and one unpublished clinical trial, summarised in ***Table 126***, ***Appendix F***. Of the six relevant ongoing clinical trials, five are being conducted in postmenopausal women and one is being conducted in women with breast cancer receiving AAIT. Two trials are being conducted in Australia/New Zealand; two trials are being conducted in Europe, including Austria, Sweden and Slovenia; and two trials are being conducted in the USA. All ongoing trials are expected to be complete between April 2021 and May 2025.

In postmenopausal women, two ongoing trials (both conducted in Australia/New Zealand) seek to compare denosumab to both zoledronate and placebo; one is actively recruiting and the other has not yet begun recruitment. One trial, enrolling by invitation, is seeking to compare denosumab to zoledronate. One trial, active and not recruiting, is seeking to compare zoledronate to placebo. One trial, active and not recruiting, is seeking to compare denosumab to placebo, with both arms crossed over to zoledronate during an extension phase.

In women with breast cancer receiving AAIT, one included RCT (ABCSG-18) is currently conducting an extension phase (active, not recruiting), with those initially assigned to denosumab crossed over to zoledronate and compared to placebo/standard care.

Based on the estimated sample sizes and designs of the identified trials, they are unlikely to contribute significant new information that would warrant reconsideration of the evidence base.

13 Conclusions

Compared to placebo and the other therapies available in Switzerland, low- to moderate-quality evidence found denosumab reported similar results in terms of the reported direction of effect in relation to vertebral fracture, nonvertebral fracture, BMD and safety outcomes. However, the analyses were largely subject to statistical imprecision. In relation to AEs, the only significant increase in treatment-related AEs was for alendronate and zoledronate in men with osteoporosis; other drugs reported similar safety profiles compared to placebo. There was no evidence investigating rebound effects in men with osteoporosis or men with prostate cancer on HAT, and insufficient evidence in postmenopausal women and women with breast cancer receiving AAIT to be able to draw conclusions.

The economic model was constructed using Swiss-specific FRAX®-derived fracture probabilities in women of postmenopausal age and at various baseline risks of fracture. The effect of treatment on fracture risk, the duration of residual benefit upon treatment discontinuation, and patient adherence to therapy were all captured within the model. At a hypothetical WTP threshold of CHF100,000, IV ibandronate was the most cost-effective antiresorptive therapy in women aged 60 years at very high risk, and in women aged 70 or 80 years at any risk level. In women aged 60 years at lower risk levels, zoledronate was shown to be the most cost-effective option. Despite cost-effectiveness frontier analysis not finding denosumab to be the most cost-effective antiresorptive therapy, denosumab was shown to have ICERs below the hypothetical WTP threshold of CHF100,000 in pairwise comparison with some comparators. The uncertainty surrounding the true effect of treatments on fracture risk evident in the network meta-analysis outputs has propagated uncertainties in economic model outcomes, therefore results should be interpreted cautiously.

Included studies reported strong patient preferences and adherence to denosumab compared to bisphosphonates. Efforts to improve adherence would need to be considered if the reimbursement status of denosumab was altered.

14 References

1. Livio F. [Pharmacovigilance update]. *Rev Med Suisse* 2018;14(588-589):81-84.
2. Heaney RP. The natural history of vertebral osteoporosis. Is low bone mass an epiphenomenon? *Bone* 1992;13 Suppl 2:S23-6.
3. Kanis JA. Osteoporosis and osteopenia. *J Bone Miner Res* 1990;5(3):209-11.
4. Dobbs MB, Buckwalter J, Saltzman CJTIoj. Osteoporosis: the increasing role of the orthopaedist. 1999;19:43.
5. Mirza F, Canalis E. Management of endocrine disease: Secondary osteoporosis: pathophysiology and management. *European journal of endocrinology* 2015;173(3):R131-51.
6. Ramin C, May BJ, Roden RBS, et al. Evaluation of osteopenia and osteoporosis in younger breast cancer survivors compared with cancer-free women: a prospective cohort study. *Breast Cancer Research* 2018;20(1):134.
7. Kawagushi H. Osteoporosis pathophysiology: the updated mechanism. *Clinical Case Reports and Reviews* 2015;1(9):194-98.
8. Gallagher JC, Riggs BL, Eisman J, et al. Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients: effect of age and dietary calcium. *The Journal of clinical investigation* 1979;64(3):729-36.
9. Haden ST, Brown EM, Hurwitz S, et al. The effects of age and gender on parathyroid hormone dynamics. 2000;52(3):329-38.
10. Healthy Bones Australia. National Strategic Action Plan for Osteoporosis 2019 [Available from: https://healthybonesaustralia.org.au/wp-content/uploads/2020/11/OA-NAP_final_24-09-19-1.pdfJanuary 2021].
11. World Health Organisation. WHO scientific group on the assessment of osteoporosis ar primary health care level - summary meeting report. In: WHO, ed. Brussels, Belgium, 2004.
12. Brunader R, Shelton DK. Radiologic bone assessment in the evaluation of osteoporosis. *American family physician* 2002;65(7):1357-64.
13. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet (London, England)* 2002;359(9321):1929-36.
14. National Institutes of Health. NIH concensus development panel on osteoporosis prevention, diagnosis, and therapy, March 7-29, 2000: Highlights of the conference. CME, 2000.
15. Centre for Metabolic Bone Diseases. Calculation Tool: University of Sheffield; 2010 [Available from: https://www.sheffield.ac.uk/FRAX/tool.aspx?country=31 accessed 2020 April 1].
16. Cranney A, Jamal SA, Tsang JF, et al. Low bone mineral density and fracture burden in postmenopausal women. *Cmaj* 2007;177(6):575-80.
17. Association Suisse contre l'Ostéoporose. Osteoporose Recommandations 2015 2015 [Available from: https://www.sgedssed.ch/fileadmin/user_upload/7_Endokrinologie/72_Empfehlungen_SGED/ASCO_Recommandations_2015.pdfJanuary 2021].
18. Meier C, Uebelhart B, Aubry-Rozier B, et al. Osteoporosis drug treatment: duration and management after discontinuation. A position statement from the SVGO/ASCO. *Swiss Med Wkly* 2017;147:w14484.
19. Schweizerische Vereinigung gegen Osteoporose. Osteoporose. Empfehlungen 2015- Prävention. Diagnostik. Behandlung.: Nachdruck nur mit Nennung der Quelle, 2015.
20. Ligue suisse contre le rhumatisme. Une personne sur trois, de plus de 65 ans, est victime d'une chute: Ligue suisse contre le rhumatisme; 2020 [Available from: https://www.ligues-rhumatisme.ch/blog/2016/une-personne-sur-trois-de-plus-de-65-ans-est-victime-dune-chute.?q=osteoporose accessed 2020 April 1].
21. Svedbom A, Ivergård M, Hernlund E, et al. Epidemiology and economic burden of osteoporosis in Switzerland. *Arch Osteoporos* 2014;9:187.
22. Ferrari S, Lippuner K, Lamy O, et al. 2020 recommendations for osteoporosis treatment according to fracture risk from the Swiss Association against Osteoporosis (SVGO). *Swiss Med Wkly* 2020;150:w20352.
23. Svedbom A, Hernlund E, Ivergård M, et al. Osteoporosis in the European Union: a compendium of country-specific reports. *Arch Osteoporos* 2013;8(1-2):137.
24. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2(6):285-9.

25. Natural Therapy Pages. World Osteoporosis Day 2019: Natural Therapy Pages; 2019 [Available from: https://www.naturaltherapypages.com.au/article/world-osteoporosis-day-2019 accessed April 1 2020].
26. Ström O, Borgström F, Kanis JA, et al. Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos* 2011;6:59-155.
27. Högnlinger ME, F.; Maurer, J. Gesundheit der Alteren Bevolkerung in der Schweiz: FORS, 2019.
28. Wasserfallen JB, Krieg MA, Greiner RA, et al. Cost effectiveness and cost utility of risedronate for osteoporosis treatment and fracture prevention in women: a Swiss perspective. *J Med Econ* 2008;11(3):499-523.
29. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet (London, England)* 2002;359(9319):1761-7.
30. Bell AB, N.; Edwaards, S.; Frank, O.; Alderman, C.P.; KAran, L.; Husband, A.; Rowett, D. Osteoporosis. Pharmacological prevention and management in older people. *Australian Family Physician* 2012;41(3):110-18.
31. Kanis JA, Cooper C, Rizzoli R, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2019;30(1):3-44.
32. Royal Australian College of General Practitioners, Osteoporosis Australia. Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age. 2nd ed. Melbourne: The Royal Australian College of General Practitioners and Osteoporosis Australia, 2017.
33. Body JJ, Bergmann P, Boonen S, et al. Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club. *Osteoporos Int* 2010;21(10):1657-80.
34. Hanley DA, Adachi JD, Bell A, et al. Denosumab: mechanism of action and clinical outcomes. *International journal of clinical practice* 2012;66(12):1139-46.
35. Swissmedicinfo. Prolia®: Refdata; 2020 [Available from: https://www.swissmedicinfo.ch/Accept.aspx?Lang=EN accessed April 1 2020].
36. Versus Arthritis. Denosumab: Versus Arthritis; 2020 [Available from: https://www.versusarthritis.org/about-arthritis/treatments/drugs/denosumab/ accessed July 28 2020].
37. Anastasilakis AD, Goulis DG, Kita M, et al. Oral bisphosphonate adverse effects in 849 patients with metabolic bone diseases. *Hormones (Athens)* 2007;6(3):233-41.
38. Lamy O, Stoll D, Aubry-Rozier B, et al. Stopping Denosumab. *Current osteoporosis reports* 2019;17(1):8-15.
39. Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. *Bone* 2017;105:11-17.
40. Amgen Inc. Xgeva: Amgen Inc.,; 2020 [Available from: accessed July 20 2020].
41. Swissmedicinfo. XGEVA®: Refdata; 2020 [Available from: https://www.swissmedicinfo.ch/default.aspx accessed 30 July 2020].
42. Real J, Galindo G, Galván L, et al. Use of oral bisphosphonates in primary prevention of fractures in postmenopausal women: a population-based cohort study. *PLoS One* 2015;10(4):e0118178.
43. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clinic proceedings* 2008;83(9):1032-45.
44. Brown JP, Prince RL, Deal C, et al. Comparison of the Effect of Denosumab and Alendronate on BMD and Biochemical Markers of Bone Turnover in Postmenopausal Women With Low Bone Mass: A Randomized, Blinded, Phase 3 Trial. *J Bone Miner Res* 2009;24(1):153-61.
45. Brown JP, Roux C, Ho PR, et al. Denosumab significantly increases bone mineral density and reduces bone turnover compared with monthly oral ibandronate and risedronate in postmenopausal women who remained at higher risk for fracture despite previous suboptimal treatment with an oral bisphosphonate. *Osteoporos Int* 2014;25(7):1953-61.
46. Freemantle N, Satram-Hoang S, Tang ET, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int* 2012;23(1):317-26.
47. Nakamura T, Matsumoto T, Sugimoto T, et al. Clinical Trials Express: Fracture Risk Reduction With Denosumab in Japanese Postmenopausal Women and Men With Osteoporosis: Denosumab Fracture Intervention Randomized Placebo Controlled Trial (DIRECT). *J Clin Endocrinol Metab* 2014;99(7):2599-607.

48. Khosla S, Melton LJ, 3rd, Riggs BL. Clinical review 144: Estrogen and the male skeleton. *J Clin Endocrinol Metab* 2002;87(4):1443-50.
49. Gennari L, Merlotti D, Nuti R. Selective estrogen receptor modulator (SERM) for the treatment of osteoporosis in postmenopausal women: focus on lasofoxifene. *Clinical interventions in aging* 2010;5:19-29.
50. Swissmedicinfo. Evista®: Refdata; 2020 [Available from: https://www.swissmedicinfo.ch/default.aspx accessed 1 April 2020].
51. Swissmedicinfo. Conbriza®: Refdata; 2020 [Available from: https://www.swissmedicinfo.ch/default.aspx accessed 1 April 2020].
52. Tella SH, Gallagher JC. Prevention and treatment of postmenopausal osteoporosis. *The Journal of steroid biochemistry and molecular biology* 2014;142:155-70.
53. Swissmedicinfo. Estalis® Refdata; 2020 [Available from: https://www.swissmedicinfo.ch/Accept.aspx?ReturnUrl=%2f%3fLang%3dEN&Lang=EN accessed July 29 2020].
54. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344(19):1434-41.
55. Swissmedicinfo. Refdata; 2020 [accessed 1 April 2020].
56. Bundesamt für Gesundheit BAG. Spezialitätenliste (SL) 2020 [Ausgabe vom 1. Februar 2020:[Available from: https://www.bag.admin.ch/dam/bag/en/dokumente/kuv-leistungen/arzneimittel/Spezialit%C3%A4tenliste/spezialitaetenliste-als-pdf-stand-vom-01-02-2020.pdf.download.pdf/Spezialit%C3%A4tenliste%20als%20PDF%20Stand%20vom%2001.02.2020.pdf].
57. European Medicines Agency. Prolia: EPAR - Product Information 2020 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001120/WC500093526.pdf; accessed February 2021].
58. Danish Medicines Agency. Medicines eligible for reimbursement 2012 [Available from: https://laegemiddelstyrelsen.dk/en/reimbursement/general-reimbursement/medicines-eligible-for-reimbursement/ accessed 19 July 2021].
59. Norwegian Medicines Agency. Legemiddelvisning: Prolia 60mg/mL 2016 [Available from: https://www.legemiddelsok.no/sider/Legemiddelvisning.aspx?pakningId=d7d3c919-08d7-434a-b972-f67df9631e4b&f=Han;Mar;par;gen&searchquery=Prolia accessed 19 July 2021].
60. The Dental and Pharmaceutical Benefits Agency. Sök i databasen: Prolia 2020 [Available from: https://www.tlv.se/beslut/sok-i-databasen.html accessed 19 July 2021].
61. Italian Medicines Agency. Elenchi farmaci di classe A e H 2020 [Available from: https://www.aifa.gov.it/liste-farmaci-a-h accessed 19 July 2021].
62. Greek Ministry of Health. POSITIVE LIST OF AUGUST 2018 - Government Gazette 3431-ΒΔ-17_8_2018 2018 [Available from: https://www.moh.gov.gr/articles/times-farmakwn/thetikh-lista/5724-thetikh-lista-aygoystoy-2018-fek-3431-b-17-8-2018].
63. French Ministry of Social Affairs and Health. PROLIA 60 mg, solution injectable en seringue préremplie 2021 [Available from: http://base-donnees-publique.medicaments.gouv.fr/extrait.php?specid=64256891 accessed 19 July 2021].
64. European Medicines Agency. Summary of opinion (post authorisation): Prolia/denosumab 2018 [Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-prolia-ii-68_en.pdf accessed 19 July 2021].
65. Amgen Inc. FDA Approves Prolia® (Denosumab) For Glucocorticoid-Induced Osteoporosis 2018 [Available from: https://www.amgen.com/newsroom/press-releases/2018/05/fda-approves-prolia-denosumab-for-glucocorticoidinduced-osteoporosis].
66. Amgen Inc. Prolia® (denosumab). Highlights of prescribing information: Amgen Inc., 2019.
67. Garvan Institute of Medical Research How did you define the risk factor? : Garvan Institute of Medical Research; 2020 [Available from: https://www.garvan.org.au/bone-fracture-risk/your-questions-answered accessed May 12 2020].
68. Bone HG, Bolognese MA, Yuen CK, et al. Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Low Bone Mass. *J Clin Endocrinol Metab* 2011;96(4):972-80.
69. Shetty S, Kapoor N, Bondu JD, et al. Bone turnover markers: Emerging tool in the management of osteoporosis. *Indian J Endocrinol Metab* 2016;20(6):846-52.
70. Tripto-Shkolnik L, Rouach V, Marcus Y, et al. Vertebral Fractures Following Denosumab Discontinuation in Patients with Prolonged Exposure to Bisphosphonates. *Calcif Tissue Int* 2018;103(1):44-49.

71. Sabate E. Adherence to long-term therapies: evidence for action. Switzerland: World Health Organization, 2003.
72. Jimmy B, Jose J. Patient medication adherence: measures in daily practice. *Oman Med J* 2011;26(3):155-59.
73. Amgen Inc. Dosing: Amgen Inc.; 2020 [Available from: https://www.prolia.com/proven-prolia-results/dosing accessed July 16 2020].
74. Royal Australian College of General Practitioners. Bisphosphonates: Royal Australian College of General Practitioners; 2020 [Available from: https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/osteoporosis/recommendations/pharmacologic-approaches-to-prevention-and-treatme/bisphosphonates accessed May 5 2020].
75. An K-C. Selective Estrogen Receptor Modulators. *Asian Spine J* 2016;10(4):787-91.
76. International Osteoporosis Foundation. accessed July 15 2020].
77. International Osteoporosis Foundation. Facts and statistics: International Osteoporosis Foundation; 2017 [Available from: https://www.iofbonehealth.org/facts-statistics accessed July 15 2020].
78. Nazrun AS, Tzar MN, Mokhtar SA, et al. A systematic review of the outcomes of osteoporotic fracture patients after hospital discharge: morbidity, subsequent fractures, and mortality. *Ther Clin Risk Manag* 2014;10:937-48.
79. Burckhardt CS, Anderson KL. The Quality of Life Scale (QOLS): reliability, validity, and utilization. *Health Qual Life Outcomes* 2003;1:60-60.
80. International Osteoporosis Foundation. Quality of Life Questionnaire-Qualeffo-41: International Osteoporosis Foundation, 1997.
81. Silverman SL. The Osteoporosis Assessment Questionnaire (OPAQ): A reliable and valid disease-targeted measure of health-related quality of life (HRQOL) in osteoporosis. *Quality of Life Research* 2000;9(1):767-74.
82. Tadic I, Vujasinovic Stupar N, Tasic L, et al. Validation of the osteoporosis quality of life questionnaire QUALEFFO-41 for the Serbian population. *Health Qual Life Outcomes* 2012;10:74.
83. NIH Osteoporosis and Related Bone Diseases National Resource Center. Bone Mass Measurement: What the Numbers Mean: National Institutes of Health, 2018.
84. Johns Hopkins. What is a bone density test? : The Johns Hopkins University, The Johns Hopkins Hospital, and Johns Hopkins Health System; 2020 [Available from: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/bone-densitometry accessed July 15 2020].
85. Sheu A, Diamond T. Bone mineral density: testing for osteoporosis. *Aust Prescr* 2016;39(2):35-39.
86. Stone KL, Seeley DG, Lui LY, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. 2003;18(11):1947-54.
87. Garvan Institute of Medical Research. Your Questions Answered: Garvan Institute of Medical Research,; 2020 [Available from: https://www.garvan.org.au/bone-fracture-risk/your-questions-answered accessed April 30 2020].
88. Overview of role of BMD measurements in managing osteoporosis. Seminars in nuclear medicine; 1997.
89. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *American journal of obstetrics and gynecology* 2006;194(2 Suppl):S3-11.
90. Bonnick SL, Shulman L. Monitoring osteoporosis therapy: bone mineral density, bone turnover markers, or both? *The American journal of medicine* 2006;119(4):S25-S31.
91. Naylor K, Eastell R. Bone turnover markers: use in osteoporosis. *Nature Reviews Rheumatology* 2012;8(7):379-89.
92. Ebeling PR, Atley LM, Guthrie JR, et al. Bone turnover markers and bone density across the menopausal transition. *The Journal of Clinical Endocrinology & Metabolism* 1996;81(9):3366-71.
93. Centre for Metabolic Bone Diseases. Welcome to FRAX®: University of Sheffield; 2008 [Available from: https://www.sheffield.ac.uk/FRAX/ accessed July 15 2020].
94. International Osteoporosis Foundation. Fracture risk assessment: International Osteoporosis Foundation; 2017 [Available from: https://www.iofbonehealth.org/osteoporosis-musculoskeletal-disorders/osteoporosis/diagnosis/fracture-risk-assessment accessed July 15 2020].

95. Centre for Metabolic Bone Diseases. Charts to download: University of Sheffield; [Available from: https://www.sheffield.ac.uk/FRAX/charts.aspx accessed July 15 2020].
96. Amgen Inc. Australian product information – prolia (r) (denosumab) solution for injection. Product Information – Prolia (R): Amgen Inc. , 2019.
97. Beaudoin C, Jean S, Bessette L, et al. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. *Osteoporos Int* 2016;27(9):2835-44.
98. Anastasilakis AD, Polyzos SA, Makras P, et al. Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases. *J Bone Miner Res* 2017;32(6):1291-96.
99. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *J Bone Miner Res* 2018;33(2):190-98.
100. American Association of Clinical Endocrinologists. AACE* guidelines: No drug holiday recommended for Prolia®1: Amgen Inc; 2019 [Available from: https://www.proliahcp.com/dosing-and-administration/aace-guidelines accessed 2020 May 1].
101. CADTH. Denosumab and Zoledronic Acid for Patients with Postmenopausal Osteoporosis: A Review of the Clinical Effectiveness, Safety, Cost Effectiveness, and Guidelines. CONTEXT AND POLICY ISSUES 2012.
102. Silva-Fernandez L, Rosario MP, Martinez-Lopez JA, et al. Denosumab for the treatment of osteoporosis: a systematic literature review. *Reumatologia clinica* 2013;9(1):42-52.
103. U.S. National Library of Medicine. Denosumab Injection: National Institutes of Health; 2020 [Available from: https://medlineplus.gov/druginfo/meds/a610023.html accessed March 10 2020].
104. Wong-Pack M, Kalani A, Hordyk J, et al. The Effects of Noncompliance to Prolia (Denosumab) on the Changes in Bone Mineral Density: A Retrospective Review. *Journal of Osteoporosis* 2016;2016:7903128.
105. Hadji P, Kyvernitakis I, Kann PH, et al. GRAND-4: the German retrospective analysis of long-term persistence in women with osteoporosis treated with bisphosphonates or denosumab. *Osteoporosis International* 2016;27(10):2967-78.
106. Suzuki T, Nakamura Y, Kamimura M, et al. Compliance and discontinuation of denosumab treatment in postmenopausal Japanese women with primary osteoporosis or rheumatoid arthritis and osteoporosis. *Osteoporosis and Sarcopenia* 2017;3(2):108-11.
107. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis 2006 [Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-treatment-primary-osteoporosis_en.pdf accessed 21 July 2021].
108. Cranney A, Welch V, Wells G, et al. Discrimination of changes in osteoporosis outcomes. *J Rheumatol* 2001;28(2):413-21.
109. Guralnik J, Bandeen-Roche K, Bhasin SAR, et al. Clinically Meaningful Change for Physical Performance: Perspectives of the ICFSR Task Force. *J Frailty Aging* 2020;9(1):9-13.
110. Mourad Ouzzani, Hossam Hammady, Zbys Fedorowicz, et al. Rayyan — a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210.
111. Swiss Broadcasting Corporation. Languages: Swiss Broadcasting Corporation; 2019 [Available from: https://www.swissinfo.ch/eng/languages/29177618 accessed March 19 2020].
112. Federal Chancellery. Romansh: Federal Chancellery; [Available from: https://www.bk.admin.ch/bk/en/home/regierungsunterstuetzung/languages/translation/raetoromanisch.html accessed March 19 2020].
113. World Health Organization. List of Member States by WHO Region and Mortality Stratum: World Health Organization; 2020 [Available from: https://www.who.int/choice/demography/mortality_strata/en/ accessed February 5 2020].
114. Ankit Rohatgi. WebPlotDigitizer: Ankit Rohatgi; 2020 [Available from: https://automeris.io/WebPlotDigitizer/ accessed Febuary 8 2020].
115. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.(doi):10.1136/bmj.l4898.
116. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist Edmonton (AB): Institute of Health Economics; 2014 [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].

117. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *PLOS ONE* 2014;9(7):e99682.
118. Higgins JPT, J.; Chandler, J.; Cumpston, M.; Li, T; Page, M.J.; Welch, V.A. (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). *Cochrane* 2020
119. Li T, Puhan MA, Vedula SS, et al. Network meta-analysis-highly attractive but more methodological research is needed. *BMC Med* 2011;9(1):79.
120. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med* 2017;12(1):103-11.
121. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology* 2015;15(1):58.
122. Béliveau A, Boyne DJ, Slater J, et al. BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. *BMC Medical Research Methodology* 2019;19(1):196.
123. Biondi-Zoccai G, D'Ascenzo F. Choosing between frequentist and bayesian frameworks and the corresponding statistical package2014:103-15.
124. Csárdi G. Package 'igraph' 2020 [Available from: https://cran.r-project.org/web/packages/igraph/igraph.pdf23 August 2021].
125. Béliveau A. BUGSnet Package Manual 2020 [Available from: https://github.com/audrey-b/BUGSnet/blob/master/manual.pdf25 March 2021].
126. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: Foundation for Statistical Computing, 2020.
127. RStudio Team. RStudio: Integrated Development for R. Boston, USA: RStudio, 2020.
128. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1: Cochrane; 2020 [cited 2021 February 02]. Available from: www.training.cochrane.org/handbook accessed September 2020].
129. Thorlund K, Thabane L, Mills EJ. Modelling heterogeneity variances in multiple treatment comparison meta-analysis – Are informative priors the better solution? *BMC Medical Research Methodology* 2013;13(1):2.
130. van Valkenhoef G, Lu G, de Brock B, et al. Automating network meta-analysis. *Res Synth Methods* 2012;3(4):285-99.
131. Brooks SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. *Journal of Computational and Graphical Statistics* 1998;7(4):434-55.
132. Gelman A, Rubin DB. Inference from Iterative Simulation Using Multiple Sequences. *Statistical Science* 1992;7(4):457-72.
133. Mills E, Thorlund K, Ioannidis J. Demystifying trial networks and network meta-analysis. *BMJ (Clinical research ed)* 2013;346:f2914.
134. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003;327(7414):557-60.
135. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3(2):80-97.
136. Tonin FS, Rotta I, Mendes AM, et al. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. *Pharm Pract (Granada)* 2017;15(1):943.
137. University of Cambridge, MRC Biostatistics Unit. DIC: Deviance Information Criteria n.d. [October 2021]. Available from: http://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-dic/].
138. Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Medical Research Methodology* 2013;13(1):35.
139. Schwarzer G. General Package for Meta-Analysis. Version 4.18–0 2021 [Available from: https://cran.r-project.org/web/packages/meta/meta.pdf].
140. Schwarzer G. Package 'netmeta' reference manual 2021 [Available from: https://cran.r-project.org/web/packages/netmeta/netmeta.pdfApril 2021].
141. Schwarzer G, Carpenter J, Rücker G. Meta-Analysis with R2015.
142. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539-58.
143. Bracken M. Statistical methods for analysis of effects of treatment in overviews of randomized trials. *Effective care of the newborn infant* 1992:13-20.
144. Lajeunesse MJ. Facilitating systematic reviews, data extraction and meta-analysis with the metagear package for r. *Methods in Ecology and Evolution* 2016;7(3):323-30.

145. Mathsisfun.com. Percentage Difference, Percentage Error, Percentage Change 2017 [Available from: https://www.mathsisfun.com/data/percentage-difference-vs-error.htmlJuly 2021].
146. Chaimani A, Higgins JPT, Mavridis D, et al. Graphical Tools for Network Meta-Analysis in STATA. *PLOS ONE* 2013;8(10):e76654.
147. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Res Synth Methods* 2012;3(2):161-76.
148. Dias S, Sutton AJ, Welton NJ, et al. Evidence Synthesis for Decision Making 3: Heterogeneity—Subgroups, Meta-Regression, Bias, and Bias-Adjustment. *Med Decis Mak* 2013;33(5):618-40.
149. Fu R, Gartlehner G, Grant M, et al. AHRQ Methods for Effective Health Care

Conducting Quantitative Synthesis When Comparing Medical Interventions: AHRQ and the Effective Health Care Program. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US) 2008.
150. Adachi JD, Bone HG, Daizadeh NS, et al. Influence of subject discontinuation on long-term nonvertebral fracture rate in the denosumab FREEDOM Extension study. *BMC Musculoskelet Disord* 2017;18(1):174.
151. Bhoopalam N, Campbell SC, Moritz T, et al. Intravenous zoledronic acid to prevent osteoporosis in a veteran population with multiple risk factors for bone loss on androgen deprivation therapy. *J Urol* 2009;182(5):2257-64.
152. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356(18):1809-22.
153. Boonen S, Orwoll ES, Wenderoth D, et al. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. *J Bone Miner Res* 2009;24(4):719-25.
154. Boonen S, Reginster JY, Kaufman JM, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. *N Engl J Med* 2012;367(18):1714-23.
155. Brown JP, Roux C, Torring O, et al. Discontinuation of denosumab and associated fracture incidence: analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. *J Bone Miner Res* 2013;28(4):746-52.
156. Cheung AS, Hoermann R, Ghasem-Zadeh A, et al. Differing Effects of Zoledronic Acid on Bone Microarchitecture and Bone Mineral Density in Men Receiving Androgen Deprivation Therapy: A Randomized Controlled Trial. *J Bone Miner Res* 2020;35(10):1871-80.
157. Choo R, Lukka H, Cheung P, et al. Randomized, double-blinded, placebo-controlled, trial of risedronate for the prevention of bone mineral density loss in nonmetastatic prostate cancer patients receiving radiation therapy plus androgen deprivation therapy. *International journal of radiation oncology, biology, physics* 2013;85(5):1239-45.
158. Christiansen C, Chesnut CH, 3rd, Adachi JD, et al. Safety of bazedoxifene in a randomized, double-blind, placebo- and active-controlled Phase 3 study of postmenopausal women with osteoporosis. *BMC Musculoskelet Disord* 2010;11:130.
159. Cummings SR, Ferrari S, Eastell R, et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. *J Bone Miner Res* 2018;33(2):190-98.
160. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361(8):756-65.
161. de Villiers TJ, Chines AA, Palacios S, et al. Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. *Osteoporos Int* 2011;22(2):567-76.
162. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002;87(8):3609-17.
163. Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol* 2008;26(30):4875-82.
164. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *Jama* 1999;282(7):637-45.
165. Fassio A, Adami G, Benini C, et al. Changes in Dkk-1, sclerostin, and RANKL serum levels following discontinuation of long-term denosumab treatment in postmenopausal women. *Bone* 2019;123:191-95.

166. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet (London, England)* 2015;386(9992):433-43.
167. Gnant M, Pfeiler G, Steger GG, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2019;20(3):339-51.
168. Gonzalez-Rodriguez E, Aubry-Rozier B, Stoll D, et al. Sixty spontaneous vertebral fractures after denosumab discontinuation in 15 women with early-stage breast cancer under aromatase inhibitors. *Breast Cancer Res Treat* 2020;179(1):153-59.
169. Greenspan SL, Bhattacharya RK, Sereika SM, et al. Prevention of bone loss in survivors of breast cancer: A randomized, double-blind, placebo-controlled clinical trial. *J Clin Endocrinol Metab* 2007;92(1):131-6.
170. Greenspan SL, Nelson JB, Trump DL, et al. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Intern Med* 2007;146(6):416-24.
171. Greenspan SL, Perera S, Ferchak MA, et al. Efficacy and safety of single-dose zoledronic acid for osteoporosis in frail elderly women: a randomized clinical trial. *JAMA Intern Med* 2015;175(6):913-21.
172. Israeli RS, Rosenberg SJ, Saltzstein DR, et al. The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. *Clin Genitourin Cancer* 2007;5(4):271-7.
173. Itabashi A, Yoh K, Chines AA, et al. Effects of bazedoxifene on bone mineral density, bone turnover, and safety in postmenopausal Japanese women with osteoporosis. *J Bone Miner Res* 2011;26(3):519-29.
174. Jacques RM, Boonen S, Cosman F, et al. Relationship of changes in total hip bone mineral density to vertebral and nonvertebral fracture risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg: the HORIZON-Pivotal Fracture Trial (PFT). *J J Bone Miner Res* 2012;27(8):1627-34.
175. Klotz LH, McNeill IY, Kebabdjian M, et al. A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: the Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) study. *Eur Urol* 2013;63(5):927-35.
176. Langdahl BL, Teglbjaerg CS, Ho PR, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. *J Clin Endocrinol Metab* 2015;100(4):1335-42.
177. Livi L, Scotti V, Desideri I, et al. Phase 2 placebo-controlled, single-blind trial to evaluate the impact of oral ibandronate on bone mineral density in osteopenic breast cancer patients receiving adjuvant aromatase inhibitors: 5-year results of the single-centre BONADIUV trial. *Eur J Cancer* 2019;108:100-10.
178. Michaelson MD, Kaufman DS, Lee H, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol* 2007;25(9):1038-42.
179. Miller PD, Epstein S, Sedarati F, et al. Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study. *Curr Med Res Opin* 2008;24(1):207-13.
180. Miller PD, Pannacciulli N, Brown JP, et al. Denosumab or Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates. *J Clin Endocrinol Metab* 2016;101(8):3163-70.
181. Morii H, Ohashi Y, Taketani Y, et al. Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. *Osteoporos Int* 2003;14(10):793-800.
182. Nakamura T, Matsumoto T, Sugimoto T, et al. Dose-response study of denosumab on bone mineral density and bone turnover markers in Japanese postmenopausal women with osteoporosis. *Osteoporos Int* 2012;23(3):1131-40.
183. Orwoll E, Teglbjaerg CS, Langdahl BL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. *J Clin Endocrinol Metab* 2012;97(9):3161-9.
184. Orwoll ES, Miller PD, Adachi JD, et al. Efficacy and safety of a once-yearly i.v. Infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male

osteoporosis: a randomized, multicenter, double-blind, active-controlled study. *J Bone Miner Res* 2010;25(10):2239-50.
185. Paggiosi MA, Peel N, McCloskey E, et al. Comparison of the effects of three oral bisphosphonate therapies on the peripheral skeleton in postmenopausal osteoporosis: the TRIO study. *Osteoporos Int* 2014;25(12):2729-41.
186. Palacios S, Silverman SL, de Villiers TJ, et al. A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. *Menopause* 2015;22(8):806-13.
187. Palomba S, Manguso F, Orio F, Jr., et al. Effectiveness of risedronate in osteoporotic postmenopausal women with inflammatory bowel disease: a prospective, parallel, open-label, two-year extension study. *Menopause* 2008;15(4 Pt 1):730-6.
188. Palomba S, Orio F, Jr., Manguso F, et al. Efficacy of risedronate administration in osteoporotic postmenopausal women affected by inflammatory bowel disease. *Osteoporos Int* 2005;16(9):1141-9.
189. Popp AW, Varathan N, Buffat H, et al. Bone Mineral Density Changes After 1 Year of Denosumab Discontinuation in Postmenopausal Women with Long-Term Denosumab Treatment for Osteoporosis. *Calcif Tissue Int* 2018;103(1):50-54.
190. Ryan CW, Huo D, Demers LM, et al. Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. *J Urol* 2006;176(3):972-8; .
191. Silverman SL, Chines AA, Kendler DL, et al. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. *Osteoporos Int* 2012;23(1):351-63.
192. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res* 2008;23(12):1923-34.
193. Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol* 2003;169(6):2008-12.
194. Smith MR, Egerdie B, Hernández Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *J N Engl J Med* 2009;361(8):745-55.
195. Chau D, Becker DL, Coombes ME, et al. Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporosis in Canada. *J Med Econ* 2012;15 Suppl 1:3-14.
196. Coyle D. Cost-Effectiveness of Pharmacological Treatments for Osteoporosis Consistent with the Revised Economic Evaluation Guidelines for Canada. *MDM Policy Pract* 2019;4(1):2381468318818843.
197. Darba J, Kaskens L, Sorio Vilela F, et al. Cost-utility of denosumab for the treatment of postmenopausal osteoporosis in Spain. *Clinicoecon Outcomes Res* 2015;7:105-17.
198. Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. *Bone* 2010;47(1):34-40.
199. Hiligsmann M, Reginster JY. Cost effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. *Pharmacoeconomics* 2011;29(10):895-911.
200. Jönsson B, Ström O, Eisman JA, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. *J Osteoporos Int* 2011;22(3):967-82.
201. Karnon J, Shafie AS, Orji N, et al. What are we paying for? A cost-effectiveness analysis of patented denosumab and generic alendronate for postmenopausal osteoporotic women in Australia. *J Cost Eff Resour Alloc* 2016;14:11.
202. Le QA. Patient-Level Modeling Approach Using Discrete-Event Simulation: A Cost-Effectiveness Study of Current Treatment Guidelines for Women with Postmenopausal Osteoporosis. *J Manag Care Spec Pharm* 2019;25(10):1089-95.
203. Makras P, Athanasakis K, Boubouchairopoulou N, et al. Cost-effective osteoporosis treatment thresholds in Greece. *Osteoporos Int* 2015;26(7):1949-57.
204. Marques A, Lourenco O, Ortsater G, et al. Cost-Effectiveness of Intervention Thresholds for the Treatment of Osteoporosis Based on FRAX((R)) in Portugal. *Calcif Tissue Int* 2016;99(2):131-41.
205. Parthan A, Kruse M, Agodoa I, et al. Denosumab: a cost-effective alternative for older men with osteoporosis from a Swedish payer perspective. *Bone* 2014;59:105-13.

