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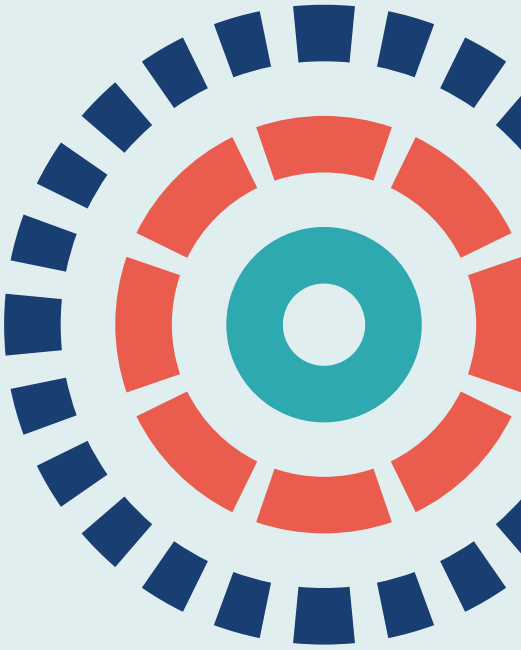

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Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation

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This report

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Abstract

Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation

Sarah Davis,[1*] Emma Simpson,[1] Jean Hamilton,[1] Marrissa Martyn-St James,[1] Andrew Rawdin,[1] Ruth Wong,[1] Edward Goka,[1] Neil Gittoes[2] and Peter Selby[3]

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Background: Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture.

Objectives: The objectives were to evaluate the clinical effectiveness, safety and cost-effectiveness of non-bisphosphonates {denosumab [Prolia®; Amgen Inc., Thousand Oaks, CA, USA], raloxifene [Evista®; Daiichi Sankyo Company, Ltd, Tokyo, Japan], romosozumab [Evenity®; Union Chimique Belge (UCB) S.A. (Brussels, Belgium) and Amgen Inc.] and teriparatide [Forsteo®; Eli Lilly and Company, Indianapolis, IN, USA]}, compared with each other, bisphosphonates or no treatment, for the prevention of fragility fracture.

Data sources: For the clinical effectiveness review, nine electronic databases (including MEDLINE, EMBASE and the World Health Organization International Clinical Trials Registry Platform) were searched up to July 2018.

Review methods: A systematic review and network meta-analysis of fracture and femoral neck bone mineral density were conducted. A review of published economic analyses was undertaken and a model previously used to evaluate bisphosphonates was adapted. Discrete event simulation was used to estimate lifetime costs and quality-adjusted life-years for a simulated cohort of patients with heterogeneous characteristics. This was done for each non-bisphosphonate treatment, a strategy of no treatment, and the five bisphosphonate treatments previously evaluated. The model was populated with effectiveness evidence from the systematic review and network meta-analysis. All other parameters were estimated from published sources. An NHS and Personal Social Services perspective was taken, and costs and benefits were discounted at 3.5% per annum. Fracture risk was estimated from patient characteristics using the QFracture® (QFracture-2012 open source revision 38, Clinrisk Ltd, Leeds, UK) and FRAX® (web version 3.9, University of Sheffield, Sheffield, UK) tools. The relationship between fracture risk and incremental net monetary benefit was estimated using non-parametric regression. A probabilistic sensitivity analysis and scenario analyses were used to assess uncertainty.

Results: Fifty-two randomised controlled trials of non-bisphosphonates were included in the clinical effectiveness systematic review and an additional 51 randomised controlled trials of bisphosphonates were included in the network meta-analysis. All treatments had beneficial effects compared with placebo for vertebral, non-vertebral and hip fractures, with hazard ratios varying from 0.23 to 0.94, depending on treatment and fracture type. The effects on vertebral fractures and the percentage change

in bone mineral density were statistically significant for all treatments. The rate of serious adverse events varied across trials (0–33%), with most between-group differences not being statistically significant for comparisons with placebo/no active treatment, non-bisphosphonates or bisphosphonates. The incremental cost-effectiveness ratios were > £20,000 per quality-adjusted life-year for all non-bisphosphonate interventions compared with no treatment across the range of QFracture and FRAX scores expected in the population eligible for fracture risk assessment. The incremental cost-effectiveness ratio for denosumab may fall below £30,000 per quality-adjusted life-year at very high levels of risk or for high-risk patients with specific characteristics. Raloxifene was dominated by no treatment (resulted in fewer quality-adjusted life-years) in most risk categories.

Limitations: The incremental cost-effectiveness ratios are uncertain for very high-risk patients.

Conclusions: Non-bisphosphonates are effective in preventing fragility fractures, but the incremental cost-effectiveness ratios are generally greater than the commonly applied threshold of £20,000–30,000 per quality-adjusted life-year.

Study registration: This study is registered as PROSPERO CRD42018107651.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 29. See the NIHR Journals Library website for further project information.

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List of abbreviations

ACTIVE	Abaloparatide Comparator Trial In Vertebral Endpoints
AE	adverse event
AG	assessment group
ALN	alendronate
ARCH	active-controlled fracture study in postmenopausal women with osteoporosis at high risk
BMD	bone mineral density
CG	clinical guideline
CHM	Commission on Human Medicines
CODA	convergence diagnosis and output analysis
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CrI	credible interval
DATA	Denosumab and Teriparatide Administration
DEN	denosumab
DES	discrete event simulation
DIC	deviance information criterion
DIRECT	Denosumab fracture Intervention RandomizEd placebo Controlled Trial
DVT	deep-vein thrombosis
DXA	dual-energy X-ray absorptiometry
EQ-5D	EuroQol-5 Dimensions
EQ-VAS	EuroQol – Visual Analogue Scale
EUROFORS	European Study of Forsteo
EVA	EVista Alendronate comparison
ExFOS	European Extended Forsteo Observational Study
FLEX	Fracture Intervention Trial Long-term Extension
FPT	Fracture Prevention Trial
FRAME	Fracture Study in Postmenopausal Women with Osteoporosis
FREEDOM	Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months
GI	gastrointestinal
GP	general practitioner
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICUROS	International Costs and Utilities Related to Osteoporotic Fractures Study
IBN	ibandronate
ICER	incremental cost-effectiveness ratio
INMB	incremental net monetary benefit
i.v.	intravenous
LOCF	last observation carried forward
MD	mean difference
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intent to treat

MTA	multiple technology appraisal
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NOGG	National Osteoporosis Guideline Group
ONJ	osteonecrosis of the jaw
PAS	Patient Access Scheme
PB	probability of being the best-ranking treatment
PE	pulmonary embolism
PrI	prediction interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QS	quality standard
QUALEFFO-41	Quality of Life Questionnaire of the European Foundation for Osteoporosis-41 items
RCT	randomised controlled trial
RevMan	Review Manager
RIS	risedronate
RLX	raloxifene
ROMO	romosozumab
RR	risk ratio
SA	sensitivity analysis
SAE	serious adverse event
s.c.	subcutaneous
ScHARR	School of Health and Related Research
SD	standard deviation
SmPC	Summary of Product Characteristics
TA	technology appraisal
TPTD	teriparatide
VBA	Visual Basic for Applications
VERO	VERtebral fracture treatment comparisons in Osteoporotic women
VTE	venous thromboembolism
WHO	World Health Organization
ZOL	zoledronic acid

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Background

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low-energy') trauma. Some people are at particularly high risk of fragility fractures. The first treatment used is often a bisphosphonate, but non-bisphosphonate treatments are alternatives.

Aims

We aimed to determine how effective non-bisphosphonates {denosumab [Prolia®; Amgen Inc., Thousand Oaks, CA, USA], raloxifene [Evista®; Daiichi Sankyo Company, Ltd, Tokyo, Japan], romosozumab [Evenity®; Union Chimique Belge (UCB) S.A. (Brussels, Belgium) and Amgen Inc.] and teriparatide [Forsteo®; Eli Lilly and Company, Indianapolis, IN, USA]} are at preventing fractures, whether or not treatment has any risks for patients and whether or not the clinical benefits are achieved at a reasonable cost.

Methods

We have systematically identified and examined trials that assessed the clinical effects of non-bisphosphonates. For each clinical outcome, we have combined data from multiple trials to estimate the clinical effectiveness of each non-bisphosphonate treatment.

We combined data from published sources in an economic model to estimate lifetime costs and clinical benefits for each non-bisphosphonate and compared these with the estimated costs and clinical outcomes for untreated patients and patients treated with bisphosphonates.

Results

All non-bisphosphonates reduced the risk of vertebral fractures compared with no treatment. For fractures at the hip or at any non-vertebral site, all of the non-bisphosphonates reduced the average number of fractures, but, for some non-bisphosphonates, we could not exclude the possibility that this was a chance finding.

The chance of patients experiencing serious side effects was generally similar regardless of whether patients took non-bisphosphonates, bisphosphonates or placebo (a dummy pill). Blood clots were more common in patients taking raloxifene than in those taking placebo, but these were still a rare outcome (fewer than 1 in 100).

The benefits of denosumab, teriparatide and romosozumab are few compared with their costs. For raloxifene, the risks generally outweigh the benefits. Treatment with bisphosphonates is likely to represent better value for money than treatment with non-bisphosphonates.

Scientific summary

Background

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture (defined by the World Health Organization as a broken bone resulting from a fall from standing height or lower). In the UK, the number of women and men aged > 50 years with osteoporosis has been estimated as 2,527,331 women and 679,424 men, with approximately 536,000 new fragility fractures, comprising 79,000 hip fractures, 66,000 vertebral fractures, 69,000 forearm fractures and 322,000 other fractures. Osteoporotic fractures cause significant pain, disability and loss of independence, and can be fatal.

Objectives

The objectives were to determine the clinical effectiveness and cost-effectiveness of denosumab (Prolia®; Amgen Inc., Thousand Oaks, CA, USA), raloxifene (Evista®; Daiichi Sankyo Company, Ltd, Tokyo, Japan), romosozumab [Evenity®; Union Chimique Belge (UCB) S.A. (Brussels, Belgium) and Amgen Inc.] and teriparatide (Forsteo®; Eli Lilly and Company, Indianapolis, IN, USA) within their licensed indications, for the prevention of osteoporotic fragility fractures, compared with each other, bisphosphonates or a non-active treatment.

Methods

A systematic review and network meta-analysis of clinical effectiveness and safety evidence for interventions of interest were conducted. Nine electronic databases (including MEDLINE, EMBASE and the World Health Organization International Clinical Trials Registry Platform) were searched up to July 2018. Studies were eligible for inclusion if they were randomised controlled trials comparing the non-bisphosphonates denosumab, raloxifene, romosozumab or teriparatide with each other, placebo or bisphosphonates within their licensed indication for an osteoporosis population, and reported either fracture or bone mineral density data. The quality of included studies was assessed using the Cochrane risk-of-bias tool.

A review of the existing cost-effectiveness literature was undertaken, including economic evaluations described in the company submissions. The identified cost-effectiveness analyses were compared with the model that was developed to inform the National Institute for Health and Care Excellence Multiple Technology Appraisal of bisphosphonates [National Institute for Health and Care Excellence. *Bisphosphonates for Treating Osteoporosis. Technology Appraisal Guidance [TA464].* 2017. URL: www.nice.org.uk/guidance/ta464/resources/bisphosphonates-for-treating-osteoporosis-pdf-82604905556677 (accessed 20 November 2018)] to identify areas of difference. The model used in Technology Appraisal Guidance 464 was then adapted to evaluate the cost-effectiveness of non-bisphosphonates when compared with either no treatment or treatment with bisphosphonates across the whole population eligible for fracture risk assessment {as defined by the National Institute for Health and Care Excellence Clinical Guideline 146 [National Institute for Health and Care Excellence. *Osteoporosis: Assessing the Risk of Fragility Fracture. Clinical Guideline [CG146].* 2012. URL: www.nice.org.uk/guidance/cg146/resources/osteoporosis-assessing-the-risk-of-fragility-fracture-pdf-35109574194373 (accessed 20 November 2018)]}. Incremental analyses were conducted for 10 risk categories based on deciles of risk when using either the QFracture® (QFracture-2012 open source revision 38, Clinrisk Ltd, Leeds, UK) or FRAX® (web version 3.9, University of Sheffield, Sheffield, UK) risk-scoring algorithms to determine risk.

In the economic analyses, treatment with romosozumab was modelled as a treatment sequence of romosozumab followed by the bisphosphonate alendronate (romosozumab/alendronate). All of the other treatment strategies modelled consisted of a single intervention followed by no treatment.

Results

The systematic review of clinical effectiveness identified 7898 citations. Fifty-two randomised controlled trials of non-bisphosphonates were included in the review, and an additional 51 randomised controlled trials of bisphosphonates were included for the network meta-analyses. Studies varied in quality, particularly on the domains of blinding and attrition, and were not all well reported.

Across studies reporting overall mortality, there were no significant differences between non-bisphosphonate treatment arms and their comparators of placebo, other non-bisphosphonates or bisphosphonates. The ranges of serious adverse event rates were as follows: denosumab, 1.6–25.8%; raloxifene, 2.0–18.6%; romosozumab, 3.2–12.9%; and teriparatide, 0.0–33.0%.