206. Parthan A, Kruse M, Yurgin N, et al. Cost effectiveness of denosumab versus oral bisphosphonates for postmenopausal osteoporosis in the US. *Appl Health Econ Health Policy* 2013;11(5):485-97.
207. Silverman S, Agodoa I, Kruse M, et al. Denosumab for Elderly Men with Osteoporosis: A Cost-Effectiveness Analysis from the US Payer Perspective. *J Osteoporos* 2015;2015:627631.
208. Ström O, Jönsson B, Kanis JA. Intervention thresholds for denosumab in the UK using a FRAX®-based cost-effectiveness analysis. *J Osteoporos Int* 2013;24(4):1491-502.
209. Alami S, Hervouet L, Poiraudeau S, et al. Barriers to Effective Postmenopausal Osteoporosis Treatment: A Qualitative Study of Patients' and Practitioners' Views. *PLoS One* 2016;11(6):e0158365.
210. Barrionuevo P, Gionfriddo MR, Castaneda-Guarderas A, et al. Women's values and preferences regarding osteoporosis treatments: A systematic review. *J Journal of Clinical Endocrinology and Metabolism* 2019;104(5):1631-36.
211. Hadji P, Papaioannou N, Gielen E, et al. Persistence, adherence, and medication-taking behavior in women with postmenopausal osteoporosis receiving denosumab in routine practice in Germany, Austria, Greece, and Belgium: 12-month results from a European non-interventional study. *Osteoporos Int* 2015;26(10):2479-89.
212. Hiligsmann M, Salas M, Hughes DA, et al. Interventions to improve osteoporosis medication adherence and persistence: a systematic review and literature appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group. *Osteoporos Int* 2013;24(12):2907-18.
213. Kendler DL, Macarios D, Lillestol MJ, et al. Influence of patient perceptions and preferences for osteoporosis medication on adherence behavior in the Denosumab Adherence Preference Satisfaction study. *Menopause* 2014;21(1):25-32.
214. Kendler DL, McClung MR, Freemantle N, et al. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. *Osteoporos Int* 2011;22(6):1725-35.
215. Modi A, Sajjan S, hi S. Challenges in implementing and maintaining osteoporosis therapy. *Int J Women's Health* 2014;6(1):759-69.
216. Naik-Panvelkar P, Norman S, Elgebaly Z, et al. Osteoporosis management in Australian general practice: an analysis of current osteoporosis treatment patterns and gaps in practice. *BMC Fam Pract* 2020;21(1):32.
217. Rabenda V, Reginster JY. Overcoming problems with adherence to osteoporosis medication. *Expert Rev Pharmacoecon Outcomes Res* 2010;10(6):677-89.
218. Yeam CT, Chia S, Tan HCC, et al. A systematic review of factors affecting medication adherence among patients with osteoporosis. *Osteoporos Int* 2018;29(12):2623-37.
219. Yu J, Brenneman SK, Sazonov V, et al. Reasons for not initiating osteoporosis therapy among a managed care population. *J Patient Preference and Adherence* 2015;9:821-30.
220. Fogelman Y, Goldshtein I, Segal E, et al. Managing osteoporosis: A survey of knowledge, attitudes and practices among primary care physicians in Israel. *J PLoS ONE* 2016;11(8):e0160661.
221. Sterne J, Savović J, Page M, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366
222. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.(doi):10.1136/bmj.i4919.
223. Orwoll E, Teglbjærg CS, Langdahl BL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. *J Clin Endocrinol Metab* 2012;97(9):3161-69.
224. BAG. STAT-TAB - interactive tables (FSO) 2019 [Available from: https://www.pxweb.bfs.admin.ch/pxweb/en/6 August 2021].
225. Dratva J, Gómez Real F, Schindler C, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. *Menopause* 2009;16(2)
226. Krieg MA, Cornuz J, Ruffieux C, et al. Prediction of hip fracture risk by quantitative ultrasound in more than 7000 Swiss women > or =70 years of age: comparison of three technologically different bone ultrasound devices in the SEMOF study. *J Bone Miner Res* 2006;21(9):1457-63.
227. Lippuner K, Johansson H, Kanis JA, et al. FRAX® assessment of osteoporotic fracture probability in Switzerland. *Osteoporosis International* 2010;21(3):381-89.

228. Svedbom A, Ivergård M, Hernlund E, et al. Epidemiology and economic burden of osteoporosis in Switzerland. *Archives of osteoporosis* 2014;9(1):187.
229. Feller A, Schmidlin K, Bordoni A, et al. Socioeconomic and demographic disparities in breast cancer stage at presentation and survival: A Swiss population-based study. *International Journal of Cancer* 2017;141(8):1529-39.
230. Ess SM, Herrmann C, Bouchardy C, et al. Impact of subtypes and comorbidities on breast cancer relapse and survival in population-based studies. *The Breast* 2018;41:151-58.
231. Zaman K, Thürlimann B, Huober J, et al. Bone mineral density in breast cancer patients treated with adjuvant letrozole, tamoxifen, or sequences of letrozole and tamoxifen in the BIG 1-98 study (SAKK 21/07). *Annals of Oncology* 2012;23(6):1474-81.
232. Schwenkglenks M, Lippuner K, Häuselmann HJ, et al. A model of osteoporosis impact in Switzerland 2000-2020. *Osteoporos Int* 2005;16(6):659-71.
233. Guessous I, Cullati S, Fedewa SA, et al. Prostate cancer screening in Switzerland: 20-year trends and socioeconomic disparities. *Preventive Medicine* 2016;82:83-91.
234. Matthes KL, Limam M, Pestoni G, et al. Impact of comorbidities at diagnosis on prostate cancer treatment and survival. *J Cancer Res Clin Oncol* 2018;144(4):707-15.
235. Dias S, Caldwell DM. Network meta-analysis explained. *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2019;104(1):F8.
236. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64(4):383-94.
237. Centre for Metabolic Bone Diseases. FRAX® Calculation Tool - Switzerland University of Sheffield, UK2021 [Available from: https://www.sheffield.ac.uk/FRAX/tool.aspx?country=15 accessed 8 August 2021].
238. Hiligsmann M, Reginster JY, Tosteson ANA, 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;30(1):45-57.
239. Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. *J Bone Miner Res* 2010;47(1):34-40.
240. Chau D, Becker DL, Coombes ME, et al. Cost-effectiveness of denosumab in the treatment of postmenopausal osteoporosis in Canada. *J Med Econ* 2012;15:3-14.
241. Darbà J, Kaskens L, Sorio Vilela F, et al. Cost-utility of denosumab for the treatment of postmenopausal osteoporosis in Spain. *Clinicoecon Outcomes Res* 2015;7:105-17.
242. de Waure C, Specchia ML, Cadeddu C, et al. The prevention of postmenopausal osteoporotic fractures: results of the Health Technology Assessment of a new antiosteoporotic drug. *Biomed Res Int* 2014;2014:975927.
243. Jönsson B, Ström O, Eisman J, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 2011;22(3):967-82.
244. Karnon J, Shafie AS, Orji N, et al. What are we paying for? A cost-effectiveness analysis of patented denosumab and generic alendronate for postmenopausal osteoporotic women in Australia. *Cost Eff Resour Alloc* 2016;14:11.
245. Ström O, Jönsson B, Kanis J. Intervention thresholds for denosumab in the UK using a FRAX-based cost-effectiveness analysis. *Osteoporos Int* 2013;24(4):1491-502.
246. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361(8):756-65.
247. Marques A, Lourenço Ó, Ortsäter G, et al. Cost-Effectiveness of Intervention Thresholds for the Treatment of Osteoporosis Based on FRAX(®) in Portugal. *Calcif Tissue Int* 2016;99(2):131-41.
248. Makras P, Athanasakis K, Boubouchairopoulou N, et al. Cost-effective osteoporosis treatment thresholds in Greece. *Osteoporos Int* 2015;26(7):1949-57.
249. Silverman S, Agodoa I, Kruse M, et al. Denosumab for Elderly Men with Osteoporosis: A Cost-Effectiveness Analysis from the US Payer Perspective. *Osteoporos Int* 2015;2015:627631.
250. Szende A, Janssen B, Cabases J. Self-Reported Population Health: An International Perspective based on EQ-5D. Dordrecht (NL): Springer 2014.
251. Svedbom A, Borgstom F, Hernlund E, et al. Quality of life for up to 18 months after low-energy hip, vertebral, and distal forearm fractures-results from the ICUROS. *Osteoporos Int* 2018;29(3):557-66.
252. *TreeAge Software, version R1.1* [program]. *Williamstown, MA; sofware available at https://www.treeage.com/*, 2021.

253. Johnell O, Kanis JA, Oden A, et al. Mortality after osteoporotic fractures. *Osteoporos Int* 2004;15(1):38-42.
254. Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos* 2013;8:136.
255. Davis S, Simpson E, Hamilton J, et al. Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation. *Health Technol Assess* 2020;24(29):1-314.
256. Federal Office of Public Health. Spezialitätenliste 2021 [Available from: http://www.spezialitaetenliste.ch/ accessed 24 May 2021].
257. Schweizerische Vereinigung gegen die Osteoporose. Osteoporose. Empfehlungen 2015-Prävention. Diagnostik. Behandlung.: Nachdruck nur mit Nennung der Quelle, 2015.
258. Lippuner K, Johansson H, Kanis JA, et al. Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women. *Osteoporos Int* 2009;20(7):1131-40.
259. Lippuner K, Johansson H, Borgstrom F, et al. Cost-effective intervention thresholds against osteoporotic fractures based on FRAX(R) in Switzerland. *Osteoporos Int* 2012;23(11):2579-89.
260. Kanis JA, Harvey NC, McCloskey E, et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporos Int* 2020;31(1):1-12.
261. McClung MR, Wagman RB, Miller PD, et al. Observations following discontinuation of long-term denosumab therapy. *Osteoporos Int* 2017;28(5):1723-32.
262. Strom O, Borgstrom F, Kanis JA, et al. Incorporating adherence into health economic modelling of osteoporosis. *Osteoporos Int* 2009;20(1):23-34.
263. Li N, Cornelissen D, Silverman S, et al. An Updated Systematic Review of Cost-Effectiveness Analyses of Drugs for Osteoporosis. *Pharmacoeconomics* 2021;39(2):181-209.
264. Karlsson L, Lundkvist J, Psachoulia E, et al. Persistence with denosumab and persistence with oral bisphosphonates for the treatment of postmenopausal osteoporosis: a retrospective, observational study, and a meta-analysis. *Osteoporos Int* 2015;26(10):2401-11.
265. Ziller V, Kostev K, Kyvernitakis I, et al. Persistence and compliance of medications used in the treatment of osteoporosis--analysis using a large scale, representative, longitudinal German database. *International journal of clinical pharmacology and therapeutics* 2012;50(5):315-22.
266. Landfeldt E, Strom O, Robbins S, et al. Adherence to treatment of primary osteoporosis and its association to fractures--the Swedish Adherence Register Analysis (SARA). *Osteoporos Int* 2012;23(2):433-43.
267. Strom O, Landfeldt E. The association between automatic generic substitution and treatment persistence with oral bisphosphonates. *Osteoporos Int* 2012;23(8):2201-9.
268. Koller G, Goetz V, Vandermeer B, et al. Persistence and adherence to parenteral osteoporosis therapies: a systematic review. *Osteoporos Int* 2020;31(11):2093-102.
269. Fahrleitner-Pammer A, Papaioannou N, Gielen E, et al. Factors associated with high 24-month persistence with denosumab: results of a real-world, non-interventional study of women with postmenopausal osteoporosis in Germany, Austria, Greece, and Belgium. *Arch Osteoporos* 2017;12(1):58.
270. World Health Organisation. Life tables by country (GHE: Life tables) 2020 [Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-ghe-life-tables-by-country accessed 9 June 2021].
271. Davis S, Martyn-St James M, Sanderson J, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. *Health Technol Assess* 2016;20(78):1-406.
272. EuroQol Research Foundation. EQ-5D: Choosing a value set 2021 [Available from: https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/valuation/choosing-a-value-set/ accessed 15 July 2021].
273. Soreskog E, Borgstrom F, Lindberg I, et al. A novel economic framework to assess the cost-effectiveness of bone-forming agents in the prevention of fractures in patients with osteoporosis. *Osteoporos Int* 2021
274. Schwenkglenks M, Lippuner K. Simulation-based cost-utility analysis of population screening-based alendronate use in Switzerland. *Osteoporos Int* 2007;18(11):1481-91.
275. Federal Statistical Office. Health - Pocket Statistics 2020. Swiss Statistics. Neuchâtel, Switzerland, 2021.

276. Lippuner K, Golder M, Greiner R. Epidemiology and direct medical costs of osteoporotic fractures in men and women in Switzerland. *Osteoporos Int* 2005;16 Suppl 2:S8-S17.
277. Trombetti A, Herrmann F, Hoffmeyer P, et al. Survival and potential years of life lost after hip fracture in men and age-matched women. *Osteoporos Int* 2002;13(9):731-7.
278. Federal Statistics Bureau. Inflation Calculator 2021 [Available from: https://lik-app.bfs.admin.ch/en/lik/rechner?periodType=Monatlich&start=06.2020&ende=06.2021&basis=AUTO accessed 29 July 2021].
279. Kanis JA, Johansson H, Harvey NC, et al. Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. *Osteoporos Int* 2020;31(10):1817-28.
280. Soreskog E, Strom O, Spangeus A, et al. Risk of major osteoporotic fracture after first, second and third fracture in Swedish women aged 50years and older. *Bone* 2020;134:115286.
281. United Nations - Department of Economic and Social Affairs. World Population Prospects 2019 2019 [Available from: https://population.un.org/wpp/ accessed 7 August 2021].
282. Federal Statistical Office. Population - Current situation and change 2020 [Available from: https://www.bfs.admin.ch/bfs/en/home/statistics/population/effectif-change.html accessed 7 August 2021].
283. IQVIA. IQVIA Switzerland 2021 [Available from: https://www.iqvia.com/locations/switzerland accessed 12 August 2021].
284. Morell S, Hemmeler C, Amsler F, et al. Adherence to osteoporosis pharmacotherapy one year after osteoporotic fracture - a Swiss trauma center secondary prevention project. *Swiss Med Wkly* 2017;147:w14451.
285. Australian Government CA. Guidance for the management of early breast cancer: Recommendations and practice points 2020 [Available from: https://www.canceraustralia.gov.au/sites/default/files/publications/guidance-management-early-breast-cancer-recommendations-and-practice-points/pdf/guidance_for_the_management_of_early_breast_cancer_recommendations_and_pps_2020_0.pdf accessed 16 July 2021].
286. Bouvard B, Confavreux CB, Briot K, et al. French recommendations on strategies for preventing and treating osteoporosis induced by adjuvant breast cancer therapies. *Joint Bone Spine* 2019;86(5):542-53.
287. Briot K, Paccou J, Beuzeboc P, et al. French recommendations for osteoporosis prevention and treatment in patients with prostate cancer treated by androgen deprivation. *Joint Bone Spine* 2019;86(1):21-28.
288. Briot K, Roux C, Thomas T, et al. 2018 update of French recommendations on the management of postmenopausal osteoporosis. *Joint Bone Spine* 2018;85(5):519-30.
289. Camacho PM, Petak SM, Binkley N, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS-2020 UPDATE. *Endocr Pract* 2020;26(Suppl 1):1-46.
290. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2021;79(2):243-62.
291. NICE. Prostate cancer: diagnosis and management 2019 [Available from: https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133 accessed 16 July 2021].
292. NOGG. Clinical guideline for the prevention and treatment of osteoporosis 2017 [Available from: https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf accessed 16 July 2021].
293. Osteologie D. Prophylaxe, Diagnostik und Therapie der Osteroporose: bei postmenopausalen Frauen und bei Männern 2017 [Available from: https://www.awmf.org/uploads/tx_szleitlinien/183-001l_S3_Osteoporose-Prophylaxe-Diagnostik-Therapie_2019-02.pdf accessed 16 July 2021].
294. Osteologie D. Prophylaxe, Diagnostik und Therapie der Osteoporose: Leitlinienreport 2018 [Available from: https://www.awmf.org/uploads/tx_szleitlinien/183-001m_S3_Osteoporose-Prophylaxe-Diagnostik-Therapie_2018-07.pdf accessed 16 July 2021].
295. Qaseem A, Forciea MA, McLean RM, et al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med* 2017;166(11):818-39.

296. RACGP. Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age: 2nd edition 2017 [Available from: https://www.racgp.org.au/getattachment/2261965f-112a-47e3-b7f9-cecb9dc4fe9f/Osteoporosis-prevention-diagnosis-and-management-in-postmenopausal-women-and-men-over-50-years-of-age.aspx accessed 16 July 2021].
297. SIGN. SIGN142: Management of osteoporosis and the prevention of fragility fractures 2020 [Available from: https://www.sign.ac.uk/media/1741/sign142.pdf accessed 16 July 2021].
298. Eastell R, Rosen CJ, Black DM, et al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline. *J Clin Endocrinol Metab* 2019;104(5):1595-622.
299. Beaudoin C, Jean S, Bessette L, et al. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. *Osteoporos Int* 2016;27(9):2835-44.
300. Davis S, Simpson E, Hamilton J, et al. Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation. *Health Technol Assess* 2020;24(29):1-314.
301. Yanbeiy ZA, Hansen KE. Denosumab in the treatment of glucocorticoid-induced osteoporosis: a systematic review and meta-analysis. *Drug Des Devel Ther* 2019;13:2843-52.
302. Federal Statistical Office. Financial markets 2021 [Available from: https://www.bfs.admin.ch/bfs/en/home/statistics/money-banks-insurance/financial-markets.html accessed 9 August 2021].
303. Cipriani A, Higgins JP, Geddes JR, et al. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013;159(2):130-7.
304. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;21(11):1559-73.
305. Cochrane Comparing Multiple Interventions Methods Group,

Li, T. Statistical considerations in indirect comparisons and network meta-analysis 2013 [Available from: https://methods.cochrane.org/sites/methods.cochrane.org.cmi/files/public/uploads/S6-L%20NMA%20with%20meta-regression.pdf].
306. Kanis JA, Cooper C, Rizzoli R, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2019;30(1):3-44.
307. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine* 2009;6(7):e1000097.
308. Canadian Agency for Drugs and Technologies in Health. Strings Attached: CADTH's Database Search Filters: Canadian Agency for Drugs and Technologies in Health; 2019 [Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters accessed January 05 2021].
309. Eastell R. TRIO Study End of Trial Report 2006 [June 2021]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2006-004738-33/1/26577].
310. Svedbom A, Ivergard M, Hernlund E, et al. Epidemiology and economic burden of osteoporosis in Switzerland. *Arch Osteoporos* 2014;9:187.

15 Appendix A: Sources of literature (databases)

Appendix A includes the sources of literature used in the systematic literature searches, and the search results from the searches conducted in each database.

15.1 Literature sources

Table 37 Biomedical bibliographic databases

Source	Website
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Embase	https://www.embase.com/
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/
York CRD	https://www.crd.york.ac.uk/CRDWeb/
International Network of Agencies for Health Technology Assessment (INAHTA)	https://database.inahta.org/
Econlit	https://www.aeaweb.org/econlit/
PsycInfo	https://www.apa.org/pubs/databases/psycinfo/
Ethmed	http://www.idem.uni-goettingen.de/en/database-ethmed.html

Table 38 Clinical trial registries

Source	Website
ClinicalTrals.gov	https://clinicaltrials.gov/
Cochrane Central Register of Controlled Trials	https://www.cochranelibrary.com/central
EU Clinical Trials Registry	https://www.clinicaltrialsregister.eu/
World Health Organization (WHO), International Clinical Trials Registry Platform	https://www.who.int/ictrp/en/
Australian New Zealand Clinical Trials Registry	http://www.anzctr.org.au/

Notes:
The MetaRegister of Controlled Trials (mRCT) searched during the scoping phase is no longer in operation.

Table 39 HTA agency websites

Source	Website
International	
International Information Network on New and Emerging Health Technologies (EuroScan International Network)	https://www.euroscan-network.global/index.php/en/47-public-features/761-database-home
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Australia and New Zealand	

Health Technology Reference Group (HTRG)	https://www.coaghealthcouncil.gov.au/AHMAC/Health-Technology-Reference-Group
Austria	
Austrian Institute of Technology Assessment (AIHTA)	https://www.oeaw.ac.at/ita/publikationen/
Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Evidence Development and Standards Branch (HQO)	http://www.hqontario.ca
Denmark	
Social and Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
Finnish Medicines Agency (FIMEA)	http://www.fimea.fi
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/
Comité d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT)	http://cedit.aphp.fr/
Germany	
Institut für Qualität und Wirtschaftlichtkeit im Gesundheitswesen (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Norway	
The Norwegian Institute of Public Health (NIPH)	http://www.fhi.no/

Singapore	
Agency for Care Effectiveness (ACE)	http://www.ace-hta.gov.sg/
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency (AETSA)	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
UK	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
USA	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html

Sources:
Based on registered INAHTA agencies located in *WHO-Mortality-Stratum A* countries.[113]

Table 40 Specialty websites

Source	Website
Geriatric	
European Geriatric Medicine Society	https://www.eugms.org/home.html
Australia and New Zealand Society for Geriatric Medicine	http://www.anzsgm.org/
Swiss Geriatric Society / Schweizerische Fachgesellschaft für Geriatrie)	https://www.sfgg.ch/
Orthopaedic	
European Society of Sport Traumatology, Knee Surgery, and Arthroscopy (ESSKA)	https://www.esska.org/page/About_Us

Source	Website
Nordic Orthopaedic Federation	https://www.norf.org/
American Orthopaedic Association	http://www.aoassn.org/aoaimis/aoanew
American Academy of Orthopaedic Surgeons	https://www.aaos.org/
Australian Orthopaedic Association	https://www.aoa.org.au/
Australian Society of Orthopaedic Surgeons	http://www.asos.org.au/
Belgian Orthopaedic Trauma Association	http://www.botatrauma.be/
British Orthopaedic Association	https://www.boa.ac.uk/
Czech Society for Orthopaedic and Traumatology	https://en.csot.cz/
Danish Orthopedic Society	https://www.ortopaedi.dk/
Deutsche Gesellschaft für Orthopädie und Unfallchirurgie (DGOU) / German Society for Orthopaedic and Trauma	https://dgou.de/en/home/
Sociedad Española De Cirugía Orthopédica Y Traumatología / Spanish Society of Orthopaedic Surgery and Traumatology	https://www.secot.es/
Société Française de Chirurgie Orthopédique et Traumatologique	http://www.sofcot.fr
Hellenic Association for Surgical Orthopaedics and Traumatology	http://eexot.gr/
Società Italiana Di Ortopedia E Traumatologia / Italian Society of Orthopaedics and Traumatology	https://siot.it/about-siot/
Irish Institute of Trauma and Orthopaedic Surgery (IITOS)	https://www.iitos.ie/
Nederlandse Orthopaedische vereniging (NOV) / Dutch Orthopedic Association	https://www.orthopeden.org/
Svensk Ortopedisk Förening / Swedish Orthopaedic Association	http://www.ortopedi.se/index1.asp?siteid=1andpageid=1
Suomen Orthopediyhdistys / Finnish Orthopaedic Association (FOA)	http://www.soy.fi/index.php?page=1340andlang=1
Swiss Orthopaedics	http://www.swissorthopaedics.ch
Osteoporosis	
International Osteoporosis Foundation	https://www.iofbonehealth.org/
European Society for Clincal and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases	http://www.esceo.org/
Osteoporosis Australia	https://www.osteoporosis.org.au/
Australian and New Zealand Bone and Mineral Society	https://www.anzbms.org.au/Index.asp
Austrian Society for Bone and Mineral Metabolism	https://www.oegkm.at/

Source	Website
Osteoporose Selbsthilfe Österreich / Osteoporosis self-help Austria	https://www.osteoporose-selbsthilfe.org/
Belgian Bone Club	http://www.bbcbonehealth.org/
Croatian Osteoporosis Society	http://www.osteoporoza.hr/
Cyprus Society Against for Osteoporosis	http://www.osteoporosis.org.cy
Czech Society for Metabolic Bone Diseases (SMOS)	http://www.smos.cz
Danish Bone Society	http://www.dkms.dk/
National Osteoporosis Foundation Denmark	http://www.osteoporoseforeningen.dk
Finish Bone Society	http://www.finnishbonesociety.org/
Finish Osteoporosis Association	http://www.osteoporoosiliitto.fi/
Research and Information Group on Osteoporosis (GRIO) (France)	http://www.grio.org
Bundesselbsthilfeverband für Osteoporose e.V. / Federal Self-Help Association for Osteoporosis (Germany)	https://www.osteoporose-deutschland.de/
Netzwerk-osteoporose e.V. / Osteoporosis Network (Germany)	https://www.netzwerk-osteoporose.de/
Osteoporose Selbsthilfegruppen Dachverband e.V. / Osteoporosis Self-help Groups Umbrella Organisation (Germany)	https://www.osd-ev.org/
Hellenic Osteoporosis Foundation (HELIOST)	http://www.heliost.gr
Hellenic Society for the Study of Bone Metabolism	http://www.eemmo.gr
Beinvernd / Icelandic Osteoporosis Foundation	http://www.beinvernd.is
Irish Osteoporosis Society (IOS)	http://www.irishosteoporosis.ie
Fondazione Italiana Ricerca Osteoporosi e Malattie Muscolo Scheletriche / Italian Foundation for Osteoporosis and Skeletal Muscle Diseases	http://www.firomms.it
Fondazione Italiana per la Ricerca Sulla Malattie Ossea / Italian Foundation for Research on Bone Disease	https://www.fondazionefirmo.com/
Federazione Italiana Osteoporosi e Malattie dello Scheletro / Italian Federation of Osteoporosis and Disease of the Skeleton	https://www.fedios.org/
Societa Italiana Osteoporosi e Malattie Metabolismo Minerale E Scheletrico (SIOMMMS) / Italian Society of Osteoporosis and Diseases Mineral and Skeletal Metabolism	https://www.siommms.it/
Osteoporose Stichting / Osteoporosis Foundation (The Netherlands)	http://www.osteoporosestichting.nl/

Source	Website
Osteoporosis Vereniging / Osteoporosis Association (The Netherlands)	http://www.osteoporosevereniging.nl
Osteoporosis New Zealand Inc.	http://www.osteoporosis.org.nz
Associação Nacional contra a Osteoporopse / National Association Against Osteoporosis (Portugal)	http://www.aporos.pt/
Portuguese Society of Osteoporosis and other Metabolic Bone Diseases (SPODOM)	http://www.spodom.org
Slovene Osteoporosis Patient Society	http://www.osteoporoza.si
Sociedad Espanola de Fracturas Osteoporoticas (SEFRAOS) / Spanish Society of Osteoporotic Fractures	http://www.sefraos.es
Fundacion Hispana de Osteoporosi Y Enfermedades Metabolicas Oseas (FHOEMO) / Hispanic Foundation of Osteoporosis and Bone Metabolic Disease (Spain)	https://www.iofbonehealth.org/societies-country-index-view/1198
Asociacion Espanola Contra La Osteoporosis (AECOS) / Spanish Association Against Osteoporosis	http://www.aecosar.es/
Osteoporosforbundet (Sweden)	https://www.osteoporos.org/
OsteoSwiss	osteoswiss.ch/de/
Schweizerische Vereinigung gegen die Osteoporose / Swiss Association Against Osteoporosis	http://www.svgo.ch/
Royal Osteoporosis Society	https://theros.org.uk/
National Osteoporosis Foundation (USA)	https://www.nof.org/
American Bone Health	https://americanbonehealth.org/
Rheumatic disease	
International League of Associations for Rheumatology (ILAR)	http://www.ilar.org/
Asia-Pacific League pf Association for Rheumatology (APLAR)	http://www.aplar.org/
European League Against Rheumatism (EULAR)	https://www.eular.org/index.cfm
Swiss Clinical Quality Management in Rheumatic Diseases (SCQM)	https://www.scqm.ch/en/ueber-uns/
Groupe des Rhumatologues Genevois (Geneva Rheumatologists Group)	http://www.rhumage.ch/
Institute of Arthritis Research (iAR):	https://www.irr-research.org/home.html
Rheumasearch Foundation	http://www.rheumasearch.ch/
Swiss Clinical Quality Management in Rheumatic Diseases	https://www.amge.ch/

Source	Website
Association Suisse des Polyarthritiques (Swiss Polyarthritis Association)	http://www.arthritis.ch/
Rheumaliga Schweiz (Swiss Association for Rheumatology Patients)	https://www.rheumaliga.ch/
Rheuma-Suisse	http://www.rheuma-schweiz.ch/
Swiss Society of Rheumatology (SGR) (Schweizerische Gesellschaft für Rheumatologie)	https://www.rheuma-net.ch/de/
American College of Rheumatology	https://www.rheumatology.org/
Australian Rheumatology Association	https://rheumatology.org.au/
Royal Australasian College of Physicians (RACP)	https://www.racp.edu.au/
Main Dans la Main Ensemble Contre Les Rhumatismes (Belgium)	https://r-humatismes.be/fr
British Society for Rheumatology	https://www.rheumatology.org.uk/
Croatian Society for Rheumatology	http://www.reumatologija.org/engKongresi_list.aspx
Croatian League Against Rheumatism	http://www.reuma.hr/
Association Française de Lutte Anti Rhumatisme (AFLAR) (France)	http://www.aflar.org
Institute of Rheumatology Research (IRR) (Germany)	https://www.irr-research.org/de/
Irish Society for Rheumatology	https://www.isr.ie/
Societa Italiana di Reumatologia/ Italian Society of Rheumatology	https://www.reumatologia.it/
Arthritis and Rheumatism Association Malta	https://www.aramalta.com/
National Association ReumaZorg Nederland (The Netherlands)	https://reumazorgnederland.nl
ReumaNederland (The Netherlands)	https://reumanederland.nl/
NorArthritis – The Norwegian Arthritis Registry	https://helse-bergen.no/en/avdelinger/revmatologisk-avdeling/norartritt
Registo Nacional de Doentes Reumáticos (Portugal)	http://www.reuma.pt/enreuma_pt.html
Spanish Society for Rheumatology	http://www.ser.es
Reumatikerförbundet (Sweden)	https://reumatiker.se/
Menopause	
International Menopause Society	https://www.imsociety.org/menopause_perspectives_around_the_world.php
Australasian Menopause Society	https://www.menopause.org.au/
European Menopause and Andropause Society	https://www.emas-online.org/
North American Menopause Society	https://www.menopause.org/home
Belgium Menopause Society	https://menopausesociety.be/en
British Menopause Society	https://thebms.org.uk/

Source	Website
Česká Menopauzální a Andropauzální Společnost / Czech Menopause and Andropause Society	http://www.meno-andro.cz/en/about-us
Groupe Etude de la Ménopause et du Vieillissement Hormonal (GEMVI) / Menopause and Hormonal Aging Study Group (France)	http://www.gemvi.org/
Deutsche Menopause Gesellschaft / German Menopause Society	http://www.menopause-gesellschaft.de/
Hellenic Society of Climacterium and Menopause (Emmino)	https://emmino.gr/en/
Societa Italiana della Menopausa (SIM) / Italian Society of Menopause	http://simenopausa.it/
De Menopauze Specialist / Dutch Menopause Society	https://demenopauzespecialist.nl/
Asociacion Espanola para el Esudio fde la Menopasuia (AEEM) / Spanish Association for the Study of Menopause	https://aeem.es/
Swiss Menopause Society / Schweizerische Menopausengesellschaft	https://meno-pause.ch
Endocrinology	
International Society of Endocrinology	https://www.isendo.org/
European Society of Endocrinology	https://www.ese-hormones.org/
Federation of International Nurses in Endocrinology (FINE)	https://finenurses.org/
International Coalition of Organisations Supporting Endocrine Patients (ICOSEP)	https://icosep.org/
Endocrine Society	https://www.endocrine.org/about-us
Hormone Health Network	https://www.hormone.org/about-us
American Association of Clinical Endocrinologist	https://www.aace.com/
Endocrine Society of Australia	https://www.endocrinesociety.org.au/
Belgian Endocrine Society	https://endocrinesociety.be/
Deutsche Gesellschaft fur Endokrinologie / German Society for Endocrinology	https://www.endokrinologie.net/
Hellenic Endocrine Society-Panhellenic Association of Endocrinologists	http://www.heliost.gr
Hellenic Endocrine Society	http://www.endo.gr/
Société Française d'Endocrinologie / French Society of Endocrinology	http://www.sfendocrino.org/
Suomen Endokrinologiyhdistys r.y./ Finnish Endocrine Society	https://www.endo.fi/
Dansk Endokrinologisk Selskab / Danish Endocrine Society	http://www.endocrinology.dk/
Hrvatsko društvo za endokrinologiju i dijabetologiju / Croatian Society for Endocrinology and Diabetology	http://www.hded.com.hr/

Source	Website
Österreichische Gesellschaft für Endokrinologie und Stoffwechsel / Austrian Society for Endocrinology and Metabolism	http://www.oeges.at/
Swiss Society for Endocrinology and Diabetology	https://www.sgedssed.ch/
Svenska Endokrinolog Föreningen / Swedish Endocrine Society	https://endokrinologforeningen.se/
Sociedad Española de Endocrinologia y Nutrición / Spainsh Society for Endocrinology and Nutrition	https://www.seen.es/inicio.aspx
Society for Endocrinology (UK)	https://www.endocrinology.org/
Združenje Endokrinologov Slovenije / Slovenian Endocrine Society	https://endodiab.si/
Sociedade Portuguesa de Endocrinologia Diabetes e Metabolismo / Portuguese Society of Endocrinology, Diabetes and Metabolism	http://www.spedm.pt/
Nederlandse Vereniging Voor Endocrinologie / Netherlands Society for Endocrinology	https://www.nve.nl/openbaar/algemeen2
Società Italiana Endocrinologia / Italian Endocrine Society	http://www.societaitalianadiendocrinologia.it/html/cnt//home.asp
Associazione Medici Endocrinologi / Endocrinologist Medical Association	http://www.associazionemediciendocrinologi.it/
Irish Endocrine Society	https://irishendocrinesociety.com/
Cancer	
International Agency for Research on Cancer (IARC)	https://www.iarc.fr/
Union for International Cancer Control (UICC)	https://www.uicc.org/
International Association of Oncology (IAO)	https://iaoncology.org/about.php
International Society of Nurses in Cancer Care	https://www.isncc.org/
International Society of Geriatric Oncology	https://www.siog.org/
International Psycho-Oncology Society	https://www.ipos-society.org/
European Society for Medical Oncology	https://www.esmo.org/
European Cancer Organisation (ECCO)	https://www.ecco-org.eu/
The Organisation of European Cancer Institutes (OECI)	www.oeci.eu
European School of Oncology	www.eso.net
European Organisation for Research and Treatment of Cancer	www.eortc.org
The European Oncology Nursing Society (EONS)	www.cancernurse.eu
European Association of Urology (EAU)	www.uroweb.org

Source	Website
European Society of Breast Cancer	www.eusoma.org
Nordic Cancer Union	http://www.ncu.nu/Default.aspx?ID=23
Clinical Oncology Society of Australia	https://www.cosa.org.au/
Cancer Council	https://www.cancer.org.au/
Cancer Australia	https://canceraustralia.gov.au/
Belgian Cancer Registry	https://kankerregister.org/Home_en
The Belgium Society of Medical Oncology (BSMO)	https://www.bsmo.be/
Cyprus Anti-Cancer Society	https://www.anticancersociety.org.cy/en/page/home
Czech National Cancer Control Programme	https://www.onconet.cz/index-en.php
Danish Cancer Society	https://www.cancer.dk/international/
Dansk Selskab for Klinisk Onkologi/ Dansish Society for Clinical Oncology	https://dsko.org/
Cancer Society of Finland	https://www.cancersociety.fi/
Fondation de France/ Foundation of France	https://www.fondationdefrance.org/en/cancer
Institut Curie/ Curie Institute (France)	https://institut-curie.org/
Institut National Du Cancer/ National cancer institute (France)	https://www.e-cancer.fr/
Société Francaise du Cancer / French Ccancer Society	https://sfc.asso.fr/
Société Francaise de Radiothérapie Oncologique / French Society of Radiation Oncology	https://www.sfro.org/
Deutsches Krebsforschungszentrum - Stiftung des öffentlichen Rechts/ German Cancer Research Center - Foundation under Public Law	https://www.dkfz.de/en/index.html
Deutsches Krebsforschungszentrum-Tumorerkrankungen (NCT) Heidelberg / National Centre for Tumour Diseases Heidelberg	https://www.nct-heidelberg.de/en/the-nct/supporting-institutions/german-cancer-research-center-dkfz.html
Deutsche Krebsgesellschaft/ German Cancer Society	https://www.krebsgesellschaft.de/german-cancer-society.html
Cancer Society (Greece)	http://www.cancer-society.gr/
Hellenic Society of Medical oncology	https://www.hesmo.gr/en/
Hellenic Cancer Society	https://cancerhellas.org/
Krabbameinsfelagid (Iceland)	https://www.krabb.is/
Irish Cancer Society	https://www.cancer.ie/
National Cancer Ireland	https://www.ncri.ie/data
Associazione Italiana Malati di Cancrio / Italian Association of Cancer Patients	https://www.aimac.it/
Istitudo di Ricovero e Cura a Carattere Scientifico (IRCCS) / Scientific Hospitalization and Care institute	https://research.fpoircc.it/

Source	Website
Institut national du cancer / National Cancer Institute (Luxembourg)	http://institutnationalducancer.lu/
Fondation Cancer / Cancer Foundation (Luxembourg)	http://www.cancer.lu/
Centre Scientifique de Monaco / Monaco Scientific Centre	https://www.centrescientifique.mc/en/article/medical-biology/cancer
Netherlands Cancer Institute	https://www.nki.nl/
Dutch Cancer Society	https://www.kwf.nl/en/english
Kreftregistry / Cancer Registry of Norway	https://www.kreftregisteret.no/en/
Ligo Portuguesa Contra o Cancro / Portuguese Cancer League	https://www.ligacontracancro.pt/
Onkološki Inštitut Ljubljana / Institute of Oncology Ljubljana (Slovenia)	https://www.onko-i.si/
Zveza slovenskih društev za boj proti raku / Association of Slovenia Cancer Societies	http://www.protiraku.si/
Asociación Española Contra el Cáncer / Spanish Association Against Cancer	https://www.aecc.es/es
Institut Catalan d'Oncologia / Catalan Institute of Oncology	http://www.iconcologia.net/
Sociedad Española de Enfermería Oncológica / Spanish Oncology Nursing Society	https://seeo.org/
Cancerfonden / Cancer Foundation (Sweden)	https://www.cancerfonden.se/
Sjuksköterskor i cancervård / Nurses in Cancer Care	https://www.swenurse.se/Sektioner-och-Natverk/Sjukskoterskoricancervard/
Krebsliga / SwissCancer League	https://www.krebsliga.ch/
NICER - Nationales Institut für Krebsepidemiologie und -registrierung / Foundation National Institute for Cancer Epidemiology and Registration (Switzerland)	https://www.nicer.org/
Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung / Swiss Group for Clinical Cancer Research	https://www.sakk.ch/en
National Cancer Institute (USA)	https://www.cancer.gov/
National Comprehensive Cancer Network (USA)	https://www.nccn.org/
American Society of Clinical Oncology (ASCO)	https://www.asco.org/
Cancer Research UK	https://www.cancerresearchuk.org/
Royal College of Radiologists (UK)	https://www.rcr.ac.uk/

15.2 Search results

15.2.1 Systematic review search results

Table 41 Summary of biomedical bibliographic database search results

Database	Results
PubMed(MEDLINE)	3,811
Embase (OVID)	14,388
Cochrane Library—Reviews	77
Cochrane Library—Protocol	23
Cochrane Library—Trials	3,612
PsycINFO–Aux only	11
ETHMED–Aux only	0
Econlit–Econ only	1
YORK CRD–Econ only	61
INAHTA—Econ only	20
Total	**22,004**

15.2.2 Efficacy, effectiveness, and safety search results

Table 42 Search strategy – PubMed [17-02-2021]

No.	Query	Results
--SEARCH STRING 1, BISPHOSPHONATE AND SERM RCTS--		
1	Osteoporosis, postmenopausal [mh]	12,985
2	Osteoporosis [mh]	55,073
3	Osteoporotic fracture [mh]	5,388
4	Osteodensitomet*[tiab]	282
5	Osteoporo* [tiab]	76,589
6	**1 OR 2 OR 3 OR 4 OR 5**	**96,185**
7	Adjuvant treatment [tiab]	13,464
8	Adjuvant therapy [tiab]	24,027
9	**7 OR 8**	**37,373**
10	Aromatase inhibitors [mh]	6,137
11	Aromatase inhibit*[tiab]	7,580
12	**10 OR 11**	**9,350**
13	Breast neoplasms [mh]	289,059
14	Breast cancer lymphedema [mh]	173
15	Breast cancer [tiab]	267,917
16	Breast cancers [tiab]	22,793
17	Breast neoplasms [tiab]	9,305

No.	Query	Results
18	Breast neoplasm [tiab]	787
19	**13 OR 14 OR 15 OR 16 OR 17 OR 18**	**367,409**
20	**9 AND 12 AND 19**	**920**
21	Ablation therapy [tw]	2,312
22	Hormon* therapy [tiab]	159,711
23	Hormon* treatment [tw]	303,438
24	Androgen suppress* [tw]	806
25	**21 OR 22 OR 23 OR 24**	**305,710**
26	Prostate neoplasms [mh]	126,497
27	Prostat* neoplasms [tiab]	6,409
28	Prostat* neoplasm [tiab]	2,010
29	Prostat* cancer [tiab]	140,660
30	Prostat* cancers [tiab]	22,117
31	**26 OR 27 OR 28 OR 29 OR 30**	**22,188**
32	**25 AND 31**	**10,393**
33	**6 OR 20 OR 32**	**116,701**
34	SERM [tw]	1,347
35	SERMs [tw]	1,514
36	Bazedoxifene [tw]	418
37	Raloxifene [tw]	3,947
38	**34 OR 35 OR 36 OR 37**	**5,575**
39	Alendron* [tw]	5,627
40	Ibandron* [tw]	1,182
41	Risedron* [tw]	2,018
42	Zoledron* [tw]	5,519
43	**39 OR 40 OR 41 OR 42**	**12,152**
44	Etidronat* [tw]	1,337
45	Clodronat* [tw]	2,141
46	Tiludronat* [tw]	145
47	Pamidronat* [tw]	3,144
48	Neridronat* [tw]	111
49	Olpadronat* [tw]	61
50	Didronel [tw]	22
51	Bonefos [tw]	23
52	Skelid [tw]	3
53	APD [tw]	5,438
54	**Aredia [tw]**	77

No.	Query	Results
55	**44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54**	**11,483**
56	**Non-nitrogenous [tw]**	88
57	**Non nitrogenous [tw]**	88
58	**56 OR 57**	88
59	None [tw]	304,383
60	Non [tw]	2,207,059
61	Nitrogenous [tw]	4,482
62	**59 AND 61**	**33**
63	**60 AND 61**	**458**
64	**55 OR 58 OR 62 OR 63**	**11,969**
65	**43 NOT 64**	**10,706**
66	**65 OR 38**	**15,951**
67	**33 AND 66**	**7,044**
68	**67 AND RCT filter**	**2,257**
--SEARCH STRING 2, DENOSUMAB, ALL LEVELS OF EVIDENCE--		
69	Denosumab [mh]	**1,574**
70	Denosumab [tiab]	**2,738**
71	Prolia [tw]	**44**
72	**69 OR 70 OR 71**	**3,348**
73	**33 AND 72**	**1,716**
--SEARCH STRING 3, COMBINATION STRING 1 OR 2--		
74	**68 OR 73**	**3,811**

Table 43 Search strategy – Embase (OVID) [16-02-2021]

No.	Query	Results
1	Exp postmenopause osteoporosis/	14,569
2	Exp Osteoporosis /	134,224
3	Exp fragility fracture /	19,434
4	Osteodensitomet.ti,ab,kw.	0
5	Osteoporo*.ti,ab,kw.	128,309
6	**1 OR 2 OR 3 OR 4 OR 5**	**170,282**
7	Exp adjuvant therapy /	169,126
8	Adjuvant treatment.ti,ab,kw	24,247
9	Adjuvant therapy.ti,ab,kw	40,645
10	**7 OR 8 OR 9**	**191,996**
11	Exp Aromatase inhibitor /	33,208

No.	Query	Results
12	Aromatase inhibit*.ti,ab,kw	13,029
13	**11 OR 12**	**34,630**
14	Exp breast tumor /	556,505
15	Exp breast cancer-related lymphedema /	549
16	Breast cancer.ti,ab,kw	421,304
17	Breast cancers.ti,ab,kw	37,035
18	Breast neoplasms.ti,ab,kw	9,914
19	Breast neoplasm.ti,ab,kw	2,000
20	**14 OR 15 OR 16 OR 17 OR 18 OR 19**	**609,804**
21	**10 AND 13 AND 20**	**6,820**
22	Exp ablation therapy /	52,296
23	Ablation therapy.ti,ab,kw	4,015
24	Hormon* therapy.ti,ab,kw	36,594
25	Hormon* treatment.ti,ab,kw	14,248
26	Androgen suppress*.ti,ab,kw	1,227
27	**22 OR 23 OR 24 OR 25 OR 26**	**103,834**
28	Exp prostate cancer/	226,437
29	Prostat* neoplasms.ti,ab,kw	8,146
30	Prostat* neoplasm.ti,ab,kw	990
31	Prostat* cancer.ti,ab,kw	193,759
32	Prostat* cancers.ti,ab,kw	9,700
33	**29 OR 30 OR 31 OR 32**	**260,113**
34	**27 AND 33**	**11,772**
35	**6 OR 21 OR 34**	**187,627**
36	SERM.ti,ab,kw.	2,262
37	SERMs.ti,ab,kw.	2,352
38	Bazedoxifene.ti,ab,kw.	676
39	Raloxifene.ti,ab,kw.	4,851
40	**36 OR 37 OR 38 OR 39**	**7,695**
41	Alendron*.ti,ab,kw.	7,894
42	Ibandron*.ti,ab,kw.	2,093
43	Risedron*.ti,ab,kw.	3,006
44	Zoledron*.ti,ab,kw.	8,942
45	**41 OR 42 OR 43 OR 44**	**18,209**
46	Etidronat*.ti,ab,kw.	1,619
47	Clodronat*.ti,ab,kw.	3,276
48	Tiludronat*.ti,ab,kw.	182

No.	Query	Results
49	Pamidronat*.ti,ab,kw.	3,822
50	Neridronat*.ti,ab,kw.	175
51	Olpadronat*.ti,ab,kw.	78
52	Didronel.ti,ab,kw.	34
53	Bonefos.ti,ab,kw.	31
54	Skelid.ti,ab,kw.	6
55	APD.ti,ab,kw.	7,863
56	**Aredia**.ti,ab,kw.	96
57	**46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56**	**16,052**
58	**40 OR 45**	**25,118**
59	**35 AND 57**	**11,851**
60	**59 NOT 57**	**11,021**
61	**68 AND RCT filter**	**4,821**
--END OF SEARCH STRING 1--		
62	Exp Denosumab /	9,663
63	Denosumab.ti,ab,kw	6,160
64	Prolia.ti,ab,kw	117
65	**35 AND 64**	**10,119**
--END OF SEARCH STRING 2--		
66	**61 OR 65**	**14,388**

Table 44 Search strategy – Cochrane Library [16-02-2021]

No.	Query	Results
1	Osteoporo*	12,390
2	Postmenopaus*	21,733
3	Fractur*	23,979
4	**#1 OR #2 OR #3**	**46,665**
5	Adjuvant treatment	22,592
6	Adjuvant therapy	24,727
7	**#5 OR #6**	**28,606**
8	Aromatase inhibitors	1,516
9	Aromatase inhibit*	2,399
10	**#8 OR #9**	**2,399**
11	Breast cancer	38,444
12	Breast cancers	2,701
13	Breast neoplasms	15,027

No.	Query	Results
14	Breast neoplasm	5,187
15	**#11 OR #12 OR #13 OR #14**	**39,135**
16	**#7 AND #10 AND #15**	**845**
17	Ablation therapy	4,532
18	Hormon* therapy	33,394
19	Hormon* treatment	33,577
20	Androgen suppress*	789
21	**#17 OR #18 OR #19 OR #20**	**46,908**
22	Prostat* neoplasms	7,508
23	Prostat* neoplasm	2,492
24	Prostat* cancer	15,796
25	Prostat* cancers	1,475
26	**#22 OR #23 OR #24 OR #25**	**16,298**
27	**#21 AND #26**	**3,448**
28	**#4 OR #16 OR #27**	**50,097**
29	Denosumab	1,039
30	Prolia	59
31	**#29 OR #30**	**1,039**
32	Selective Estrogen Receptor Modulators	624
33	(SERM):ti,ab,kw	201
34	(SERMs):ti,ab,kw	144
35	(Bazedoxifene):ti,ab,kw	172
36	(Raloxifene):ti,ab,kw	971
37	**#32 OR #33 OR #34 OR #35 OR #36**	**1,488**
38	Bisphosphonat*	2,421
39	Diphosphonat*	1,396
40	**#38 OR #39**	**3,237**
41	**#31 OR #37 OR #40**	**5,345**
42	**#28 AND #41**	**3,730**
Filtered		
63	**#62 in Cochrane Reviews**	**77**
64	**#62 in Cochrane Protocols**	**23**
65	**#62 in Trials**	**3,612**

15.2.3 Auxiliary and economic search results

Table 45 PsycINFO (OVID) search strategy – AUX only [17-02-2021]

No.	Query	Results
1	Exp Osteoporosis /	1,104
2	Osteodensitomet.ti,ab.	0
3	Osteoporo*.ti,ab.	2,082
4	Postmenopaus*.ti,ab.	2,607
5	Menopaus*.ti,ab.	4,768
6	Fractures, bone/	0
7	**Or/1-6**	**8,168**
8	Adjuvant treatment.ti,ab.	385
9	Adjuvant therapy.ti,ab.	455
10	**Or/8-9**	**796**
11	Aromatase inhibit*.ti,ab.	281
12	Exp Breast neoplasms/	10,213
13	Breast cancer.ti,ab.	12,288
14	Breast cancers.ti,ab.	178
15	Breast neoplasms.ti,ab.	4
16	Breast neoplasm.ti,ab.	5
17	**Or/12-16**	**13,176**
18	**10 AND 11 AND 17**	**15**
19	Ablation therapy.ti,ab.	9
20	Hormon* therapy.ti,ab.	1,321
21	Hormon* treatment.ti,ab.	772
22	Androgen suppress*.ti,ab.	12
23	**Or/19-22**	**2,014**
24	Exp Prostate cancer/	4,859
25	Prostat* neoplasms.ti,ab.	5
26	Prostat* neoplasm.ti,ab.	0
27	Prostat* cancer.ti,ab.	3,021
28	Prostat* cancers.ti,ab.	85
29	**Or/24-28**	**7,488**
30	**23 AND 29**	**95**
31	**7 OR 18 OR 30**	**8,261**
32	Denosumab.ti,ab.	16
33	Prolia.ti,ab.	0
34	**Or/32-33**	**16**
35	**31 AND 34**	**11**

Table 46 ETHMED search strategy – AUX only [17-02-2021]

Search strings	Results
Auxiliary search strings:*Ethical, social, legal*	
Osteoporosis	6
Denosumab	0
Prolia	0

Table 47 EconLit (EBSCO) search strategy – Cost-effectiveness only [17-02-2021]

No.	Query	Results
1	TX "Osteoporo*"	30
2	TX "Postmenopaus*"	13
3	TX "Fractur*"	447
4	**1 OR 2 OR 3**	499
5	TX "Adjuvant treatment"	3
6	TX "Adjuvant therapy"	2
7	**5 OR 6**	4
8	TX "Aromatase inhibitors"	2
9	TX "Aromatase inhibit*"	2
10	**8 OR 9**	2
11	TX "Breast neoplasms"	0
12	TX "Breast cancer"	2
13	TX "Breast cancers"	310
14	TX "Breast neoplasm"	0
15	**11 OR 12 OR 13 OR 14**	317
16	**7 AND 10 AND 15**	0
17	TX "Ablation therapy"	0
18	TX "Hormon* therapy"	7
19	TX "Hormon* treatment"	1
20	TX "Androgen suppress*"	0
21	**17 OR 18 OR 19 OR 20**	8
22	TX "Prostat* neoplasm"	0
23	TX "Prostat* cancer"	94
24	TX "Prostat* cancers"	3
25	**22 OR 23 OR 24**	95
26	**21 AND 25**	**2**
27	**4 OR 16 OR 26**	501
28	TX "Denosumab"	2
29	TX "Prolia"	0

No.	Query	Results
30	**28 OR 29**	2
31	**27 AND 30**	**1**

Table 48 York CRD – Cost-effectiveness only [17-02-2021]

Search strings	Results
Cost-effectiveness	
Denosumab	61

Table 49 INAHTA – International HTA Database – Cost-effectiveness only [17-02-2021]

Search strings	Results
Cost-effectiveness	
Denosumab	20

15.2.4 Clinical trials search results

Table 50 Clinical trials search strategy [03-03-2021]

Database	Search strategy	Results
Clinicaltrials.gov	Intervention AND Osteoporosis AND (Denosumab OR Alendronate OR Ibandronate OR Risedronate OR Zoledronate OR Bazedoxifene OR Raloxifene)	Denosumab: 28 Alendronate: 118 Ibandronate: 39 Risedronate: 65 Zoledronate: 86 Bazedoxifene: 11 Raloxifene: 27 **Sub-total**: **374**
EU Clinical trials registry	Adult AND Osteoporosis AND (Denosumab OR Alendronate OR Ibandronate OR Risedronate OR Zoledronate OR Bazedoxifene OR Raloxifene)	Denosumab: 12 Alendronate: 37 Ibandronate: 0 Risedronate: 19 Zoledronate: 4 Bazedoxifene: 3 Raloxifene: 6 **Sub-total**: **81**
Cochrane clinical trials registry	Osteoporosis AND Denosumab	15
ISRCTN	Osteoporosis AND Denosumab	4
ANZCTR	Osteoporosis AND Denosumab	11
	Total	**497**

15.2.5 Methodological search filters

Table 51 Search filter – PubMed (RCTs)

No.	Query
1	Randomized Controlled Trial [pt]
2	Controlled Clinical Trial [pt]
3	Pragmatic Clinical Trial [pt]
4	Equivalence Trial [pt]
5	Clinical Trial, Phase III [pt]
6	Randomized Controlled Trial [mh]
7	Randomized Controlled Trials as Topic [mh]
8	Controlled Clinical Trial [pt]
9	Controlled Clinical Trials as Topic [mh]
10	Randomization [tw]
11	Random Allocation [mh]
12	Double-Blind Method [mh]
13	Double Blind Procedure [tw]
14	Double-Blind Studies [tw]
15	Single-Blind Method [mh]
16	Single Blind Procedure [tw]
17	Single-Blind Studies [tw]
18	Placebos [mh]
19	Placebo Effect [mh]
20	Control Groups [mh]
21	Control Group* [tiab]
22	Allocated [tw]
23	(Nonrandom* [tw] OR quasirandom* [tw] OR quasi-random* [tw] OR non-random* [tw])
24	(pragmatic study [tw] OR pragmatic studies [tw])
25	(random* [tw] OR Sham* [tw] OR Placebo* [tw])
26	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25**
27	(singl* [tw] OR doubl* [tw])
28	(blind* [tw] OR dumm* [tw] OR mask* [tw])
29	**27 AND 28**
30	(tripl* [tw] OR trebl* [tw])
31	**30 AND 28**
32	(Study [tw] OR studies [tw] OR trial* [tw] OR group* [tw])
33	control* [tw]
34	**32 AND 33**

No.	Query
35	(open label [tw] OR open-label [tw])
36	**32 AND 35**
37	(Equivalence [tw] OR superiority[tw] OR non-inferiority[tw] OR noninferiority [tw])
38	**32 AND 37**
39	(Phase III [tw] OR Phase 3 [tw])
40	**32 AND 39**
41	(Pragmatic [tw] OR practical [tw])
42	trial* [tw]
43	**41 AND 42**
44	(Quasiexperimental [tw] OR quasi-experimental [tw])
45	**42 AND 44**
46	**26 OR 29 OR 31 OR 34 OR 36 OR 38 OR 40 OR 43 OR 45**

Sources:
CADTH[308]

16 Appendix B: Evidence pertaining to effectiveness and safety outcomes

Appendix B includes tables that outline the characteristics of the studies included in the clinical evaluation of safety and effectiveness outcomes (***Table 52***), and the outcome data included in the clinical data analysis (***Table 53*** to ***Table 66***).

Table 52 Characteristics of included RCTs (per publication) assessing clinical effectiveness and safety

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
Postmenopausal women with osteoporosis									
Cummings et al. 2009[160] FREEDOM NCT00089791	RCT, double blind, multicentre (214 sites)	USA, Canada, Argentina, Brazil, Mexico, Australia, New Zealand, Australia, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK, Czech Republic, Estonia, Greece, Serbia, Hungary, Latvia, Lithuania,	Postmenopausal women, T-score <-2.5 at LS or TH	DEN (60 mg/6mo) n=3902	PL n=3906	Overall FREEDOM population: 72.3±5.2	36mo	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (LS, TH) *Safety:* Mortality, AEs, SAEs, AEs upon discontinuation of DEN	Amgen Inc.

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
		Malta, Poland, Slovak Republic, Romania, Bulgaria							
Adachi et al. 2017[150] FREEDOM NCT00089791 FREEDOM Extension NCT00523341	OL crossover, extension study (214 centres)* *Only data to 36mo extracted. Crossover data was not utilised.	Refer to countries in Cummings et al. 2009	Postmenopausal women, T-score <-2.5 at LS or TH	FREEDOM-DEN (60 mg/6mo) Long-term DEN: n=2343 Crossover DEN: n=2207	NA	FREEDOM-DEN: 72.3±5.2 PL: 72.3±5.2 FREEDOM Extension- Long-term DEN: 74.9±5.0 Crossover DEN: 74.8±5.1	96mo (long-term DEN)* 60mo (DEN in crossover)* *Crossover data not utilised.	*Safety:* Withdrawal due to AEs	Amgen Inc.
Brown et al. 2013[155] FREEDOM NCT00089791	Retrospective analysis, multicentre (214 centres)	Refer to countries in Cummings et al. 2009	FREEDOM trial participants who discontinued treatment after 2-5 doses of DEN or PL and continued participation for ≥7mo (≥6mo since last dose + 1mo study visit window)	DEN (60 mg/6mo) n=327	PL n=470	DEN: 73±5 PL: 73±5	24mo (maximum off treatment observation period) 10mo (mean follow-up)	*Safety:* AEs upon discontinuation of DEN	Amgen Inc.
Cumming et al. 2018[159] FREEDOM NCT00089791 FREEDOM Extension	Retrospective/ post-hoc analysis, multicentre (214 centres)	Refer to countries in Cummings et al. 2009	FREEDOM and FREEDOM Extension participants who discontinued treatment after ≥2 doses of DEN or	DEN (60 mg/6mo) n=327 FREEDOM Extension-Crossover:	PL:470	FREEDOM-DEN: 73±5 PL: 73±5 FREEDOM Extension-	FREEDOM-DEN: median 0.5 (0.2-1.4) PL: median 0.5 (0.3-1.4)	*Safety:* AEs upon discontinuation of DEN	Amgen Inc.

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
NCT00523341			PL and continued participation for ≥7mo (≥6mo since the last dose + 1mo study visit window)	678		Crossover: 73	FREEDOM Extension- Crossover: median 0.2 (0.1-0.7)		
Nakamura et al. 2012[182] NR	RCT, double blind, multicentre (NR)	Japan	Postmenopausal women, T-score -2.5 to -4.0 at LS, or -2.5 to -3.5 at FN or TH	DEN (14 mg/6mo)[a] n=53 DEN (60 mg/6mo)[a] n=54 DEN (100 mg/ 6mo)[a] n=50	PL n=55	DEN (14 mg): 65.9±7.1 DEN (60 mg): 65.1±6.3 DEN (100 mg): 64.6±7.1 PL: 64.6±7.0	12mo	*Effectiveness:* Vertebral fracture, BMD (TH) *Safety:* AEs, SAEs	Amgen Inc.
Miller et al. 2016[180] NCT01732770	RCT, double blind, double dummy, multicentre (37 sites)	Belgium, Denmark, Poland, Spain, Canada, USA, Australia	Postmenopausal women, ≥2y bisphosphonate therapy prior to screening if T-score ≤-2.5 at LS, TH, FN	DEN (60 mg/6mo) n=321	ZOL (IV 5 mg/ once yearly) n=322	DEN: 65.1±7.6 ZOL: 69.5±7.7	12mo	*Effectiveness:* BMD (FN, TH) *Safety:* Withdrawal due to AEs, AEs, SAEs	Amgen Inc.
Morii et al. 2003[181 181] NR	RCT, double blind, multicentre (26 sites)	Japan	Postmenopausal women, ≥2y PM, T-score <-2.5 at LS	RLX (oral 60 mg/d) n=92 RLX (oral 120 mg/day)[b] n=95	PL n=97	RLX (60 mg): 65.2±6.2 RLX (120 mg): 64.7±6.2 PL: 64.3±6.5	12mo	*Effectiveness:* Vertebral and nonvertebral fracture *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Eli Lilly and Company and Chugai Pharmaceutical Company
Ettinger et al. 1999[164]	RCT, double blind,	Argentina, Australia,	Postmenopausal women, ≥2y PM,	RLX (oral 60 mg/day)	PL n=2576	Overall MORE population: 67	36mo	*Effectiveness:* Vertebral	Eli Lilly and Company

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
MORE	multicentre (180 sites)	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, the Netherlands, New Zealand, Poland, Singapore, Slovak Republic, Slovenia, Spain, Sweden, UK, USA, Canada	Group 1: T-score <-2.5 at LS or FN Group 2: Low BMD with ≥1 moderate or severe vertebral fractures, or ≥2 moderate fractures regardless of BMD	n=2557 RLX (oral 120 mg/day)[c] n=2572				fracture, BMD (FN, LS)	
Delmas et al. 2002[162] MORE	RCT, double blind, multicentre (180 sites)	Refer to countries in Ettinger et al. 1999	Postmenopausal women, ≥2y PM, Group 1: T-score <-2.5 at LS or FN Group 2: Low BMD with ≥1 moderate or severe vertebral fractures, or ≥2 moderate fractures regardless of BMD	RLX (oral 60 mg/day) n=2557 RLX (oral 120 mg/day)[c] n=2572	PL n=2576	Overall MORE population: 67	48mo	*Safety:* Mortality	Eli Lilly and Company
Silverman et al. 2008[192]	RCT, double blind,	Argentina, Australia,	Postmenopausal women, ≥2y PM,	BAZ (oral 20 mg/day)	RLX (oral 60 mg/day)	BAZ 20 mg: 66.5±6.5	36mo	*Effectiveness:* Nonvertebral	Pfizer Inc.

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
NCT00205777	multicentre (206 sites)	Belgium, Brazil, Bulgaria, Canada, Chile, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Mexico, The Netherlands, New Zealand, Norway, Poland, Romania, Russia, Slovakia, South Africa, Spain, USA	T-score -2.5 to -4.0 at LS or FN, or prevalent vertebral facture and T-score not below -4.0 at LS or FN	n=1886 BAZ (oral 40 mg/day)[d] n=1872	n=1849 PL n=1885	BAZ 40 mg: 66.2±6.8 RLX 60 mg: 66.4±6.7 PL: 66.5±6.8		fracture, BMD (LS, TH)	
Christiansen et al. 2010[158] NCT00205777	RCT, double blind, multicentre (206 sites)	Refer to countries in Silverman et al. 2008	Postmenopausal women, ≥2y PM, T-score -2.5 to -4.0 at LS or FN, or prevalent vertebral facture and T-score not below -4.0 at LS or FN	BAZ (oral 20 mg/day) n=1866 BAZ (oral 40 mg/day)[d] n=1872	RLX (oral 60 mg/day) n=1849 PL n=1885	BAZ 20 mg: 66.5±6.5 BAZ 40 mg: 66.2±6.8 RLX 60 mg: 66.4±6.7 PL: 66.5±6.8	36mo	*Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Pfizer Inc.
de Villiers et al. 2009[161] NCT00205777 Extension I	RCT, double blind, multicentre (206 sites),	Refer to countries in Silverman et al. 2008	Postmenopausal women, ≥2y PM, T-score -2.5 to -4.0 at LS or FN, or	MORE- BAZ (oral 20 mg/day) → BAZ (oral 20	PL n=1058	Extension I- BAZ 20 mg: 65.9±6.3 BAZ 40/20 mg:	60mo	*Safety:* Mortality	Pfizer Inc.

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
	extension study		prevalent vertebral facture and T-score not below -4.0 at LS or FN	mg/day) n=1047 MORE Extension I-BAZ (oral 40 mg/day) → BAZ (oral 20 mg/day)[e] n=1041		65.7±6.4 PL: 65.9±6.5			
Silverman et al. 2012[191] NCT00205777 Extension I	RCT, double blind, multicentre (206 sites), extension study	Refer to countries in Silverman et al. 2008	Postmenopausal women, ≥2y PM, T-score -2.5 to -4.0 at LS or FN, or prevalent vertebral facture and T-score not below -4.0 at LS or FN	MORE-BAZ (oral 20 mg/day) → BAZ (oral 20 mg/day) n=1047 MORE Extension I-BAZ (oral 40 mg/day) → BAZ (oral 20 mg/day)[e] n=1041	PL n=1058	Extension I-BAZ 20 mg: 65.9±6.3 BAZ 40/20 mg: 65.7±6.4 PL: 65.9±6.5	60mo	*Safety:* Mortality	Pfizer Inc.
Palacios et al. 2015b[186] NCT00205777 Extension II	RCT, double blind, multicentre (206 sites), extension study	Refer to countries in Silverman et al. 2008	Postmenopausal women, ≥2y PM, T-score -2.5 to -4.0 at LS or FN, or prevalent vertebral facture and T-score not below -4.0 at LS or FN	MORE-BAZ (oral 20 mg/day) → BAZ (oral 20 mg/day) n=560 MORE Extension I-BAZ (oral 40 mg/day) → BAZ (oral 20 mg/day)[e]	PL n=590	Extension II-BAZ 20 mg and 40/20 mg combined: 65.7±6.2 PL: 65.7±6.1	84mo	*Effectiveness:* Vertebral fracture	Pfizer Inc.

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
				n=1142					
Itabashi et al. 2011[173] NCT00238745	RCT, double blind, multicentre (17 sites)	Japan	Postmenopausal women, intact uterus, ≥2y PM, no prevalent vertebral fracture and T-score <-2.5 or prevalent vertebral fracture and T-score <-1.7 (approximately)	BAZ (oral 20 mg/day) n=143 BAZ (oral 40 mg/day)[d] n=140	PL n=142	BAZ 20 mg: 63.0±6.4 BAZ 40 mg: 63.2±6.3 PL: 64.1±6.6	24mo	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Pfizer Inc.
Miller et al. 2008[179] MOTION MM17385	RCT, double blind, double dummy, non-inferiority, multicentre (65 sites)	North America, Latin America, Europe, South Africa	Postmenopausal women, ≥5y PM, ambulatory, T-score <-2.5 to ≥-5.0 at LS	IBN (oral 150 mg/once monthly) n=887	ALN (oral 70 mg/once weekly) n=873	IBN: 65.6 ALN: 65.6	12mo	*Effectiveness:* BMD (FN) *Safety:* AEs, SAEs	F. Hoffmann-La Roche Ltd.
Paggiosi et al. 2014[185] TRIO NCT00666627	RCT, OL, multicentre (NR)	UK	Postmenopausal women, ≥5y PM, ambulatory, T-score ≤-2.5 at LS or PF or T-score ≤-1.0 at LS or PF and a previous fracture from a fall at standing height	IBN (oral 150 mg/ once monthly) n=57	ALN (oral 70 mg/once weekly) n=57 RIS (oral 35 mg/ once weekly) n=58	IBN: 66.9±7.2 ALN: 67.8±7.8 RIS: 66.8±6.7	24mo	*Effectiveness:* BMD (FN, LS) *Safety:* SAEs	Warner Chilcott
Greenspan et al. 2015[171] ZEST NCT00558012	RCT, OL, single centre	USA	Frail women with osteoporosis residing in nursing homes or assisted-living facilities, with a history of vertebral or hip	ZOL (IV 5 mg/once yearly) n=89	PL n=92	ZOL: 85.4±0.6 PL: 85.5±0.5	24mo	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Mortality, AEs, SAEs	NIH/National Institute on Aging, The National Institute of Diabetes and Digestive and Kidney Diseases, Pittsburgh Older Americans

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
			fracture or T-score <-2.0 at LS, TH or radius						Independence Center, Pharmaceutical Outcomes Research Program in Aging award, Clinical Translational Science Institute NIH/National Center for Research Resources
Palomba et al. 2005[188] NR	RCT, double blind, multicentre (2 sites)	Italy	Postmenopausal women, IBD in remission(≥6mo), ambulatory, T-score ≤-2.5 at posterior-anterior LS	RIS (oral 35 mg/once weekly) n=45	PL n=45	RIS: 52.3±3.2 PL: 51.4±3.0	12mo	*Effectiveness:* Vertebral fracture	NA
Palomba et al. 2008[187] Extension NR	RCT, OL, multicentre (2 sites), extension study	Italy	Postmenopausal women, IBD in remission(≥6mo), ambulatory, T-score ≤-2.5 at posterior-anterior LS	RIS (oral 35 mg/once weekly) n=45	PL n=45	RIS: 52.3±3.2 PL: 51.4±3.0	36mo	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS) *Safety:* AEs	NA
Black et al. 2007[152] HORIZON-PFT NCT00049829	RCT, double blind, multicentre (240 sites)	Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Columbia, Finland,	Postmenopausal women, T-score <-2.5 at FN with or without vertebral fracture, or T-score <-1.5 with radiologic	ZOL (IV 5 mg/once yearly) n=3889	PL n=3876	ZOL:73.1±5.34 PL: 73.0±5.40	36mo	*Effectiveness:* Nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs,	Novartis Pharma

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
		France, Germany, Hong Kong, Hungary, Israel, Italy, Korea, Mexico, New Zealand, Norway, Poland, Russia, Sweden, Switzerland, Taiwan, Thailand, UK, USA	evidence of ≥2 mild vertebral fractures or 1 moderate vertebral fracture Stratum 1: No osteoporosis medication at BL Stratum 2: Taking osteoporosis medication at BL					Mortality, AEs, SAEs	
Jacques et al. 2012[174] HORIZON-PFT NCT00049829	RCT, double blind, multicentre (240 sites), subgroup analysis	Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Columbia, Finland, France, Germany, Hong Kong, Hungary, Israel, Italy, Korea, Mexico, New Zealand, Norway, Poland, Russia, Sweden, Switzerland, Taiwan, Thailand, UK,	Postmenopausal women, T-score <-2.5 at FN with or without vertebral fracture, or T-score <-1.5 with radiologic evidence of ≥2 mild vertebral fractures or 1 moderate vertebral fracture Stratum 1: No osteoporosis medication at BL Stratum 2: Taking osteoporosis medication at BL	ZOL (IV 5 mg/once yearly) n=3889	PL n=3876	ZOL:73.1±5.34 PL: 73.0±5.40	36mo	*Effectiveness:* Vertebral fracture	Novartis Pharma

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
		USA	BTM subgroup						
Women with breast cancer receiving AAIT who have an increased fracture risk									
Ellis et al. 2008[163] NCT00089661	RCT, double blind, multicentre (53 sites)	USA, Canada	Early-stage histologically or cytologically confirmed breast cancer, hormone-receptor positive, undergoing AAIT, completed treatment via radiation and/or chemotherapy or surgery ≥4w before study entry, low bone mass or FN T-score of -1.0 to -2.5	DEN (60 mg/6mo) n=125	PL n=127	DEN: 59.2±8.9 PL: 59.7±9.7	24mo	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH, Trochanteric) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Amgen Inc.
Gnant et al. 2015[166] ABCSG-18 NCT00556374	RCT, double blind, multicentre (58 sites)	Austria, Sweden	Postmenopausal women (defined as those who have undergone bilateral oophorectomy, ≥60yo or <60yo with follicle-stimulating hormone and oestradiol levels in PM range), histologically confirmed breast cancer, receptor positive, receiving	DEN (60 mg/6mo) n=1711	PL n=1709	Total ABCSG-18 population: median 64 (58-70)	36mo	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH)	Amgen Inc.

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
			AAIT						
Gnant et al. 2019[167] ABCSG-18 NCT00556374	RCT, OL, multicentre (58 sites)	Austria, Sweden	Postmenopausal women (defined as those who have undergone bilateral oophorectomy, ≥60yo or <60yo with follicle-stimulating hormone and oestradiol levels in PM range), histologically confirmed breast cancer, receptor positive, receiving AAIT	DEN (60 mg/6mo) n=1711	PL n=1709	Total ABCSG-18 population: median 64 (58-70)	OL phase-73mo (median duration of follow-up)[f]	*Safety:* Mortality, AEs, SAEs	Amgen Inc.
Greenspan et al. 2007[169] NCT00118508	RCT, double blind, single centre	USA	Newly postmenopausal women (≤8y) with breast cancer, treated with chemotherapy with or without tamoxifen or AAIT	RIS (oral 35 mg/ once weekly) n=43	PL n=44	RIS: 50.1±5.1 PL: 49±5.9	12mo	*Effectiveness:* BMD (LS, TH, Trochanteric)	NIH/National Institute of Diabetes and Digestive and Kidney Diseases, Alliance for Better Bone (Procter and Gamble)
Livi et al. 2019[177] BONADIUV NCT02616744	RCT, single blind, single centre	Italy	Postmenopausal women with early breast cancer, hormone receptor-positive, receiving AAIT	IBN (oral 150 mg/ once monthly) n=89	PL n=82	IBN: median 60.5 (54.3-67.0) PL: median 59.6 (53.9-68.0)	63.3mo (median follow-up)[g]	*Effectiveness:* BMD (LS, TH) *Safety:* SAEs	NA
Men with osteoporosis who have an increased fracture risk									
Orwoll et al.	RCT, double	Belgium,	Ambulatory men	DEN (60	PL	DEN: 64.9±9.8	12mo	*Effectiveness:*	Amgen Inc.