Network meta-analyses were conducted for vertebral fractures (46 randomised controlled trials, 11 interventions), non-vertebral fractures (42 randomised controlled trials, 11 interventions), hip fractures (23 randomised controlled trials, nine interventions), wrist fractures (15 randomised controlled trials, eight interventions), proximal humerus fractures (13 proximal humerus fractures, eight interventions) and percentage change in femoral neck bone mineral density (73 proximal humerus fractures, 12 interventions). For vertebral, non-vertebral and hip fractures and for femoral neck bone mineral density, all treatments were associated with beneficial effects relative to placebo. For both vertebral fractures and percentage change in femoral neck bone mineral density, the treatment effects were statistically significant at a conventional 5% level for all treatments. For vertebral, non-vertebral and hip fractures, teriparatide provided the largest treatment effect, although, in general, the ranking of treatments varied for the different outcomes. For wrist and proximal humerus fractures, there was less randomised controlled trial evidence, and so there is considerable uncertainty in treatment effects for certain interventions in these networks. Sensitivity analyses conducted to assess the impact of assessment method for vertebral fractures (radiographic or clinical), duration of study, issues with data quality and effect of prior bisphosphonate treatment demonstrated that the results of the network meta-analysis were robust to these potential issues.

In the economic evaluation conducted by the assessment group, the incremental cost-effectiveness ratios were found to be > £30,000 per quality-adjusted life-year for all of the non-bisphosphonate treatments (raloxifene, denosumab, teriparatide and romosozumab/alendronate) compared with no treatment across all 10 risk categories when using either QFracture or FRAX to estimate the 10-year absolute risk of fracture. This finding was unchanged when sensitivity analyses were conducted exploring alternative assumptions regarding the duration of persistence with treatment and the duration of time it takes for the treatment effect to fall to zero after treatment stops (the offset period). The results of the regression of incremental net monetary benefit against fracture risk predicted a positive incremental net monetary benefit for denosumab compared with no treatment when valuing a quality-adjusted life-year at £30,000 at very high levels of risk (FRAX score of > 45%), but the estimates of cost-effectiveness are very uncertain at this level of risk. Otherwise, the results of the regression analysis were consistent with the findings based on the 10 risk categories. An exploratory scenario analysis examining an example high-risk patient also suggested that the cost-effectiveness of denosumab may be more favourable among high-risk patients with specific characteristics.

Discussion

Fracture and bone mineral density data were available for all four non-bisphosphonate interventions. All of these interventions were associated with beneficial effects compared with placebo.

One of the strengths of this analysis is that we have been able to estimate the cost-effectiveness of each intervention across the broad range of absolute fracture risk observed in the population eligible for risk assessment under Clinical Guideline 146. However, the downside of the approach we have taken is that the estimates of cost-effectiveness are uncertain for patients at high risk of fracture (e.g. > 30%), as they are informed by fewer simulated patients.

The results of the assessment group's economic evaluation differ from the cost-effectiveness results presented in the submissions by the companies for denosumab and romosozumab. However, the review of cost-effectiveness analyses highlighted a number of important differences between these economic evaluations.

Conclusions

The non-bisphosphonate interventions (raloxifene, denosumab, teriparatide and romosozumab) are all clinically effective at reducing vertebral fracture risk when compared with placebo. However, the effectiveness estimates for other fracture sites are more uncertain and the treatment effects were not statistically significant at a conventional 5% level for all non-bisphosphonate treatments for non-vertebral fractures.

The incremental cost-effectiveness ratios compared with no treatment are above the National Institute for Health and Care Excellence threshold of £20,000 per quality-adjusted life-year for all non-bisphosphonate interventions across the range of QFracture and FRAX scores expected in the population eligible for fracture risk assessment. The incremental cost-effectiveness ratio for denosumab was < £30,000 per quality-adjusted life-year for very high-risk patients (FRAX score of > 45%), based on the regression, but the estimates of cost-effectiveness for high-risk patients are very uncertain.

Study registration:

This study is registered as PROSPERO CRD42018107651.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 29. See the NIHR Journals Library website for further project information.

Chapter 1 Background

Description of the health problem

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture (a broken bone as a result of a fall from standing height or lower). The definition provided by the World Health Organization (WHO)[1] defines the condition as bone mineral density (BMD) that is 2.5 standard deviations (SDs) below the average peak bone mass of healthy females aged 20–29 years, as measured by dual-energy X-ray absorptiometry (DXA). The WHO operational definition is updated to refer specifically to DXA at the femoral neck.[2] The term 'established osteoporosis' includes the presence of a fragility fracture.[1] Primary osteoporosis can occur in both men and women, but is most common in women after menopause, when it is termed postmenopausal osteoporosis. In contrast, secondary osteoporosis may occur in anyone as a result of medications, specifically glucocorticoids, or in the presence of particular hormonal disorders and other chronic diseases.[3]

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low-energy') trauma, quantified as forces equivalent to a fall from a standing height or lower.[1] Although osteoporosis is an important predictor of the risk of fragility fracture, 70% of fragility fractures in postmenopausal women occur in those who do not meet the criteria for osteoporosis.[4]

The prevalence of osteoporosis in the EU has been estimated at 22 million women and 5.5 million men.[5] In the UK, the number of women and men aged > 50 years with osteoporosis has been estimated as 2,527,331 women and 679,424 men, with approximately 536,000 new fragility fractures, comprising 79,000 hip fractures, 66,000 vertebral fractures, 69,000 forearm fractures and 322,000 other fractures (i.e. fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum and other femoral fractures).[6]

In 2010, the number of postmenopausal women living with osteoporosis in the UK, based on the definition of a BMD at least 2.5 SDs lower than a young healthy woman (*T*-score of ≤ -2.5 SDs), was predicted to increase to 2.1 million in 2020 (+ 16.5%).[7] The prevalence of osteoporosis in the general population of women aged ≥ 50 years in the UK was assumed to remain stable over time, at approximately 15.5%.

Current service provision

Clinical guidelines

Currently, related National Institute for Health and Care Excellence (NICE) guidance includes a clinical guideline (CG) for identifying women and men at risk of fracture (CG146[8]) and four technology appraisals (TAs) of treatments for osteoporosis (TA464,[9] TA204,[10] TA161[11] and TA160[12]).

Current National Institute for Health and Care Excellence technology appraisal guidance

The NICE guidance TA464[9] recommends oral bisphosphonates [alendronate (ALN), ibandronate (IBN) and risedronate (RIS)] and intravenous (i.v.) bisphosphonates [IBN and zoledronic acid (ZOL)] as options for treating osteoporosis in people who are eligible for risk assessment, as defined in NICE's CG146 on osteoporosis,[8] depending on the person's risk of fragility fracture.[9] However, the risk level at which oral bisphosphonates are cost-effective is not a clinical intervention threshold. NICE guidance TA464[9] should be applied clinically in conjunction with the NICE quality standard (QS) 149 on osteoporosis,[13]

which defines the clinical intervention thresholds. These thresholds are based on the NICE-accredited National Osteoporosis Guideline Group (NOGG) guideline.[14]

The NICE guidance TA204[10] recommends denosumab (DEN) (Prolia®; Amgen Inc., Thousand Oaks, CA, USA) for the primary prevention of fragility fractures in postmenopausal women at specified fracture risks, defined by age, *T*-score and number of independent clinical risk factors for fracture, who have osteoporosis and who are unable to comply with the special instructions for administering ALN and either RIS or etidronate (which is no longer marketed in the UK), or have an intolerance of, or a contraindication to, those treatments. TA204[10] also recommends DEN for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are at an increased risk of fractures and who are unable to comply with the special instructions for administering ALN and either RIS or etidronate, or have an intolerance of, or a contraindication to, ALN and either RIS or etidronate.

The NICE guidance TA161[11] recommends raloxifene (RLX) (Evista®; Daiichi Sankyo Company, Ltd, Tokyo, Japan) and strontium ranelate (discontinued at the time this research was conducted), and teriparatide (TPTD) (Forsteo®; Eli Lilly and Company, Indianapolis, IN, USA) at specified fracture risks, defined by age, *T*-score and number of independent clinical risk factors for fracture, for women who have already sustained a fracture and who cannot take ALN.[11] NICE guidance TA160[12] does not recommend RLX as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.[12]

Current service cost

Hernlund *et al.*[5] reviewed the literature on fracture incidence and costs of fractures in the 27 EU countries and incorporated data into a model estimating the clinical and economic burden of osteoporotic fractures in 2010. The cost of osteoporosis, including pharmacological intervention in the EU in 2010 was estimated at €37B. Costs of treating incident fractures represented 66% of this cost, pharmacological prevention represented 5% and long-term fracture care represented 29%. Excluding the costs of pharmacological prevention, hip fractures represented 54% of the costs, vertebral and forearm fractures represented 5% and 1%, respectively, of the costs and 'other fractures' represented 39%. The estimated number of life-years lost in the EU as a result of incident fractures was approximately 26,300 in 2010. The total health burden, measured in terms of lost quality-adjusted life-years (QALYs), was estimated at 1,180,000 QALYs for the EU.

In the UK, the cost of osteoporosis (excluding the value of QALYs lost) in 2010 was estimated by Hernlund *et al.*[5] at €103M (£91.8M in 2017 prices) for pharmacological fracture prevention, €3977M (£3546M in 2017 prices) for cost of fractures, and €1328M (£1185M in 2017 prices) for cost of long-term disability. The 2010 cost of UK osteoporosis fracture in relation to population and health-care spending was €5408M (£4822M in 2017 prices). The 2010 prices reported by Hernlund *et al.*[5] in euros were converted back to Great British pounds (2006 prices). The conversion ratio from 2006 prices to 2010 prices used by Hernlund *et al.*[5] was estimated by the School of Health and Related Research (ScHARR) as 1.4065 by comparing the unit cost for nursing home stay against the cited UK-specific source data from 2006.[15] Costs were then uplifted to 2017 prices using the Hospital and Community Health Service inflation indices from the Personal Social Services Research Unit (PSSRU)[16] (302.3 for 2016/17 vs. 240.9 for 2005/6).

Current treatment pathway

The NICE 2018 osteoporosis overview pathway[17] and fragility fracture risk assessment pathway[18] cover NICE guidance on osteoporosis in adults (aged $\geq$ 18 years), including assessing the risk of fragility fracture and drug treatment for the primary and secondary prevention of osteoporotic fragility fractures. (The recommendations on assessment of fracture risk in CG146[8] are summarised in *Measurement of disease*.)

Description of the technology under assessment

Interventions considered in the scope of this report

Four interventions are considered in this assessment: DEN, RLX, romosozumab (ROMO) [Evenity®; Union Chimique Belge (UCB) S.A. (Brussels, Belgium) and Amgen Inc.] and TPTD.

Mode of action

Treatments for osteoporosis generally fall into two classes: bone-forming agents (ROMO and TPTD) and anti-resorptive agents (bisphosphonates, DEN and RLX). Bone-forming agents are used for shorter durations of treatment, often in patients at very high risk of fracture, whereas anti-resorptive agents are used as long-term treatments and sometimes after bone-forming agents.[19] It should be noted that the company submission by UCB S.A. states that ROMO leads to 'an increase in bone formation and reduction in bone resorption', suggesting that it has both bone-forming and anti-resportive properties.[20]

Marketing licence and administration method

Denosumab is a monoclonal antibody that reduces osteoclast activity, and so reduces bone breakdown. It is administered as a single 60-mg subcutaneous (s.c.) injection once every 6 months. DEN has a marketing authorisation in the UK for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.[19] DEN also has a marketing authorisation for the treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.[21]

Raloxifene is a selective oestrogen receptor modulator. It is administered orally at a dose of 60 mg daily. RLX has a marketing authorisation in the UK for the treatment and prevention of osteoporosis in postmenopausal women. Non-proprietary RLX [Sandoz International GmBH (Holzkirchen, Germany), Consilient Health Ltd (Dublin, Ireland), Actavis UK (now Accord-UK Ltd, Barnstaple, UK), Mylan Pharma UK Ltd (Sandwich, UK)] is also available for the same indication.[19]

Romosozumab is a monoclonal antibody that inhibits the protein sclerostin, increasing bone formation and decreasing bone breakdown. It has been studied in clinical trials as 12 months of ROMO followed by at least 12 months of ALN, compared with at least 24 months of ALN alone, in postmenopausal women. It has also been studied in a randomised, placebo-controlled clinical trial for treating osteoporosis in men.[19] This report was prepared while ROMO was still being assessed by the European Medicines Agency; therefore, it was based on the anticipated licensed indication for ROMO. A marketing authorisation was issued in December 2019; the recommended dose is 210 mg (administered as two s.c. injections of 105 mg each) once monthly for 12 months. This is consistent with the anticipated licensed indication used in preparation of this report.

Teriparatide is a recombinant fragment of human parathyroid hormone and, as an anabolic agent, it stimulates formation of new bone and increases resistance to fracture. It is administered subcutaneously at a dose of 20 µg daily for up to 24 months. TPTD has a marketing authorisation in the UK for treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. It also has a marketing authorisation in the UK for treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture. Biosimilar versions of TPTD [Movymia, Internis Pharmaceuticals Ltd (Huddersfield, UK);[22] Terrosa, Gedeon Richter plc (Budapest, Hungary)[23]] have been licensed for the same indications.[19]

Contraindications, special warnings and precautions

The Summary of Product Characteristics (SmPC) for each intervention describes the contraindications and special warnings for bisphosphonates.[20,24,25]

A s.c. injection of 60 mg of DEN once every 6 months is contraindicated in patients with hypocalcaemia or hypersensitivity to the active substance or to any of its excipients. Adequate intake of calcium and vitamin D is important in all patients.[24] Special warnings and precautions include hypocalcaemia, renal impairment, skin infections, osteonecrosis of the jaw (ONJ) and atypical femoral fracture.[24]

A 60-mg daily oral dose of RLX is contraindicated in women with child-bearing potential and in patients with an active or past history of venous thromboembolism (VTE), including deep-vein thrombosis (DVT), pulmonary embolism (PE) and retinal vein thrombosis; hepatic impairment including cholestasis; severe renal impairment; unexplained uterine bleeding; signs or symptoms of endometrial cancer; or hypersensitivity to the active substance or to any of the excipients.[25]

The draft SmPC for ROMO notes special precautions in patients (confidential information has been removed). Special warnings and precautions include (confidential information has been removed).[20]

Teriparatide administered subcutaneously at a dose of 20 µg daily is contraindicated in women who are pregnant or breastfeeding and in patients with pre-existing hypercalcaemia, severe renal impairment, metabolic bone diseases (including hyperparathyroidism and Paget's disease of bone) (other than primary osteoporosis or glucocorticoid-induced osteoporosis), unexplained elevations of alkaline phosphatase, prior external beam or implant radiation therapy to the skeleton, skeletal malignancies or bone metastases, or hypersensitivity to the active substance or to any of the excipients.[25] Precautions include elevations of serum calcium concentrations, active or recent urolithiasis, orthostatic hypotension and renal impairment.[25]

Place in treatment pathway

Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fracture who are unable to comply with the special instructions for administering ALN and either RIS or etidronate, or have an intolerance of, or a contraindication to, those treatments and who have a sufficiently high risk of fracture as determined by a combination of *T*-score, age and number of independent clinical risk factors for fracture.[10] DEN is also recommended 'as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments' (TA204)[10] (© NICE 2010 *Denosumab for the Prevention of Osteoporotic Fractures in Postmenopausal Women. Technology Appraisal Guidance [TA204].* Available from www.nice.org.uk/guidance/ta204. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication.). DEN has a marketing authorisation in the UK for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and for the treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.[21]

Raloxifene is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to comply with the special instructions for the administration of ALN and RIS, or have a contraindication to, or are intolerant of, ALN and RIS and who also are at a sufficiently high risk of fracture as determined by a combination of *T*-score, age and number of independent clinical risk factors for fracture.

Romosozumab is not currently part of any NICE osteoporosis treatment pathway.

Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to take ALN and RIS, or who have a contraindication to or are intolerant of ALN and RIS, or who have had an unsatisfactory response to treatment with ALN or RIS, and who are aged $\geq$ 65 years and have a *T*-score of $\leq$ –4.0 SD,

or a *T*-score of ≤ −3.5 SD plus more than two fractures, or who are aged 55–64 years and have a *T*-score of ≤ −4 SD plus more than two fractures.[12]

Identification of important subgroups

The final NICE scope specified subgroups based on patient characteristics that increase the risk of fracture (those specified in NICE CG146[8]) or that affect the impact of fracture on lifetime costs and outcomes.[19]

Current usage in the NHS

Data from the 2017 Prescription Cost Analysis[26] were analysed to determine the level of non-bisphosphonate usage in primary care across England in 2017. It can be seen from the data summarised in *Table 1* that generic RLX was the most commonly prescribed preparation in primary care. The prescribing costs in hospitals and the community in England in 2016/17 for treatment of osteoporosis was £11,930,475 for DEN, £355,530 for RLX and £4,409,696 for TPTD.[27]

Anticipated costs associated with interventions

Table 2 summarises the 2018 net costs associated with the interventions, based on their list prices.[28]

TABLE 1 Primary care prescribing of non-bisphosphonates per annum in 2017

Drug	Generic or branded	Dosing schedule	Prescriptions in thousands[a]	Description of preparations
DEN	Branded	Once every 6 months	43.063	Prolia injection, 60 mg/1 ml pre-filled syringe
RLX	Branded	Daily	1.738	Evista tablet, 60 mg
	Generic	Daily	57.301	RLX hydrochloride tablet, 60 mg
TPTD	Branded	Daily	0.964	Forsteo injection, 250 µg/ml, 2.4 ml pre-filled pen

a Prescription items dispensed in the community in 2017.[26]

TABLE 2 Acquisition costs associated with DEN, RLX and TPTD

Drug	Generic or branded	Unit type and dose	Price per unit[28]
DEN	Branded	Prolia injection, 60 mg/1 ml, one pre-filled disposable injection	• NHS indicative price = £183.00 • Drug Tariff (Part VIIIA Category C) price = £183.00
RLX	Branded	Evista tablet, 60 mg, 28 tablets	• NHS indicative price = £17.06 • Drug Tariff (Part VIIIA Category M) price = £3.27
	Generic	RLX HCl tablet, 60 mg, 28 tablets	Activis UK: • NHS indicative price = £4.60 • Drug Tariff (Part VIIIA Category M) price = £3.27
TPTD	Branded	Forsteo injection, 250 µg/ml 2.4 ml pre-filled pen, one pre-filled disposable injection (i.e. 30 daily doses)	• NHS indicative price = £271.88 • Drug Tariff (Part VIIIA Category C) price = £271.88

Impact of health problem

Significance for patients

Fractures cause significant pain, disability and loss of independence and can be fatal.[1] In the UK, the number of fracture-related deaths in 2010 was estimated at 6059.[6] Hip, vertebral and other fractures accounted for 2764, 1795 and 1500 deaths, respectively.[6]

Significance for the NHS

The cost of osteoporosis in the UK in 2010 was estimated at £4.4B. First-year costs, subsequent-year costs and pharmacological fracture prevention costs amounted to £3.2B, £1.1B and £84M, respectively.[6]

Measurement of disease

Quantitative diagnosis in the UK relies on the assessment of BMD, usually by central DXA. BMD at the femoral neck provides the reference site. It is defined as a value for BMD of $\geq$ 2.5 SDs below the young female adult mean (i.e. a *T*-score of $\leq$ −2.5 SDs). Severe osteoporosis (established osteoporosis) describes osteoporosis in the presence of one or more fragility fractures.[29]

The NICE CG146[8] recommends the estimation of absolute risk of fragility fracture when assessing risk of fracture and recommends the use either FRAX® (web version 3.9, University of Sheffield, Sheffield, UK)[30] (without a BMD value if DXA has not previously been undertaken) or QFracture® (QFracture-2012 open source revision 38, Clinrisk Ltd, Leeds, UK),[31] within their allowed age ranges, to estimate the 10-year predicted absolute fracture risk when assessing risk of fracture.[8] Above the upper age limits defined by the tools, people are considered to be at high risk.[8]

The guideline[8] recommends that assessment is indicated in all women aged $\geq$ 65 years and all men aged $\geq$ 75 years and in women aged $<$ 65 years and men aged $<$ 75 years in the presence of risk factors (i.e. previous fragility fracture, current use or frequent recent use of oral or systemic glucocorticoids, history of falls, family history of hip fracture, other causes of secondary osteoporosis, low body mass index, smoking and alcohol intake of $>$ 14 units per week for women and of $>$ 21 units per week for men). The guideline[8] recommends not routinely assessing fracture risk in people aged $<$ 50 years unless they have major risk factors (i.e. current or frequent recent use of systemic corticosteroids, untreated premature menopause or previous fragility fracture). The guideline[8] also recommends interpretation with caution of the estimated absolute risk of fracture in people aged $>$ 80 years, because predicted 10-year fracture risk may underestimate their short-term fracture risk.

Chapter 2 Definition of the decision problem

Decision problem

This assessment addresses the following question: what is the clinical effectiveness and cost-effectiveness of DEN, RLX, ROMO and TPTD, within their licensed indications, for the prevention of osteoporotic fragility fractures, as compared with each other, bisphosphonates or a non-active treatment?

Overall aims and objectives of the assessment

- To evaluate the clinical effectiveness of each intervention in terms of osteoporotic fragility fractures, and femoral neck BMD.
    - Population: adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE CG146.[8]
    - Interventions: DEN, RLX, ROMO and TPTD.
    - Comparators: placebo or no active treatment control; interventions compared with each other; the bisphosphonates ALN, RIS, IBN (oral or i.v.) and ZOL.
    - Outcomes: osteoporotic fragility fracture, BMD at the femoral neck, adverse events (AEs) and health-related quality of life (HRQoL).
- To evaluate the incremental cost-effectiveness of each intervention compared with (1) each other, (2) the bisphosphonates ALN, IBN (oral or i.v.), RIS and ZOL and (3) no active treatment.

From here on, the term bisphosphonates will be used to refer only to those bisphosphonates included as comparators in this assessment, namely ALN, RIS, IBN (oral or i.v.) and ZOL.

Chapter 3 Assessment of clinical effectiveness

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

A systematic review of the literature and network meta-analyses (NMAs) were conducted to evaluate the clinical effectiveness of DEN, RLX, ROMO and TPTD in the treatment of adults with osteoporosis in terms of preventing osteoporotic fragility fractures.

The systematic review of the evidence was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[32,33]

Methods for reviewing effectiveness

Search strategy

A comprehensive search was undertaken to systematically identify clinical effectiveness literature relating to the bisphosphonates ALN, IBN, RIS and ZOL, and the non-bisphosphonates DEN, RLX, ROMO and TPTD, within their licensed indications, for the prevention of fragility fractures.

The search strategy comprised the following main elements:

- searching of electronic databases
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

The following database and trials registries were searched on 11 July 2018:

- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and MEDLINE (via Ovid), searched from 1946 to 2018
- EMBASE (via Ovid), searched from 1974 to 2018
- Cochrane Database of Systematic Reviews (via Wiley Online Library), searched from 1996 to 2018
- Database of Abstracts of Reviews of Effects (via Wiley Online Library), searched from 1995 to 2015
- Cochrane Central Register of Controlled Trials (via Wiley Online Library), searched from 1898 to 2018
- Health Technology Assessment Database (via Wiley Online Library), searched from 1995 to 2016
- Science Citation Index Expanded (via Web of Science), searched from 1900 to 2018
- Conference Proceedings Citation Index – Science (via Web of Science), searched from 1990 to 2018
- WHO International Clinical Trials Registry Platform.

Existing evidence reviews commissioned by NICE, which included literature published up to September 2014, were assumed to have identified all papers published prior to 2014 that were relevant to this review.

Searches were not restricted by language or publication type. Subject headings and keywords for 'osteoporosis' were combined with each of the named drug interventions. The MEDLINE search strategy is presented in *Appendix 1*. The search was adapted across the other databases. Highly sensitive study design filters were used to retrieve clinical trials and systematic reviews on MEDLINE and other databases, when appropriate. Industry submissions and relevant systematic reviews were also hand-searched to identify any further relevant clinical trials. The WHO International Clinical Trials Registry Platform was searched for ongoing and recently completed research projects. Citation searches of key included studies were also

undertaken using the Web of Science database. All potentially relevant citations were downloaded to the bibliographic software EndNote version X9.1 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] and deduplication of citation records undertaken.

Other resources

In addition to database searches, the reference lists of relevant studies were checked. Identified systematic reviews were checked to identify any additional trials meeting the inclusion criteria.

Bisphosphonate studies were identified from the assessment report[34] used to inform the development of NICE TA464.[9] As the searches for this TA were last updated in September 2014, more recent studies were sought from the database searches.

When data from included trials were missing, the company submissions were checked. Any academic or commercial-in-confidence data taken from a company submission were underlined and highlighted in the assessment report.

Study selection

All titles and abstracts identified by the searches were screened by one reviewer, and 10% were screened by a second reviewer. Full-text articles were assessed by one reviewer, with queries addressed by a second reviewer; discrepancies were resolved by discussion.

Inclusion and exclusion criteria for the selection of clinical effectiveness evidence were defined according to the decision problem outlined in the NICE scope.[19]

Inclusion criteria

Population

Adults at risk of osteoporotic fragility fracture, according to the recommendations in NICE CG146[8] (see *Chapter 1*, *Measurement of disease*).

Interventions

Four interventions are considered in this assessment: DEN, RLX, ROMO and TPTD. These four interventions were assessed in accordance with their licensed indications, at licensed doses. At the time that searches were conducted, ROMO did not have a marketing authorisation in the UK for treating osteoporosis, but had been submitted to the European Medicines Agency, given as monthly 210-mg s.c. injections (draft SmPC, as provided in the company submission).[20]

Comparators

Interventions may be compared with placebo, no active treatment control, each other or the bisphosphonates ALN, RIS, IBN (oral or i.v.) and ZOL, within their licensed indications (including s.c. and i.v. where licensed).

Studies that allowed concomitant treatment with calcium and/or vitamin D for patients in both the intervention and comparator arms were included.

Studies that planned treatment sequences or open-label extensions with participants in allocated randomised groups were included.

Outcomes

The main outcome sought was osteoporotic fragility fracture. Vertebral fractures, when data allowed, were considered separately for clinical/symptomatic fractures and morphometric/radiographic fractures. Radiographic fractures, defined according to Genant *et al.*,[35] were those resulting in a $\geq$ 20% reduction in vertebral height; however, if a study did not specify that the Genant *et al.*[35] definition was used, morphometric/radiographic fracture data were still included. Non-vertebral fracture data were sought, and, when reported, hip, wrist and proximal humerus fractures were considered separately. Although planned, data on concordance were not extracted owing to time constraints.