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
2012[183] ADAMO NCT00980174	blind, multicentre (27 sites)	Canada, Denmark, France, Poland, Sweden, USA	with osteoporosis, T-score between ≤-2.0 and ≥-3.5 at LS or FN, or had a previous MOF and T-score between ≤-1.0 and ≥-3.5 at LS or FN and had ≥2 vertebral fractures, 1 femur and 1 forearm evaluated by DXA	mg/6mo) n=121	n=121	PL: 65.0±9.1		Vertebral and nonvertebral fracture	
Langdahl et al. 2015[176] ADAMO NCT00980174	RCT, OL, multicentre (27 sites), crossover study	Belgium, Canada, Denmark, France, Poland, Sweden, USA	Ambulatory men with osteoporosis, T-score between ≤-2.0 and ≥-3.5 at LS or FN, or had a previous MOF and T-score between ≤-1.0 and ≥-3.5 at LS or FN and had ≥2 vertebral fractures, 1 femur and 1 forearm evaluated by DXA	ADAMO: DEN (60 mg/6mo) n=111 ADAMO OL phase: DEN → DEN (continued intervention long-term) n=117	NA	Long-term DEN: 65.0±10.2 Crossover DEN: 65.1±9.2	24mo	*Effectiveness:* BMD (FN, LS, TH, Trochanteric), *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Amgen Inc.
Boonen et al. 2009[153] NR	RCT, double blind, multicentre (25 sites)	USA, Australia, Lebanon, France, Belgium, UK, Czech Republic, Hungary, Poland, the	Ambulatory men with osteoporosis, T-score ≤-2.5 at LS and ≤-1 at FN or T-score ≤-1 at LS and ≤-2 at FN	RIS (oral 35 mg/ once weekly) n=191	PL n=93	RIS: 60±11 PL: 62±11	24mo	*Effectiveness:* BMD (FN, LS, TH, Trochanteric) *Safety:* Mortality, AEs, SAEs	Alliance for Better Bone (Procter and Gamble)

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
		Netherlands							
Boonen et al. 2012[154] NCT00439647	RCT, double blind, multicentre (NR)	Australia, Africa, South America, Belgium, Switzerland, Argentina, Denmark, Austria, Norway, Brazil, Czech Republic, Finland, Germany, Hungary, Iceland, Poland, Portugal, Romania, Russia, Slovakia, Spain, Sweden, UK	Men with primary osteoporosis or osteoporosis from low testosterone levels, T-score ≤-1.5 at TH or FN, and 1-3 prevalent vertebral fractures. If no fracture, T-score of ≤-2.5 at TH, FN, LS	ZOL (IV 5 mg/ once yearly) n=588	PL n=611	ZOL: median 66 (50-85) PL: median 66 (50-85)	24mo	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Novartis Pharma
Orwoll et al. 2010[184] NR	RCT, double blind, double dummy, non-inferiority, multicentre (30 sites)	Australia and North America	Men with primary osteoporosis or osteoporosis associated with hypogonadism, T-score of -2.0 at FN and -1.0 at LS, or -1.0 at FN and a prior low trauma vertebral or nonvertebral fracture or with a	ZOL (IV 5 mg/ once yearly) n=154	ALN (oral 70 mg/once weekly) n=148	ZOL: 64.5±9.90 ALN: 63.5±10.98	24mo	*Effectiveness:* Vertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Novartis Pharma

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
			confirmed radiographic vertebral fracture						
Men with prostate cancer on HAT who have an increased fracture risk									
Smith et al. 2009a[194] NCT00089674	RCT, double blind, multicentre (156 sites)	Canada, USA, Finland, Czech Republic	Men with histologically confirmed prostate cancer on HAT, ≥70yo or if <70yo had history of osteoporotic fracture or T-score <-1.0 at LS, TH or FN, had either received bilateral orchiectomy or are on ADT for at least next 12mo	DEN (60 mg/6mo) n=734	PL n=734	DEN: 75.3±7.0 PL: 75.5±7.1	36mo	*Effectiveness:* Vertebral and nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	Amgen Inc.
Michaelson et al. 2007[178] NR	RCT, double blind, multicentre (2 sites)	USA	Men with prostate adenocarcinoma, receiving GnRH agonists, T-score ≥-2.5 at LS or FN	ZOL (IV 4 mg/ once yearly) n=22	PL n=22	ZOL: 65±8 PL: 66±11	12mo	*Effectiveness:* BMD (FN, LS, TH)	Novartis Pharma
Choo et al. 2013[157] NR	RCT, double blind, multicentre (2 sites)	USA	*"Prostate adenocarcinoma with 1 of the following 3 clinical conditions: (1) T3N0M0, Gleason score >7, or prostate specific antigen (PSA)*	RIS (oral 35 mg/ once weekly) n=52	PL n=52	RIS: 67.5 PL: 66.8	24mo	*Effectiveness:* BMD (FN, LS) *Safety:* SAEs	Aventis Pharma and Procter and Gamble

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
			>15 ng/mL (Group A); (2) pathologic T3 and/or positive surgical margin after radical prostatectomy (Group B); and (3) Rising PSA or clinically palpable local recurrence after radical prostatectomy (Group C). Patients had to have serum creatinine <120 µmol/L. All were to be treated with external beam RT plus 2-3y of ADT using LHRH analogues." T-score >-2.5 at LS						
Greenspan et al. 2007b[170] NCT00048841	RCT, double blind, single centre	USA	Men with prostate cancer receiving ADT	ALN (oral 70 mg/once weekly) n=56	PL n=56	ALN: 70.8±7.9 PL: 72.2±8.8	12mo	*Effectiveness:* Nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Mortality, AEs, SAEs	NIH/National Institute of Diabetes and Digestive and Kidney Diseases and NIH/National Center for Research Resources
Israeli et al. 2007[172] NR	RCT, double blind, single centre	USA	Men with histologically confirmed prostate cancer	ZOL (IV 4 mg/ 3mo) n=112	PL n=110	ZOL: median 74 (44-88) PL: median 73 (47-89)	12mo	*Effectiveness:* Nonvertebral fracture, BMD (LS, TH)	Novartis Pharma

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
			within 1y of starting ADT, received orchiectomy, T-score of ≥-2 at LS and TH					*Safety:* Withdrawal due to AEs, Mortality, AEs, SAEs	
Bhoopalam et al. 2009[151] NR	RCT, double blind, multicentre (11 sites)	USA	Men with histologically confirmed prostate cancer, on or initiating ADT (LHRH agonist with or without antiandrogen or bilateral orchiectomy), T-score of ≥-2 at LS and TH	ZOL (IV 4 mg/ 3mo) n=48	PL n=45	ZOL: Stratum 1- 69.1±10.7 Stratum 2- 71.2±6.8 PL: Stratum 1- 68.4±6.0 Stratum 2- 73.7±.2	12mo	*Effectiveness:* BMD (LS, TH) *Safety:* Withdrawal due to AEs, Mortality, AEs	Novartis Pharma
Cheung et al. 2020[156] NCT01006395	RCT, double blind, single centre	Australia	Men with prostate cancer prior to commence GnRH agonists therapy, ADT intended for at least 2y	ZOL (IV 5 mg/ single dose) n=39	PL n=37	ZOL: median 68.8 (63.1-73.2) PL: median 67.5 (65.2-74.3)	24mo	*Effectiveness:* Nonvertebral fracture, BMD (LS, TH) *Safety:* Withdrawal due to AEs, AEs, SAEs	NHMRC
Klotz et al. 2013[175] NR	RCT, double blind, multicentre (30 sites)	Canada	Men with histologically confirmed prostate cancer, >1yr of ADT indicated (treatment with an antiandrogen for	ALN (oral 70 mg/ once weekly) n=84	PL n=102	ALN: 73.5±8.1 PL: 73.7±8.6	12mo	*Effectiveness:* Nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, SAEs	Abbot Laboratories Canada

Study	Study design	Country	Population	Intervention Sample size	Comparator(s) Sample size	Mean age (y) ±SD	Duration	Outcome(s)	Funding
			up to 30d prior to initiation of LHRH therapy was permitted)						
Ryan et al. 2006[190] NR	RCT, double blind, multicentre (19 sites)	USA	Men with prostate adenocarcinoma who were planning to receive ADT or who had initiated ADT within the previous 12mo, T-score >-2.5 at FN, TH or LS	ZOL (IV 4 mg/3mo) n=61	PL n=61	ZOL: median 73 (67-80) PL: 71 (64-77)	12mo	*Effectiveness:* Nonvertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, SAEs	Novartis Pharma
Smith et al. 2003[193] NR	RCT, double blind, double dummy, multicentre (16 sites)	USA	Men with prostate cancer, initiating ADT with a GnRH agonist with or without an antiandrogen	ZOL (4 mg/3mo) n=55	PL n=51	ZOL: 71.1±8.6 PL 70.2±9.3	12mo	*Effectiveness:* Vertebral fracture, BMD (FN, LS, TH) *Safety:* Withdrawal due to AEs, Mortality, SAEs	Novartis Pharma

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **ADT**: androgen deprivation therapy; **AEs**: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **BL**: baseline; **BMD**: bone mineral density; **BTM**: bone turnover markers; **DEN**: denosumab; **DXA**: dual-energy x-ray absorptiometry; **FN**: femoral neck; **GnRH**: gonadotropin-releasing hormone; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **Inc**.: incorporated; **IV**: intravenous, **LHRH**: luteinising hormone-releasing hormone; **LS**: lumbar spine; mo: months; **PF**: proximal femur; **PL**: placebo; **PM**: postmenopausal; **RCT**: randomised controlled trial; **RLX**: raloxifene; **RIS**: risedronate; **SAEs**: serious adverse events; **TH**: total hip; **mg**: milligrams; **MOF**: major osteoporotic fracture; **NA**: not applicable; **ng/dL**: nanograms per decilitre; **ng/mL**: nanograms per millilitre; **NR**: not reported; **UK**: United Kingdom; **USA**: United States of America; **w**: week/s; **y**: year/s; **yo**: years old; **ZOL**: zoledronate.
Notes:
[a] DEN 60 mg/6mo data extracted and analysed. DEN 14 mg/6mo and 100 mg/6mo excluded as this is not a reimbursed dosage of denosumab in Switzerland.
[b] Raloxifene 60 mg and 120 mg included in Morii et al. 2003[181] . Only 60 mg dosage (I.e., dosage of interest) reported in table.
[c] RLX oral 120 mg/day data in all MORE trial publications were not extracted or analysed, as this is not a reimbursed dosage of raloxifene in Switzerland.
[d] BAZ oral 40 mg/day data were not extracted or analysed, as this is not a reimbursed dosage of bazedoxifene in Switzerland.

[e] Crossover data for BAZ (oral 40 mg/day) to BAZ (oral 20 mg/day) were not extracted or analysed, as no drug washout was undertaken between dosage periods and may bias results.
[f] Data from the outcome presented at median timepoint of 73 months in Gnant 2019[167] were not utilised, only relevant safety data presented at 36 months were extracted from this publication.
[g] Data from the outcome presented at median timepoint of 63.3 months in Livi 2019[177] were not utilised, only relevant effectiveness/safety data presented to 24 months were extracted from this publication.

Table 53 Vertebral fracture extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Postmenopausal women with osteoporosis					
FREEDOM	Cummings et al. 2009[160]	DEN	36	86	3702
FREEDOM	Cummings et al. 2009[160]	PLB	36	264	3691
Nakamura et al. 2012	Nakamura et al. 2012[182]	DEN	12	0	54
Nakamura et al. 2012	Nakamura et al. 2012[182]	PLB	12	0	55
Morii et al. 2003	Morii et al. 2003[181]	RLX	12	0	90
Morii et al. 2003	Morii et al. 2003[181]	PLB	12	2	97
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	24	5	132
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	24	6	128
ZEST	Greenspan et al. 2015[171]	ZOL	24	6	89
ZEST	Greenspan et al. 2015[171]	PLB	24	8	92
Palomba et al.	Palomba et al. 2005[188] Palomba et al. 2008[187]	RIS	36	12	40
Palomba et al.	Palomba et al. 2005[188] Palomba et al. 2008[187]	PLB	36	30	41
HORIZON-PFT	Jacques et al. 2012[174]	ZOL	36	98	2931
HORIZON-PFT	Jacques et al. 2012[174]	PLB	36	308	2976
MORE	Ettinger et al. 1999[164]	RLX	36	148	2259
MORE	Ettinger et al. 1999[164]	PLB	36	231	2292
NCT00205777	Palacios et al. 2015b[186]	BAZ	84	14	506
NCT00205777	Palacios et al. 2015b[186]	PLB	84	15	535
Women with breast cancer receiving AAIT who have an increased fracture risk					
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	24	0	106
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	24	0	99
ABCSG-18	Gnant et al. 2015[166]	DEN	36	27	835
ABCSG-18	Gnant et al. 2015[166]	PLB	36	49	809
Men with osteoporosis who have an increased fracture risk					
ADAMO	Orwoll et al. 2012[183]	DEN	12	0	120
ADAMO	Orwoll et al. 2012[183]	PLB	12	1	120
Boonen et al. 2012	Boonen et al. 2012[154]	ZOL	24	1	588
Boonen et al. 2012	Boonen et al. 2012[154]	PLB	24	3	611
Orwoll et al. 2010	Orwoll et al. 2010[184]	ZOL	24	4	154
Orwoll et al. 2010	Orwoll et al. 2010[184]	ALN	24	6	148
Men with prostate cancer on HAT who have an increased fracture risk					
NCT00089674	Smith et al. 2009[194]	DEN	12	2	679
NCT00089674	Smith et al. 2009[194]	PLB	12	13	673
Smith et al. 2003	Smith et al. 2003[193]	ZOL	12	5	55
Smith et al. 2003	Smith et al. 2003[193]	PLB	12	3	51

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

Table 54 Nonvertebral fracture extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Postmenopausal women with osteoporosis					
FREEDOM	Cumming et al. 2009[160]	DEN	24	264	3902
FREEDOM	Cumming et al. 2009[160]	PLB	24	336	3906
Morii et al. 2003	Morii et al. 2003[181]	RLX	12	1	90
Morii et al. 2003	Morii et al. 2003[181]	PLB	12	4	97
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	24	5	132
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	24	4	128
ZEST	Greenspan et al. 2015[171]	ZOL	24	12	89
ZEST	Greenspan et al. 2015[171]	PLB	24	7	92
Palomba et al. ‖	Palomba et al. 2008[187] ‖	RIS	36	1	40
Palomba et al. ‖	Palomba et al. 2008[187] ‖	PLB	36	7	41
HORIZON-PFT	Black et al. 2007[152]	ZOL	36	1	3861
HORIZON-PFT	Black et al. 2007[152]	PLB	36	4	3875
NCT00205777	Silverman et al. 2008[192]	BAZ	36	89	1886
NCT00205777	Silverman et al. 2008[192]	RLX	36	89	1849
NCT00205777	Silverman et al. 2008[192]	PLB	36	99	1885
Women with breast cancer receiving AAIT who have an increased fracture risk					
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	24	8	106
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	24	8	99
ABCSG-18	Gnant et al. 2015[166]	DEN	36	65	835
ABCSG-18	Gnant et al. 2015[166]	PLB	36	129	809
Men with osteoporosis who have an increased fracture risk					
ADAMO	Orwoll et al. 2012[183]	DEN	12	1	120
ADAMO	Orwoll et al. 2012[183]	PLB	12	2	120
Boonen et al. 2012	Boonen et al. 2012[154]	ZOL	24	5	588
Boonen et al. 2012	Boonen et al. 2012[154]	PLB	24	8	611
Men with prostate cancer on HAT who have an increased fracture risk					
NCT00089674	Smith et al. 2009[194]	DEN	36	38	734
NCT00089674	Smith et al. 2009[194]	PLB	36	53	734
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	ALN	12	1	56
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	PLB	12	1	56
Israeli et al. 2007	Israeli et al. 2007[172]	ZOL	12	2	112
Israeli et al. 2007	Israeli et al. 2007[172]	PLB	12	3	110
Cheung et al. 2020	Cheung et al. 2020[156]	ZOL	24	2	38
Cheung et al. 2020	Cheung et al. 2020[156]	PLB	24	0	36
Klotz et al. 2013	Klotz et al. 2013[175]	ALN	12	1	84
Klotz et al. 2013	Klotz et al. 2013[175]	PLB	12	3	102

Ryan et al. 2006	Ryan et al. 2006[190]	ZOL	12	2	61
Ryan et al. 2006	Ryan et al. 2006[190]	PLB	12	0	59

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
‖ Palomba et al. 2008[187] was included in the main analysis and excluded during the sensitivity analysis (presented in the HTA Supplement).

Table 55 FN BMD extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
Postmenopausal women with osteoporosis						
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	16	1.57	4.99 †	132
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	16	-1.20	3.81 †	128
MOTION	Miller et al. 2008[179]	ALN	12	2.30	1.81 *	714
MOTION	Miller et al. 2008[179]	IBN	12	2.07	1.57 *	720
TRIO	Paggiosi et al. 2014[185]	IBN	24	3.00	2.81	30
TRIO	Paggiosi et al. 2014[185]	ALN	24	3.97	3.51	33
TRIO	Paggiosi et al. 2014[185]	RIS	24	1.91	3.61	30
ZEST	Greenspan et al. 2015[171]	ZOL	24	0.12	5.24 *	54
ZEST	Greenspan et al. 2015[171]	PLB	24	-3.03	6.01 *	63
Palomba et al.	Palomba et al. 2008[187]	RIS	24	8.20	4.60	40
Palomba et al.	Palomba et al. 2008[187]	PLB	24	-6.40	6.20	41
HORIZON-PFT	Black et al. 2007[152]	ZOL	24	3.38	6.63 *	3234
HORIZON-PFT	Black et al. 2007[152]	PLB	24	-0.50	7.32 *	3254
MORE	Ettinger et al. 1999[164]	RLX	24	1.52	4.83 †	1490
MORE	Ettinger et al. 1999[164]	PLB	24	-0.34	1.08 †	1522
Miller et al. 2016	Miller et al. 2016[180]	DEN	12	1.20	3.66 *	321
Miller et al. 2016	Miller et al. 2016[180]	ZOL	12	-0.10	3.20 *	322
Women with breast cancer receiving AAIT who have an increased fracture risk						
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	12	1.93	4.21 *	123
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	12	-0.56	4.45 *	122
ABCSG-18	Gnant et al. 2015[166]	DEN	12	2.22	4.29 *	490
ABCSG-18	Gnant et al. 2015[166]	PLB	12	-1.08	4.36 *	505
Men with osteoporosis who have an increased fracture risk						
ADAMO	Langdahl et al. 2015[176]	DEN	12	2.2	3.46 *	111
ADAMO	Langdahl et al. 2015[176]	PLB	12	-0.1	3.47 *	117
Boonen et al. 2009	Boonen et al. 2009[153]	RIS	12	1.49	4.33 *	183
Boonen et al. 2009	Boonen et al. 2009[153]	PLB	12	0.63	3.83	83
Boonen et al. 2012	Boonen et al. 2012[154]	ZOL	12	2.1	3.58 *	58

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
Boonen et al. 2012	Boonen et al. 2012[154]	PLB	12	0.6	3.6 *	64
Orwoll et al. 2010	Orwoll et al. 2010[184]	ZOL	12	2.79	8.19 *	144
Orwoll et al. 2010	Orwoll et al. 2010[184]	ALN	12	2.14	8.38 *	136
Men with prostate cancer on HAT who have an increased fracture risk						
NCT00089674	Smith et al. 2009[194]	DEN	12	1.846	4.0846 *	700
NCT00089674	Smith et al. 2009[194]	PLB	12	-0.889	4.09151 *	706
Michaelson et al. 2007	Michaelson et al. 2007[178]	ZOL	12	2	2.814 *	22
Michaelson et al. 2007	Michaelson et al. 2007[178]	PLB	12	-0.1	4.6904 *	22
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	ALN	12	1.6	4.48093 *	56
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	PLB	12	-0.7	2.9872 *	56
Klotz et al. 2013	Klotz et al. 2013[175]	ALN	12	1.65	7.53	45
Klotz et al. 2013	Klotz et al. 2013[175]	PLB	12	-2.06	5.71	53
Ryan et al. 2006	Ryan et al. 2006[190]	ZOL	12	1.3	4.277 *	41
Ryan et al. 2006	Ryan et al. 2006[190]	PLB	12	-2.4	4.4403 *	44
Smith et al. 2003	Smith et al. 2003[193]	ZOL	12	1.2	3.888 *	42
Smith et al. 2003	Smith et al. 2003[193]	PLB	12	-2.1	4.257 *	37
Choo et al. 2013	Choo et al. 2013[157]	RIS	12	1.02	19.553 *	30
Choo et al. 2013	Choo et al. 2013[157]	PLB	12	-5.55	35.556*	35

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **FN**: femoral neck; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate; **% change**: percentage change.
Notes:
* SD calculated from sample size and SE or sample size, mean and 95% CIs as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)*.[128]
† SD imputed in *R* ('metagear' package) where data were not available to calculate SD.[126 127 143 144]

Table 56 LS BMD extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
Postmenopausal women with osteoporosis						
FREEDOM	Cummings et al. 2009[160]	DEN	24	7.76	5.07 *	232
FREEDOM	Cummings et al. 2009[160]	PLB	24	0.09	4.39 *	209
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	24	2.43	4.02 *	132
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	24	-0.65	4.04 *	128
TRIO	Paggiosi et al. 2014[185]	IBN	24	6.68	4.14	31
TRIO	Paggiosi et al. 2014[185]	ALN	24	6.84	3.85	33
TRIO	Paggiosi et al. 2014[185]	RIS	24	3.04	3.65	30
ZEST	Greenspan et al. 2015[171]	ZOL	24	4.50	5.93 *	55

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
ZEST	Greenspan et al. 2015[171]	PLB	24	0.70	4.09 *	67
Palomba	Palomba et al. 2008[187]	RIS	24	10.6	5.4	40
Palomba	Palomba et al. 2008[187]	PLB	24	-6.6	7.4	41
HORIZON-PFT	Black et al. 2007[152]	ZOL	24	5.76	6.22 *	236
HORIZON-PFT	Black et al. 2007[152]	PLB	24	-0.14	5.92 *	226
MORE	Ettinger et al. 1999[164]	RLX	24	2.86	4.96 †	1490
MORE	Ettinger et al. 1999[164]	PLB	24	0.33	0.57 †	1522
NCT00205777	Silverman et al. 2008[192]	BAZ	24	1.97	6.95 *	1886
NCT00205777	Silverman et al. 2008[192]	RLX	24	2.73	6.88 *	1849
NCT00205777	Silverman et al. 2008[192]	PLB	24	0.47	6.94 *	1885
Women with breast cancer receiving AAIT who have an increased fracture risk						
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	12	4.8	3.20 *	123
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	12	-0.7	2.76 *	122
ABCSG-18	Gnant et al. 2015[166]	DEN	12	3.94	4.02 *	480
ABCSG-18	Gnant et al. 2015[166]	PLB	12	-1.81	4.13 *	506
Greenspan et al. 2007a	Greenspan et al. 2007a[169]	RIS	12	1.2	3.28 *	43
Greenspan et al. 2007a	Greenspan et al. 2007a[169]	PLB	12	-0.9	3.32 *	44
Livi et al. 2019	Livi et al. 2019[177]	IBN	12	2.96	4.10 †	72
Livi et al. 2019	Livi et al. 2019[177]	PLB	12	-2.29	4.15 †	72
Men with osteoporosis who have an increased fracture risk						
ADAMO	Langdahl et al. 2015[176]	DEN	12	5.8	3.11 *	111
ADAMO	Langdahl et al. 2015[176]	PLB	12	0.8	3.03 *	117
Boonen et al. 2009	Boonen et al. 2009[153]	RIS	12	4.6	4.87 *	183
Boonen et al. 2009	Boonen et al. 2009[153]	PLB	12	1.4	4.37 *	83
Boonen et al. 2012	Boonen et al. 2012[154]	ZOL	12	5.5	3.64 *	60
Boonen et al. 2012	Boonen et al. 2012[154]	PLB	12	0.8	3.7 *	62
Orwoll et al. 2010	Orwoll et al. 2010[184]	ZOL	12	4.17	3.77 *	142
Orwoll et al. 2010	Orwoll et al. 2010[184]	ALN	12	4.94	3.87 *	136
Men with prostate cancer on HAT who have an increased fracture risk						
NCT00089674	Smith et al. 2009[194]	DEN	12	4.254	4.42 *	714
NCT00089674	Smith et al. 2009[194]	PLB	12	-0.742	4.15 *	715
Michaelson et al. 2007	Michaelson et al. 2007[178]	ZOL	12	4	4.69 *	22
Michaelson et al. 2007	Michaelson et al. 2007[178]	PLB	12	-3.1	4.69 *	22
Choo et al. 2013	Choo et al. 2013[157]	RIS	12	-0.12	7.74 *	36
Choo et al. 2013	Choo et al. 2013[157]	PLB	12	-5.77	29.47 *	40
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	ALN	12	3.7	8.98 *	56
Greenspan et al.	Greenspan et al. 2007b[170]	PLB	12	-1.4	5.99 *	56

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
2007b						
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	ZOL	12	4.9825 ±	6.8544 †	48
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	PLB	12	-1.20733 ±	3.3478 †	45
Klotz et al. 2013	Klotz et al. 2013[175]	ALN	12	1.71	4.06	77
Klotz et al. 2013	Klotz et al. 2013[175]	PLB	12	-1.89	4.31	90
Ryan et al. 2006	Ryan et al. 2006[190]	ZOL	12	4.6	5.23 *	41
Ryan et al. 2006	Ryan et al. 2006[190]	PLB	12	-2.1	5.20 *	43
Smith et al. 2003	Smith et al. 2003[193]	ZOL	12	5.6	4.73 *	35
Smith et al. 2003	Smith et al. 2003[193]	PLB	12	-2.2	5.25 *	34
Israeli et al. 2007	Israeli et al. 2007[172]	ZOL	12	4.7	4.27 *	76
Israeli et al. 2007	Israeli et al. 2007[172]	PLB	12	-2	4.39 *	91
Cheung et al. 2020	Cheung et al. 2020[156]	ZOL	12	1.9747 ‡	4.58 *	38
Cheung et al. 2020	Cheung et al. 2020[156]	PLB	12	-4.3371 ‡	5.17 *	36

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **LS**: lumbar spine; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate; **% change**: percentage change.
Notes:
* SD calculated from sample size and SE or sample size, mean and 95% CIs as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)*.[128]
† SD imputed in *R* ('metagear' package) where data were not available to calculate SD.[126 127 143 144]
± Means combined using formulae detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)* were used.[128]
‡ Means converted from g/cm2 to percentage change.[145]

Table 57 TH BMD extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
Postmenopausal women with osteoporosis						
FREEDOM	Cummings et al. 2009[160]	DEN	24	4.01	3.4 *	232
FREEDOM	Cummings et al. 2009[160]	PLB	24	-0.78	3.23 *	209
Nakamura et al. 2012	Nakamura et al. 2012[182]	DEN	12	3.09	2.75 *	54
Nakamura et al. 2012	Nakamura et al. 2012[182]	PLB	12	-0.61	2.54 *	55
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	24	1.1	5.775 †	132
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	24	-0.97	5.093 †	128
ZEST	Greenspan et al. 2015[171]	ZOL	24	2.6	4.41 *	54
ZEST	Greenspan et al. 2015[171]	PLB	24	-1.5	5.56 *	63
HORIZON-PFT	Black et al. 2007[152]	ZOL	24	3.72	6.05 *	3228
HORIZON-PFT	Black et al. 2007[152]	PLB	24	-0.98	7.23 *	3248
NCT00205777	Silverman et al. 2008[192]	BAZ	24	0.82	5.21 *	1886
NCT00205777	Silverman et al. 2008[192]	RLX	24	1.37	5.16 *	1849
NCT00205777	Silverman et al. 2008[192]	PLB	24	-0.35	5.21 *	1885
Miller et al. 2016	Miller et al. 2016[180]	DEN	12	1.9	17.82 *	321

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
Miller et al. 2016	Miller et al. 2016[180]	ZOL	12	0.6	5.04 *	322
Women with breast cancer receiving AAIT who have an increased fracture risk						
Ellis et al. 2008	Ellis et al. 2008[163]	12	DEN	3.03	2.32 *	123
Ellis et al. 2008	Ellis et al. 2008[163]	12	PLB	-0.72	2.59 *	122
ABCSG-18	Gnant et al. 2015[166]	12	DEN	2.67	3.83 *	488
ABCSG-18	Gnant et al. 2015[166]	12	PLB	-1.2	4.35 *	504
Greenspan et al. 2007a	Greenspan et al. 2007a[169]	12	RIS	1.3	1.039 *	43
Greenspan et al. 2007a	Greenspan et al. 2007a[169]	12	PLB	-0.8	1.019 *	44
Livi et al. 2019	Livi et al. 2019[177]	12	IBN	1.49	1.2617 †	72
Livi et al. 2019	Livi et al. 2019[177]	12	PLB	-3.19	4.2959 †	72
Men with osteoporosis who have an increased fracture risk						
ADAMO	Langdahl et al. 2015[176]	12	DEN	2.3	2.15 *	111
ADAMO	Langdahl et al. 2015[176]	12	PLB	0.3	2.23 *	117
Boonen et al. 2009	Boonen et al. 2009[153]	12	RIS	1.38	2.84 *	183
Boonen et al. 2009	Boonen et al. 2009[153]	12	PLB	0.73	2.64 *	83
Boonen et al. 2012	Boonen et al. 2012[154]	12	ZOL	1.7	2.21 *	58
Boonen et al. 2012	Boonen et al. 2012[154]	12	PLB	0.3	2.24 *	64
Orwoll et al. 2010	Orwoll et al. 2010[184]	12	ZOL	1.77	2.83 *	144
Orwoll et al. 2010	Orwoll et al. 2010[184]	12	ALN	2.03	2.97 *	136
Men with prostate cancer on HAT who have an increased fracture risk						
NCT00089674	Smith et al. 2009[194]	12	DEN	2.055	3.226 *	700
NCT00089674	Smith et al. 2009[194]	12	PLB	-1.108	3.24 *	706
Michaelson et al. 2007	Michaelson et al. 2007[178]	12	ZOL	0.7	2.345 *	22
Michaelson et al. 2007	Michaelson et al. 2007[178]	12	PLB	-1.9	3.283 *	22
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	12	ZOL	1.148	3.1382 †	48
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	12	PLB	-0.931	2.6908 †	45
Klotz et al. 2013	Klotz et al. 2013[175]	12	ALN	0.23	5.17	75
Klotz et al. 2013	Klotz et al. 2013[175]	12	PLB	1.18	16.5	88
Ryan et al. 2006	Ryan et al. 2006[190]	12	ZOL	1.4	2.814 *	40
Ryan et al. 2006	Ryan et al. 2006[190]	12	PLB	-2.4	2.888 *	42
Smith et al. 2003	Smith et al. 2003[193]	12	ZOL	1.1	3.708 *	55
Smith et al. 2003	Smith et al. 2003[193]	12	PLB	-2.8	4.285 *	51
Israeli et al. 2007	Israeli et al. 2007[172]	12	ZOL	1.6	3.226 *	76
Israeli et al. 2007	Israeli et al. 2007[172]	12	PLB	-2.1	3.279 *	93
Cheung et al. 2020	Cheung et al. 2020[156]	12	ZOL	-19.07 ‡	2.358 *	38
Cheung et al. 2020	Cheung et al. 2020[156]	12	PLB	-3.53 ‡	2.586 *	36
Greenspan et al. 2007b	Greenspan et al.	12	ALN	0.7	4.864 *	56

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
	2007b[170]					
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	12	PLB	-0.7	5.238 *	56

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **TH**: total hip; **ZOL**: zoledronate; **% change**: percentage change.
Notes:
* SD calculated from sample size and SE or sample size, mean and 95% CIs as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)*.[128]
† SD imputed in *R* ('metagear' package) where data were not available to calculate SD.[126 127 143 144]
‡ Means converted from g/cm2 to percentage change.[145]

Table 58 Trochanteric BMD extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Mean (% change)	SD	Sample size (n)
Women with breast cancer receiving AAIT who have an increased fracture risk						
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	12	4.3	4.39 *	123
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	12	-0.32	4.59 *	122
Greenspan et al. 2007a	Greenspan et al. 2007a[169]	RIS	12	1.76	1.69 *	43
Greenspan et al. 2007a	Greenspan et al. 2007a[169]	PLB	12	-0.48	1.64 *	44
Men with osteoporosis who have an increased fracture risk						
ADAMO	Langdahl et al. 2015[176]	DEN	12	3.2	3.6 *	111
ADAMO	Langdahl et al. 2015[176]	PLB	12	0.8	3.59 *	117
Boonen et al. 2009	Boonen et al. 2009[153]	RIS	12	1.88	4.06 *	183
Boonen et al. 2009	Boonen et al. 2009[153]	PLB	12	0.81	3.74 *	83

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **DEN**: denosumab; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **SD**: standard deviation; **% change**: percentage change.
Notes:
* SD calculated from sample size and SE or sample size, mean and 95% CIs as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.1)*.[128]
† SD imputed in *R* ('metagear' package) where data were not available to calculate SD.[126 127 143 144]

Table 59 Mortality extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Postmenopausal women with osteoporosis					
FREEDOM	Cummings et al. 2009[160]	DEN	36	70	3886
FREEDOM	Cummings et al. 2009[160]	PLB	36	90	3876
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	24	0	143
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	24	0	140
ZEST	Greenspan et al. 2015[171]	ZOL	24	14	89

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
ZEST	Greenspan et al. 2015[171]	PLB	24	12	92
HORIZON-PFT	Black et al. 2007[152]	ZOL	36	130	3862
HORIZON-PFT	Black et al. 2007[152]	PLB	36	112	3852
MORE	Delmas et al. 2002[162]	RLX	48	23	2557
MORE	Delmas et al. 2002[162]	PLB	48	36	2576
NCT00205777	Christiansen et al. 2010[158]	RLX	36	19	1849
NCT00205777	de Villiers et al. 2009[161] Silverman et al. 2012[191]	BAZ	60	24	1886
NCT00205777	de Villiers et al. 2009[161] Silverman et al. 2012[191]	PLB	60	13	1885
Morii et al. 2003	Morii et al. 2003[181]	RLX	12	0	92
Morii et al. 2003	Morii et al. 2003[181]	PLB	12	0	97
Women with breast cancer receiving AAIT who have an increased fracture risk					
ABCSG-18	Gnant et al. 2019[167]	DEN	36	98	1711
ABCSG-18	Gnant et al. 2019[167]	PLB	36	109	1709
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	24	1	129
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	24	1	120
Men with osteoporosis who have an increased fracture risk					
ADAMO	Langdahl et al. 2015[176]	DEN	12	1	120
ADAMO	Langdahl et al. 2015[176]	PLB	12	1	120
Boonen et al. 2009	Boonen et al. 2009[153]	RIS	24	2	191
Boonen et al. 2009	Boonen et al. 2009[153]	PLB	24	3	93
Boonen et al. 2012	Boonen et al. 2012[154]	ZOL	24	15	588
Boonen et al. 2012	Boonen et al. 2012[154]	PLB	24	18	611
Orwoll et al. 2010	Orwoll et al. 2010[184]	ZOL	24	1	153
Orwoll et al. 2010	Orwoll et al. 2010[184]	ALN	24	1	148
Men with prostate cancer on HAT who have an increased fracture risk					
NCT00089674	Smith et al. 2009[194]	DEN	36	44	731
NCT00089674	Smith et al. 2009[194]	PLB	36	46	725
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	ALN	12	1	56
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	PLB	12	1	56
Israeli et al. 2007	Israeli et al. 2007[172]	ZOL	12	1	112
Israeli et al. 2007	Israeli et al. 2007[172]	PLB	12	0	110
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	ZOL	12	0	48
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	PLB	12	1	45
Smith et al. 2003	Smith et al. 2003[193]	ZOL	12	1	55
Smith et al. 2003	Smith et al. 2003[193]	PLB	12	0	51

Abbreviations:

AAIT: adjuvant aromatase inhibitor therapy; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

Table 60 Treatment-related adverse events extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Postmenopausal women with osteoporosis					
FREEDOM	Cummings et al. 2009[160]	DEN	36	3605	3886
FREEDOM	Cummings et al. 2009[160]	PLB	36	3607	3876
Nakamura et al. 2012	Nakamura et al. 2012[182]	DEN	12	47	54
Nakamura et al. 2012	Nakamura et al. 2012[182]	PLB	12	49	54
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	24	134	143
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	24	126	140
MOTION	Miller et al. 2008[179]	ALN	12	632	859
MOTION	Miller et al. 2008[179]	IBN	12	659	874
ZEST	Greenspan et al. 2015[171]	ZOL	24	87	89
ZEST	Greenspan et al. 2015[171]	PLB	24	88	92
Palomba et al. 2008	Palomba et al. 2008[187]	RIS	36	13	40
Palomba et al. 2008	Palomba et al. 2008[187]	PLB	36	12	41
HORIZON-PFT	Black et al. 2007[152]	ZOL	36	3688	3862
HORIZON-PFT	Black et al. 2007[152]	PLB	36	3616	3852
NCT00205777	Christiansen et al. 2010[158]	BAZ	36	1807	1886
NCT00205777	Christiansen et al. 2010[158]	RLX	36	1777	1849
NCT00205777	Christiansen et al. 2010[158]	PLB	36	1814	1885
Morii et al. 2003	Morii et al. 2003[181]	RLX	12	32	92
Morii et al. 2003	Morii et al. 2003[181]	PLB	12	33	97
Miller et al. 2016	Miller et al. 2016[180]	DEN	12	199	320
Miller et al. 2016	Miller et al. 2016[180]	ALN	12	199	320
TRIO ∞	Paggiosi et al. 2014[185] ∞	IBN	24	52	57
TRIO ∞	Paggiosi et al. 2014[185] ∞	ALN	24	55	57
TRIO ∞	Paggiosi et al. 2014[185] ∞	RIS	24	51	56
Women with breast cancer receiving AAIT who have an increased fracture risk					
ABCSG-18	Gnant et al. 2019[167]	DEN	36	1367	1636
ABCSG-18	Gnant et al. 2019[167]	PLB	36	1339	1646
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	24	117	129
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	24	108	120
Men with osteoporosis who have an increased fracture risk					
ADAMO	Langdahl et al. 2015[176]	DEN	12	87	120
ADAMO	Langdahl et al. 2015[176]	PLB	12	87	120
Boonen et al. 2009	Boonen et al. 2009[153]	RIS	24	134	191
Boonen et al. 2009	Boonen et al. 2009[153]	PLB	24	68	93
Boonen et al. 2012	Boonen et al. 2012[154]	ZOL	24	534	588

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Boonen et al. 2012	Boonen et al. 2012[154]	PLB	24	466	611
Orwoll et al. 2010	Orwoll et al. 2010[184]	ZOL	24	143	153
Orwoll et al. 2010	Orwoll et al. 2010[184]	ALN	24	138	148
Men with prostate cancer on HAT who have an increased fracture risk					
NCT00089674	Smith et al. 2009[194]	DEN	36	638	731
NCT00089674	Smith et al. 2009[194]	PLB	36	627	725
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	ALN	12	43	56
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	PLB	12	46	56
Israeli et al. 2007	Israeli et al. 2007[172]	ZOL	12	39	112
Israeli et al. 2007	Israeli et al. 2007[172]	PLB	12	10	110
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	ZOL	12	20	48
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	PLB	12	23	45
Cheung et al. 2020	Cheung et al. 2020[156]	ZOL	24	27	38
Cheung et al. 2020	Cheung et al. 2020[156]	PLB	24	22	36

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **AEs**: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
∞ Information extracted from the TRIO study summary report.[309]

Table 61 Serious adverse events extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Postmenopausal women with osteoporosis					
FREEDOM	Cummings et al. 2009[160]	DEN	36	1004	3886
FREEDOM	Cummings et al. 2009[160]	PLB	36	972	3876
Nakamura et al. 2012	Nakamura et al. 2012[182]	DEN	12	4	54
Nakamura et al. 2012	Nakamura et al. 2012[182]	PLB	12	4	54
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	24	9	143
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	24	14	140
MOTION	Miller et al. 2008[179]	ALN	12	55	859
MOTION	Miller et al. 2008[179]	IBN	12	39	874
TRIO ∞	Paggiosi et al. 2014[185] ∞	IBN	24	7	57
TRIO ∞	Paggiosi et al. 2014[185] ∞	ALN	24	3	57
TRIO ∞	Paggiosi et al. 2014[185] ∞	RIS	24	11	56
ZEST	Greenspan et al. 2015[171]	ZOL	24	60	89
ZEST	Greenspan et al. 2015[171]	PLB	24	55	92
HORIZON-PFT	Black et al. 2007[152]	ZOL	36	1126	3862
HORIZON-PFT	Black et al. 2007[152]	PLB	36	1158	3852
NCT00205777	Christiansen et al. 2010[158]	BAZ	36	382	1886
NCT00205777	Christiansen et al. 2010[158]	RLX	36	344	1849
NCT00205777	Christiansen et al. 2010[158]	PLB	36	354	1885
Morii et al. 2003	Morii et al. 2003[181]	RLX	12	5	92
Morii et al. 2003	Morii et al. 2003[181]	PLB	12	7	97
Miller et al. 2016	Miller et al. 2016[180]	DEN	12	25	320
Miller et al. 2016	Miller et al. 2016[180]	ALN	12	29	320
Women with breast cancer receiving AAIT who have an increased fracture risk					
ABCSG-18	Gnant et al. 2019[167]	DEN	36	521	1636
ABCSG-18	Gnant et al. 2019[167]	PLB	36	515	1646
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	24	19	129
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	24	11	120
Livi et al. 2019	Livi et al. 2019[177]	IBN	24	5	72
Livi et al. 2019	Livi et al. 2019[177]	PLB	24	2	72
Men with osteoporosis who have an increased fracture risk					
ADAMO	Langdahl et al. 2015[176]	DEN	12	13	120
ADAMO	Langdahl et al. 2015[176]	PLB	12	11	120
Boonen et al. 2009	Boonen et al. 2009[153]	RIS	24	29	191
Boonen et al. 2009	Boonen et al. 2009[153]	PLB	24	15	93
Boonen et al. 2012	Boonen et al. 2012[154]	ZOL	24	149	588
Boonen et al. 2012	Boonen et al. 2012[154]	PLB	24	154	611

Orwoll et al. 2010	Orwoll et al. 2010[184]	ZOL	24	27	153
Orwoll et al. 2010	Orwoll et al. 2010[184]	ALN	24	31	148
Men with prostate cancer on HAT who have an increased fracture risk					
NCT00089674	Smith et al. 2009[194]	DEN	36	253	731
NCT00089674	Smith et al. 2009[194]	PLB	36	222	725
Choo et al. 2013	Choo et al. 2013[157]	RIS	24	2	52
Choo et al. 2013	Choo et al. 2013[157]	PLB	24	0	52
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	ALN	12	11	56
Greenspan et al. 2007b	Greenspan et al. 2007b[170]	PLB	12	15	56
Israeli et al. 2007	Israeli et al. 2007[172]	ZOL	12	24	112
Israeli et al. 2007	Israeli et al. 2007[172]	PLB	12	22	110
Cheung et al. 2020	Cheung et al. 2020[156]	ZOL	24	11	38
Cheung et al. 2020	Cheung et al. 2020[156]	PLB	24	11	36
Klotz et al. 2013	Klotz et al. 2013[175]	ALN	12	7	84
Klotz et al. 2013	Klotz et al. 2013[175]	PLB	12	8	102
Ryan et al. 2006	Ryan et al. 2006[190]	ZOL	12	13	61
Ryan et al. 2006	Ryan et al. 2006[190]	PLB	12	18	59
Smith et al. 2003	Smith et al. 2003[193]	ZOL	12	13	55
Smith et al. 2003	Smith et al. 2003[193]	PLB	12	20	51

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **AEs**: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
∞ Information extracted from the TRIO study summary report.[309]

Table 62 Study withdrawal due to treatment-related AEs extracted data

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Postmenopausal women with osteoporosis					
FREEDOM	Adachi et al. 2017[150]	DEN	36	93	3902
FREEDOM	Adachi et al. 2017[150]	PLB	36	81	3906
Itabashi et al. 2011	Itabashi et al. 2011[173]	BAZ	24	21	143
Itabashi et al. 2011	Itabashi et al. 2011[173]	PLB	24	13	140
HORIZON-PFT	Black et al. 2007[152]	ZOL	36	80	3862
HORIZON-PFT	Black et al. 2007[152]	PLB	36	70	3852
NCT00205777	Christiansen et al. 2010[158]	BAZ	36	278	1886
NCT00205777	Christiansen et al. 2010[158]	RLX	36	273	1849
NCT00205777	Christiansen et al. 2010[158]	PLB	36	253	1885
Morii et al. 2003	Morii et al. 2003[181]	RLX	12	7	92
Morii et al. 2003	Morii et al. 2003[181]	PLB	12	3	97
Miller et al. 2016	Miller et al. 2016[180]	DEN	12	4	320
Miller et al. 2016	Miller et al. 2016[180]	ALN	12	9	320
Women with breast cancer receiving AAIT who have an increased fracture risk					
Ellis et al. 2008	Ellis et al. 2008[163]	DEN	24	2	129
Ellis et al. 2008	Ellis et al. 2008[163]	PLB	24	5	120
Men with osteoporosis who have an increased fracture risk					
ADAMO	Langdahl et al. 2015[176]	DEN	12	4	120
ADAMO	Langdahl et al. 2015[176]	PLB	12	0	120
Boonen et al. 2012	Boonen et al. 2012[154]	ZOL	24	11	588
Boonen et al. 2012	Boonen et al. 2012[154]	PLB	24	11	611
Orwoll et al. 2010	Orwoll et al. 2010[184]	ZOL	24	6	153
Orwoll et al. 2010	Orwoll et al. 2010[184]	ALN	24	12	148
Men with prostate cancer on HAT who have an increased fracture risk					
NCT00089674	Smith et al. 2009[194]	DEN	36	29	731
NCT00089674	Smith et al. 2009[194]	PLB	36	23	725
Klotz et al. 2013	Klotz et al. 2013[175]	ALN	12	0	77
Klotz et al. 2013	Klotz et al. 2013[175]	PLB	12	6	90
Israeli et al. 2007	Israeli et al. 2007[172]	ZOL	12	8	112
Israeli et al. 2007	Israeli et al. 2007[172]	PLB	12	6	110
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	ZOL	12	2	48
Bhoopalam et al. 2009	Bhoopalam et al. 2009[151]	PLB	12	0	45
Cheung et al. 2020	Cheung et al. 2020[156]	ZOL	24	6	38
Cheung et al. 2020	Cheung et al. 2020[156]	PLB	24	5	36
Ryan et al. 2006	Ryan et al. 2006[190]	ZOL	12	1	61

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Ryan et al. 2006	Ryan et al. 2006[190]	PLB	12	1	59
Smith et al. 2003	Smith et al. 2003[193]	ZOL	12	2	55
Smith et al. 2003	Smith et al. 2003[193]	PLB	12	3	51

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **AEs**: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **mo**: month/s; **n**: number; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.

Table 63 Adverse events upon discontinuation: Vertebral and nonvertebral fracture outcomes in postmenopausal women (RCT and single-arm trials)

Trial	Author/Year	Treatment	Follow-up (mo)	Events (n)	Sample size (n)
Postmenopausal women with osteoporosis					
Vertebral fracture: RCT evidence					
FREEDOM	Cummings et al. 2009[160]	DEN	BL	929	3902
FREEDOM	Cummings et al. 2009[160]	PL	BL	915	3906
FREEDOM	Cummings et al. 2018[159]	DEN	4.2 §	56	1001
FREEDOM	Cummings et al. 2018[159]	PL	4.2 §	31	470
FREEDOM	Brown et al. 2013[155]	DEN	6 §	15	327
FREEDOM	Brown et al. 2013[155]	PL	6 §	35	470
Vertebral fracture: Single-arm study evidence					
FREEDOM	Popp et al. 2018[189]	DEN	BL	2	9
FREEDOM	Popp et al. 2018[189]	DEN	12 §	4	9
Nonvertebral fracture: RCT evidence					
FREEDOM	Cummings et al. 2009[160]	DEN	BL	264	3902
FREEDOM	Cummings et al. 2009[160]	PL	BL	336	3906
FREEDOM	Cummings et al. 2018[159]	DEN	4.2 §	23	1001
FREEDOM	Cummings et al. 2018[159]	PL	4.2 §	14	470
FREEDOM	Brown et al. 2013[155]	DEN	6 §	11	327
FREEDOM	Brown et al. 2013[155]	PL	6 §	16	470

Abbreviations:
AEs: adverse events; **DEN**: denosumab; **mo**: month/s; **n**: number; **PLB**: placebo; **RCT**: randomised controlled trial.
Notes:
§ Months since loss of denosumab effect #
# Loss of effect defined as 6 months post-last dose of denosumab.[155 159 189] An additional 1-month study visit window was also reported in Brown et al. 2013 and Cummings et al. 2018.[155 159]

Table 64 Adverse events upon discontinuation: BMD outcomes in postmenopausal women (single-arm trials)

Trial	Author/Year	Treatment	Follow-up (mo)	Metric	Mean	SD	Sample size (n)
Postmenopausal women with osteoporosis							
Femoral neck							
FREEDOM	Cummings et al. 2009[160]	DEN	BL	T-score	-2.15	0.72	3902
FREEDOM	Popp et al. 2018[189]	DEN	12 §	% change	-11	†	9
FREEDOM	Popp et al. 2018[189]	DEN	12 §	T-score ¶	-1.887 ¶	0.303 ¶	9
Lumbar spine							
FREEDOM	Cummings et al. 2009[160]	DEN	BL	T-score	-2.82	0.7	3902
FREEDOM	Popp et al. 2018[189]	DEN	12 §	% change	-9.1	†	9
FREEDOM	Popp et al. 2018[189]	DEN	12 §	T-score ¶	-3.273 ¶	0.480 ¶	9
Total hip							
FREEDOM	Cummings et al. 2009[160]	DEN	BL	T-score	-1.89	0.81	3902
FREEDOM	Popp et al. 2018[189]	DEN	12 §	% change	-12.7	†	9
FREEDOM	Popp et al. 2018[189]	DEN	12 §	T-score ¶	-2.254 ¶	0.397 ¶	9

Abbreviations:
AEs: adverse events; **BL**: baseline; **BMD**: bone mineral density**; DEN**: denosumab; **mo**: month/s; **n**: number; **SD**: standard deviation; **% change**: percentage change.
Notes:
¶ Percentage change data reported in Popp et al. 2018[189] converted to T-score.
† SD imputed in *R* ('metagear' package) where data were not available to calculate SD.[126 127 143 144]
§ Months since loss of denosumab effect [#]
[#] Loss of effect defined as 6 months post-last dose of denosumab.[189]

Table 65 Adverse events upon discontinuation: BTM outcomes in postmenopausal women (single-arm trials)

Trial	Author/Year	Treatment	Follow-up (mo)	Metric	Mean	SD	Sample size (n)
Postmenopausal women with osteoporosis							
B-ALP							
FREEDOM	Popp et al. 2008[189]	DEN	BL	IU/L	85.1	11.2	9
FREEDOM	Popp et al. 2008[189]	DEN	12 §	IU/L	59.3	2.8	9
CTX							
Fassio et al. 2019	Fassio et al. 2019[165]	DEN	BL	ng/ml	0.76	0.43	15
Fassio et al. 2019	Fassio et al. 2019[165]	DEN	3 §	ng/ml	1.066	0.5	15
Fassio et al. 2019	Fassio et al. 2019[165]	DEN	12 §	ng/ml	0.891	0.123	15

Abbreviations:
AEs: adverse events; **BL**: baseline; **BTM**: bone turnover marker**; B-ALP**: bone-specific alkaline phosphatase**; CTX**: C-terminal telopeptide of type 1 collagen; **DEN**: denosumab; **mo**: month/s; **n**: number; **SD**: standard deviation.
Notes:
§ Months since loss of denosumab effect #
# Loss of effect defined as 6 months post-last dose of denosumab.[165 189]

Table 66 Adverse events upon discontinuation: BMD outcomes in women with breast cancer receiving AAIT who have an increased fracture risk (single-arm trials)

Trial	Author/Year	Treatment	Follow-up (mo)	Metric	Mean	SD	Sample size (n)
Women with breast cancer receiving AAIT who have an increased fracture risk							
Femoral neck							
Gonzalez-Rodriguez 2020	Gonzalez-Rodriguez 2020[168]	DEN	BL	T-score	-2.1	0.5	15
Gonzalez-Rodriguez 2020	Gonzalez-Rodriguez 2020[168]	DEN	4.2 §	T-score	-1.87	0.57	15
Lumbar spine							
Gonzalez-Rodriguez 2020	Gonzalez-Rodriguez 2020[168]	DEN	BL	T-score	-2.08	0.61	15
Gonzalez-Rodriguez 2020	Gonzalez-Rodriguez 2020[168]	DEN	4.2 §	T-score	-1.72	0.52	15
Total hip							
Gonzalez-Rodriguez 2020	Gonzalez-Rodriguez 2020[168]	DEN	BL	T-score	-1.65	0.4	15
Gonzalez-Rodriguez 2020	Gonzalez-Rodriguez 2020[168]	DEN	4.2 §	T-score	-1.47	0.41	15

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **AEs**: adverse events; **BL**: baseline; **BMD**: bone mineral density**; DEN**: denosumab; **mo**: month/s; **n**: number; **SD**: standard deviation.
Notes:
§ Months since loss of denosumab effect #
# Loss of effect defined as 6 months post-last dose of denosumab.[168]

17 Appendix C: Pairwise summary tables

Appendix C includes pairwise summary tables (i.e. league tables) that report the results of the NMA for each outcome, in each population. Explanatory notes are included under each table, to assist in the interpretation of the results.

17.1 Findings efficacy and effectiveness

17.1.1 Vertebral Fractures

Postmenopausal women with osteoporosis

Table 67 League table of summary estimates for vertebral fractures in postmenopausal women with osteoporosis

DEN	2.55 (0.26,12.00)	3.09 (0.17 ,14.51)	2.70 (0.18, 10.56)	5.06 (0.46, 22.33)	4.74 (0.90, 17.88)
1.07 (0.08, 3.79)	ZOL *bisphosphonate*	1.66 (0.12, 6.65)	1.67 (0.12, 5.10)	2.91 (0.33, 10.11)	2.90 (0.69, 7.33)
1.34 (0.07, 5.75)	1.85 (0.15, 8.36)	RIS *bisphosphonate*	2.01 (0.10, 7.67)	3.67 (0.26, 15.70)	3.52 (0.50, 12.80)
1.17 (0.09, 5.58)	1.64 (0.20, 8.38)	2.00 (0.13, 10.12)	RLX *SERM*	3.20 (0.34, 15.40)	2.97 (0.69, 12.18)
0.55 (0.04, 2.18)	0.75 (0.10, 3.08)	0.87 (0.06, 3.83)	0.85 (0.06, 2.91)	BAZ *SERM*	1.48 (0.36, 4.31)
0.37 (0.06, 1.11)	0.48 (0.14, 1.45)	0.55 (0.08, 2.02)	0.58 (0.08, 1.46)	0.99 (0.23, 2.80)	PLB

RR (95% CrI)
Abbreviations:
BAZ: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate.
Notes:
Credible interval: An interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
**statistical significance
- Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- RR less than 1 favours the column-defining treatment.
- RR greater than 1 favours the row-defining treatment.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Men with osteoporosis who have an increased fracture risk

Table 68 League table of summary estimates for vertebral fractures in men with osteoporosis who have an increased fracture risk

ALN *bisphosphonate*	.	.	1.56 (0.45, 5.42)
1.62 (0.03, 98.21)	DEN *bisphosphonate*	0.33 (0.01, 8.10)	.
0.54 (0.04, 7.14)	0.33 (0.01, 8.10)	PLB	0.35 (0.04, 3.32)
1.56 (0.45, 5.42)	0.96 (0.02, 48.03)	0.35 (0.04, 3.32)	ZOL *bisphosphonate*

RR (95% CI)
Abbreviations:
ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
**statistical significance
- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:
RR calculated from indirect evidence.
RR calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 69 League table of summary estimates for vertebral fractures in men with prostate cancer on HAT

DEN	0.15 (0.03, 0.67) **	.
0.15 (0.03, 0.67) **	PLB	1.55 (0.39, 6.14)
0.10 (0.01, 0.75) **	1.55 (0.39, 6.14)	ZOL *bisphosphonate*

RR (95% CI)
Abbreviations:
CI: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.
Notes:
**statistical significance
- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:
RR calculated from indirect evidence.
RR calculated from direct evidence.

17.1.2 Nonvertebral Fractures

Postmenopausal women with osteoporosis

Table 70 League table of summary estimates for nonvertebral fractures in postmenopausal women with osteoporosis

RIS *bisphosphonate*	244.38 (0.45, 280.72)	287.93 (0.63, 344.17)	1303.80 (0.81, 416.22)	418.11 (1.03, 357.61)	757.85 (0.70, 501.24)
0.41 (0.00, 2.20)	RLX *SERM*	1.58 (0.35, 5.65)	2.30 (0.34, 10.44)	1.84 (0.51, 6.24)	3.01 (0.25, 14.03)
0.31 (0.00, 1.59)	1.03 (0.18, 2.87)	BAZ *SERM*	1.73 (0.26, 6.99)	1.44 (0.39, 4.13)	2.21 (0.19, 9.53)
0.25 (0.00, 1.23)	0.98 (0.10, 2.96)	1.18 (0.14, 3.89)	ZOL *bisphosphonate*	1.21 (0.30, 3.01)	1.78 (0.14, 6.95)
0.20 (0.00, 0.97) **	0.81 (0.16, 1.98)	0.96 (0.24, 2.56)	1.14 (0.33, 3.36)	PLB	1.43 (0.22, 5.04)
0.30 (0.00, 1.44)	1.05 (0.07, 3.94)	1.30 (0.10, 5.30)	1.60 (0.14, 7.06)	1.29 (0.20, 4.56)	DEN

RR (95% CrI)

Abbreviations:

BAZ: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate.

Notes:

Credible interval: An interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]

**statistical significance

- Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- RR less than 1 favours the column-defining treatment.
- RR greater than 1 favours the row-defining treatment.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Men with osteoporosis who have an increased fracture risk

Table 71 League table of summary estimates for nonvertebral fractures in men with osteoporosis who have an increased fracture risk

DEN	0.50 (0.05, 5.44)	.
0.50 (0.05, 5.44)	PLB	0.65 (0.21, 1.97)
0.77 (0.06, 10.72)	0.65 (0.21, 1.97)	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.

**statistical significance

Notes:

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 72 League table of summary estimates for nonvertebral fractures in men with prostate cancer on HAT

ALN *bisphosphonate*	.	0.58 (0.10, 3.31)	.
0.81 (0.14, 4.83)	DEN	0.72 (0.48, 1.07)	.
0.58 (0.10, 3.31)	0.72 (0.48, 1.07)	PLB	1.48 (0.38, 5.76)
0.39 (0.04, 3.58)	0.49 (0.12, 2.01)	1.48 (0.38, 5.76)	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.

**statistical significance

Notes:

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

17.1.3 Bone mineral density (BMD)

Femoral neck (FN)

Postmenopausal women with osteoporosis

Table 73 League table of summary estimates for bone mineral density (BMD) measured at femoral neck (FN) in postmenopausal women with osteoporosis

ALN *bisphosphonate*	-0.45 (-4.47, 3.36)	-1.80 (-7.06, 3.40)	-11.47 (-21.96, -1.39) **	-12.76 (-21.60, -4.23)**	-13.67 (-23.20, -4.15) **	-14.58 (-24.04, -5.07) **	-16.44 (-24.27, -8.73) **
0.45 (-3.36, 4.47)	IBN *bisphosphonate*	-1.35 (-6.54, 3.93)	-11.02 (-21.37, -0.82) **	-12.32 (-21.05, -3.66) **	-13.22 (-22.70, -3.59) **	-14.13 (-23.48, -4.52) **	-15.99 (-23.64, -8.12) **
1.80 (-3.40, 7.06)	1.35 (-3.93, 6.54)	RIS *bisphosphonate*	-9.67 (-18.72, -0.88) **	-10.97 (-18.08, -4.06) **	-11.88 (-19.74, -3.90) **	-12.78 (-20.67, -4.85) **	-14.64 (-20.38, -8.88) **
11.47 (1.39, 21.96) **	11.02 (0.82, 21.37) **	9.67 (0.88, 18.72) **	DEN	-1.29 (-6.81, 4.24)	-2.20 (-10.77, 6.77)	-3.11 (-11.65, 5.80)	-4.97 (-11.63, 1.97)
12.76 (4.23, 21.60) **	12.32 (3.66, 21.05) **	10.97 (4.06, 18.08) **	1.29 (-4.24, 6.81)	ZOL *bisphosphonate*	-0.91 (-7.50, 6.10)	-1.81 (-8.31, 5.06)	-3.68 (-7.46, 0.40)
13.67 (4.15, 23.20) **	13.22 (3.59, 22.70) **	11.88 (3.90, 19.74) **	2.20 (-6.77, 10.77)	0.91 (-6.10, 7.50)	BAZ *SERM*	-0.90 (-8.60, 6.88)	-2.77 (-8.30, 2.78)
14.58 (5.07, 24.04) **	14.13 (4.52, 23.48) **	12.78 (4.85, 20.67) **	3.11 (-5.80, 11.65)	1.81 (-5.06, 8.31)	0.90 (-6.88, 8.60)	RLX *SERM*	-1.87 (-7.33, 3.58)
16.44 (8.73, 24.27) **	15.99 (8.12, 23.64) **	14.64 (8.88, 20.38) **	4.97 (-1.97, 11.63)	3.68 (-0.40, 7.46)	2.77 (-2.78, 8.30)	1.87 (-3.58, 7.33)	PLB

MD (95% CrI)

Abbreviations:

ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **CrI**: credible interval; **DEN**: denosumab; **FN**: femoral neck; **IBN**: ibandronate; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate.

Notes:

Credible interval: An interval within which MD values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
**statistical significance
- Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- MD less than 0 favours the column-defining treatment.
- MD greater than 0 favours the row-defining treatment.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Men with osteoporosis who have an increased fracture risk

Table 74 League table of summary estimates for bone mineral density (BMD) measured at femoral neck (FN) in men with osteoporosis who have an increased fracture risk

ALN *bisphosphonate*	.	.	.	-0.65 (-2.59, 1.29)
-1.45 (-3.94, 1.04)	DEN	2.30 (1.40, 3.20) **	.	.
0.85 (-1.47, 3.17)	2.30 (1.40, 3.20) **	PLB	0.86 (-0.18, 1.89)	1.50 (0.22, 2.78) **
-0.01 (-2.55, 2.53)	1.44 (0.07, 2.81) **	0.86 (-0.18, 1.89)	RIS *bisphosphonate*	.
-0.65 (-2.59, 1.29)	0.80 (-0.76, 2.36)	1.50 (0.22, 2.78) **	-0.64 (-2.28, 1.00)	ZOL *bisphosphonate*

MD (95% CI)
Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **FN**: femoral neck; **MD**: Mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.
Notes:
**statistical significance
- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:
MD calculated from indirect evidence.
MD calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 75 League table of summary estimates for bone mineral density (BMD) measured at femoral neck (FN) in men with prostate cancer on HAT

ALN *bisphosphonate*	.	2.61 (1.36, 3.85) **	.	.
-0.13 (-1.45, 1.19)	DEN	2.74 (2.31, 3.16) **	.	.
2.61 (1.36, 3.85) **	2.73 (2.31, 3.16) **	PLB	6.57 (- 7.13, 20.27)	3.16 (2.03, 4.28) **
-3.96 (-17.72, 9.79)	-3.84 (-17.54, 9.87)	6.57 (- 7.13, 20.27)	RIS *bisphosphonate*	.
-0.55 (-2.23, 1.13)	-0.42 (-1.63, 0.78)	3.16 (2.03, 4.28) **	3.41 (-10.33, 17.16)	ZOL *bisphosphonate*

MD (95% CI)
Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **FN**: femoral neck; **HAT**: hormone ablation therapy; **MD**: Mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.
Notes:
**statistical significance

- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

MD calculated from indirect evidence.
MD calculated from direct evidence.

Lumbar spine (LS)

Postmenopausal women with osteoporosis

Table 76 League table of summary estimates for bone mineral density (BMD) measured at lumbar spine (LS) in postmenopausal women with osteoporosis

ALN *bisphosphonate*	-0.15 (-4.94, 4.65)	-3.80 (-8.55, 0.96)	-13.32 (-21.64, -4.90) **	-15.96 (-23.79, -8.33) **	-18.41 (-26.00, -10.75) **	-18.78 (-26.30, -10.99) **	-20.98 (-27.95, -13.93) **
0.15 (-4.65, 4.94)	IBN *bisphosphonate*	-3.64 (-8.44, 1.16)	-13.16 (-21.50, -4.75) **	-15.81 (-23.71, -8.09) **	-18.25 (-25.89, -10.52) **	-18.63 (-26.17, -10.83) **	-20.83 (-27.86, -13.73) **
3.80 (-0.96, 8.55)	3.64 (-1.16, 8.44)	RIS *bisphosphonate*	-9.52 (-16.37, -2.66) **	-12.17 (-18.39, -6.13) **	-14.61 (-20.57, -8.58) **	-14.99 (-20.89, -8.89) **	-17.19 (-22.33, -12.00) **
13.32 (4.90, 21.64) **	13.16 (4.75, 21.50) **	9.52 (2.66, 16.37) **	DEN	-2.65 (-8.38, 2.87)	-5.09 (-10.55, 0.44)	-5.47 (-10.88, 0.16)	-7.67 (-12.22, -3.11) **
15.96 (8.33, 23.79) **	15.81 (8.09, 23.71) **	12.17 (6.13, 18.39) **	2.65 (-2.87, 8.38)	ZOL *bisphosphonate*	-2.44 (-6.84, 2.24)	-2.82 (-7.14, 1.95)	-5.02 (-8.22, -1.59) **
18.41 (10.75, 26.00) **	18.25 (10.52, 25.89) **	14.61 (8.58, 20.57) **	5.09 (-0.44, 10.55)	2.44 (-2.24, 6.84)	RLX *SERM*	-0.38 (-4.02, 3.36)	-2.58 (-5.69, 0.48)
18.78 (10.99, 26.30) **	18.63 (10.83, 26.17) **	14.99 (8.89, 20.89) **	5.47 (-0.16, 10.88)	2.82 (-1.95, 7.14)	0.38 (-3.36, 4.02)	BAZ *SERM*	-2.20 (-5.39, 0.80)
20.98 (13.93, 27.95) **	20.83 (13.73, 27.86) **	17.19 (12.00, 22.33) **	7.67 (3.11, 12.22) **	5.02 (1.59, 8.22) **	2.58 (-0.48, 5.69)	2.20 (-0.80, 5.39)	PLB

MD (95% CrI)

Abbreviations:

ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **CrI**: credible interval; **DEN**: denosumab; **BN**: ibandronate; **LS**: lumbar spine; **MD**: mean difference; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate.

Notes:

Credible interval: An interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]

**statistical significance

- Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- MD less than 0 favours the column-defining treatment.
- MD greater than 0 favours the row-defining treatment.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Women with breast cancer receiving AAIT who have an increased fracture risk

Table 77 League table of summary estimates for bone mineral density (BMD) measured at lumbar spine (LS) in women with breast cancer receiving AAIT who have an increased fracture risk

DEN	.	5.67 (5.25, 6.09) **	.
0.42 (-0.76, 1.60)	IBN *bisphosphonate*	5.25 (4.15, 6.35) **	.
5.67 (5.25, 6.09) **	5.25 (4.15, 6.35) **	PLB	2.10 (0.71, 3.49) **
3.57 (2.12, 5.02) **	3.15 (1.38, 4.92) **	2.10 (0.71, 3.49) **	RIS *Bisphosphonate*

MD (95% CI)

Abbreviations:

AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **LS**: lumbar spine; **IBN**: ibandronate; **MD**: Mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

MD calculated from indirect evidence.
MD calculated from direct evidence.

Men with osteoporosis who have an increased fracture risk

Table 78 League table of summary estimates for bone mineral density (BMD) measured at lumbar spine (LS) in men with osteoporosis who have an increased fracture risk

ALN *bisphosphonate*	.	.	.	0.77 (-0.13, 1.67)
0.47 (-1.30, 2.24)	DEN	5.00 (4.20, 5.80) **	.	.
5.47 (3.89, 7.05) **	5.00 (4.20, 5.80) **	PLB	3.20 (2.02, 4.38) **	4.70 (3.40, 6.00) **
2.27 (0.30, 4.24) **	1.80 (0.38, 3.22) **	3.20 (2.02, 4.38) **	RIS *bisphosphonate*	.
0.77 (-0.13, 1.67)	0.30 (-1.23, 1.83)	4.70 (3.40, 6.00) **	-1.50 (-3.25, 0.25)	ZOL *bisphosphonate*

MD (95% CI)

Abbreviations:

ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **LS**: lumbar spine; **MD**: Mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

MD calculated from indirect evidence.
MD calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 79 League table of summary estimates for bone mineral density (BMD) measured at lumbar spine (LS) in men with prostate cancer on HAT

ALN *bisphosphonate*	.	3.85 (2.69, 5.01) **	.	.
-1.14 (-2.39, 0.10)	DEN	5.00 (4.55, 5.44) **	.	.
3.85 (2.69, 5.01) **	5.00 (4.55, 5.44) **	PLB	-5.65 (-15.13, 3.83)	-6.74 (-7.56, -5.93) **
-1.80 (-11.35, 7.75)	-0.65 (-10.14, 8.83)	-5.65 (-15.13, 3.83)	RIS *bisphosphonate*	.
-2.89 (-4.31, -1.47) **	-1.75 (-2.68, -0.82) **	-6.74 (-7.56, -5.93) **	-1.09 (-10.60, 8.42)	ZOL *bisphosphonate*

MD (95% CI)

Abbreviations:

ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **LS**: lumbar spine; **MD**: Mean difference; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

MD calculated from indirect evidence.
MD calculated from direct evidence.

Total hip (TH)

Postmenopausal women with osteoporosis

Table 80 League table of summary estimates for bone mineral density (BMD) measured at total hip (TH) in postmenopausal women with osteoporosis

DEN	-0.23 (-2.26, 1.42)	-2.67 (-5.23, -0.05) **	-3.07 (-5.21, -0.75) **	-4.55 (-6.05, -3.08) **
0.23 (-1.42, 2.26)	ZOL *bisphosphonate*	-2.44 (-4.82, 0.42)	-2.83 (-4.82, -0.29) **	-4.31 (-5.67, -2.60) **
2.67 (0.05, 5.23) **	2.44 (-0.42, 4.82)	RLX *SERM*	-0.39 (-2.47, 1.78)	-1.87 (-4.05, 0.20)
3.07 (0.75, 5.21) **	2.83 (0.29, 4.82) **	0.39 (-1.78, 2.47)	BAZ *SERM*	-1.48 (-3.25, 0.08)
4.55 (3.08, 6.05) **	4.31 (2.60, 5.67) **	1.87 (-0.20, 4.05)	1.48 (-0.08, 3.25)	PLB

MD (95% CrI)

Abbreviations:

BAZ: bazedoxifene; **BMD**: bone mineral density; **CrI**: credible interval; **DEN**: denosumab; **MD**: mean difference; **PLB**: placebo; **RLX**: raloxifene; **SERM**: selective oestrogen receptor modulator; **TH**: total hip; **ZOL**: zoledronate.

Notes:

Credible interval: An interval within which MD values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]

**statistical significance

- Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- MD less than 0 favours the column-defining treatment.
- MD greater than 0 favours the row-defining treatment.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Women with breast cancer receiving AAIT who have an increased fracture risk

Table 81 League table of summary estimates for bone mineral density (BMD) measured at total hip (TH) in women with breast cancer receiving AAIT who have an increased fracture risk

DEN	.	3.82 (3.43, 4.21) **	.
-0.86 (-1.96, 0.25)	IBN *bisphosphonate*	4.68 (3.65, 5.71) **	.
3.82 (3.43, 4.21) **	4.68 (3.65, 5.71) **	PLB	2.10 (1.67,2.53) **
1.72 (1.14, 2.31) **	2.58 (1.46, 3.70) **	2.10 (1.67,2.53) **	RIS *bisphosphonate*

MD (95% CI)

Abbreviations:

AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **MD**: Mean difference; **PLB**: placebo; **RIS**: risedronate; **TH**: total hip.

Notes:

**statistical significance

- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.\
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

MD calculated from indirect evidence.
MD calculated from direct evidence.

Men with osteoporosis who have an increased fracture risk

Table 82 League table of summary estimates for bone mineral density (BMD) measured at total hip (TH) in men with osteoporosis who have an increased fracture risk

ALN *bisphosphonate*	. .	.	.	0.26 (-0.42, 0.94)
-0.34 (-1.53, 0.85)	DEN	2.00 (1.43, 2.57) **	.	.
-0.47 (-2.11, 1.17)	-0.13 (-1.51, 1.25)	2.13 (0.87, 3.39) **	.	.
1.66 (0.62, 2.70) **	2.00 (1.43, 2.57) **	PLB	0.65 (-0.05,1.35)	1.40 (0.61, 2.19) **
1.01 (-0.25, 2.27)	1.35 (0.45, 2.25) **	0.65 (-0.05, 1.35)	RIS *bisphosphonate*	.
0.26 (-0.42, 0.94)	0.60 (-0.37, 1.57)	1.40 (0.61, 2.19) **	-0.75 (-1.81, 0.31)	ZOL *bisphosphonate*

MD (95% CI)

Abbreviations:

ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **MD**: Mean difference; **PLB**: placebo; **RIS**: risedronate; **TH**: total hip; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

MD calculated from indirect evidence.
MD calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 83 League table of summary estimates for bone mineral density (BMD) measured at total hip (TH) in men with prostate cancer on HAT

ALN *bisphosphonate*	.	0.25 (-11.25, 11.74)	.
-2.92 (-22.62, 16.79)	DEN	3.16 (-12.84, 19.17)	.
0.25 (-11.25, 11.74)	3.16 (-12.84, 19.17)	PLB	-0.08 (-6.64, 6.47)
0.16 (-13.07, 13.39)	3.08 (-14.21, 20.37)	-0.08 (-6.64, 6.47)	ZOL *bisphosphonate*

MD (95% CI)
Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **MD**: Mean difference; **PLB**: placebo; **TH**: total hip; **ZOL**: zoledronate.
Notes:
**statistical significance
- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:
MD calculated from indirect evidence.
MD calculated from direct evidence.

Trochanter

Women with breast cancer receiving AAIT who have an increased fracture risk

Table 84 League table of summary estimates for bone mineral density (BMD) measured at trochanter in women with breast cancer receiving AAIT who have an increased fracture risk

DEN	4.62 (3.50, 5.74) **	.
4.62 (3.50, 5.74) **	PLB	2.24 (1.54, 2.94) **
2.38 (1.06, 3.70) **	2.24 (1.54 ,2.94) **	RIS *bisphosphonate*

MD (95% CI)
Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **MD**: Mean difference; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
**statistical significance
- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:
MD calculated from indirect evidence.
MD calculated from direct evidence.

Men with osteoporosis who have an increased fracture risk

Table 85 League table of summary estimates for bone mineral density (BMD) measured at trochanter in men with osteoporosis who have an increased fracture risk

DEN	2.40 (1.45, 3.35) **	.
2.40 (1.45, 3.35) **	PLB	1.07 (0.27, 1.87) **
1.33 (0.09, 2.57) **	1.07 (0.27, 1.87) **	RIS *bisphosphonate*

MD (95% CI)
Abbreviations:
BMD: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **MD**: Mean difference; **PLB**: placebo; **RIS**: risedronate.
Notes:
**statistical significance
- Each MD (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:
MD calculated from indirect evidence.
MD calculated from direct evidence.