In addition, BMD at the femoral neck (assessed by DXA) data were sought. Only femoral neck BMD data were included in the NMA; however, when trials did not report these data, BMD measured at the lumbar spine was tabulated.

The following outcome measures were also included: mortality (overall or following fracture), AEs of treatment, and HRQoL.

Study design

Randomised controlled trials (RCTs) were included. Studies published as abstracts or conference presentations were included only if sufficient details were presented to allow both an appraisal of the methodology and an assessment of the results to be undertaken. Systematic reviews and CGs were used only as potential sources of additional RCTs of efficacy evidence.

Exclusion criteria

- Studies with patients with normal or unspecified BMD.
- Studies with patients with other indications for the same drugs. Cancer populations at risk of osteoporosis that are covered by NICE guideline (NG) 101[36] and NICE CG175.[37]
- Studies in which interventions were administered not in accordance with licensed indications.
- Studies in which interventions were co-administered with any other therapy with the potential to augment bone, unless concomitant treatments are specified in the SmPC.
- Studies that were considered methodologically unsound in terms of study design or the method used to assess outcomes.
- Reports published as abstracts or conference presentations only, for which insufficient details are reported to allow an assessment of study quality or results.
- Studies that were published in languages other than English.
- Studies based on animal models, and pre-clinical and biological studies.
- Narrative reviews, editorials, opinions.

Data extraction and critical appraisal

Data relevant to the decision problem were extracted by one reviewer and checked by a second reviewer. Discrepancies were resolved by discussion. Data were extracted without blinding to authors or journal. Data from study arms for which intervention treatments were administered in line with licensed indications were extracted; data from unlicensed treatment arms were not extracted.

For studies included in NICE TA464, the data used were those previously extracted.[34]

Methodological quality of RCTs identified for inclusion were assessed using the Cochrane Collaboration risk-of-bias assessment criteria.[38] Two independent reviewers undertook quality assessment. Risk-of-bias plots were produced using Cochrane Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

The revised tool (RoB 2.0)[39] to assess the risk of bias in randomised trials,[39] published in September 2018, was not applied as this review commenced prior to the publication of the revised risk-of-bias tool.

Randomised controlled trials were classified as being at high risk of attrition bias when the dropout rate in any treatment arm was $\geq$ 10%.[40]

Data synthesis

The extracted data and quality assessment variables were presented for each study, both in structured tables and as a narrative description. Information on between-group differences extracted from included studies were presented. When these were not reported by included studies, these were estimated using Cochrane RevMan version 5.3, as either risk ratio (RR) or mean difference (MD).

Data were pooled across studies in NMAs, the methods of which are described in *Methods for the network meta-analysis*.

Results

Quantity of research available

Study selection is shown in *Figure 1*. As a result of the searches described in *Search strategy*, a total of 7898 citations were identified for the clinical review. At abstract sift, 7792 were excluded. At full-text sift, 34 records were excluded. These are listed in *Appendix 2*, along with reasons for exclusion. Fifty-two RCTs of the interventions of interest were included (published in 69 articles; see *Table 3*).

In addition, three bisphosphonate RCTs were identified and added to the 48 RCTs of bisphosphonates identified from TA464[34] (see *Appendix 3*).

Randomised controlled trials included in the systematic review of clinical effectiveness of fracture and femoral neck BMD are presented in *Table 3*; data from licensed dose arms only for DEN, RLX, ROMO and TPTD were extracted and presented in this assessment report.

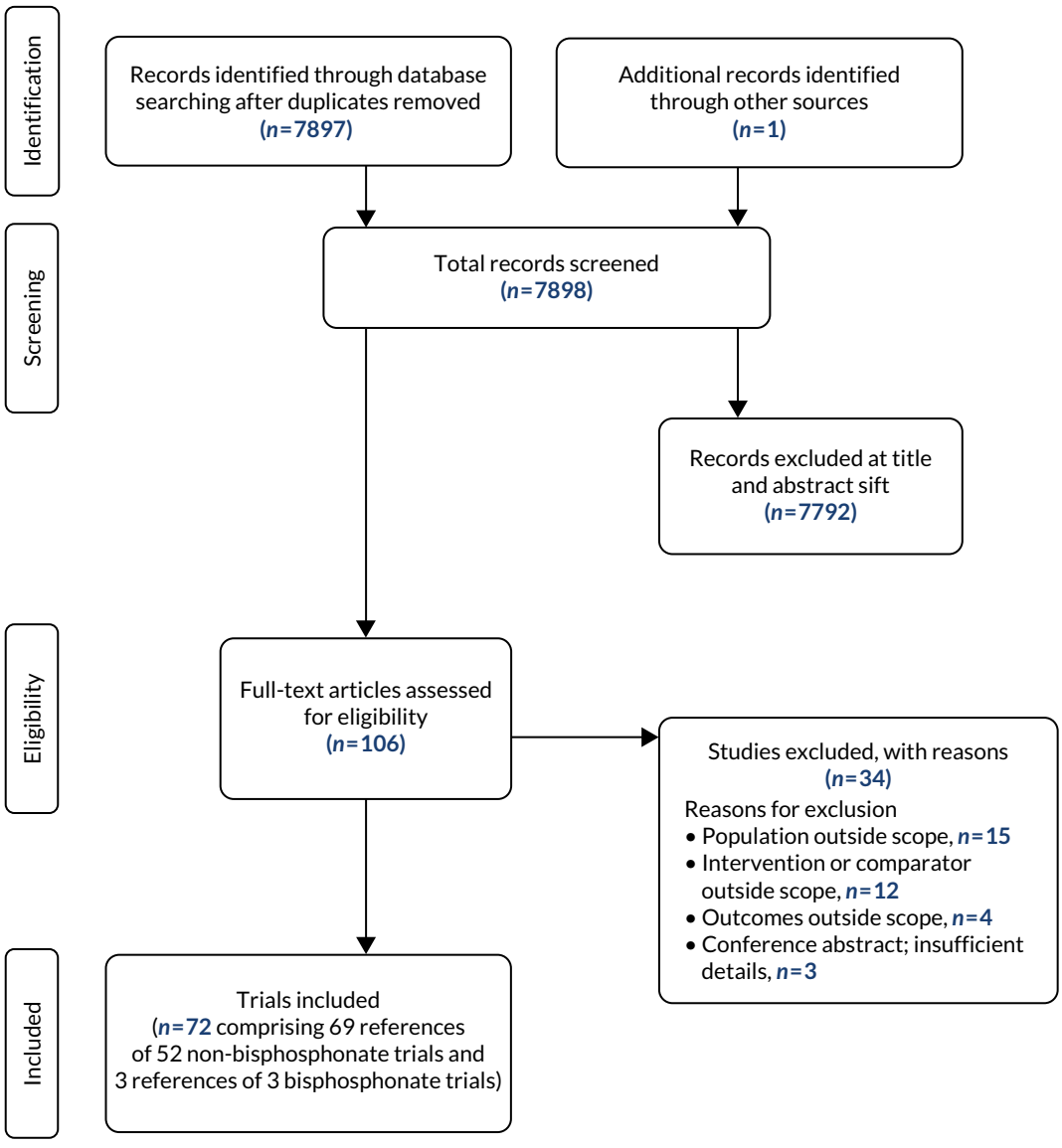

FIGURE 1 The PRISMA flow diagram of study selection.

TABLE 3 Trials included in the review

Trial	Intervention and comparators	Population	Reported vertebral fracture data	Reported femoral neck BMD data
DEN vs. placebo				
FREEDOM[41]	• DEN • Placebo	Postmenopausal women with osteoporosis	Yes	Yes
ADAMO (Orwoll 2012)[42]	• DEN • Placebo	Men with osteoporosis	Yes	Yes
DIRECT[43]	• DEN followed by DEN • Placebo followed by DEN	Postmenopausal women with osteoporosis and men with osteoporosis	Yes	Yes
Nakamura 2012[44]	• DEN • Placebo	Postmenopausal women with osteoporosis	Yes	No
Koh 2016[45]	• DEN • Placebo	Postmenopausal women with osteoporosis	No	Yes
RLX vs. placebo				
Adami 2008[46]	• RLX • Placebo	Postmenopausal women with osteoporosis	No	Yes
Morii 2003[47]	• RLX • Placebo	Postmenopausal women with osteoporosis	Yes	No
Liu 2004[48]	• RLX • Placebo	Postmenopausal women with osteoporosis	Yes	Yes
Gorai 2012[49]	• RLX • RLX plus alfacalcidol • Alfacalcidol	Postmenopausal women with osteoporosis	No	No, lumbar spine BMD
Silverman 2008[50]	• RLX • Placebo	Postmenopausal women with osteoporosis	Yes	Yes
MORE[51]	• RLX • Placebo	Postmenopausal women with osteoporosis	Yes	Yes
Lufkin 1998[52]	• RLX • Control	Postmenopausal women with osteoporosis	Yes	No
Mok 2011[53]	• RLX • Placebo	Postmenopausal women with osteoporosis	Yes	Yes
ROMO vs. placebo				
FRAME[54]	• ROMO followed by DEN • Placebo followed by DEN	Postmenopausal women with osteoporosis	Yes	Yes
Ishibashi 2017[55]	• ROMO • Placebo	Postmenopausal women with osteoporosis	No	Yes
BRIDGE[56]	• ROMO • Placebo	Men with osteoporosis	No	Yes
TPTD vs. placebo				
Orwoll 2003[57]	• TPTD • Placebo	Men with osteoporosis	No	Yes
Miyauchi 2010[58]	• TPTD • Placebo	Women and men with osteoporosis	Yes	Yes
Miyauchi 2008[59]	• TPTD • Placebo	Women with osteoporosis	No	Yes

continued

TABLE 3 Trials included in the review (*continued*)

Trial	Intervention and comparators	Population	Reported vertebral fracture data	Reported femoral neck BMD data
ACTIVE[60]	• TPTD • Placebo	Postmenopausal women with osteoporosis	Yes	Yes
Leder 2015[61]	• TPTD • Placebo	Postmenopausal women with osteoporosis	No	Yes
FPT[62]	• TPTD • Placebo	Postmenopausal women with prior fractures	Yes	Yes
Sethi 2008[63]	• TPTD • Control	Postmenopausal women with osteoporosis	No	Yes
Head-to-head non-bisphosphonates				
• DATA[64] • DATA-Switch[65]	• DEN (then switch to TPTD) • TPTD (then switch to DEN) • Combined DEN and TPTD (then switch to DEN)	Postmenopausal women with osteoporosis	No	Yes
EUROFORS[66]	• TPTD followed by RLX • TPTD	Postmenopausal women with osteoporosis	Yes	Yes
STRUCTURE[67]	• ROMO • TPTD	Postmenopausal women with osteoporosis	Yes	Yes
McClung 2014[68] (also bisphosphonate comparator)	• ROMO • TPTD • ALN • Placebo	Postmenopausal women with osteoporosis	No	Yes
DEN vs. bisphosphonates				
DECIDE[69]	• DEN plus placebo • ALN plus placebo	Postmenopausal women with osteoporosis	No	Yes
STAND[70]	• DEN • ALN • (Both arms received ALN prior to being randomised to either DEN or ALN)	Postmenopausal women with osteoporosis	No	Yes
DAPS[71]	• DEN followed by ALN • ALN followed by DEN	Postmenopausal women with osteoporosis	No	Yes
AMG 162 Bone Loss study[72]	• DEN • ALN • Placebo	Postmenopausal women with osteoporosis	No	Yes
Recknor 2013[73]	• DEN • IBN (oral)	Postmenopausal women with osteoporosis	No	Yes
Saag 2018[74]	• DEN • RIS	Glucocorticoid-induced osteoporosis (men and women)	No	Yes
Miller 2016[75]	• DEN plus placebo • ZOL plus placebo	Postmenopausal women with osteoporosis	No	Yes
RLX vs. bisphosphonates				
EFFECT (international)[76]	• RLX plus placebo • ALN plus placebo	Postmenopausal women with osteoporosis	Yes	Yes
EFFECT (USA)[77]	• RLX plus placebo • ALN plus placebo	Postmenopausal women with osteoporosis	No	Yes
Johnell 2002[78]	• RLX • ALN	Postmenopausal women with osteoporosis	No	Yes

TABLE 3 Trials included in the review (*continued*)

Trial	Intervention and comparators	Population	Reported vertebral fracture data	Reported femoral neck BMD data
Muscoso 2004[79]	• RLX • ALN • RIS	Postmenopausal women with osteoporosis	Yes	No
EVA[80]	• RLX • ALN	Postmenopausal women with osteoporosis	Yes	Yes
Sanad 2011[81]	• RLX • ALN	Postmenopausal women with osteoporosis	No	Yes
Michalská 2006[82]	• RLX • ALN • Placebo	Postmenopausal women with osteoporosis	No	Yes
ROMO vs. bisphosphonates				
ARCH[83]	• ROMO followed by ALN • ALN	Postmenopausal women with osteoporosis	Yes	Yes
TPTD vs. bisphosphonates				
FACT[84]	• TPTD plus placebo • ALN plus placebo	Postmenopausal women with osteoporosis	No	Yes
Saag 2009[85]	• TPTD • ALN	Glucocorticoid-induced osteoporosis (men and women)	Yes	Yes
Panico 2011[86]	• TPTD • ALN	Postmenopausal women with osteoporosis	Yes	Yes
EuroGIOPs[87]	• TPTD • RIS	Glucocorticoid-induced osteoporosis (men)	No	Yes
Anastasilakis 2008[88]	• TPTD • RIS	Postmenopausal women with osteoporosis	No	No, lumbar spine BMD
Walker 2013[89]	• TPTD • RIS	Glucocorticoid-induced osteoporosis (men)	Yes	Yes
VERO[90]	• TPTD plus placebo • RIS plus placebo	Postmenopausal women with osteoporosis	Yes	No
Hadji 2012[91]	• TPTD plus placebo • RIS plus placebo	Postmenopausal women with osteoporosis	Yes	Yes
MOVE[92]	• TPTD plus placebo • RIS plus placebo	Post surgery for osteoporotic hip fracture	Yes	Yes
Cosman 2011[93]	• TPTD • ZOL	Postmenopausal women with osteoporosis	Yes	Yes

ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; ARCH, Active-controlled fracture study in postmenopausal women with osteoporosis at high risk; BRIDGE, phase III randomized placeBo-contRolled double-blind study evaluatIng the efficacy and safety of Romosozumab in treatinG mEn with osteoporosis; DAPS, Denosumab Adherence Preference Satisfaction; DATA, Denosumab and Teriparatide Administration; DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus alendronate; DIRECT, Denosumab fracture Intervention RandomizEd placebo Controlled Trial; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; EUROFORS, European Study of Forsteo; EVA, EVista Alendronate comparison; FACT, Forteo Alendronate Comparator Trial; FPT, Fracture Prevention Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months; MORE, Multiple Outcomes for Raloxifene Evaluation; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy; VERO, VERtebral fracture treatment comparisons in Osteoporotic women.