17.2 Findings safety

17.2.1 Mortality

Postmenopausal women with osteoporosis

Table 86 League table of summary estimates for mortality in postmenopausal women with osteoporosis

DEN	1.19 (0.40, 2.81)	1.39 (0.61, 2.78)	1.66 (0.57, 3.87)	1.83 (0.50, 4.67)
1.06 (0.36, 2.51)	RLX *SERM*	1.29 (0.66, 2.29)	1.53 (0.60, 3.29)	1.62 (0.63, 3.34)
0.82 (0.36, 1.64)	0.85 (0.44, 1.51)	PLB	1.19 (0.64, 2.04)	1.31 (0.51, 2.69)
0.75 (0.26, 1.75)	0.78 (0.30, 1.66)	0.91 (0.49, 1.57)	ZOL *bisphosphonate*	1.20 (0.37, 2.81)
0.74 (0.21, 2.01)	0.74 (0.30, 1.59)	0.90 (0.37, 1.94)	1.08 (0.36, 2.67)	BAZ *SERM*

RR (95% CrI)
Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate.
Notes:
Credible interval: An interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
**statistical significance
- Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- RR less than 1 favours the column-defining treatment.
- RR greater than 1 favours the row-defining treatment.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Men with osteoporosis who have an increased fracture risk

Table 87 League table of summary estimates for mortality in men with osteoporosis who have an increased fracture risk

ALN *bisphosphonate*	.	.	.	1.03 (0.07, 16.38)
0.90 (0.02, 47.11)	DEN	1.00 (0.06, 15.80)	.	.
0.90 (0.05, 15.38)	1.00 (0.06, 15.80)	PLB	0.32 (0.06, 1.91)	0.87 (0.44, 1.70)
2.76 (0.10, 78.67)	3.08 (0.12, 81.87)	0.32 (0.06, 1.91)	RIS *bisphosphonate*	.
1.03 (0.07, 16.38)	1.15 (0.07, 19.80)	0.87 (0.44, 1.70)	0.37 (0.06, 2.50)	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RR**: risk ratio; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 88 League table of summary estimates for mortality in men with prostate cancer on HAT who have an increased fracture risk

ALN *bisphosphonate*	.	1.00 (0.06, 15.59)	.
1.05 (0.07, 16.92)	DEN	0.95 (0.64, 1.42)	.
1.00 (0.06, 15.59)	0.95 (0.64, 1.42)	PLB	1.37 (0.22, 8.56)
0.73 (0.03, 19.95)	0.69 (0.11, 4.55)	1.37 (0.22, 8.56)	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

17.2.2 Treatment-related adverse events (AEs)

Postmenopausal women with osteoporosis

Table 89 League table of summary estimates for treatment-related adverse events (AEs) in postmenopausal women with osteoporosis

RIS *bisphosphonate*	1.03 (0.86, 1.22)	1.03 (0.86, 1.24)	1.04 (0.86, 1.26)	1.04 (0.86, 1.26)	1.03 (0.92, 1.17)	1.03 (0.92, 1.17)	1.05 (0.87, 1.27)
0.98 (0.82, 1.16)	DEN	1.01 (0.95, 1.08)	1.01 (0.93, 1.12)	1.01 (0.94, 1.11)	1.01 (0.88, 1.15)	1.01 (0.87, 1.17)	1.03 (0.95, 1.12)
0.97 (0.80, 1.16)	0.99 (0.93, 1.05)	PLB	1.00 (0.94, 1.08)	1.01 (0.96, 1.07)	1.00 (0.87, 1.16)	1.00 (0.85, 1.17)	1.02 (0.96, 1.08)
0.97 (0.79, 1.16)	0.99 (0.90, 1.08)	1.00 (0.93, 1.06)	RLX *SERM*	1.00 (0.94, 1.08)	1.00 (0.85, 1.16)	1.00 (0.84, 1.18)	1.02 (0.93, 1.10)
0.97 (0.79, 1.16)	0.99 (0.90, 1.06)	1.00 (0.93, 1.05)	1.00 (0.93, 1.07)	BAZ *SERM*	1.00 (0.85, 1.16)	1.00 (0.83, 1.17)	1.01 (0.93, 1.09)
0.97 (0.85, 1.09)	0.99 (0.87, 1.13)	1.00 (0.87, 1.16)	1.01 (0.86, 1.18)	1.01 (0.86, 1.18)	ALN *bisphosphonate*	1.00 (0.93, 1.07)	1.02 (0.87, 1.19)
0.97 (0.85, 1.09)	0.99 (0.86, 1.15)	1.00 (0.85, 1.18)	1.01 (0.85, 1.20)	1.01 (0.85, 1.20)	1.00 (0.93, 1.08)	IBN *bisphosphonate*	1.02 (0.86, 1.21)
0.96 (0.78, 1.15)	0.98 (0.89, 1.06)	0.98 (0.93, 1.04)	0.99 (0.91, 1.08)	0.99 (0.92, 1.08)	0.99 (0.84, 1.15)	0.99 (0.83, 1.16)	ZOL *bisphosphonate*

RR (95% CrI)

Abbreviations:

AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate.

Notes:

Credible interval: An interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]

**statistical significance

- Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- RR less than 1 favours the column-defining treatment.
- RR greater than 1 favours the row-defining treatment.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Men with osteoporosis who have an increased fracture risk

Table 90 League table of summary estimates for treatment-related adverse events (AEs) in men with osteoporosis who have an increased fracture risk

ALN *bisphosphonate*	.	.	.	1.00 (0.94, 1.06)
1.19 (1.00, 1.41)	DEN	1.00 (0.86, 1.17)	.	.
1.19 (1.10, 1.29) **	1.00 (0.86, 1.17)	PLB	1.04 (0.89, 1.22)	0.84 (0.80, 0.88) **
1.24 (1.04, 1.47) **	1.04 (0.84, 1.30)	1.04 (0.89, 1.22)	RIS *bisphosphonate*	.
1.00 (0.94, 1.06)	0.84 (0.71, 0.99) **	0.84 (0.80, 0.88) **	0.81 (0.69, 0.95) **	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

AEs: adverse events; **ALN**: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RR**: risk ratio; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 91 League table of summary estimates for treatment-related adverse events (AEs) in men with prostate cancer on HAT who have an increased fracture risk

ALN *bisphosphonate*	.	0.93 (0.29, 3.06)	.
0.93 (0.17, 4.92)	DEN	1.01 (0.31, 3.26)	.
0.93 (0.29, 3.06)	1.01 (0.31, 3.26)	PLB	1.47 (0.71, 3.06)
0.64 (0.16, 2.56)	0.69 (0.17, 2.73)	1.47 (0.71, 3.06)	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

AEs: adverse events; **ALN**: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

17.2.3 Serious adverse events (SAEs)

Postmenopausal women with osteoporosis

Table 92 League table of summary estimates for serious adverse events (SAEs) in postmenopausal women with osteoporosis

RLX *SERM*	1.58 (0.32, 5.46)	1.11 (0.52, 2.02)	1.18 (0.67, 2.28)	1.24 (0.49, 2.88)	1.27 (0.57, 2.91)	1.68 (0.41, 4.91)	3.96 (0.56, 14.25)
1.14 (0.18, 3.15)	IBN *bisphosphonate*	1.19 (0.19, 3.24)	1.23 (0.26, 3.35)	1.16 (0.30, 2.78)	1.32 (0.24, 3.86)	1.27 (0.54, 2.20)	2.65 (0.78, 6.49)
1.00 (0.50, 1.91)	1.50 (0.31, 5.24)	BAZ *SERM*	1.12 (0.66, 2.17)	1.18 (0.48, 2.75)	1.20 (0.56, 2.79)	1.60 (0.40, 4.70)	3.76 (0.55, 13.72)
0.92 (0.44, 1.50)	1.27 (0.30, 3.85)	0.97 (0.46, 1.51)	PLB	1.04 (0.50, 1.83)	1.06 (0.61, 1.79)	1.39 (0.39, 3.42)	3.19 (0.52, 10.44)
0.97 (0.35, 2.04)	1.21 (0.36, 3.38)	1.02 (0.36, 2.07)	1.05 (0.55, 1.98)	DEN	1.12 (0.47, 2.52)	1.33 (0.50, 2.88)	3.02 (0.61, 9.40)
0.93 (0.34, 1.76)	1.31 (0.26, 4.15)	0.98 (0.36, 1.79)	1.01 (0.56, 1.65)	1.05 (0.40, 2.14)	ZOL *bisphosphonate*	1.41 (0.33, 3.73)	3.28 (0.46, 11.02)
0.90 (0.20, 2.43)	0.89 (0.45, 1.85)	0.94 (0.21, 2.48)	0.98 (0.29, 2.54)	0.92 (0.35, 2.00)	1.05 (0.27, 3.02)	ALN *bisphosphonate*	2.23 (0.69, 5.73)
0.55 (0.07, 1.77)	0.51 (0.15, 1.28)	0.57 (0.07, 1.83)	0.59 (0.10, 1.91)	0.56 (0.11, 1.63)	0.64 (0.09, 2.16)	0.60 (0.17, 1.45)	RIS *bisphosphonate*

RR (95% CrI)

Abbreviations:

ALN: alendronate; **BAZ**: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SAEs**: serious adverse events; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate.

Notes:

Credible interval: An interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]

**statistical significance

- Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- RR less than 1 favours the column-defining treatment.
- RR greater than 1 favours the row-defining treatment.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Women with breast cancer receiving AAIT who have an increased fracture risk

Table 93 League table of summary estimates for serious adverse events (SAEs) in women with breast cancer receiving AAIT who have an increased fracture risk

DEN	.	1.12 (0.78, 1.60)
0.45 (0.08, 2.42)	IBN *bisphosphonate*	2.50 (0.48, 13.06)
1.12 (0.78, 1.60)	2.50 (0.48, 13.06)	PLB

RR (95% CI)

Abbreviations:

AAIT: adjuvant aromatase inhibitors therapy; **CI**: confidence interval; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RR**: risk ratio; **SAEs**: serious adverse events.

Notes:

**statistical significance

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

Men with osteoporosis who have an increased fracture risk

Table 94 League table of summary estimates for serious adverse events (SAEs) in men with osteoporosis who have an increased fracture risk

ALN *bisphosphonate*	.	.	.	1.19 (0.75, 1.89)
1.01 (0.41, 2.52)	DEN	1.18 (0.55, 2.53)	.	.
1.19 (0.72, 1.97)	1.18 (0.55, 2.53)	PLB	0.94 (0.53, 1.67)	1.01 (0.83, 1.22)
1.27 (0.59, 2.72)	1.26 (0.48, 3.26)	0.94 (0.53, 1.67)	RIS *bisphosphonate*	.
1.19 (0.75, 1.89)	1.18 (0.54, 2.58)	1.01 (0.83, 1.22)	0.94 (0.51, 1.71)	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RR**: risk ratio; **SAEs**: serious adverse events; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 95 League table of summary estimates for serious adverse events (SAEs) in men with prostate cancer on HAT who have an increased fracture risk

ALN *bisphosphonate*	.	0.83 (0.47, 1.45)	.	.
0.73 (0.41, 1.31)	DEN	1.13 (0.97, 1.31)	.	.
0.83 (0.47, 1.45)	1.13 (0.97, 1.31)	PLB	5.00 (0.25, 101.66)	0.82 (0.61, 1.10)
0.17 (0.01, 3.55)	0.23 (0.01, 4.61)	5.00 (0.25, 101.66)	RIS *bisphosphonate*	.
1.01 (0.54, 1.91)	1.38 (0.99, 1.92)	0.82 (0.61, 1.10)	6.11 (0.30, 126.00)	ZOL *bisphosphonate*

Abbreviations:
ALN: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **RIS**: risedronate; **RR**: risk ratio; **SAEs**: serious adverse events; **ZOL**: zoledronate.
Notes:
**statistical significance
- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:
RR calculated from indirect evidence.
RR calculated from direct evidence.

17.2.4 Withdrawal due to treatment-related adverse events (AEs)

Postmenopausal women with osteoporosis

Table 96 League table of summary estimates for withdrawals due to adverse events (AEs) in postmenopausal women with osteoporosis

PLB	1.23 (0.46, 2.74)	1.24 (0.47, 2.74)	1.31 (0.67, 2.67)	1.29 (0.69, 2.47)	4.44 (0.60, 16.89)
0.97 (0.37, 2.16)	ZOL *bisphosphonate*	1.22 (0.29, 3.53)	1.29 (0.39, 3.67)	1.26 (0.39, 3.46)	4.39 (0.43, 18.41)
0.96 (0.36, 2.14)	1.19 (0.28, 3.48)	DEN	1.28 (0.39, 3.64)	1.25 (0.39, 3.42)	3.56 (0.68, 12.05)
0.85 (0.37, 1.48)	1.04 (0.27, 2.58)	1.05 (0.27, 2.58)	RLX *SERM*	1.05 (0.46, 2.07)	3.75 (0.40, 14.79)
0.85 (0.41, 1.45)	1.04 (0.29, 2.57)	1.05 (0.29, 2.58)	1.07 (0.48, 2.19)	BAZ *SERM*	3.77 (0.42, 14.82)
0.47 (0.06, 1.66)	0.58 (0.05, 2.32)	0.48 (0.08, 1.48)	0.63 (0.07, 2.49)	0.61 (0.07, 2.38)	ALN *bisphosphonate*

RR (95% CrI)
Abbreviations:
AEs: adverse events; **BAZ**: bazedoxifene; **CrI**: credible interval; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **RR**: risk ratio; **SERM**: selective oestrogen receptor modulator; **ZOL**: zoledronate.
Notes:
Credible interval: An interval within which RR values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[235]
**statistical significance
Each RR (95% CrI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
RR less than 1 favours the column-defining treatment.
RR greater than 1 favours the row-defining treatment.
This is a league table of summary estimates that is the result of a network meta-analysis performed using a Bayesian inference.

Men with osteoporosis who have an increased fracture risk

Table 97 League table of summary estimates for withdrawals due to adverse events (AEs) in men with osteoporosis who have an increased fracture risk

ALN *bisphosphonate*	.	.	2.07 (0.80, 5.37)
0.24 (0.01, 5.70)	DEN	9.00 (0.49, 165.35)	.
2.15 (0.61, 7.60)	9.00 (0.49, 165.35)	PLB	0.1.04 (0.45, 2.38)
2.07 (0.80, 5.37)	8.66 (0.42, 178.60)	0.1.04 (0.45, 2.38)	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

AEs: adverse events; **ALN**: alendronate; **CI**: confidence interval; **DEN**: denosumab; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

Men with prostate cancer on HAT who have an increased fracture risk

Table 98 League table of summary estimates for withdrawals due to adverse events (AEs) in men with prostate cancer on HAT who have an increased fracture risk

ALN *bisphosphonate*	.	0.09 (0.01, 1.57)	.
0.07 (0.00, 1.32)	DEN	1.25 (0.73, 2.14)	.
0.09 (0.01, 1.57)	1.25 (0.73, 2.14)	PLB	1.17 (0.61, 2.24)
0.08 (0.00, 1.44)	1.07 (0.46, 2.48)	1.17 (0.61, 2.24)	ZOL *bisphosphonate*

RR (95% CI)

Abbreviations:

AEs: adverse events; **ALN**: alendronate; **CI**: confidence interval; **DEN**: denosumab; **HAT**: hormone ablation therapy; **PLB**: placebo; **RR**: risk ratio; **ZOL**: zoledronate.

Notes:

**statistical significance

- Each RR (95% CI) in a cell should be interpreted as a comparison between the column-defining treatment against the row-defining treatment.
- Inconsistency does not appear to be present in the network as the direct and indirect comparisons are equal.
- This is a league table of summary estimates that is the result of a network meta-analysis performed using a frequentist inference.

Legend:

RR calculated from indirect evidence.
RR calculated from direct evidence.

18 Appendix D: Assessment of inconsistency and heterogeneity

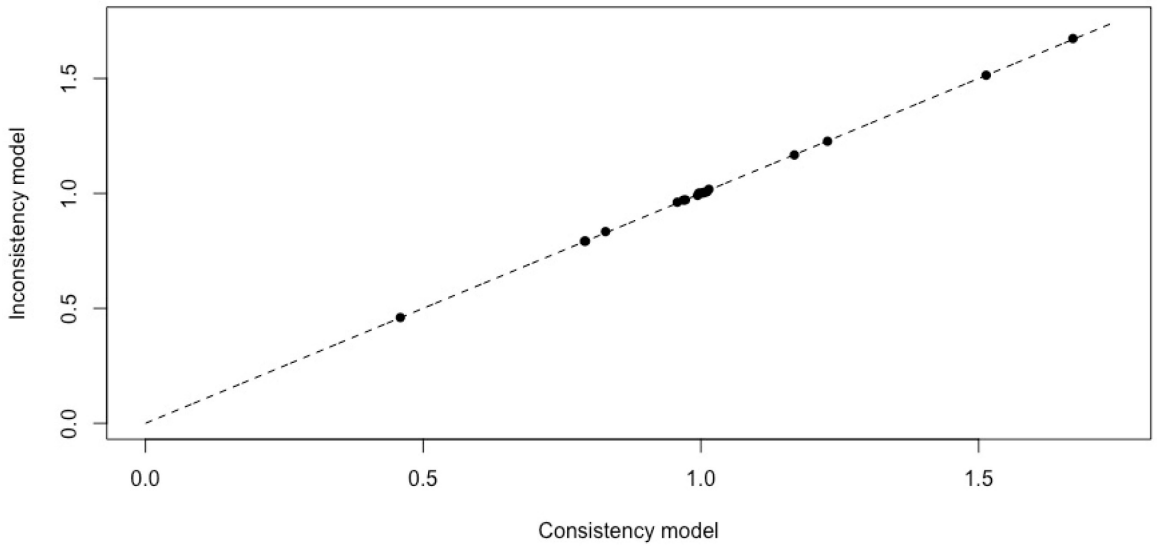
Appendix D includes the results of the assessment of inconsistency and heterogeneity in the analyses reporting in ***Section 7***.

18.1 Findings efficacy and effectiveness

18.1.1 Vertebral fractures

Postmenopausal women with osteoporosis

Figure 99 Assessment of local inconsistency in the network meta-analysis for vertebral fractures in postmenopausal women with osteoporosis



Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 99 Assessment of heterogeneity in the network meta-analysis for vertebral fractures in postmenopausal women with osteoporosis

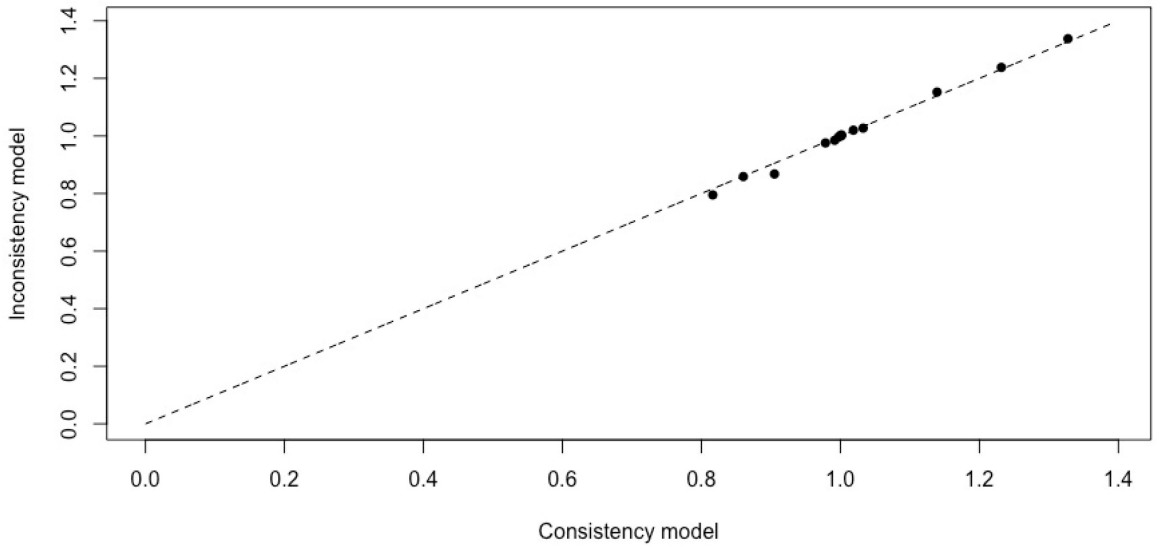
Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	3.30	3	0.1018	0.09
Comparison-specific heterogeneity				
PLB vs BAZ	0.08	1	0.7743	0
PLB vs RLX	0.51	1	0.4750	0
PLB vs ZOL	2.71	1	0.0995	63.2

Abbreviations:
BAZ: bazedoxifene; **df**: degrees of freedom; **NA**: not applicable; **PLB:** placebo; **RLX:** raloxifene; **ZOL:** zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

18.1.2 Nonvertebral fractures

Postmenopausal women with osteoporosis

Figure 100 Assessment of local inconsistency in the network meta-analysis for nonvertebral fractures in postmenopausal women with osteoporosis



Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 100 Assessment of global inconsistency in the network meta-analysis for nonvertebral fractures in postmenopausal women with osteoporosis

Item	DIC	Dres	Importance of difference
Consistency model	28.80	15.30	NA
Inconsistency model	28.76	15.26	NA
Difference between models	0.04	0.04	Minimal

Abbreviations:
DIC: deviance information criterion; **Dres**: residual deviance; **NA**: not applicable.
Notes:
This table presents the inconsistency result of a network meta-analysis performed using a Bayesian inference.

Table 101 Assessment of heterogeneity in the network meta-analysis for nonvertebral fractures in postmenopausal women with osteoporosis

Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	4.87	3	0.0411	38.4
Comparison-specific heterogeneity				
PLB vs RLX PLB vs BAZ PLB vs ZOL	1.20 0.20 3.47	1 1 1	0.2733 0.6571 0.0625	16.7 0.0 71.2

Abbreviations:
BAZ: bazedoxifene; **df**: degrees of freedom; **NA**: not applicable, **PLB:** placebo; **RLX:** raloxifene; **ZOL:** zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

Men with prostate cancer on HAT who have an increased fracture risk

Table 102 Assessment of heterogeneity in the network meta-analysis for nonvertebral fractures in men with prostate cancer on HAT

Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	2.24	3	0.5250	0
Comparison-specific heterogeneity				
PLB vs ALN PLB vs ZOL	0.25 1.99	1 2	0.6173 0.3705	0 0

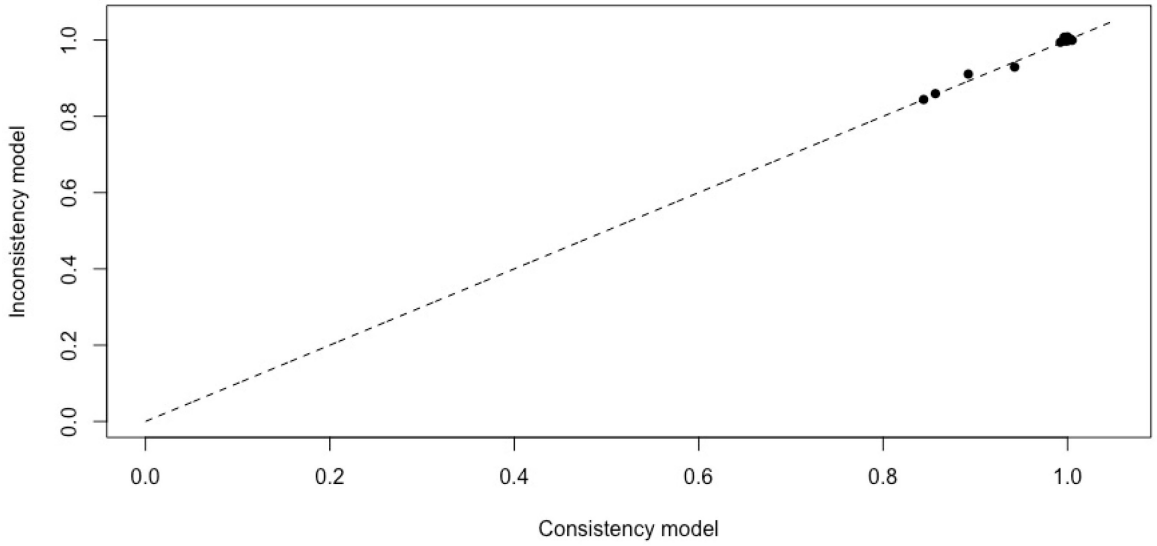
Abbreviations:
ALN: alendronate; **df**: degrees of freedom; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

18.1.3 Bone mineral density (BMD)

18.1.3.1 Femoral neck (FN)

Postmenopausal women with osteoporosis

Figure 101 Assessment of local inconsistency in the network meta-analysis for BMD measured at FN in postmenopausal women with osteoporosis



Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 103 Assessment of global inconsistency in the network meta-analysis for BMD measured at FN in postmenopausal women with osteoporosis

Item	DIC	Dres	Importance of difference
Consistency model	32.80	16.53	NA
Inconsistency model	32.88	16.56	NA
Difference between models	0.08	0.03	Minimal

Abbreviations:
DIC: deviance information criterion; **Dres**: residual deviance; **NA**: not applicable.
Notes:
This table presents the inconsistency result of a network meta-analysis performed using a Bayesian inference.

Table 104 Assessment of heterogeneity in the network meta-analysis for bone mineral density (BMD) measured at femoral neck (FN) in postmenopausal women with osteoporosis

Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	2.71	2	0.6136	26.19
Comparison-specific heterogeneity				
PLB vs ZOL IBN vs ALN	0.48 2.23	1 1	0.4887 0.1350	0 55.20

Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **df**: degrees of freedom; **FN**: femoral neck; **IBN**: ibandronate; **NA**: not applicable; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

Men with prostate cancer on HAT who have an increased fracture risk

Table 105 Assessment of heterogeneity in the network meta-analysis for bone mineral density (BMD) measured at femoral neck (FN) in men with prostate cancer on HAT

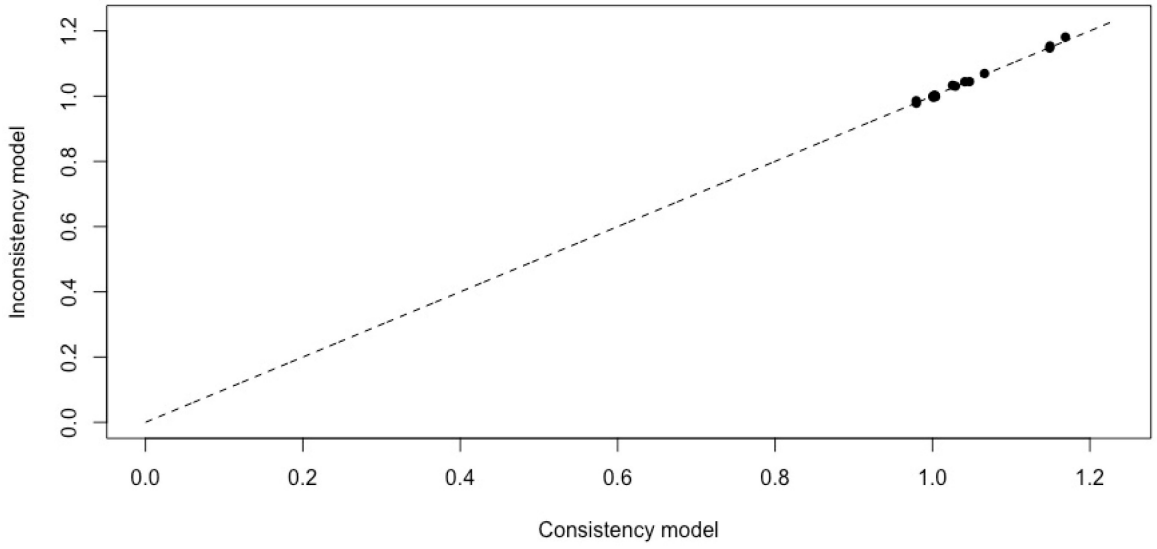
Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	2.01	3	0.5711	0
Comparison-specific heterogeneity				
PLB vs ALN PLB vs ZOL	0.83 1.18	1 2	0.3621 0.5556	0 0

Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **df**: degrees of freedom; **FN**: femoral neck; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

18.1.3.2 Lumbar spine (LS)

Postmenopausal women with osteoporosis

Figure 102 Assessment of local inconsistency in the network meta-analysis for BMD measured at LS in postmenopausal women with osteoporosis



Abbreviations:
BMD: bone mineral density; **LS**: lumbar spine
Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 106 Assessment of global inconsistency in the network meta-analysis for BMD measured at LS in postmenopausal women with osteoporosis

Item	DIC	Dres	Importance of difference
Consistency model	36.64	18.65	NA
Inconsistency model	36.66	18.67	NA
Difference between models	0.02	0.02	Minimal

Abbreviations:
DIC: deviance information criterion; **Dres**: residual deviance; **NA**: not applicable.
Notes:
This table presents the inconsistency result of a network meta-analysis performed using a Bayesian inference.

Table 107 Assessment of heterogeneity in the network meta-analysis for bone mineral density (BMD) measured at lumbar spine (LS) in postmenopausal women with osteoporosis

Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	13.02	3	0.0187	76.90
Comparison-specific heterogeneity				
PLB vs BAZ PLB vs ZOL PLB vs DEN	8.29 3.65 1.08	1 1 1	0.0040 0.0561 0.2990	87.90 72.60 7.30

Abbreviations:
BAZ: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **df**: degrees of freedom; **LS**: lumbar spine; **PLB**: placebo; **ZOL**: zoledronate
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

Women with breast cancer receiving AAIT who have an increased fracture risk

Table 108 Assessment of heterogeneity in the network meta-analysis for bone mineral density (BMD) measured at lumbar spine (LS) in women with breast cancer receiving AAIT who have an increased fracture risk

Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	0.29	1	0.5881	0
Comparison-specific heterogeneity				
PLB vs DEN	0.29	1	0.5881	0

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **DEN**: denosumab; **df**: degrees of freedom; **LS**: lumbar spine; **PLB**: placebo.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

Men with prostate cancer on HAT who have an increased fracture risk

Table 109 Assessment of heterogeneity in the network meta-analysis for bone mineral density (BMD) measured at lumbar spine (LS) in men with prostate cancer on HAT

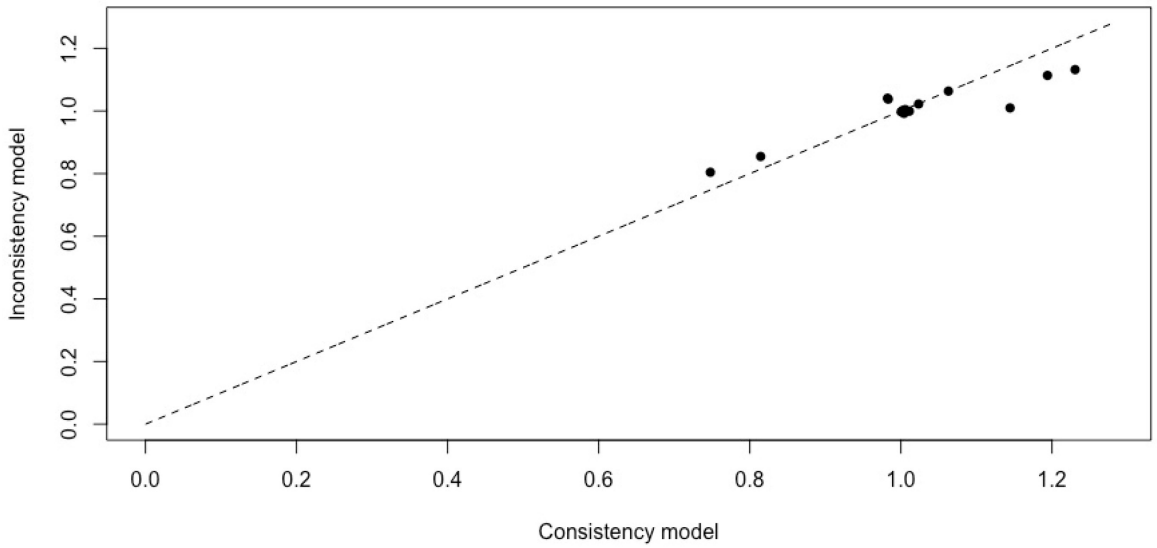
Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	2.13	6	0.9071	0
Comparison-specific heterogeneity				
PLB vs ALN PLB vs ZOL	0.90 1.23	1 5	0.3428 0.9414	0 0

Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **df**: degrees of freedom; **HAT**: hormone ablation therapy; **LS**: lumbar spine; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

18.1.3.3 Total hip (TH)

Postmenopausal women with osteoporosis

Figure 103 Assessment of local inconsistency in the network meta-analysis for BMD measured at TH in postmenopausal women with osteoporosis



Abbreviations:
BMD: bone mineral density; **TH**: total hip
Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 110 Assessment of global inconsistency in the network meta-analysis for BMD measured at TH in postmenopausal women with osteoporosis

Item	DIC	Dres	Importance of difference
Consistency model	29.05	15.21	NA
Inconsistency model	29.38	15.07	NA
Difference between models	0.33	0.14	Minimal

Abbreviations:
DIC: deviance information criterion; **Dres**: residual deviance; **NA**: not applicable.
Notes:
This table presents the inconsistency result of a network meta-analysis performed using a Bayesian inference.

Table 111 Assessment of heterogeneity in the network meta-analysis for bone mineral density (BMD) measured at total hip (TH) in postmenopausal women

Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	5.91	3	0.1109	49.24
Comparison-specific heterogeneity				
PLB vs BAZ PLB vs ZOL PLB vs DEN	2.17 0.41 3.33	1 1 1	0.1411 0.5220 0.0681	53.8 0.0 69.9

Abbreviations:
BAZ: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **df**: degrees of freedom; **TH**: total hip; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

Women with breast cancer receiving AAIT who have an increased fracture risk

Table 112 Assessment of heterogeneity in the network meta-analysis for bone mineral density (BMD) measured at total hip (TH) in women with breast cancer receiving AAIT who have an increased fracture risk

Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	0.09	1	0.7686	0
Comparison-specific heterogeneity				
PLB vs DEN	0.09	1	0.7686	0

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **BMD**: bone mineral density; **DEN**: denosumab; **df**: degrees of freedom; **PLB**: placebo; **TH**: total hip.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

Men with prostate cancer on HAT who have an increased fracture risk

Table 113 Assessment of heterogeneity in the network meta-analysis for bone mineral density (BMD) measured at total hip (TH) in men with prostate cancer on HAT

Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	861.77	6	<0.0001	99.30
Comparison-specific heterogeneity				
PLB vs ALN PLB vs ZOL	1.27 860.51	1 5	0.2605 <0.0001	21.26 99.42

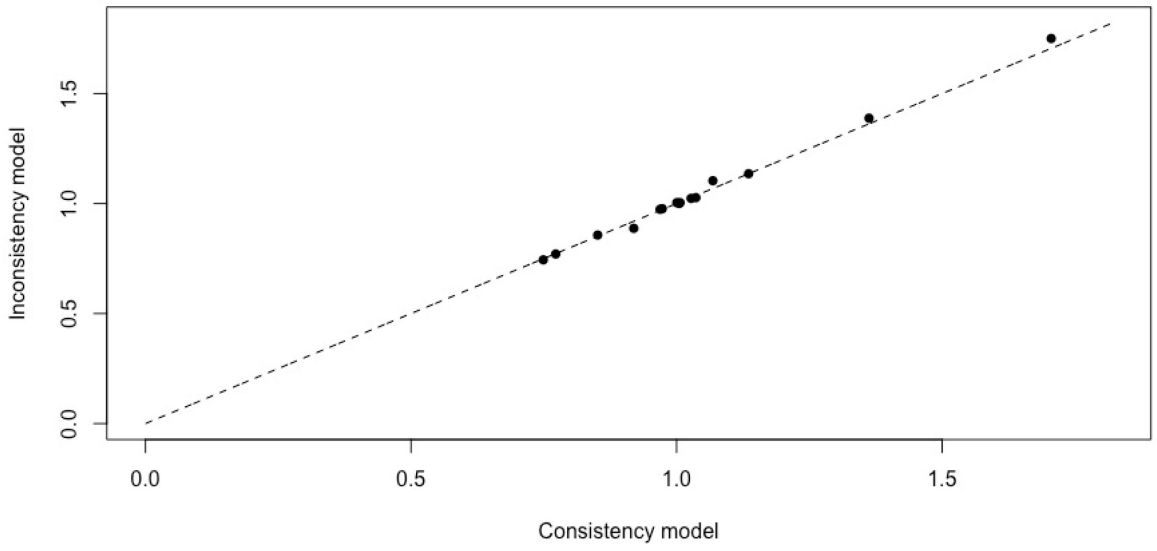
Abbreviations:
ALN: alendronate; **BMD**: bone mineral density; **df**: degrees of freedom; **HAT**: hormone ablation therapy; **PLB**: placebo; **TH**: total hip; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

18.2 Findings safety

18.2.1 Mortality

Postmenopausal women with osteoporosis

Figure 104 Assessment of local inconsistency in the network meta-analysis for mortality in postmenopausal women with osteoporosis



Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 114 Assessment of heterogeneity in the network meta-analysis for mortality in postmenopausal women with osteoporosis

Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	3.55	2	0.0569	43.7
Comparison-specific heterogeneity				
PLB vs ZOL PLB vs RLX	0.01 3.54	1 1	0.9156 0.0599	0.0 71.8

Abbreviations:
df: degrees of freedom; **NA**: not applicable; **PLB**: placebo; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

Men with prostate cancer on HAT who have an increased fracture risk

Table 115 Assessment of heterogeneity in the network meta-analysis for mortality men with prostate cancer on HAT who have an increased fracture risk

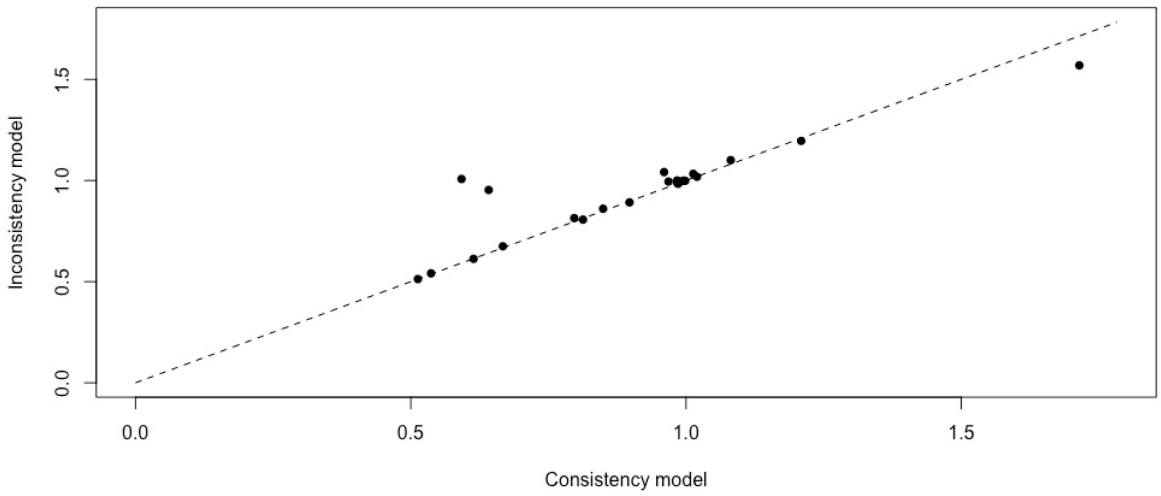
Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	1.24	2	0.54	0
Comparison-specific heterogeneity				
PLB vs ZOL	1.24	2	0.54	0

Abbreviations:
df: degrees of freedom; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

18.2.2 Treatment-related adverse events (AEs)

Postmenopausal women with osteoporosis

Figure 105 Assessment of local inconsistency in the network meta-analysis for treatment-related AEs in postmenopausal women with osteoporosis



Abbreviations:
AEs: adverse events
Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 116 Assessment of global inconsistency in the network meta-analysis for treatment-related adverse events (AEs) in postmenopausal women with osteoporosis

Item	DIC	Dres	Importance of difference
Consistency model	40.49	21.81	NA
Inconsistency model	42.25	22.59	NA
Difference between models	1.76	0.78	Minimal

Abbreviations:
DIC: deviance information criterion; **Dres**: residual deviance; **NA**: not applicable.
Notes:
This table presents the inconsistency result of a network meta-analysis performed using a Bayesian inference.

Table 117 Assessment of heterogeneity in the network meta-analysis for treatment-related adverse events (AEs) in postmenopausal women with osteoporosis

Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	2.21	5	0.6806	0
Comparison-specific heterogeneity				
PLB vs ZOL	0.03	1	0.8693	0
PLB vs RLX	0.01	1	0.9070	0
PLB vs DEN	0.32	1	0.5735	0
PLB vs BAZ	1.53	1	0.2158	34.7
IBN vs ALN	0.32	1	0.5718	0

Abbreviations:
AEs: adverse events; **BAZ**: bazedoxifene; **DEN:** denosumab; **df**: degrees of freedom; **NA**: not applicable; **PLB:** placebo; **RLX:** raloxifene; **ZOL:** zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

Men with prostate cancer on HAT who have an increased fracture risk

Table 118 Assessment of heterogeneity in the network meta-analysis for treatment-related adverse events (AEs) in men with prostate cancer on HAT who have an increased fracture risk

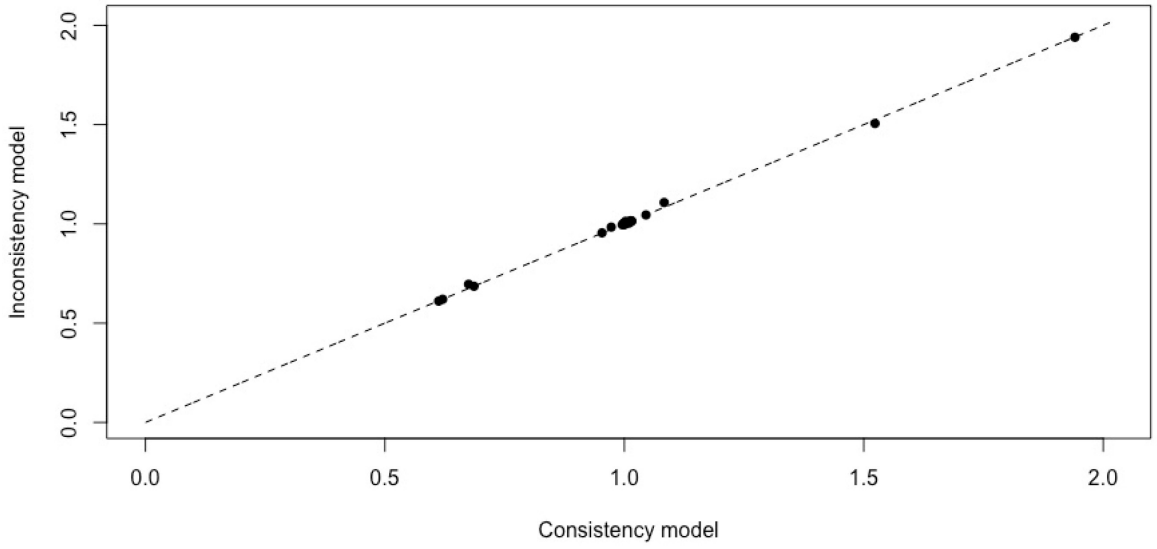
Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	15.45	2	0.0004	87.1
Comparison-specific heterogeneity				
PLB vs ZOL	15.45	2	0.0004	87.1

Abbreviations:
AEs: adverse events; **df**: degrees of freedom; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

18.2.3 Serious adverse events (SAEs)

Postmenopausal women with osteoporosis

Figure 106 Assessment of local inconsistency in the network meta-analysis for SAEs in postmenopausal women with osteoporosis



Abbreviations:
SAEs: serious adverse events
Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 119 Assessment of global inconsistency in the network meta-analysis for SAEs in postmenopausal women with osteoporosis

Item	DIC	Dres	Importance of difference
Consistency model	41.16	22.17	NA
Inconsistency model	41.20	22.22	NA
Difference between models	0.04	0.05	Minimal

Abbreviations:
DIC: deviance information criterion; **Dres**: residual deviance; **NA**: not applicable.
Notes:
This table presents the inconsistency result of a network meta-analysis performed using a Bayesian inference.

Table 120 Assessment of heterogeneity in the network meta-analysis for serious adverse events (SAEs) in postmenopausal women with osteoporosis

Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	4.03	5	0.1582	0
Comparison-specific heterogeneity				
ALN vs IBN	0.49	1	0.4840	0
PLB vs BAZ	1.68	1	0.1950	40.4
PLB vs DEN	0.00	1	0.9651	0
PLB vs RLX	0.23	1	0.6313	0
PLB vs ZOL	1.63	1	0.2022	38.5

Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **DEN:** denosumab; **df**: degrees of freedom; **IBN:** ibandronate; **NA**: not applicable; **PLB:** placebo; **RLX:** raloxifene; **SAEs**: serious adverse events; **ZOL:** zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

Women with breast cancer receiving AAIT who have an increased fracture risk

Table 121 Assessment of heterogeneity in the network meta-analysis for serious adverse events (SAEs) in women with breast cancer receiving AAIT who have an increased fracture risk

Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	1.60	1	0.2056	37.6
Comparison-specific heterogeneity				
PLB vs DEN	1.60	1	0.2056	37.6

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **DEN**: denosumab; **df**: degrees of freedom; **PLB**: placebo; **SAEs**: serious adverse events.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

Men with prostate cancer on HAT who have an increased fracture risk

Table 122 Assessment of heterogeneity in the network meta-analysis for serious adverse events (SAEs) in men with prostate cancer on HAT who have an increased fracture risk

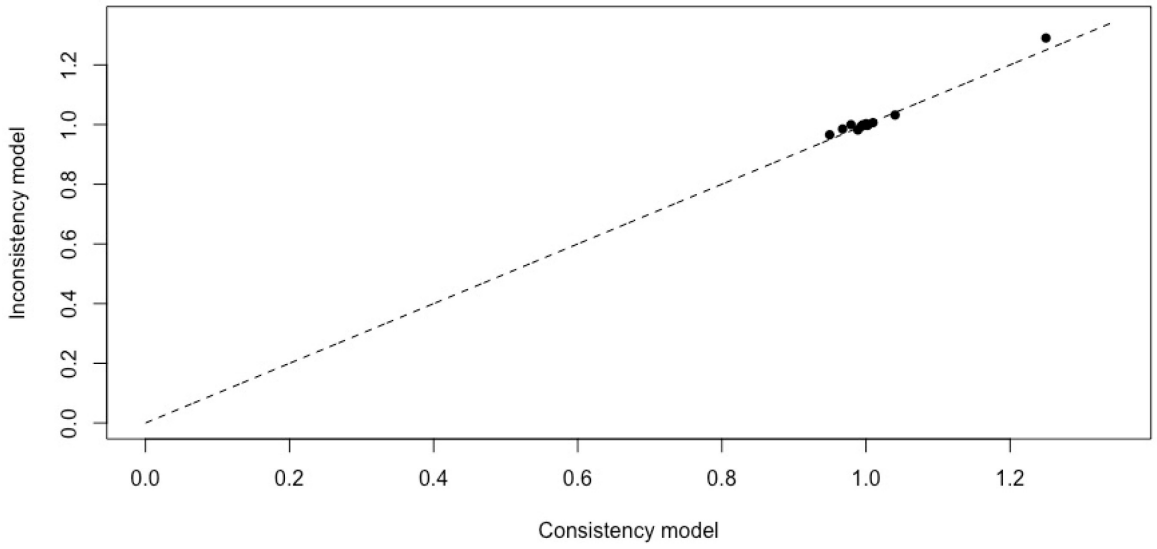
Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	2.89	4	0.5757	0
Comparison-specific heterogeneity				
PLB vs ALN PLB vs ZOL	0.37 2.52	1 3	0.5411 0.4716	0 0

Abbreviations:
ALN: alendronate; **df**: degrees of freedom; **HAT**: hormone ablation therapy; **PLB**: placebo; **SAEs**: serious adverse events; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

18.2.4 Withdrawal due to treatment-related adverse events (AEs)

Postmenopausal women with osteoporosis

Figure 107 Assessment of local inconsistency in the network meta-analysis for withdrawal due to treatment-related AEs in postmenopausal women with osteoporosis



Abbreviations:
AEs: adverse events
Notes:
- Each point represents a treatment-arm's contribution to posterior deviance for the consistency model and inconsistency model.[122]
- Correlation along the y=x line indicates consistency among the two models.[122]
- This forest plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 123 Assessment of global inconsistency in the network meta-analysis for withdrawal due to treatment-related AEs in postmenopausal women with osteoporosis

Item	DIC	Dres	Importance of difference
Consistency model	24.90	13.18	NA
Inconsistency model	24.95	13.25	NA
Difference between models	0.05	0.07	Minimal

Abbreviations:
DIC: deviance information criterion; **Dres**: residual deviance; **NA**: not applicable.
Notes:
This table presents the inconsistency result of a network meta-analysis performed using a Bayesian inference.

Table 124 Assessment of heterogeneity in the network meta-analysis for withdrawal due to treatment-related adverse events (AEs) in postmenopausal women with osteoporosis

Item	Q-statistic	df	P-value	I^2
Total/within-design heterogeneity	2.54	2	0.1703	21.2
Comparison-specific heterogeneity				
PLB vs BAZ PLB vs RLX	1.14 1.40	1 1	0.2862 0.2361	12.1 28.7

Abbreviations:
AEs: adverse events; **BAZ**: bazedoxifene; **df**: degrees of freedom; **NA**: not applicable; **PLB:** placebo; **RLX:** raloxifene; **--**: not generated
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a Bayesian inference.

Men with prostate cancer on HAT who have an increased fracture risk

Table 125 Assessment of heterogeneity in the network meta-analysis for withdrawals due to treatment-related adverse events (AEs) in men with prostate cancer on HAT who have an increased fracture risk

Item	Q-statistic (Q^{het})	df	P-value	I^2
Total/within-design heterogeneity	1.40	4	0.8447	0
Comparison-specific heterogeneity				
PLB vs ZOL	1.40	4	0.8447	0

Abbreviations:
AEs: adverse events; **df**: degrees of freedom; **HAT**: hormone ablation therapy; **PLB**: placebo; **ZOL**: zoledronate.
Notes:
This table presents the heterogeneity result of a network meta-analysis performed using a frequentist inference.

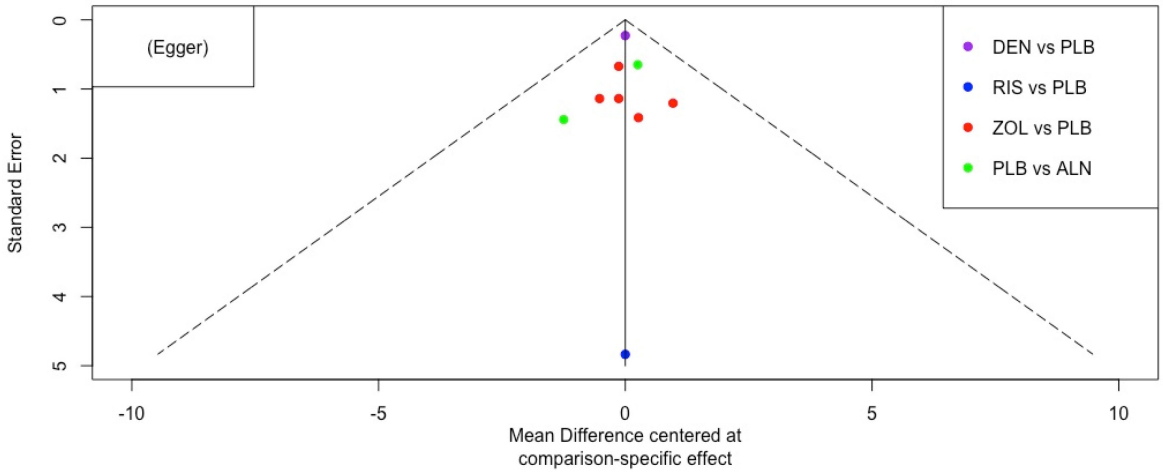
19 Appendix E: Assessment of publication bias

Appendix E includes funnel plots for investigating the impact of missing results on the outcome of the analysis (i.e. publication bias). As noted in the methods section, the analysis of funnel plot asymmetry was only conducted for outcomes with 10 or more studies included in the analysis. None of the included analyses identified the presence of publication bias on the results.

19.1 Lumbar spine (LS) BMD

Men with prostate cancer on HAT with an increased fracture risk

Figure 108 Assessment of publication bias in the network meta-analysis for LS BMD in men with prostate cancer on HAT with an increased fracture risk



Abbreviations:
ALN: alendronate; **BMD:** bone mineral density; **DEN**: denosumab; **LS**: lumbar spine; **PLB**: placebo; **RIS**: risedronate; **ZOL**: zoledronate.
Notes:

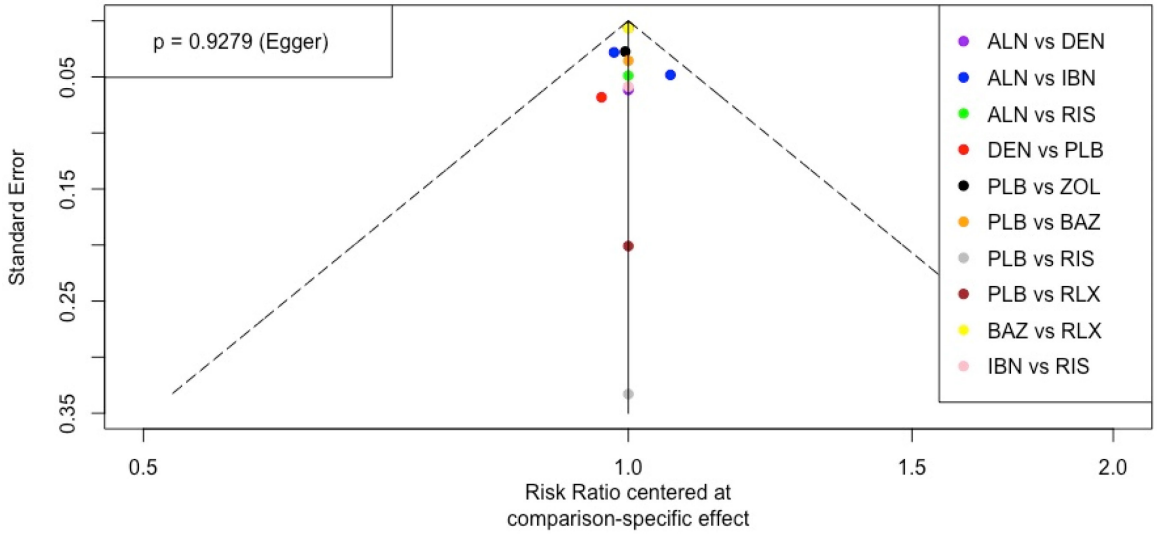
- Egger score: p= 0.7731
- This is a funnel plot assessing publication bias in the network meta-analysis.
- The purpose of the plot is to detect asymmetry.

-

19.2 Treatment-related adverse events (AEs)

Postmenopausal women with osteoporosis

Figure 109 Assessment of publication bias in the network meta-analysis for treatment-related AEs in postmenopausal women with osteoporosis

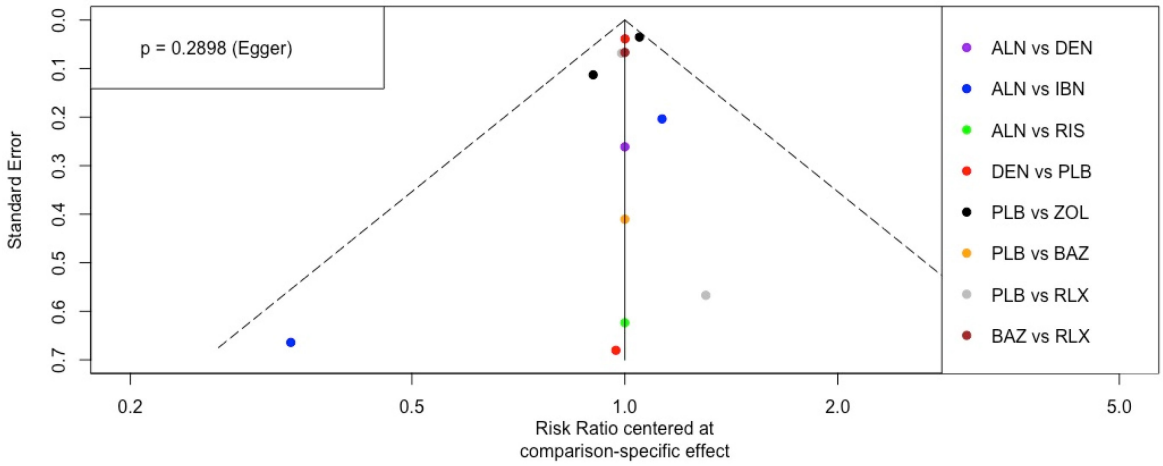


Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
- This is a funnel plot assessing publication bias in the network meta-analysis.
- The purpose of the plot is to detect asymmetry.

19.3 Serious adverse events (SAEs)

Postmenopausal women with osteoporosis

Figure 110 Assessment of publication bias in the network meta-analysis for SAEs in postmenopausal women with osteoporosis



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SAEs**: serious adverse events; **ZOL**: zoledronate.
Notes:
- This is a funnel plot assessing publication bias in the network meta-analysis.
- The purpose of the plot is to detect asymmetry.

20 Appendix F: Ongoing and recently completed clinical trials

Appendix F includes a table of ongoing and recently completed clinical trials that meet the inclusion criteria for this assessment. The aim of this table is to outline any upcoming evidence, in order to determine if new evidence that may affect the results of this assessment is likely to be published in the near future.

Table 126 Ongoing clinical trials fitting the inclusion criteria

Trial registry ID; Country	Indication; Sample size (n)	Intervention	Comparator	Primary outcomes	Recruitment status; Expected completion date
ClinicalTrials.gov					
NCT02753283 USA	Postmenopausal women n = 201	Denosumab (Prolia®) then zoledronate (5 mg IV/year)	Placebo then zoledronic acid (5 mg IV/year)	*Effectiveness*- BMD (TH, LS)	Active, not recruiting September 2023
NCT04085419 Slovenia	Postmenopausal women with secondary osteoporosis due to primary hyperparathyroidism n = 40	Denosumab (Prolia®)	Zoledronate (5 mg IV/year)	*Effectiveness*- BMD BTM (CTX, P1NP, B-ALP)	Enrolling by invitation May 2022
NCT04608630 Australia, NZ	Postmenopausal women n = 450	Denosumab (Prolia®)	Zoledronate (5 mg IV/year) Placebo (matched denosumab or zoledronate)	*Effectiveness*- BMD (FN, LS) Fracture HRQoL BTM (CTX, P1NP) *Safety*- Mortality	Not yet recruiting May 2025
NCT02589600 (ZEST II) USA	Postmenopausal women n = 310	Zoledronate (IV 5 mg/year)	Placebo (matched)	*Effectiveness*- Fracture	Active, not recruiting March 2023
NCT00556374 (ABCSG-18 Extension) Austria, Sweden	Women with breast cancer receiving AAIT n = 3420	Denosumab (Prolia®) Extension: Zoledronate (5 mg IV/year)	Placebo (matched denosumab) Extension: Standard care	*Effectiveness*- BMD (LS, TH, FN) Fracture	Active, not recruiting July 2022
NCT00859703 France	Women with breast cancer receiving AAIT	Risedronate (35 mg/weekly)	Placebo	*Effectiveness*- BMD (LS, FN) BTM	Complete October 2013

Trial registry ID; Country	Indication; Sample size (n)	Intervention	Comparator	Primary outcomes	Recruitment status; Expected completion date
	n = 20			Fracture	(No results posted or published)
Australian New Zealand Clinical Trials Registry (ANZCTR)					
372599 Australia, NZ	Postmenopausal women n = 30	Denosumab (Prolia®)	Zoledronate (5 mg IV/year) Placebo (matched denosumab or zoledronate)	*Effectiveness*- BTM (CTX, P1NP) BMD (LS) *Safety*- AEs Serious AEs	Active, recruiting April 2021

Abbreviations:
AAIT: adjuvant aromatase inhibitor therapy; **AE**: adverse event; **B-ALP**: bone-specific alkaline phosphatase; **BMD**: bone mineral density; **BTM**: bone turnover makers; **CTX**: c-terminal telopeptide of type 1 collagen; **FN**: femoral neck; **HRQoL**: health-related quality of life; **IV**: intravenous; **LS**: lumbar spine; **NZ**: New Zealand; **P1NP**: procollagen type 1 N propeptide; **TH**: total hip; **mg**: milligrams; **USA**: United States of America.

21 Appendix G: Economics reporting standards, osteoporosis

Appendix G includes a table outlining a set of minimum criteria for an economic evaluation in osteoporosis. The economic model designed for this assessment report was based on these criteria.

Table 127 A set of minimum criteria for an economic evaluation in osteoporosis

- Cost-utility analysis with QALY as outcome
- Modelling technique (with limited restrictions)
- Long-term (lifetime) horizon
- Payer and/or societal perspective
- At a minimum hip and clinical vertebral fracture
- Excess mortality after hip and clinical vertebral fractures
- Short-term/long-term effects of fracture on utility
- Long-term cost of hip and clinical vertebral fractures
- Treatment characteristics*: effect on fractures during treatment and after discontinuation; medication adherence; side effects; therapy costs
- Multiple scenarios (age, fracture risk, BMD)
- Presentation of disaggregated outcomes, incremental costs, and outcomes for each interventional and incremental cost-effectiveness ratio
- One-way and probabilistic sensitivity analyses

Abbreviations:
QALY: quality-adjusted life years; **BMD**: bone mineral density
Notes:
*medication adherence and side effects could be included in sensitivity analyses
Source:
Hiligsmann et al. 2019[238]: Table 3, p.51

22 Appendix H: Economic evaluation input tables

Appendix H includes tables that summarise the probabilities (probability of nursing home admission after hip fracture, death after vertebral fracture, or death after hip fracture; ***Table 128***), utilities (index population norms, ***Table 129***; utility multipliers applied to the population norms after a fracture event, ***Table 130***) and costs (intervention-related costs, ***Table 131***; fracture-related costs ***Table 132***) used in the economic evaluation.

22.1 Probabilities

Table 128 Probability inputs used in the economic model upon fracture events

Age (years)	Nursing home admission after hip fracture	Death from vertebral fracture	Death from hip fracture
50	0.04	0.005	0.004
55	0.04	0.007	0.006
60	0.07	0.010	0.009
65	0.07	0.013	0.012
70	0.12	0.016	0.016
75	0.12	0.019	0.020
80	0.21	0.021	0.024
85	0.21	0.038	0.049
90	0.33	–	–

Source:
Relative risks of death due to hip or vertebral from Hernlund et al. 2013;[254] original source is Johnell et al. 2004.[253] It was assumed that 30% of the excess mortality after fractures was directly attributable to the fracture event
Age dependent probabilities of nursing home admission from Davis et al. 2020[255]

22.2 Utilities

Table 129 Age dependent baseline population utility values for women used in the economic model

Age range	Base utility inputs	Utilities (France)	Utilities (Germany)	Utilities (Italy)
45 – 54	**0.937**	0.920	0.950	0.941
55 – 64	**0.896**	0.843	0.917	0.929
65 – 74	**0.841**	0.771	0.874	0.879
75 +	**0.785**	0.717	0.820	0.817

Source:
Age-specific EQ-5D-3L index population norms for women in France, Germany, and Italy sourced from Szende, Janssen and Cabases 2014[250]. Simple average calculated for the purposes of this evaluation

Table 130 Utility multipliers used in the economic model following fracture events

	Utility multipliers

Time after fracture	Hip fracture	Vertebral fracture	NHNV fracture
First year after fracture	0.545	0.671	0.791
Subsequent years	0.857	0.841	0.952

Abbreviations:
NHNV: non-hip nonvertebral
Source:
Utility multipliers source from Soreskog et al. 2021;[273] originally sourced from ICUROS.[251]

22.3 Costs

Table 131 Medication cost data informing the economic model

Medication costs (CHF/year)		Unit costs (CHF)	
DEN	604.90	Physician visit	68.41
Oral bisphosphonates	326.94	DXA scan	50.84
IV IBN	269.87	Injection by a specialist	53.35
ZOL	284.45	Injection by non-medical personnel	22.11
RLX	367.02	Non-medical care for outpatient (60 min)	13.51
BAZ	495.31		

Abbreviations:
BAZ: bazedoxifene; **CHF**: Swiss francs; **DEN**: denosumab; **IBN**: ibandronate; **IV**: intravenous; **RLX**: raloxifene.
Notes:
The cost for oral bisphosphonates is an average cost across alendronate, oral IBN and risedronate, weighted based on 2020 sales data (packs sold) from © COGE GmbH. Tarifpool. © SASIS AG.
Source:
Drug prices sourced from Spezialitätenliste; outpatient unit costs sourced from TARMED.

Table 132 Fracture-related costs used in the economic model

Cost input	Base case cost (CHF)	Sensitivity analysis cost (CHF)
Hip fracture (event cost)	56,527.10	37,940.91
Vertebral fracture (event cost)	16,456.75	29,221.42
NHNV fracture (event cost)	12,131.38	23,016.29
Nursing home (annual cost)	112,055.00	NA

Abbreviations:
CHF: Swiss francs; **NHNV**: non-hip nonvertebral.
Notes:
Cost for NHNV is an average across costs for vertebral and forearm
Source:
Costing approach informed by previous publications,[28 259 274 310] and current data on hospital, rehabilitation and nursing home costs,[275] and inflation rates.[278]

23 Appendix I: Economic evaluation outcomes

Appendix I presents the detailed results tables from the economic evaluation, and provides an investigation of the key drivers with each pairwise comparison between denosumab and the comparators, individually.

First, cost and QALY outcomes for each treatment under the scenario analyses on age and baseline risk are presented (***Table 133***, ***Table 134***, and ***Table 135***). ICERs calculated under both a cost-effectiveness frontier analysis framework, and as pairwise comparisons are also presented.

Second, cost and QALY outcomes for each treatment under the deterministic sensitivity analyses performed on the base case cohort (age 70 years; high risk) are presented (***Table 136***) Again, ICERs calculated under both a cost-effectiveness frontier analysis framework, and as pairwise comparisons are presented.

Lastly, results from the pairwise comparisons made under each of the deterministic sensitivity analysis scenarios are assessed in order to provide insight into the key drivers within each pairwise comparison. Narrative descriptions of the drivers within each comparison are provided, and tornado diagrams (***Figure 111*** to ***Figure 118***) are included to provide a visual summary.

23.1 Age and baseline risk scenarios

Table 133 Cost-effectiveness outcomes for a start age of 60 years at various risk levels

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
Age 60 years; moderate risk				
No treatment	17,247	13.2659		102,189
Oral BIS	17,624	13.2839	**20,890** (vs. no treatment)	647,247
ZOL	17,649	13.2845	**47,817** (vs. oral BIS)	793,656
RLX	17,722	13.2825	Dominated	399,925
IV IBN	18,046	13.2870	**156,524** (vs. ZOL)	DEN dominated
BAZ	18,051	13.2753	Dominated	37,436
DEN	19,363	13.2866	Dominated	
Age 60 years; high-risk				
No treatment	27,192	13.1406		63,193
Oral BIS	27,495	13.1648	**12,514** (vs. no treatment)	274,761
RLX	27,508	13.1638	Dominated	231,517

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
ZOL	27,639	13.1694	**31,075** (vs. oral BIS)	1,230,256
IV IBN	27,843	13.1690	Dominated	805,230
BAZ	27,875	13.1557	Dominated	81,392
DEN	29,090	13.1706	**1,230,256** (vs. ZOL)	
Age 60 years; very-high risk				
IV IBN	51,233	12.8485		501,781
ZOL	51,422	12.8478	Dominated	342,177
Oral BIS	51,543	12.8417	Dominated	113,023
RLX	51,594	12.8370	Dominated	72,790
BAZ	52,109	12.8194	Dominated	16,388
No treatment	52,488	12.7991	Dominated	2,775
DEN	52,633	12.8513	**501,781** (vs. IV IBN)	

Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **CHF**: Swiss francs; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous; **QALY**: quality-adjusted life year; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
Interventions have been ranked in order of least to most costly. For the cost-effectiveness frontier analysis, ICERs have been calculated for interventions that are neither dominated nor extendedly dominated. For the pairwise comparison between DEN and each comparator, ICERs have been calculated as DEN vs. the comparator.

Table 134 Cost-effectiveness outcomes for a start age of 70 years at various risk levels

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
Age 70 years; moderate risk				
Oral BIS	17,392	8.8281		333,449
IV IBN	17,743	8.8323	**82,710** (vs. oral BIS)	1,499,549
No treatment	17,823	8.8130	Dominated	63,751
RLX	17,834	8.8250	Dominated	154,917
BAZ	18,230	8.8162	Dominated	51,754
ZOL	18,258	8.8243	Dominated	96,015
DEN	19,115	8.8333	**1,499,549** (vs. IV. IBN)	
Age 70 years; high-risk – Base case scenario				
IV IBN	29,144	8.7176		615,149
Oral BIS	29,214	8.7117	Dominated	166,451
RLX	29,573	8.7082	Dominated	86,776
ZOL	29,601	8.7108	Dominated	107,460
BAZ	30,028	8.6957	Dominated	23,135
No treatment	30,084	8.6883	Dominated	15,927
DEN	30,589	8.7200	**615,149** (vs. IV IBN)	
Age 70 years; very-high risk				
IV IBN	51,678	8.5019		438,327
Oral BIS	51,702	8.4932	Dominated	131,187
RLX	52,489	8.4863	Dominated	44,299
ZOL	52,772	8.4900	Dominated	36,509
DEN	53,347	8.5057	**438,327** (vs. IV IBN)	
BAZ	53,514	8.4641	Dominated	DEN dominant
No treatment	53,680	8.4558	Dominated	DEN dominant

Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **CHF**: Swiss francs; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous; **QALY**: quality-adjusted life year; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
Interventions have been ranked in order of least to most costly. For the cost-effectiveness frontier analysis, ICERs have been calculated for interventions that are neither dominated nor extendedly dominated. For the pairwise comparison between DEN and each comparator, ICERs have been calculated as DEN vs. the comparator.

Table 135 Cost-effectiveness outcomes for a start age of 80 years at various risk levels

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
Age 80 years; moderate risk				
Oral BIS	10,469	4.2669		479,535
No treatment	10,632	4.2587	Dominated	122,815
IV IBN	10,664	4.2690	**93,418** (vs. oral BIS)	1,149,246
RLX	10,852	4.2655	Dominated	255,829
BAZ	11,381	4.2588	Dominated	58,672
ZOL	11,986	4.2628	Dominated	8,661
DEN	12,050	4.2702	**1,149,246** (vs. IV IBN)	
Age 80 years; high-risk				
Oral BIS	18,880	4.2086		427,633
IV IBN	19,009	4.2117	**41,188** (vs. oral BIS)	1,616,479
RLX	19,153	4.2067	Dominated	248,060
No treatment	19,708	4.1924	Dominated	46,285
BAZ	20,242	4.1959	Dominated	24,209
DEN	20,649	4.2127	**1,616,479** (vs. IV IBN)	
ZOL	21,028	4.2025	Dominated	DEN dominant
Age 80 years; very-high risk				
IV IBN	32,775	4.1215		1,051,800
Oral BIS	32,850	4.1159	Dominated	253,116
RLX	33,145	4.1132	Dominated	157,648
No treatment	34,377	4.0910	Dominated	11,688
BAZ	34,665	4.0953	Dominated	3,264
DEN	34,757	4.1234	**1,051,800** (vs. IV IBN)	
ZOL	35,737	4.1073	Dominated	DEN dominant

Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **CHF**: Swiss francs; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous; **QALY**: quality-adjusted life year; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
Interventions have been ranked in order of least to most costly. For the cost-effectiveness frontier analysis, ICERs have been calculated for interventions that are neither dominated nor extendedly dominated. For the pairwise comparison between DEN and each comparator, ICERs have been calculated as DEN vs. the comparator.