Of the 52 RCTs included, 23 compared non-bisphosphonates with placebo, four were head-to-head comparisons of non-bisphosphonates (of which one RCT also included a bisphosphonate arm) and 25 RCTs compared a non-bisphosphonate with a bisphosphonate.

Listed treatment arms were all at licensed doses.

Trial characteristics are shown in *Appendix 4*. All 52 included trials were RCTs, with the majority being multicentre studies. All trials providing data for the NMAs involved concomitant treatment with calcium and vitamin D. The most common primary outcome measure was percentage change in BMD from baseline.

The majority of RCTs had populations of postmenopausal women. Population baseline characteristics of RCTs are shown in *Appendix 4*. There was some variation between trials in baseline BMD *T*-scores and the percentage of participants with fractures at baseline. In the RCTs, population baseline characteristics were balanced between treatment arms.

Quality of research available

Results of the risk-of-bias assessment

Non-bisphosphonates versus placebo

A summary of the Cochrane risk-of-bias assessment across the placebo-controlled non-bisphosphonate studies is presented in *Figure 2*.

Denosumab versus placebo

None of the five studies comparing DEN with placebo[41–45] reported how the random sequence was generated, and only two reported that allocation to treatment groups was concealed.[41,42]

Four of the five studies reported that participants and personnel were blinded to treatment allocation.[41–43,45] Four studies reported that fracture assessment was blinded to treatment allocation.[42–45] However, only one reported that BMD assessment was blinded to treatment allocation.[42]

One study was considered to have a high risk of attrition bias for both fracture and BMD outcomes as ≥ 10% of participants in both treatment groups did not complete the study.[41]

Only one study did not report the location of a study protocol, against which the reported outcomes could be checked for selective reporting.[44] The remaining four studies of DEN vs. placebo were all considered to have a low risk of bias for this domain.[41–43,45]

Raloxifene versus placebo

Of the eight studies comparing RLX with placebo,[46–48,50–53,94] only one reported how the random sequence was generated (it was computer generated), and was considered to have a low risk of bias for this domain.[50] Only three of the eight studies reported that allocation to treatment groups was concealed.[47,50,51]

Six of the studies reported that participants and personnel were blinded to treatment allocation.[47,48,50–53] One study was considered to have a high risk of bias for this domain as it was described as open label.[94]

Four of the studies comparing RLX with placebo reported that fracture assessment was blinded to treatment allocation,[47,50,51,53] and three reported that BMD assessment was blinded to treatment allocation.[46,47,53] One study reported that BMD assessment was not blinded to treatment allocation;[94] this study was therefore considered to have a high risk of bias for this domain.

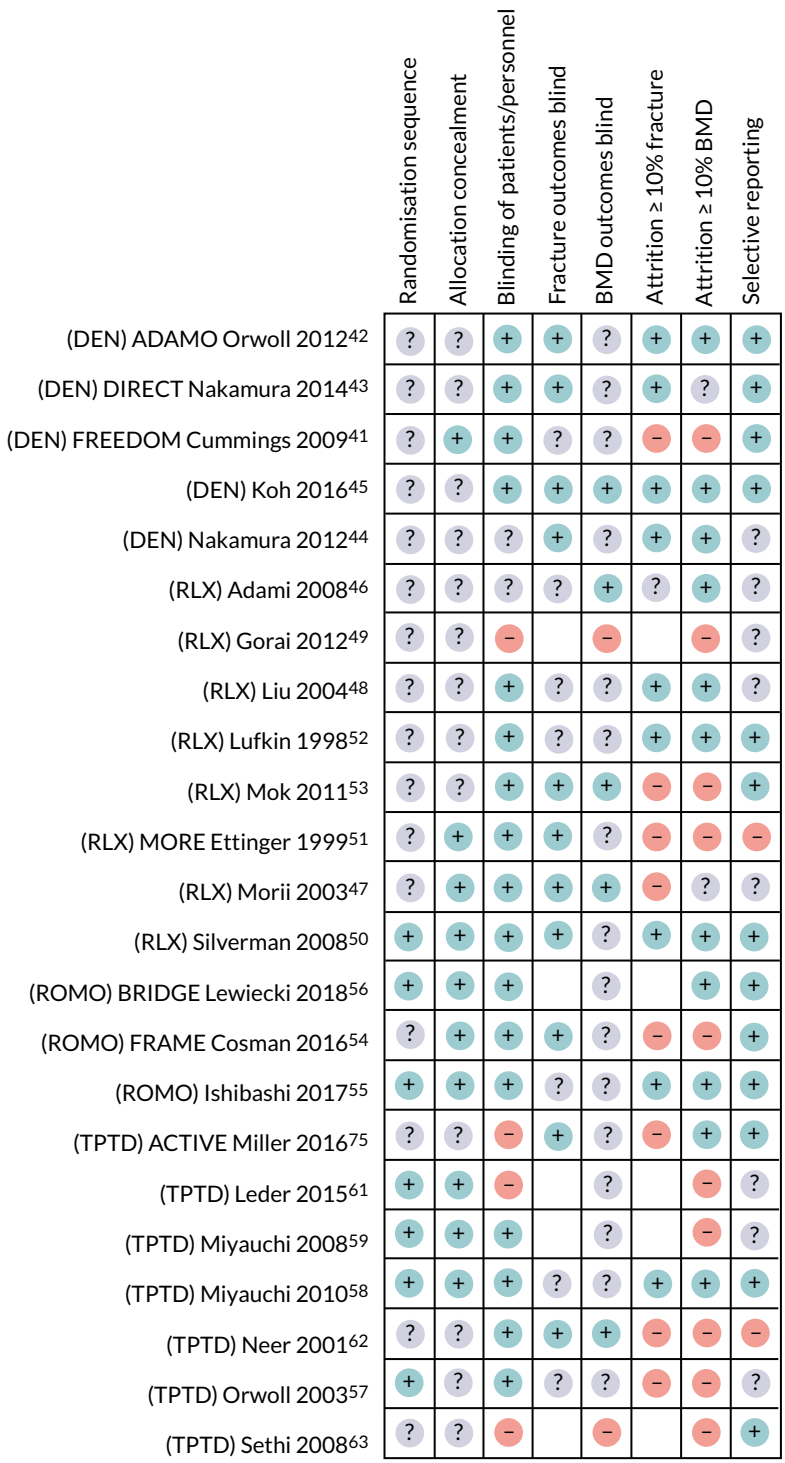

FIGURE 2 Cochrane risk-of-bias summary across placebo-controlled non-bisphosphonate studies. ?, Unclear-risk of bias; +, low-risk of bias; –, high-risk of bias; blank cells, not a study outcome. ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; BRIDGE, phase III randomized placeBo-contRolled double-blind study evaluatIng the efficacy and safety of Romosozumab in treatinG mEn with osteoporosis; DIRECT Denosumab fracture Intervention RandomizEd placebo Controlled Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months; MORE, Multiple Outcomes for Raloxifene Evaluation.

Four studies were considered to have a high risk of attrition bias for fracture and/or BMD outcomes, as ≥ 10% of participants did not complete the study.[47,51,53,94]

Only three studies reported the location of a protocol, against which outcomes could be checked;[50,52,53] these studies were considered to have a low risk of bias, as all outcomes in the protocol had been reported.[50,52,53]

In one study, which did not report a protocol location, BMD was reported for only a subset of participants and AEs were not reported by the different RLX doses.[51] This study was considered to have a high risk of bias for selective reporting.

Romosozumab versus placebo

All three of the studies comparing ROMO with placebo reported that allocation to treatment groups was concealed,[54–56] and two reported how the random sequence was generated (all adequate methods).[55,56] All three reported that participants and personnel were blinded to treatment allocation.[54–56]

All three studies assessed BMD,[54–56] but none reported whether or not the assessment was blinded. Only one[54] of the two studies[54,55] assessing fracture reported that this outcome was blinded to treatment allocation.

One study was considered to have a high risk of attrition bias (≥ 10% participants did not complete the study) for both BMD and fracture outcomes,[54] and one study was considered to have a low risk of bias for BMD and fracture outcomes,[55] as was one study that assessed only BMD.[56]

All three studies reported the location of the protocol and all items in the protocol were reported in all three study publications.[54–56]

Teriparatide versus placebo

Across the seven studies comparing TPTD with placebo,[57–59,61–63,95] four reported a method for the random sequence generation (all adequate)[57–59,61] and three reported that allocation to treatment groups was concealed.[58,59,61]

Three of the studies were described as open label and were considered to have a high risk of bias for blinding of participants and study personnel.[63,65,95] The other four trials were considered to have a low risk of bias for this domain.[57–59,62]

When fractures and/or BMD were outcomes, only two of the studies reported that fracture assessment was blinded[62,95] and only one reported that BMD assessment was blinded to treatment allocation.[62] One study that reported that BMD assessment was unblinded (fractures were not an outcome) was considered to have a high risk of bias for this domain.[63]

Attrition bias of ≥ 10% was evident for reporting of fracture outcomes in three studies,[57,62,95] and evident for five studies reporting BMD outcomes, all of which were judged to be at high risk of attrition bias.[57,59,62,63,65]

Three studies reporting the location of a protocol were judged to be at low risk of selective reporting bias.[58,63,95] One study was judged to be at high risk of selective reporting bias[62] as safety outcomes were not clearly reported in the publication and, although the online protocol described safety as a planned outcome, no results for any outcome had been posted.[96]

When considering studies of non-bisphosphonates compared with placebo, those reporting fracture data had a similar risk of bias to those reporting BMD data, although a higher percentage of studies reporting fracture data reported blinding of outcome assessors than did those reporting BMD data. [97]

Head-to-head non-bisphosphonates

The summary of the Cochrane risk-of-bias assessment across the head-to-head non-bisphosphonate studies is presented in *Figure 3*.

Of the four head-to-head studies,[64,66–68] three reported the method for the random sequence generation,[64,66,67] and three reported that allocation was concealed.[66–68]

All four studies were reported as open label and were considered to have a high risk of bias for blinding of participants and personnel.[64,66–68]

All four studies reported fractures as an outcome;[64,66–68] of these, two studies reported that fracture assessment was not blinded to treatment allocation.[66,67] All four studies assessed BMD and three were considered to have a low risk of bias for the blinding of BMD assessments.[64,66,67]

Two[66,67] of the three studies assessing fracture were considered to have a low risk of attrition bias (< 10% of participants withdrew/were not included in the analysis).[64,66,67] All four studies reported BMD outcomes;[64,66–68] one of these was considered to have a high risk of attrition bias (≥ 10% of participants in both treatment groups did not complete the study) for this domain.[68] All other studies were considered to have a low risk of bias.

Three studies reporting the location of a protocol were judged to be at low risk of selective reporting bias.[64,67,68]

Non-bisphosphonates versus bisphosphonates

The summary of the Cochrane risk-of-bias assessment across the non-bisphosphonate versus bisphosphonate studies is presented in *Figure 4*.

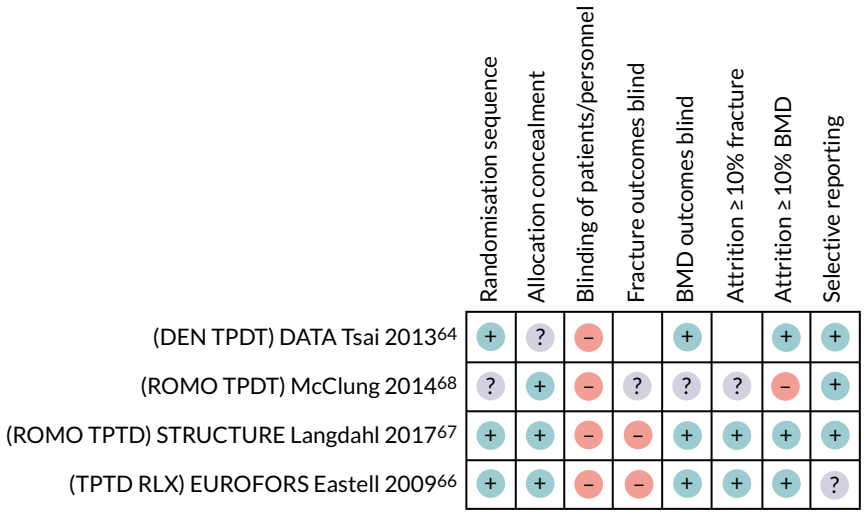

FIGURE 3 Cochrane risk-of-bias summary across head-to-head non-bisphosphonate studies. ?, Unclear-risk of bias; +, low-risk of bias; –, high-risk of bias; blank cells, not a study outcome. DATA, Denosumab and Teriparatide Administration; DIRECT, Denosumab fracture Intervention RandomizEd placebo Controlled Trial; EUROFORS, European Study of Forsteo; EVA, EVista Alendronate comparison; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy.

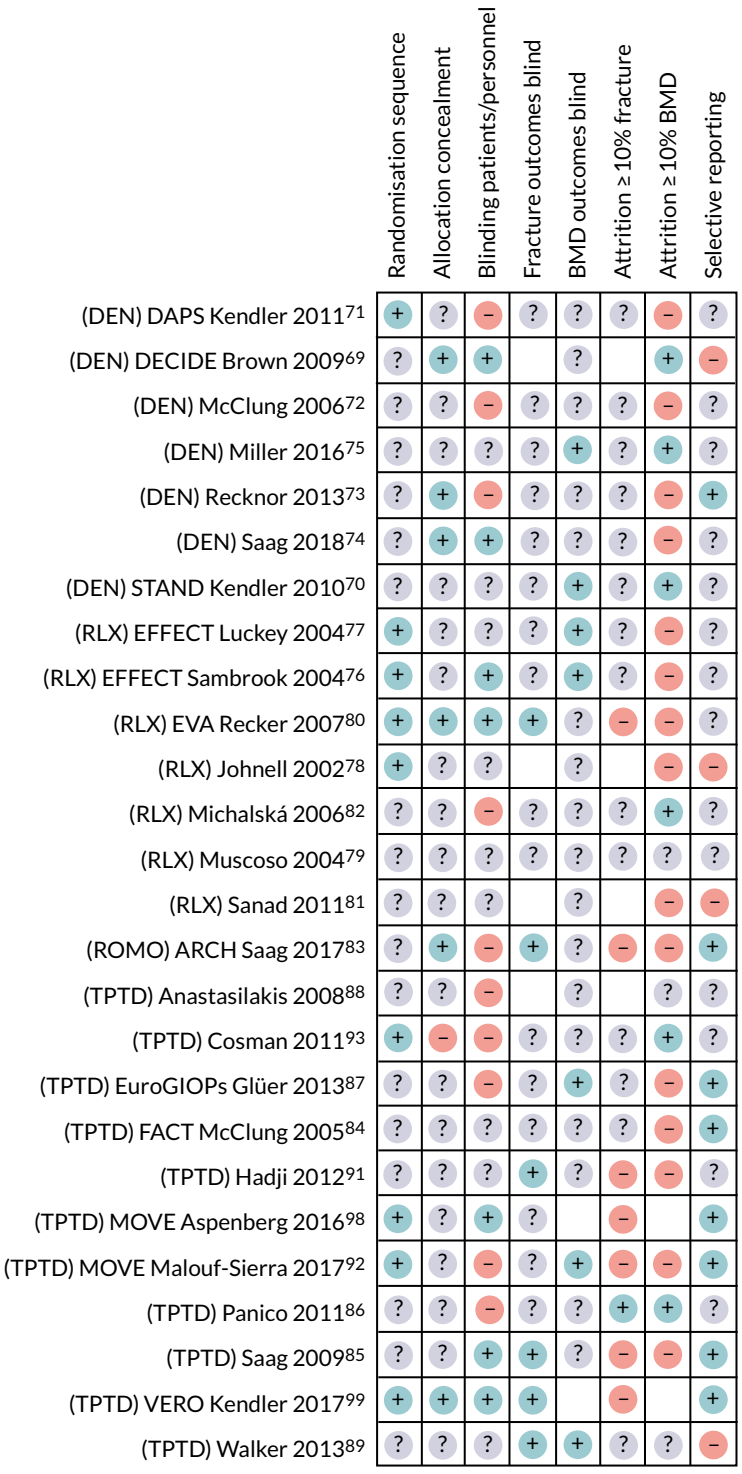

FIGURE 4 Cochrane risk-of-bias summary across non-bisphosphonate vs. bisphosphonate studies. ?, Unclear-risk of bias; +, low-risk of bias; –, high-risk of bias; blank cells, not a study outcome. ARCH, Active-controlled fracture study in postmenopausal women with osteoporosis at high risk; DAPS, Denosumab Adherence Preference Satisfaction; DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus alEndronate; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; EVA, EVista Alendronate comparison; FACT, Forteo Alendronate Comparator Trial; STAND, Study of Transitioning from Alendronate to Denosumab; VERO, VERtebral fracture treatment comparisons in Osteoporotic women.

Denosumab versus bisphosphonates

Of the seven studies comparing DEN with a bisphosphonate,[69–75] only one reported the method for the random sequence generation,[71] and only three reported the method of treatment allocation concealment.[69,73,74]

Three studies comparing DEN with a bisphosphonate were reported as open label and were considered to have a high risk of bias for blinding of participants and personnel.[71–73]

All seven studies assessed BMD as an outcome, but only one reported that the assessment was blinded to treatment allocation.[75] The remaining six studies were considered to have an unclear risk of bias for this domain.[69–74] Four of these studies were also considered to have a high risk of attrition bias (≥ 10% of participants in both treatment groups did not complete the study) for BMD outcomes.[71–74]

The six studies that assessed fracture as an outcome were all considered at unclear-risk of bias for blinded assessment.[70–75] All six studies were also considered at unclear risk of attrition bias (≥ 10% of participants in both treatment groups did not complete the study) for BMD outcomes.

Only one of the studies comparing DEN with a bisphosphonate reported the location of a protocol against which to check outcomes; this study was considered to have a low risk of bias for selective reporting.[73]

For one study,[69] HRQoL was reported as an outcome in the manufacturer's company submission.[100] However, this outcome was not reported in the published study, which was considered to have a high risk of bias for selective reporting.[69]

Raloxifene versus bisphosphonates

Of the seven studies comparing RLX with a bisphosphonate,[76–82] four reported the method for the random sequence generation (all adequate).[76–78,80] However, only one reported a method of treatment allocation concealment.[80]

Two of the studies comparing RLX with a bisphosphonate reported that participants and personnel were blinded to treatment allocation (low risk of bias)[76,80] and one study reported an open-label design (high risk of bias).[82] All other studies comparing RLX with a bisphosphonate were considered to have an unclear risk of bias for blinding of participants and study personnel.[77–79,81]

Across studies comparing RLX with a bisphosphonate that assessed fracture and/or BMD,[76–82] only one study reported that the fracture assessment was blinded to treatment allocation,[80] and only two reported that fracture assessment was blinded to treatment allocation.[76,77]

One study comparing RLX with a bisphosphonate that reported fracture outcomes was considered to have a high risk of attrition bias (≥ 10% of participants in both treatment groups did not complete the study),[80] and four studies assessing BMD were considered to have a high risk of attrition bias (≥ 10% of participants in both treatment groups did not complete the study).[76–78,80]

No study comparing RLX with a bisphosphonate reported the location of a study protocol. In one of the studies, AEs were not fully reported in the study publication,[78] and one study reported that fracture was an assessed outcome, but did not report any results in the study publication.[81] These two studies were considered to have a high risk of selective reporting.

Romosozumab versus bisphosphonates

In the one study that compared ROMO with a bisphosphonate,[83] the method for the sequence generation was not reported, although the method for allocation concealment was. This study was described as open label and was considered to have a high risk of bias for blinding of participants and

study personnel. Blinding of fracture outcome assessment was reported; however, blinding of BMD assessment was not. Both fracture and BMD outcomes were considered to have a high risk of attrition bias (≥ 10% of participants in both treatment groups did not complete the study). All outcomes in the study protocol were reported.

Teriparatide versus bisphosphonates

Across the 11 studies that compared TPTD with a bisphosphonate,[84–89,91–93,99,101] four[92,93,99,101] reported an adequate method of random sequence generation and only one study reported an adequate method of treatment allocation concealment.[99] One study reported that unblinded pharmacists distributed the study drug, and was considered to have a high risk of bias for allocation concealment.[93]

Three of the studies comparing TPTD with a bisphosphonate reported that participants and personnel were blinded to treatment allocation (low risk of bias),[85,99,101] and five studies reported an open-label design (high risk of bias).[86–88,92,93] The other three studies comparing TPTD with a bisphosphonate were considered to have an unclear risk of bias for blinding of participants and study personnel.[84,89,91]

Four of the studies comparing TPTD with a bisphosphonate reported that fracture assessment was blinded to treatment allocation,[85,89,91,99] and three reported that BMD assessment was blinded to treatment allocation.[87,89,92]

Five of the studies (comparing TPTD with a bisphosphonate) that reported fracture outcomes were considered to have a high risk of attrition bias (≥ 10% of participants in both treatment groups did not complete the study),[85,91,92,99,101] and five studies assessing BMD were considered to have a high risk of attrition bias (≥ 10% of participants in both treatment groups did not complete the study).[84,85,87,91,92]

Six studies (comparing TPTD with a bisphosphonate) that reported the location of a protocol against which to check outcomes were considered to have a low risk of selective reporting bias.[84,85,87,92,99,101] One study reporting an intention-to-treat and a per-protocol analysis stated in the study publication that the data from the per-protocol analysis were not reported.[89] This study was considered to have a high risk of selective reporting.[89]

Assessment of effectiveness: fractures

Here we summarise the fracture results for the individual non-bisphosphonate RCTs included in the review. The results of the NMAs, which include both the bisphosphonate and non-bisphosphonate studies, are summarised in *Results of the network meta-analysis*.

Vertebral fractures

Results for vertebral fractures reported in the included studies are presented in *Appendix 5*, *Table 17*, for the non-bisphosphonate treatments compared with placebo, non-bisphosphonate treatments compared head to head, and non-bisphosphonate treatments compared with bisphosphonates. Fracture data used in the NMAs are shown in *Appendix 9*.

Clinical vertebral fractures: efficacy

Non-bisphosphonates versus placebo: clinical vertebral fractures One study comparing DEN with placebo reported a statistically significant between-group difference in clinical vertebral fractures at 36 months in favour of DEN in postmenopausal women with osteoporosis ($p < 0.001$).[41]

Three of the studies comparing RLX with placebo in postmenopausal women with osteoporosis reported on clinical vertebral fractures.[48,50,102] One of these reported a statistically significant between-group difference in favour of RLX at 12 months in postmenopausal women with osteoporosis ($p < 0.001$).[102] In the other two studies comparing RLX with placebo,[48,50] the between-group difference was not statistically significant (RLX, 0% vs. placebo, 4.90%; $p > 0.05$;[48] and RLX, 2.36% vs. placebo, 4.10%; $p = 0.89$[50]).

None of the studies comparing ROMO with placebo reported on clinical vertebral fractures.

Only one study comparing TPTD (prescribed open label) with placebo reported on clinical vertebral fractures at 18 months in postmenopausal women with osteoporosis.[95] The estimated between-group difference was not statistically significant (TPTD, 0.40% vs. placebo, 1.10%; $p = 0.10$).