23.2 Deterministic sensitivity analyses: tabulated

Table 136 Cost-effectiveness outcomes under a series of sensitivity analyses

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
RRs for all treatments equal				
ZOL	28,782	8.7239		DEN dominated
IV IBN	29,653	8.7175	Dominated	388,763
Oral BIS	29,664	8.7117	Dominated	111,822
BAZ	29,842	8.7103	Dominated	77,549
RLX	29,993	8.7092	Dominated	55,573
No treatment	30,084	8.6883	Dominated	15,927
DEN	30,589	8.7200	Dominated	
RRs for vertebral fracture set equal (differential effect on non-vertebral fracture only)				
IV IBN	29,026	8.7238		DEN dominated
Oral BIS	29,150	8.7172	Dominated	528,722
RLX	29,540	8.7138	Dominated	169,706
ZOL	29,550	8.7159	Dominated	259,205
BAZ	29,842	8.7103	Dominated	77,549
No treatment	30,084	8.6883	Dominated	15,927
DEN	30,589	8.7200	Dominated	
RRs for non-vertebral fracture set equal (differential effect on vertebral fracture only)				
ZOL	28,840	8.7187		1,388,977
Oral BIS	29,720	8.7062	Dominated	63,131
IV IBN	29,776	8.7114	Dominated	95,381
BAZ	30,028	8.6957	Dominated	23,135
RLX	30,039	8.7037	Dominated	33,902
No treatment	30,084	8.6883	Dominated	15,927
DEN	30,589	8.7200	1,388,977	
No offset period for denosumab				
IV IBN	29,144	8.7176		DEN dominated
Oral BIS	29,214	8.7117	Dominated	548,512
RLX	29,573	8.7082	Dominated	232,165
ZOL	29,601	8.7108	Dominated	353,069
BAZ	30,028	8.6957	Dominated	60,933
No treatment	30,084	8.6883	Dominated	42,125
DEN	31,225	8.7154	Dominated	
Offset period for denosumab equal to treatment duration				
IV IBN	29,144	8.7176		146,777
Oral BIS	29,214	8.7117	Dominated	81,895
RLX	29,573	8.7082	Dominated	46,083
ZOL	29,601	8.7108	Dominated	51,782

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
BAZ	30,028	8.6957	Dominated	12,147
No treatment	30,084	8.6883	Dominated	8,275
DEN	30,398	8.7261	**146,777** (*vs.* IV IBN)	
Offset period for raloxifene equal to treatment duration				
IV IBN	29,144	8.7176		615,149
RLX	29,168	8.7122	Dominated	182,056
Oral BIS	29,214	8.7117	Dominated	166,451
ZOL	29,601	8.7108	Dominated	107,460
BAZ	30,028	8.6957	Dominated	23,135
No treatment	30,084	8.6883	Dominated	15,927
DEN	30,589	8.7200	**615,149** (*vs.* IV IBN)	
Offset period for ZOL equal to treatment duration				
IV IBN	29,144	8.7176		615,149
Oral BIS	29,214	8.7117	Dominated	166,451
ZOL	29,522	8.7038	Dominated	65,861
RLX	29,573	8.7082	Dominated	86,776
BAZ	30,028	8.6957	Dominated	23,135
No treatment	30,084	8.6883	Dominated	15,927
DEN	30,589	8.7200	**615,149** (*vs.* IV IBN)	
No offset period for any treatment				
Oral BIS	29,555	8.7056		171,957
IV IBN	29,765	8.7091	**60,807** (*vs.* oral BIS)	233,337
RLX	29,974	8.7050	Dominated	121,152
No treatment	30,084	8.6883	Dominated	42,125
ZOL	30,233	8.6997	Dominated	63,366
BAZ	30,359	8.6948	**Dominated**	42,050
DEN	31,225	8.7154	**233,337** (*vs.* IV IBN)	
Increased persistence with denosumab				
IV IBN	29,144	8.7176		233,427
Oral BIS	29,214	8.7117	Dominated	129,355
RLX	29,573	8.7082	Dominated	83,044
ZOL	29,601	8.7108	Dominated	95,203
BAZ	30,028	8.6957	Dominated	33,033
No treatment	30,084	8.6883	Dominated	24,949
DEN	31,016	8.7256	**233,427** (*vs.* IV IBN)	

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
Decreased persistence with denosumab				
IV IBN	29,144	8.7176		DEN dominated
Oral BIS	29,214	8.7117	Dominated	424,203
RLX	29,573	8.7082	Dominated	120,661
ZOL	29,601	8.7108	Dominated	199,654
BAZ	30,028	8.6957	Dominated	14,522
No treatment	30,084	8.6883	Dominated	8,196
DEN	30,297	8.7142	Dominated	
Alternate source of persistence data for all				
Oral BIS	29,165.1	8.7078		174,742
IV IBN	29,213	8.7137	**8,094** (*vs.* oral BIS)	1,873,380
ZOL	29,216	8.7067	Dominated	142,987
RLX	29,420	8.7063	Dominated	110,109
BAZ	29,765	8.6957	Dominated	28,639
No treatment	30,084	8.6883	Dominated	8,196
DEN	30,297	8.7142	**1,873,380** (*vs.* IV IBN)	
Full persistence for all				
Oral BIS	28,618	8.7447		DEN dominated
IV IBN	29,603	8.7475	**353,654** (*vs.* oral BIS)	DEN dominated
RLX	29,766	8.7307	Dominated	1,064,599
No treatment	30,084	8.6883	Dominated	36,132
ZOL	30,601	8.7170	Dominated	69,481
BAZ	31,562	8.6959	Dominated	3,286
DEN	31,683	8.7325	Dominated	
Intended duration of therapy with denosumab (10 years)				
IV IBN	29,144	8.7176		136,026
Oral BIS	29,214	8.7117	Dominated	101,126
RLX	29,573	8.7082	Dominated	76,299
ZOL	29,601	8.7108	Dominated	82,602
BAZ	30,028	8.6957	Dominated	41,898
No treatment	30,084	8.6883	Dominated	34,308
DEN	31,747	8.7367	**136,026** (*vs.* IV IBN)	
Intended duration of therapy with IV IBN (3 years)				
IV IBN	29,007	8.7103		163,203
Oral BIS	29,214	8.7117	**144,533** (*vs.* IV IBN)	166,451
RLX	29,573	8.7082	Dominated	86,776
ZOL	29,601	8.7108	Dominated	107,460

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
BAZ	30,028	8.6957	Dominated	23,135
No treatment	30,084	8.6883	Dominated	15,927
DEN	30,589	8.7200	**166,451** (*vs.* oral BIS)	
Cost of administration, denosumab				
IV IBN	29,144	8.7176		534,084
Oral BIS	29,214	8.7117	Dominated	143,395
RLX	29,573	8.7082	Dominated	70,517
ZOL	29,601	8.7108	Dominated	86,746
BAZ	30,028	8.6957	Dominated	15,280
No treatment	30,084	8.6883	Dominated	9,916
DEN	30,398	8.7200	**534,084** (*vs.* IV IBN)	
Alternate source of fracture event costs				
IV IBN	29,767	8.7176		596,939
Oral BIS	29,835	8.7117	Dominated	161,605
RLX	30,249	8.7082	Dominated	78,596
ZOL	30,252	8.7108	Dominated	99,858
No treatment	30,753	8.6883	Dominated	13,143
BAZ	30,822	8.6957	Dominated	14,328
DEN	31,169	8.7200	**596,939** (*vs.* IV IBN)	
Time Horizon: 10 years				
Oral BIS	12,659	6.3475		286,445
IV IBN	12,884	6.3512	**60,371** (*vs.* oral BIS)	668,667
RLX	13,112	6.3456	Dominated	159,016
No treatment	13,282	6.3305	Dominated	46,954
ZOL	13,374	6.3449	Dominated	115,355
BAZ	13,569	6.3362	Dominated	45,884
DEN	14,355	6.3534	**668,667** (*vs.* IV IBN)	
Discount rate: 0% p.a.				
IV IBN	40,470	10.8335		545,916
Oral BIS	40,690	10.8257	Dominated	125,464
ZOL	40,974	10.8256	Dominated	97,062
RLX	41,078	10.8210	Dominated	61,237
BAZ	41,569	10.8055	Dominated	14,351
No treatment	41,872	10.7963	Dominated	3,481
DEN	42,011	10.8363	**545,916** (*vs.* IV IBN)	

Treatment	Cost (CHF)	Effect (QALYs)	ICER: *cost-effectiveness frontier analysis*	ICER: *pairwise comparisons (DEN vs.)*
Discount rate: 6% p.a.				
Oral BIS	21,682	7.2042		208,113
IV IBN	21,713	7.2088	**6,490** (*vs.* oral BIS)	678,506
RLX	22,007	7.2016	Dominated	114,447
ZOL	22,125	7.2028	Dominated	117,402
No treatment	22,334	7.1851	Dominated	28,311
BAZ	22,435	7.1912	Dominated	32,092
DEN	23,062	7.2108	**678,506** (*vs.* IV IBN)	
No excess death after vertebral fracture				
IV IBN	29,230	8.7280		1,081,415
Oral BIS	29,280	8.7226	Dominated	202,753
RLX	29,653	8.7192	Dominated	98,487
ZOL	29,690	8.7203	Dominated	106,167
BAZ	30,092	8.7071	Dominated	25,026
No treatment	30,171	8.6994	Dominated	15,967
DEN	30,650	8.7293	**1,081,415** (*vs.* IV IBN)	
No excess death after hip fracture				
IV IBN	29,689	8.7316		496,497
Oral BIS	29,743	8.7257	Dominated	158,744
RLX	30,093	8.7221	Dominated	84,810
ZOL	30,135	8.7252	Dominated	108,683
BAZ	30,549	8.7100	Dominated	24,207
No treatment	30,649	8.7040	Dominated	16,134
DEN	31,141	8.7345	**496,497** (*vs.* IV IBN)	
Exclude probability of nursing home admission				
No treatment	14,169	8.6883		54,229
Oral BIS	14,237	8.7117	**2,905** (*vs.* no treatment)	199,760
RLX	14,410	8.7082	Dominated	126,048
IV IBN	14,501	8.7176	**44,749** (vs. oral BIS)	589,773
ZOL	14,583	8.7108	Dominated	141,818
BAZ	14,872	8.6957	Dominated	41,852
DEN	15,886	8.7200	**589,773** (*vs.* IV IBN)	

Abbreviations:
BAZ: bazedoxifene; **BIS**: bisphosphonates; **CHF**: Swiss francs; **DEN**: denosumab; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV**: intravenous; **p.a.**: per annum; **QALY**: quality-adjusted life year; **RLX**: raloxifene; **RR:** risk ratio; **ZOL**: zoledronate.
Notes:
Interventions have been ranked in order of least to most costly. For the cost-effectiveness frontier analysis, ICERs have been calculated for interventions that are neither dominated nor extendedly dominated. For the pairwise comparison between DEN and each comparator, ICERs have been calculated as DEN vs. the comparator.

23.3 Deterministic sensitivity analyses: key drivers within each pairwise comparison

The sensitivity of each pairwise comparison (denosumab versus a comparator) to the scenario analyses were explored in more detail. Scenarios resulting in a situation of dominance (in favour of either denosumab or the comparator) were noted. Next, tornado diagrams were constructed to provide a visual representation of the key drivers of ICER outcomes for each pairwise comparison (***Figure 113*** to ***Figure 118***). Scenarios under which dominancy was observed were excluded from the tornadoes. For the denosumab versus IV ibandronate comparison, in which dominancy was observed under four scenarios, tornadoes showing the key drivers of incremental QALY and incremental cost outcomes were also presented (***Figure 111*** and ***Figure 112***).

In most pairwise comparisons (denosumab versus IV ibandronate, oral bisphosphonates, raloxifene, bazedoxifene and no treatment), age had an interesting impact on cost-effectiveness outcomes. Denosumab showed its best economic outcomes at a start age of 70 years, the ICER worsening (i.e., increasing) when the start age was either reduced to 60 years or increased to 80 years. This may be due to the differing relative prevalence of fracture types at differing ages. The start age (60 or 80 years) having the greatest impact on the ICER was included in the tornado diagram.

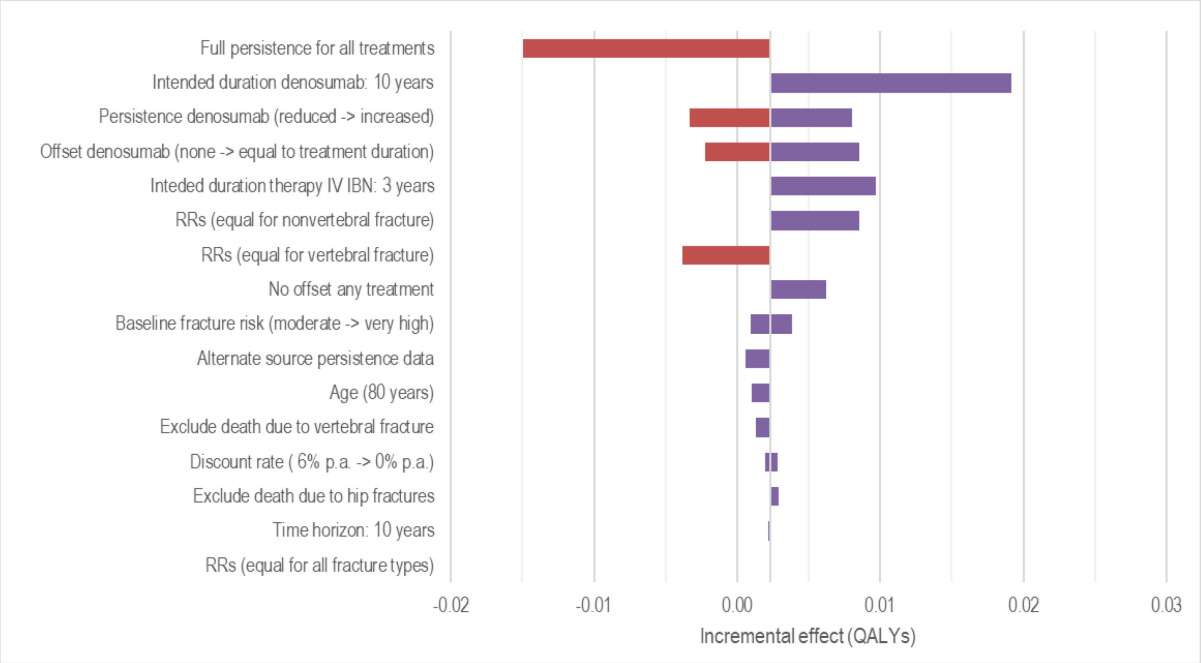
For the pairwise comparison between denosumab and zoledronate, patients' baseline fracture risk had an interesting impact on economic outcomes, denosumab showing its worst economic outcomes at the base case 'high-risk' level. The cost-effectiveness of denosumab was improved for women starting therapy with either a moderate fracture risk (ICER of CHF96,015; ***Table 134***) or very-high fracture risk (ICER of CHF36,509; ***Table 134***). Again, the baseline risk having the greatest impact on the ICER was included in the tornado diagram.

23.3.1 Denosumab versus IV ibandronate

Sensitivity analyses of the pairwise comparison between denosumab and IV ibandronate showed IV ibandronate to be dominant over denosumab on four occasions: *(1)* when the offset period of denosumab was removed, *(2)* when patient persistence with denosumab was decreased, *(3)* when the effectiveness of each treatment in reducing the risk of vertebral fracture was assumed equivalent, and *(4)* when full persistence was assumed for all treatments (***Table 136***). This dominance was driven by a reduction in incremental QALYs to below zero (***Figure 111***).

An increase in the intended duration of denosumab therapy also had a significant impact on incremental QALYs, seeing an increase in the incremental QALYs for denosumab over IV ibandronate (***Figure 111***).

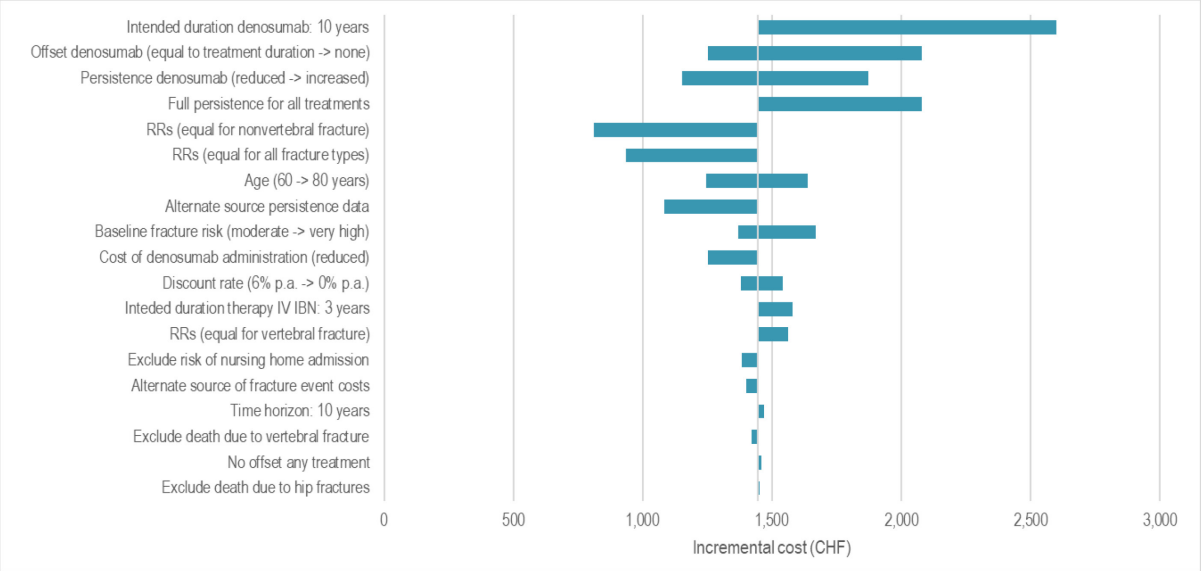
Figure 111 Tornado diagram for the denosumab versus IV ibandronate comparison, incremental QALYs



Abbreviations:
IBN: ibandronate; **IV**: intravenous; **p.a.:** per annum; **QALY**: quality-adjusted life year; **RR**: risk ratio
Notes:
The red bars highlight scenarios in which the incremental QALYs were negative (i.e., favoured the comparator).

The top four scenarios influencing incremental QALYs were the same four scenarios that the incremental cost outcome was most sensitive to: *(1)* inclusion of non-persistence in the model, *(2)* intended duration of denosumab, *(3)* patient persistence with denosumab, and *(4)* the assumed duration of residual benefit (i.e., the offset period) for denosumab (***Figure 111*** and ***Figure 112***). Under three of these scenarios, IV ibandronate was dominant (due to negative incremental QALYs). The fourth scenario (increased intended therapy duration for denosumab) increased both the incremental QALYs and incremental costs, resulting in an ICER of CHF136,026 (***Table 136***).

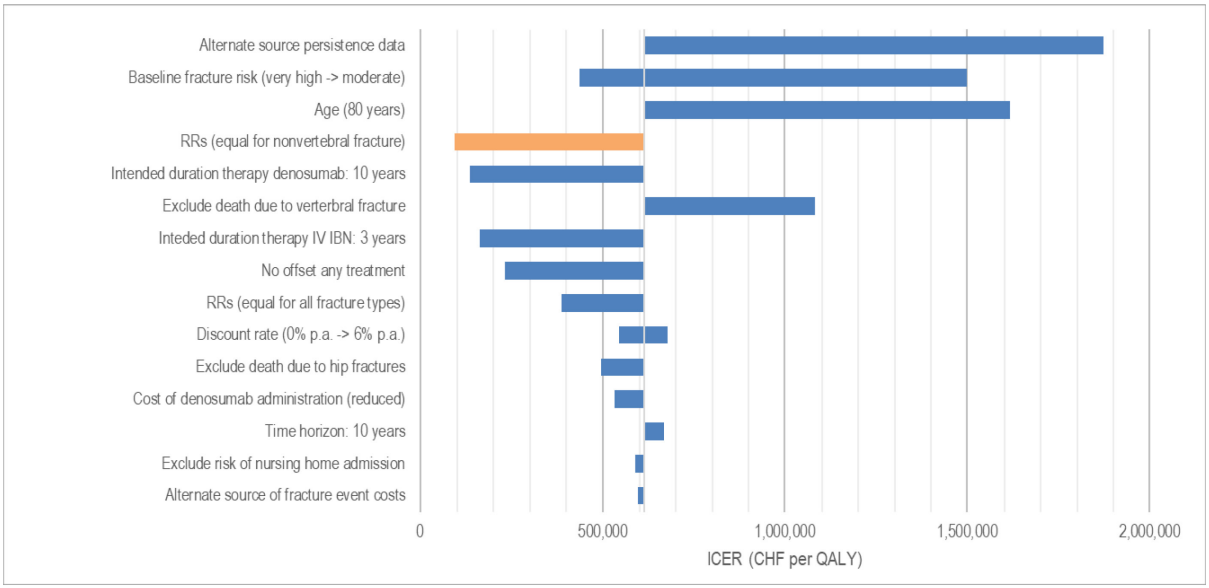
Figure 112 Tornado diagram for the denosumab versus IV ibandronate comparison, incremental costs



Abbreviations:
CHF: Swiss franc; **IBN**: ibandronate; **IV**: intravenous; **p.a.**: per annum; **RR**: risk ratio.

Excluding scenarios under which dominancy was observed, the ICER was most sensitive to the source of persistence data, patients' baseline risk of fracture, and the age at which patients begin antiresorptive therapy (***Figure 113***). Scenario analyses on all three variables pushed the ICER to at or above CHF1.5 million (***Figure 113*** and ***Table 136***). The ICER fell below the hypothetical WTP threshold of CHF100,000 on one occasion, when the effectiveness of each treatment in reducing the risk of nonvertebral fracture was assumed equivalent (ICER of CHF95,381; ***Figure 113*** and ***Table 136***).

Figure 113 Tornado diagram for the denosumab versus IV ibandronate comparison, ICER



Abbreviations:
CHF: Swiss franc; **IBN**: ibandronate; **ICER**: incremental cost-effectiveness ratio; **IV:** intravenous; **p.a.**: per annum **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
The orange bar highlights the scenario in which the ICER fell below a hypothetical willingness-to-pay of CHF100,000.

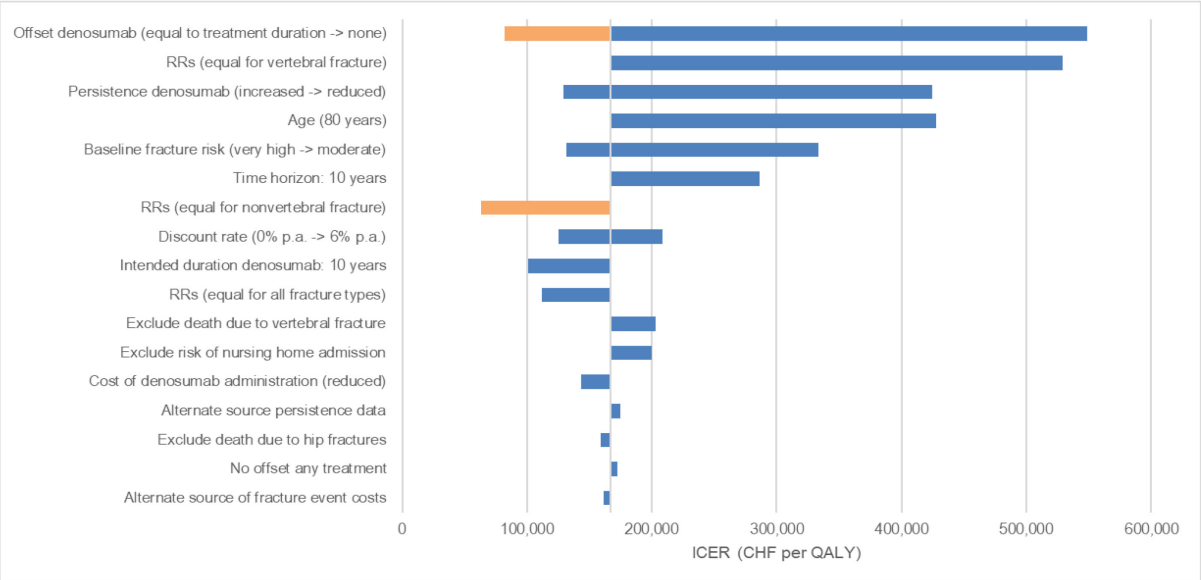
23.3.2 Denosumab versus oral bisphosphonates

Sensitivity analyses of the pairwise comparison between denosumab and oral bisphosphonates showed oral bisphosphonates to be dominant over denosumab when full persistence was assumed for both therapies (***Table 136***). This dominance was driven by a reduction in incremental QALYs to below zero (QALYs of 8.7325 and 8.7447 for denosumab and oral bisphosphonates; ***Table 136***).

Excluding the scenario under which dominancy was observed, the ICER was most sensitive to the assumed duration of residual benefit for denosumab, the difference in the treatments' efficacies on reducing the risk of vertebral fracture, patient persistence with denosumab, and the age at which patients start therapy (***Figure 114***).

The ICER fell below the hypothetical WTP threshold of CHF100,000 on two occasions (***Figure 114***): *(1)* when the offset period for denosumab was assumed to equal treatment duration (ICER of CHF91,895), and *(2)* when the effectiveness of each treatment in reducing the risk of nonvertebral fracture was assumed equivalent (ICER of CHF63,131). While the latter scenario (equivalent RRs for nonvertebral fracture) is plausible (given overlapping 95% CRIs), the former (extended offset period for denosumab) is unlikely (see ***Section 8.4.3.1***). When the intended duration of denosumab was extended to 10 years (an optimistic assumption; ***Section 8.4.3.1***), an ICER of CHF101,126 was observed (***Table 136***).

Figure 114 Tornado diagram for the denosumab versus oral bisphosphonates comparison, ICER



Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **p.a.**: per annum; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
The orange bars highlight scenarios in which the ICER fell below a hypothetical willingness-to-pay threshold of CHF100,000.

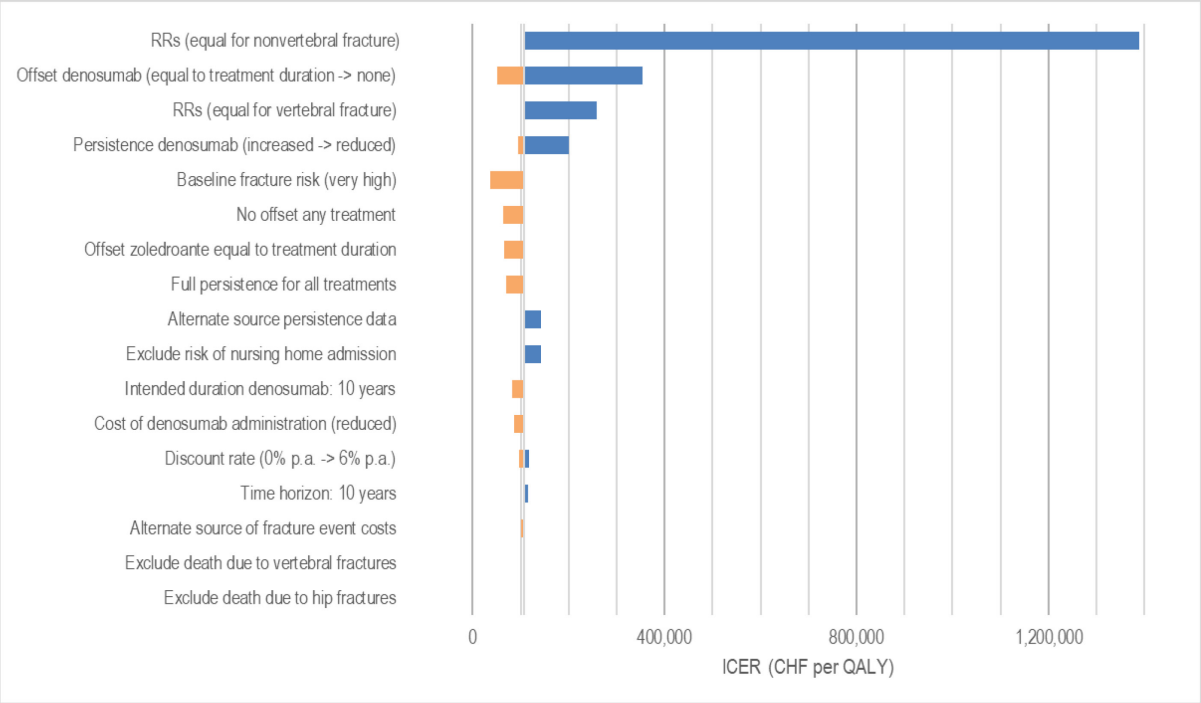
23.3.3 Denosumab versus zoledronate

Sensitivity analyses of the pairwise comparison between denosumab and zoledronate showed denosumab to be dominant over zoledronate in women starting therapy at age 80 years (***Table 136***). This dominance was driven by a reduction in the incremental cost to below zero (costs of CHF20,649 and CHF21,028 for denosumab and zoledronate, respectively ***Table 136***). Zoledronate was found to be dominant over denosumab when the efficacy of each treatment in reducing the risk of both vertebral and nonvertebral fractures were assumed equivalent (***Table 136***). In this case, dominancy was driven by a reduction in incremental QALYs to below zero (QALYs of 8.7200 and 8.7239 for denosumab and zoledronate, respectively; ***Table 136***).

Excluding the two scenarios under which dominancy was observed, the ICER was shown to be most sensitive to (in descending order) the difference in the treatments' efficacies on reducing nonvertebral fracture risk, the assumed duration of residual benefit (i.e., the offset period) for denosumab, and the difference in the treatments' efficacies on reducing vertebral fracture risk (***Figure 115***). Assuming equivalence in efficacy on nonvertebral risk reduction (a plausible scenario given overlapping 95% CRIs; ***Section 8.4.3.1***) had a considerable impact on the ICER, increasing it to CHF1.39 million (***Figure 115*** and ***Table 136***).

The ICER fell below the hypothetical WTP threshold of CHF100,000 on several occasions (***Figure 115***); as could be expected given the base case ICER lay close to the WTP value, at CHF107,460.

Figure 115 Tornado diagram for the denosumab versus zoledronate comparison; ICER



Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **p.a.**: per annum; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
The orange bars highlight scenarios in which the ICER fell below a hypothetical willingness-to-pay threshold of CHF100,000.

23.3.4 Denosumab versus raloxifene

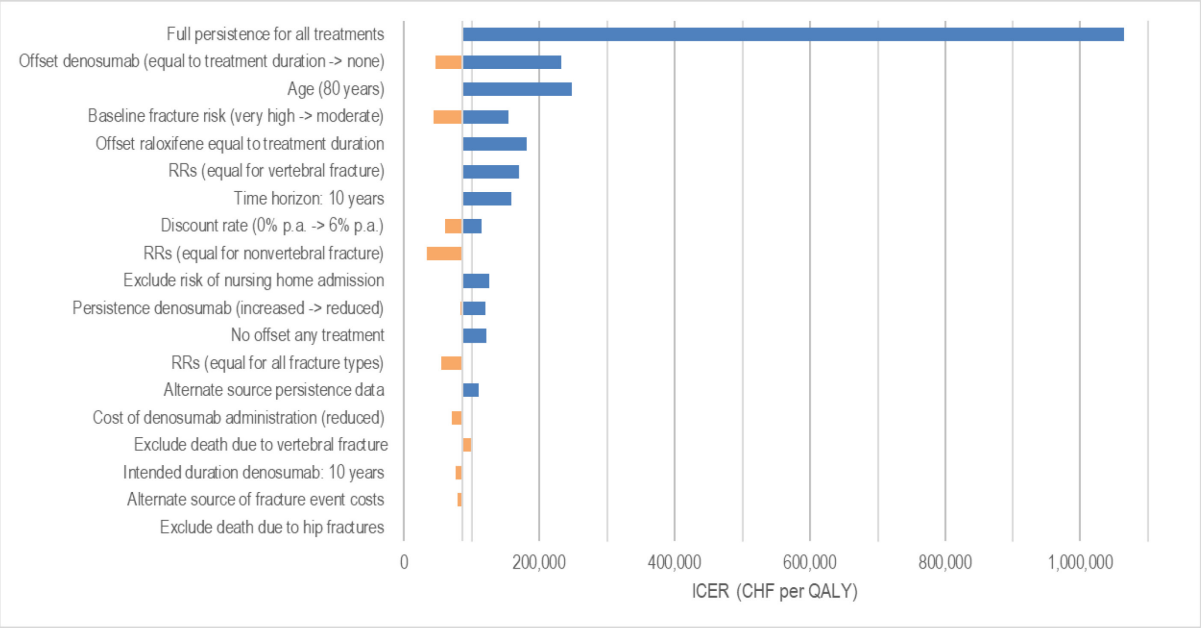
In the pairwise comparison between denosumab and raloxifene, the ICER was shown to be most sensitive to (in descending order), the inclusion of non-persistence data in the model, the assumed duration of residual benefit (i.e., the offset period) for denosumab, the age at which patients start therapy, patients' baseline fracture risk, and the assumed duration of residual benefit for raloxifene (***Figure 116***). Dominancy was not observed under any scenario.

The base case ICER for the pairwise comparison between denosumab and raloxifene was below the hypothetical WTP threshold of CHF100,000, at CHF86,776 (***Table 21***, ***Section 8.4.1***). The ICER increased to above CHF100,000 on several occasions (***Figure 116***), as could be expected given the proximity of the base case ICER to the hypothetical WTP value.

The largest ICER of CHF1.06 million was observed when full persistence was assumed for both raloxifene and denosumab – an unlikely scenario to observe in practice; however, one which provides useful insight, indicating the poor performance of raloxifene relative to denosumab may be driven by

the reduced persistence with oral versus alternate administration routes. An ICER of CHF248,060 was observed when the start age of therapy was set at 80 years of age (***Figure 116***), while an ICER of CHF231,51 was observed for a start age of 60 years (see ***Table 136***; data not included in tornado).

Figure 116 Tornado diagram for the denosumab versus raloxifene comparison; ICER



Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **p.a.**: per annum; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
The orange bars highlight scenarios in which the ICER remained below a hypothetical willingness-to-pay threshold of CHF100,000.

23.3.5 Denosumab versus bazedoxifene

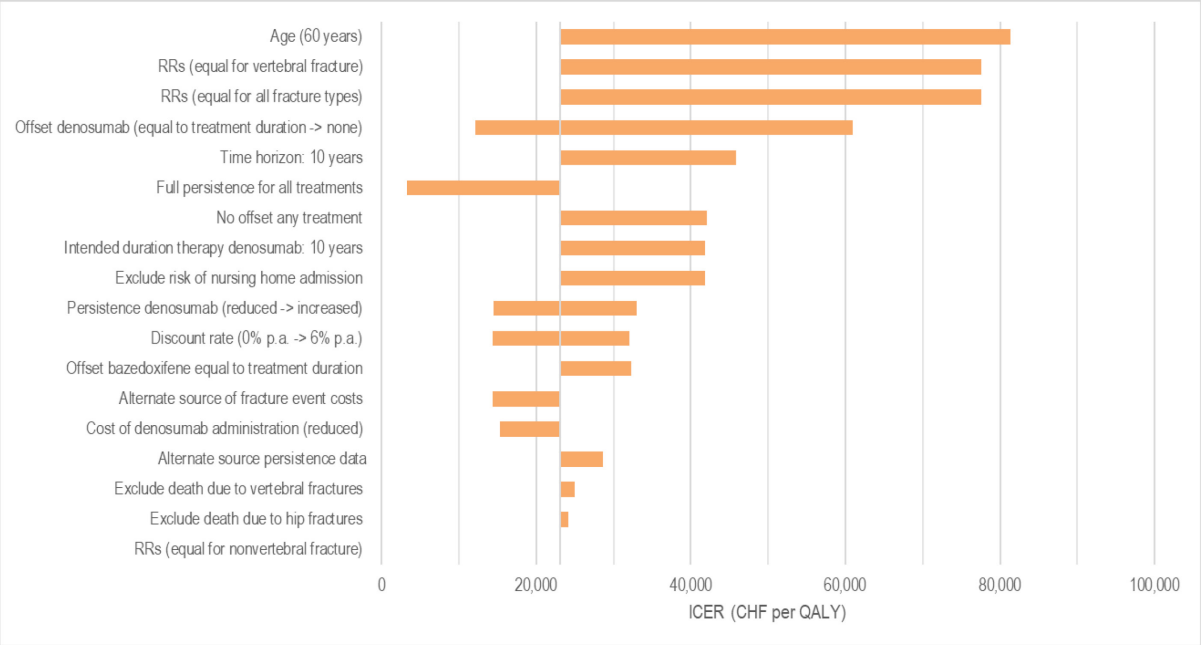
Sensitivity analyses of the pairwise comparison between denosumab and bazedoxifene showed denosumab to be dominant over bazedoxifene in women with a very high baseline risk of fracture (***Table 136).*** This dominance was driven by a reduction in the incremental cost to below zero (costs of CHF53,347 and CHF53,514 for denosumab and bazedoxifene; ***Table 136***).

Excluding the scenario under which dominancy was observed, the ICER was shown to be most sensitive to (in descending order) the age at which patients start therapy, the difference in the treatments' efficacies in reducing vertebral fracture risk, the difference in the treatments' efficacies in reducing fracture risk overall, and the assumed duration of residual benefit (i.e., the offset period) for denosumab (***Figure 117***).

The base case ICER for the pairwise comparison between denosumab and bazedoxifene was below the hypothetical WTP threshold of CHF100,000, at CHF23,135 (***Table 21***, ***Section 8.4.1***). The ICER never increased to a value above the hypothetical WTP threshold (***Figure 117)***. Similarly, in scenario

analyses on both age *and* baseline fracture risk, the ICER for denosumab versus bazedoxifene never increased above the hypothetical WTP threshold (see ***Table 133*** to ***Table 135***, ***Section 23.1***).

Figure 117 Tornado diagram for the denosumab versus bazedoxifene comparison; ICER



Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **p.a.**: per annum; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
The orange bars highlight scenarios in which the ICER remained below a hypothetical willingness-to-pay threshold of CHF100,000.

23.3.6 Denosumab versus no treatment

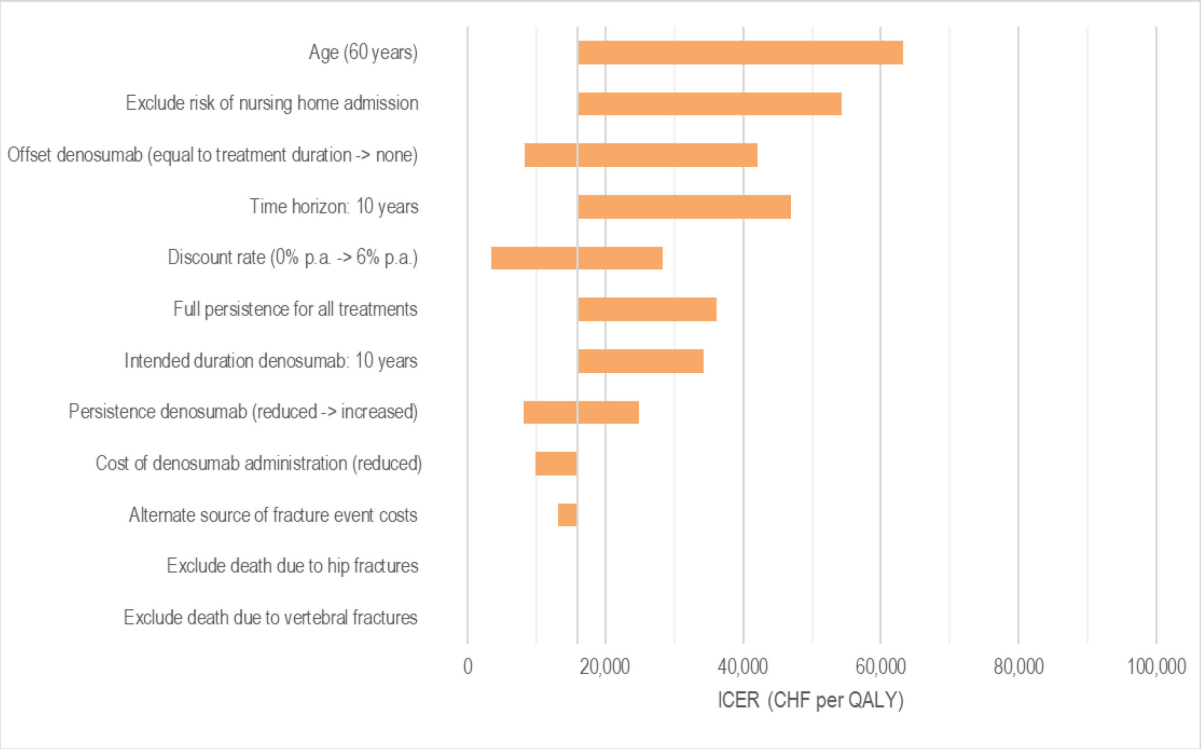
Sensitivity analyses of the pairwise comparison between denosumab and no treatment showed denosumab to be dominant over no treatment in women with very high baseline fracture risk (***Table 136).*** This dominance was driven by a reduction in the incremental cost to below zero (costs of CHF53,347 and CHF53,680 for denosumab and no treatment; ***Table 136***).

Excluding the scenario under which dominancy was observed, the ICER was shown to be most sensitive to (in descending order) the age at which patients start therapy, the inclusion of nursing home admissions after hip fracture within the model structure, and the assumed duration of residual benefit (i.e., the offset period) for denosumab (***Figure 118***).

The base case ICER for the pairwise comparison between denosumab and no treatment was below the hypothetical WTP threshold of CHF100,000, at CHF15,927 (***Table 21***, ***Section 8.4.1***). The ICER never increased to a value above the hypothetical WTP threshold across the deterministic sensitivity analyses conducted (***Figure 118***). However, in scenario analyses on both age *and* baseline fracture

risk, ICERs of CHF102,189 and CHF122,815 were observed for denosumab versus no treatment in women age 60 or 80 years, respectively, at moderate fracture risk (see ***Table 133*** and ***Table 135***, ***Section 23.1***).

Figure 118 Tornado diagram for the denosumab versus no treatment comparison; ICER



Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **p.a.**: per annum; **QALY**: quality-adjusted life year.
Notes:
The orange bars highlight scenarios in which the ICER remained below a hypothetical willingness-to-pay threshold of CHF100,000.