Non-bisphosphonates compared head to head: clinical vertebral fractures One study comparing TPTD with RLX in an open-label design, in postmenopausal women with severe osteoporosis who were all pre-treated with TPTD for 12 months prior to randomisation, reported that there was no statistically significant between-group difference in clinical vertebral fractures at 12 months following randomisation (TPTD, 1.32% vs. RLX, 0%; *p*-value not reported).[66]

Non-bisphosphonates versus bisphosphonates: clinical vertebral fractures The estimated between-group difference in clinical vertebral fractures for one study comparing DEN with RIS in women and men receiving glucocorticoids was not statistically significant at 12 months (DEN, 3.00% vs. RIS, 4.00%; $p = 0.34$).[74]

The estimated between-group difference in clinical vertebral fractures for one study comparing RLX with ALN in postmenopausal women with osteoporosis was not statistically significant after approximately 45 weeks of treatment (study stopped early owing to difficulty in finding treatment-naive women) (ALN, 3.14% vs. RLX, 1.93%; $p = 0.20$).[80]

The reported between-group difference in clinical vertebral fractures for one study comparing ROMO with ALN in postmenopausal women with osteoporosis was not statistically significant at 12 months (ALN, 0.9% vs. ROMO, 0.50%; $p = 0.14$).[83]

The reported between-group difference in clinical vertebral fractures for one study comparing TPTD with ALN in women and men receiving glucocorticoids was not statistically significant at 18 months ($p = 0.07$).[103] However, the between-group difference at 36 months was statistically significant, in favour of TPTD ($p = 0.037$).[103]

Morphometric vertebral fractures: efficacy Morphometric assessment was not always defined, but for studies that assessed vertebral fracture as an efficacy measure, this was most often reported as using the method described by Genant *et al.*[35]

Non-bisphosphonates versus placebo: new morphometric vertebral fractures One study comparing DEN with placebo in postmenopausal women with osteoporosis reported a statistically significant between-group difference at 36 months in new morphometric vertebral fractures in favour of DEN ($p < 0.001$).[41] The estimated between-group differences for this study over 0-12, 12-24 and 24-36 months were also statistically significant in favour of DEN ($p < 0.05$).[104] However, the estimated between-group difference at the end of the 7-year open-label extension to this study following treatment-switching (all participants received DEN) was not statistically significant (placebo switched to DEN, 7.30% vs. continued DEN, 7.04%; $p = 0.76$).[105]

In a single study comparing DEN with placebo in women and men with osteoporosis, the reported between-group difference in new morphometric vertebral fractures at 24 months was statistically significant in favour of DEN ($p < 0.0001$).[43] The estimated between-group difference was also statistically significant in favour of DEN at 36 months, including a 12-month open-label extension following treatment-switching (all participants received DEN) ($p < 0.0001$).[106] The estimated between-group difference for the 12-month open-label extension alone was $p = 0.05$ (placebo switched to DEN, 2.00% vs. continued DEN, 0.25%).[106]

Across two studies comparing RLX with placebo in postmenopausal women with osteoporosis, at 36 months the reported or estimated between-group differences were statistically significant in favour of RLX in reducing new morphometric vertebral fractures ($p < 0.05$).[50,51] However, the between-group difference was not statistically significant in two studies of postmenopausal women with osteoporosis that reported this outcome at 12 months (placebo, 2.30% vs. RLX, 0%; estimated $p = 0.33$[47] and placebo, 40.00% vs. RLX, 48.84%; estimated $p = 0.41$[52]) and in one study of postmenopausal women on long-term glucocorticoids that reported this outcome at 12 months (placebo, 5.36% vs. RLX, 0%; reported $p = 0.24$).[53]

In the one study that compared ROMO with placebo in postmenopausal women with osteoporosis, statistically significant between-group differences in new morphometric vertebral fractures in favour of ROMO were reported at 12 months ($p < 0.001$) and 24 months ($p < 0.001$).[54] Following treatment-switching to DEN (all participants), (confidential information has been removed) between-group differences in new vertebral fracture (confidential information has been removed) group were reported at 36 months (confidential information has been removed).[20]

In one study comparing TPTD with placebo in postmenopausal women with osteoporosis, the reported between-group difference at 18 months was statistically significant in favour of TPTD in reducing new morphometric vertebral fractures ($p < 0.001$).[95] However, the estimated between-group difference was not statistically significant in one study in postmenopausal women with osteoporosis that reported this outcome at 12 months (placebo, 5.97% vs. TPTD, 3.68%; $p = 0.46$).[58]

Non-bisphosphonates compared head to head: new morphometric vertebral fractures New morphometric vertebral fracture was not an outcome in the study comparing TPTD with RLX in postmenopausal women with osteoporosis.[66]

Non-bisphosphonates versus bisphosphonates: new morphometric vertebral fractures The estimated between-group difference in new morphometric vertebral fractures after approximately 45 weeks of treatment in one study comparing RLX with ALN in postmenopausal women with osteoporosis (study stopped early owing to difficulty in finding treatment-naive women) was not statistically significant (ALN, 3.14% vs. RLX, 1.93%; $p = 0.39$).[80]

The reported between-group difference between new morphometric vertebral fractures for one study comparing ROMO with ALN in postmenopausal women with osteoporosis was statistically significant at 12 months [modified intent to treat (mITT), $p = 0.003$; last observation carried forward (LOCF), $p = 0.008$] and 24 months following treatment-switching to ALN, in favour of the group that switched from ROMO to ALN (mITT and LOCF, $p < 0.001$).[83]

The reported between-group difference in new morphometric vertebral fractures for one study comparing TPTD with ALN in women and men receiving glucocorticoids was statistically significant at 18 months ($p = 0.004$) and 36 months ($p = 0.007$) in favour of TPTD.[103] However, the estimated between-group difference at 18 months for men and women separately was not statistically significant (men: ALN, 4.48% vs. TPTD, 0.72%; $p = 0.09$; women: ALN, 12.90% vs. TPTD, 0%; $p = 0.13$).[107] One open-label study of postmenopausal women with severe osteoporosis receiving treatment for osteoporosis reported that there was no statistically significant difference between TPTD and ALN at 18 months (p-value not reported) (ALN, 15.7% vs. TPTD, 2.4%; estimated $p = 0.08$).[86]

Across studies comparing TPTD with RIS, no statistically significant between-group differences in new morphometric vertebral fractures were evident at 18 months in men with osteoporosis (RIS, 10.00% vs. TPTD, 0%; estimated $p = 0.52$)[89] or at 6 months in postmenopausal women with osteoporosis (RIS, 5.10% vs. TPTD, 4.20%; reported $p = 0.6$).[91] However, statistically significant between-group differences in new morphometric vertebral fractures in postmenopausal women with osteoporosis in favour of TPTD were reported at 18 months ($p = 0.01$)[91] and at 24 months ($p < 0.0001$).[99]

Vertebral fractures assessed as safety or when the efficacy assessment method was not reported One study comparing DEN with placebo in men with osteoporosis reported that there was no statistically significant between-group difference in clinical fractures assessed as a safety outcome at 12 months (placebo, 0.83% vs. DEN, 0%; $p = 0.50$).[42]

One study comparing RLX with ALN in postmenopausal women with osteoporosis reported vertebral fractures as a safety outcome, but did not report the assessment method.[76] Zero events were reported in both treatment groups in this study.[76] One study comparing RLX, ALN and RIS in postmenopausal women with osteoporosis reported vertebral fractures as an efficacy outcome, but did not report the assessment method.[79] When estimable, the between-group difference was not statistically significant in this study (ALN, 0.2% vs. RLX, 0%; $p = 0.66$; RIS, 0% vs. RLX, 0%; p-value not estimable).[79]

In one study comparing TPTD with RIS in women and men with low BMD following hip fracture surgery, for which clinical vertebral fractures were a safety outcome,[108] zero events were reported in both groups at 6 months. The between-group difference at 18 months was not statistically significant (RIS, 1.00% vs. TPTD, 0%; $p = 1.00$).[92]

One study of postmenopausal women with osteoporosis comparing TPTD (plus a placebo for ZOL) with ZOL (without a placebo for TPTD) also reported vertebral fractures as a safety outcome (the assessment method was not reported).[93] The estimated between-group difference at 12 months was not statistically significant (TPTD + placebo, 0.70% vs. ZOL, 3.70%; $p = 0.14$).[93]

Summary: clinical vertebral fractures There is evidence from a single study[41] that DEN is statistically more effective than placebo at reducing clinical vertebral fractures at 36 months in postmenopausal women with osteoporosis. There is also evidence from a single study[48] that RLX is statistically more effective than placebo at reducing clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. Evidence from a single open-label study[95] has found no statistical difference between TPTD and placebo on clinical vertebral fractures at 18 months in postmenopausal women with osteoporosis. There are, at present, no placebo-controlled studies of ROMO that evaluate clinical vertebral fractures.

There is evidence from a single study that there is no statistically significant difference between DEN and RIS,[74] between RLX and ALN,[76] and between ROMO and ALN[83] in the reduction of clinical vertebral fractures at up to 12 months in postmenopausal women with osteoporosis.

There is also evidence from a single study[103] that there is a statistically significant between-group difference between TPTD and ALN in favour of TPTD in the reduction of clinical vertebral fractures at 36 months in women and men receiving glucocorticoids.

Summary: new morphometric vertebral fractures There is evidence from a single study[41] that DEN is statistically more effective than placebo at reducing new morphometric vertebral fractures at 24 months and 36 months in postmenopausal women with osteoporosis, and at 24 months in men and women with osteoporosis. There is evidence from two studies[50,51] that RLX is statistically more effective than placebo at reducing new morphometric vertebral fractures at 36 months in postmenopausal women with osteoporosis. There is evidence from a single study[54] that ROMO is statistically more effective than placebo at reducing new morphometric vertebral fractures at 12 and 24 months in postmenopausal women with osteoporosis. There is also evidence from a single study[95] that TPTD is statistically more effective than placebo at reducing new morphometric vertebral fractures at 18 months in postmenopausal women with osteoporosis.

There is evidence from a single study that there is no statistically significant difference in new morphometric vertebral fractures between RLX and ALN at approximately 45 weeks (study stopped early owing to difficulty in finding treatment-naive women) in postmenopausal women with osteoporosis,[80] between TPTD and ALN at 18 months in women with severe osteoporosis receiving

treatment for osteoporosis,[103] and between TPTD and RIS at 18 months in men with osteoporosis.[89] However, there is evidence from a single study that ROMO is significantly more effective than ALN at reducing new morphometric vertebral fractures at 12 months in postmenopausal women with osteoporosis,[83] and that TPTD is significantly more effective than ALN at reducing new morphometric vertebral fractures at 18 and 36 months in women and men receiving glucocorticoids.[103] There is also evidence from two studies[89,99] that TPTD is significantly more effective than RIS at reducing new morphometric vertebral fractures at 18 and 24 months in postmenopausal women with osteoporosis.

Non-vertebral fractures

Non-vertebral fracture outcomes were reported in 28 RCTs and are shown in *Appendix 5*, *Table 18*. Hip, wrist and proximal humerus fracture outcomes were reported separately in 22 RCTS; these are shown in *Appendix 5*, *Table 19*. These fractures are also counted among the non-vertebral fracture total. Results of the NMAs for these outcomes are shown in *Results of the network meta-analysis*. Fracture data used in the NMAs are shown in *Appendix 9*.

Non-bisphosphonates versus placebo

The Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial[41] reported a significant ($p = 0.01$) advantage in non-vertebral fractures for DEN (6.1%) over placebo (7.5%) at 36 months for postmenopausal women. The FREEDOM trial[41] also had a lower rate of non-vertebral fractures for DEN (7.3%) than for placebo/DEN (9.9%) (significance not reported; estimated in RevMan as $p = 0.01$) 84 months into the open-label extension. At 36 months, the FREEDOM trial[41] reported a significantly ($p = 0.04$) lower rate of hip fracture for DEN (0.7%) than for placebo (1.2%) (see *Appendix 5*, *Table 19*). The Denosumab fracture Intervention RandomizEd placebo Controlled Trial (DIRECT),[43] a RCT of postmenopausal women and of men, did not find a difference in the number of non-vertebral fractures at 24 months between the DEN and placebo groups (both 4.1%), although there was a trend ($p = 0.0577$) towards fewer major non-vertebral fractures in the DEN group (1.6%) than in the placebo group (3.7%). The rate of non-vertebral fractures in the DEN group at 24 months of the international population of FREEDOM[41] was similar to that of the Japanese population of DIRECT.[43] Following a further year during which all participants received DEN, DIRECT[106] reported non-vertebral fracture rates of 6.7% for placebo/DEN and 5.2% for DEN, with rates of major non-vertebral fractures of 5.4% and 2.0%, respectively. At 24 months, DIRECT[43] reported 0% hip fractures for DEN and 0.4% for placebo.

Of the RLX versus placebo RCTs, the Morii *et al.*[47] and Lufkin *et al.*[52] studies were not powered to detect a difference between groups; however, both studies had a 0% rate of non-vertebral fractures in the RLX group at 12 months. In the Silverman *et al.*[50] RCT, there was no significant difference (estimated in RevMan as $p = 0.6409$) in non-vertebral fractures at 36 months between the RLX (6.3%) and placebo (5.7%) groups (see *Appendix 5*, *Table 18*), with rates of hip fracture of 0.3% in both groups (see *Appendix 5*, *Table 19*).

The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME)[54] reported a non-significant ($p = 0.096$) difference between ROMO (1.6%) and placebo (2.1%) at 12 months for non-vertebral fractures. At 24 months, FRAME[54] reported a significant advantage for ROMO/DEN over placebo/DEN in non-vertebral fractures (2.7% vs. 3.6%; $p = 0.029$), with a trend ($p = 0.059$) favouring ROMO/DEN for hip fractures (0.3%) over placebo/DEN (0.6%).

The Miyauchi *et al.*[58] trial, which included women and men, reported a lower (significance not reported; estimated in RevMan as $p = 0.1838$) rate of non-vertebral fractures for TPTD (2.2%) than for placebo (6.0%) at 12 months. In postmenopausal women, the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE)[95] did not find a significant difference ($p = 0.22$) between TPTD (3.3%) and placebo (4.7%) in the prevention of non-vertebral fractures at 18 months. In ACTIVE,[95] no hip fractures were reported in the TPTD group, whereas 0.2% of participants in the placebo group reported hip fractures. The Fracture Prevention Trial (FPT)[62] found a significant ($p = 0.04$) advantage of TPTD (6.3%) over

placebo (9.7%) in the prevention of non-vertebral fractures. The FPT[62] reported hip fracture rates of 0.4% in the TPTD group and of 0.7% in the placebo group. The population in the FPT[62] all had vertebral fractures at baseline, in contrast to ACTIVE,[95] in which two-thirds had prior fractures at baseline. The FPT[62] was blinded, whereas the TPTD arm in ACTIVE[95] was open label, as the trial was designed compare abaloparatide with placebo.

Studies reporting non-vertebral fracture rates as safety data reported, for postmenopausal women, the 6-month non-vertebral fracture rates for DEN (1.5%) and placebo (1.5%)[45] and the 12-month rates for ROMO (3.2%) and placebo 1.6%,[55] and, for men, the 12-month rates of DEN (0.8%) and placebo (1.7%).[42]

Head-to-head non-bisphosphonates

The European Study of Forsteo (EUROFORS)[66] reported fractures as an efficacy outcome, and found no significant difference between TPTD (2.96%) and RLX (2.06%) in non-vertebral fractures at 12 months' follow-up in postmenopausal women with prior TPTD treatment. Rates of hip fracture were 0.3% for TPTD and 0% for RLX.

The STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy (STRUCTURE)[67] reported fractures as a safety outcome in postmenopausal women. The rates of non-vertebral fractures at 12 months were 3.21% for ROMO and 3.67% for TPTD. Rates of hip fracture were 0.5% for ROMO and 0% for TPTD.[67]

Non-bisphosphonates versus bisphosphonates

Saag *et al.*[74] reported rates (no significance reported; estimated in RevMan as $p = 0.1781$) of non-vertebral fractures of 4.0% for DEN and 3.0% for RIS at 12 months' follow-up, and hip fracture rates of 0.3% for both groups.

Muscoso *et al.*[79] reported rates of non-vertebral fractures of 0% in both the RLX and RIS groups and of 0.2% in the ALN group in both the first and second years of the RCT. The EVista Alendronate comparison (EVA)[80] RCT found no significant difference (estimated in RevMan as $p = 0.8092$) between rates of non-vertebral fracture in the RLX (2.2%) and ALN (2.0%) groups. The EVA[80] RCT reported hip fracture rates of 0.3% for RLX and 0.1% for ALN.

The Active-controlled fracture study in postmenopausal women with osteoporosis at high risk (ARCH)[83] reported a trend ($p = 0.057$) favouring ROMO (3.4%) over ALN (4.6%) for the prevention of non-vertebral fractures at 12 months; for the prevention of major non-vertebral fractures (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm and hip), there was a significant ($p = 0.019$) difference between the groups (2.9% for ROMO and 4.3% for ALN). There was no significant ($p = 0.19$) difference in hip fracture rates at 12 months.[83] The results of the primary analysis show that there was a significant ($p = 0.037$) advantage of ROMO/ALN (8.7%) over ALN (10.6%) in the prevention of non-vertebral fractures, as well as the prevention of major non-vertebral fractures ($p = 0.004$) and hip fractures ($p = 0.015$).

Saag *et al.*[103] found no significant ($p = 0.6$) difference between rates of non-vertebral fractures for TPTD (5.6%) and ALN (3.7%) at 18 months, and also no significant treatment difference for subgroups of men ($p = 0.6$) or women ($p = 0.3$). Two RCTs of postmenopausal women comparing TPTD with RIS found no significant treatment difference for the prevention of non-vertebral fractures: VERtebral fracture treatment comparisons in Osteoporotic women (VERO) (Kendler *et al.*)[99] at 24 months (TPTD, 4.0% and RIS, 6.0%; $p = 0.10$) and Hadji *et al.*[91] at 6 months (TPTD, 7.8% and RIS, 8.3%; $p = 0.89$). The population in the Hadji *et al.*[91] study were selected because they had back pain due to vertebral fracture, which may explain why the rates were higher in both these groups than they were in VERO.[99] The rates of hip fracture were 0.3% for TPTD and 0.7% for RIS in VERO,[99] and 1.4% for TPTD and 0.6% for RIS in Hadji *et al.*[91]

For studies reporting fractures as safety data, non-vertebral fracture rates for postmenopausal women at 12 months were 0.8% for DEN and 0.9% for ALN,[109] 3.9% for RLX and 2.5% for ALN,[77] 5.1% for TPTD,[93] 5.8% for ZOL[93] and, for women pre treated (with ALN), 3.2% for DEN and 1.6% for ALN.[70] At 24 months, non-vertebral fracture rates were 3.0% for RLX, 3.0% for ALN and 6.0% for placebo for women pre treated (with ALN).[82] Hip fracture rates at 12 months were reported as 0.4% for RLX and 0.0% for ALN.[76] For men with glucocorticoid-induced osteoporosis, non-vertebral fracture rates of 0.0% for TPTD and 10.6% for RIS (trend $p = 0.056$) were reported at 18 months.[87] In a population that had had hip surgery, at 18 months' follow-up reported non-vertebral fracture rates were 4.7% for TPTD and 9.1% for RIS; hip fracture rates were 1.9% for TPTD and 6.4% for RIS.[92]

Across placebo-controlled trials and trials with comparators of non-bisphosphonates or bisphosphonates, when reported, non-bisphosphonates had wrist fracture rates of no more than 2.5% and proximal humerus fracture rates of no more than 1.1%.

Assessment of effectiveness: bone mineral density

Here we summarise the BMD results of the individual non-bisphosphonate RCTs included in the review. The results of the NMAs, which include both the bisphosphonate and non-bisphosphonate studies, are summarised in *Results of the network meta-analysis*. Given the multiple time points often reported for BMD, we decided to focus on annual or final follow-up.

Femoral neck bone mineral density

Results for femoral neck BMD reported by the included studies are presented in *Appendix 5*, *Table 20*, for the non-bisphosphonate treatments compared with placebo, non-bisphosphonate treatments compared head to head, and non-bisphosphonate treatments compared with bisphosphonates.

Non-bisphosphonates versus placebo: femoral neck bone mineral density

Three studies comparing DEN with placebo reported a statistically significant between-group difference in femoral neck BMD in favour of DEN: at 6 months in postmenopausal women with osteoporosis ($p = 0.0042$),[45] at 12 months in men with osteoporosis ($p < 0.0001$)[42] and at 24 months in women and men with osteoporosis ($p < 0.0001$).[43] The estimated between-group differences were also statistically significant in favour of DEN in the open-label extensions to these studies. However, the open-label extension estimates were all reliant on data extracted from graphs.

Statistically significant between-group differences in femoral neck BMD in favour of RLX over placebo were evident at 36 months for two studies of postmenopausal women with osteoporosis ($p < 0.00001$[50] and $p < 0.001$[51]) and at 12 months for one study of postmenopausal women with osteoporosis who were pre treated with TPTD ($p < 0.001$).[46] However, the between-group difference in the open-label extensions to the study of postmenopausal women with osteoporosis pre treated with TPTD was not statistically significant (see *Appendix 5*, *Table 20*).[46] The estimated between-group difference at 12 months in one study of postmenopausal women with osteoporosis was not statistically significant,[48] nor was the between-group difference at 12 months in one study of postmenopausal women receiving long-term glucocorticoids (data estimated from graph).[53]

Statistically significant between-group differences in femoral neck BMD in favour of ROMO over placebo were reported at 12 months for two studies of postmenopausal women with osteoporosis ($p < 0.001$[54] and $p < 0.00001$[55]), and at 12 months in one study of men with osteoporosis ($p < 0.001$).[56] The reported between-group difference was also statistically significant at 24 months in one study following an open-label treatment-switching extension, favouring switching from ROMO to DEN over switching from placebo to DEN ($p < 0.001$)[54] (see *Appendix 5*, *Table 20*). A study of postmenopausal women with osteoporosis reported statistically significant between-group differences in femoral neck BMD in favour of ROMO over ALN at 12 months ($p < 0.001$), and in favour of ROMO/ALN over ALN/ALN at 24 and 36 months ($p < 0.001$).

Four studies comparing TPTD with placebo reported a statistically significant between-group difference in femoral neck BMD in favour of TPTD at 6 months in postmenopausal women with osteoporosis ($p < 0.01$).[61] Statistically significant between-group differences in favour of TPTD at 12 months were also reported by one study ($p = 0.015$),[58] at 18 months by one study ($p < 0.0001$)[95] and at 24 months by one study ($p < 0.001$).[62] The estimated between-group difference was also statistically significant in favour of continued TPTD in the open-label extension in one of these studies, compared with switching from placebo to TPTD at 18 months ($p = 0.03$), but not at 24 months (see *Appendix 5*, *Table 20*).[58] The estimated between-group difference at 6 months for one study comparing TPTD with placebo in postmenopausal women with osteoporosis was not statistically significant,[59] nor was the estimated between-group difference at 6 months of one study comparing TPTD plus calcium and vitamin D with calcium and vitamin D alone.[63]

Non-bisphosphonates compared head to head: femoral neck bone mineral density

One study comparing TPTD with DEN in postmenopausal women with osteoporosis reported no statistically significant between-group difference in femoral neck BMD at either 12[64] or 24 months.[110] However, statistically significant differences were reported in the open-label extension following treatment-switching, in favour of the group switching from TPTD to DEN, at 24 and 48 months following switching.[65]

A statistically significant between-group difference in femoral neck BMD at 12 months in postmenopausal women with osteoporosis, who were pre treated with ALN prior to randomisation, was reported by one study comparing TPTD with ROMO, in favour of ROMO ($p < 0.0001$).[67]

One study comparing TPTD, RLX and a non-active control in postmenopausal women with osteoporosis who were pre treated with ALN reported on the between-group difference in femoral neck BMD for TPTD compared with control only; the result was statistically significantly in favour of the non-active treatment ($p < 0.05$).[66] No variance estimates were reported by this study. Therefore, the other between-group comparisons could not be estimated.

The estimated between-group difference in femoral neck BMD at 12 months for one study comparing TPTD with ROMO in postmenopausal women was not statistically significant.[68] In this study, the estimated between-group differences for both non-bisphosphonates compared with placebo were statistically significant in favour of the active treatment (TPTD, $p = 0.0007$; ROMO, $p = 0.0002$). However, when comparing ROMO with ALN and TPTD with ALN, the results were not statistically significant.

Non-bisphosphonates versus bisphosphonates: femoral neck bone mineral density

Across two open-label studies comparing DEN with ALN, statistically significant between-group differences in femoral neck BMD in favour of DEN were reported at 12 months in one study of postmenopausal women with osteoporosis ($p = 0.0001$),[69] and at 12 months in one study of postmenopausal women with osteoporosis already receiving ALN ($p < 0.0121$).[70] The estimated between-group difference for one study comparing DEN with ALN in postmenopausal women with osteoporosis, which was not powered for femoral neck BMD, was not statistically significant (see *Appendix 5*, *Table 20*).[71]

In one open-label study comparing DEN with IBN (oral) in postmenopausal women with osteoporosis, at 12 months the between-group difference in femoral neck BMD was statistically significant in favour of DEN ($p < 0.001$).[73]

Statistically significant between-group differences in femoral neck BMD in favour of DEN at 12 months were also reported by one study comparing DEN with RIS in women and men with osteoporosis who were continuing or initiating glucocorticoids (continuing: $p = 0.004$; initiating: $p = 0.020$),[74] and at 12 months by one study comparing DEN with ZOL in postmenopausal women with osteoporosis previously treated with bisphosphonates ($p < 0.0001$).[75]

Two studies comparing RLX with ALN in postmenopausal women with osteoporosis reported statistically significant between-group differences in femoral neck BMD in favour of RLX at 12 months ($p = 0.0001$)[76] and 24 months ($p = 0.002$).[80] However, one study comparing RLX with ALN in postmenopausal women with osteoporosis,[77] and one study comparing RLX with ALN in postmenopausal women with osteoporosis who were previously treated with bisphosphonates,[82] reported that the between-group difference at 12 months was not statistically significant. In one of these studies,[82] the estimated between-group difference following a 12-month open-label extension to 24 months (data estimated from graph) was statistically significant in favour of ALN ($p = 0.03$). One other study comparing RLX with ALN in postmenopausal women with osteoporosis also reported a statistically significant between-group difference in favour of ALN at 12 months ($p < 0.05$).[78]

One study comparing TPTD with ALN in women and men with osteoporosis receiving glucocorticoids reported a statistically significant between-group difference in femoral neck BMD at 36 months ($p < 0.001$).[103] The between-group difference reported by one study comparing TPTD with ALN at 18 months in postmenopausal women with osteoporosis was $p = 0.05$.[84]

Across three studies comparing TPTD with RIS, statistically significant between-group differences in femoral neck BMD in favour of TPTD were reported at 18 months: in men with osteoporosis receiving glucocorticoids ($p = 0.026$),[87] in postmenopausal women with osteoporosis ($p = 0.02$)[91] and in women and men with low BMD following hip fracture surgery ($p = 0.003$).[92] However, one of these studies[91] reported an imbalance in femoral neck BMD across study groups at baseline. One study comparing TPTD with RIS in men with osteoporosis reported that the between-group difference at 18 months was not statistically significant.[89]

One study comparing TPTD (plus a placebo for ZOL) with ZOL (without a placebo for TPTD) reported a statistically significant between-group difference in femoral neck BMD in favour of ZOL at 12 months in postmenopausal women with osteoporosis ($p < 0.05$).[93]

Summary: femoral neck bone mineral density

There is evidence that DEN is statistically more effective than placebo at increasing femoral neck BMD at 6 months in postmenopausal women with osteoporosis,[45] at 12 months in men with osteoporosis[42] and at 24 months in women and men with osteoporosis.[43]

The evidence is mixed for RLX increasing femoral neck BMD, compared with placebo. There is evidence from a single study that RLX is statistically more effective than placebo at 36 months in postmenopausal women with osteoporosis[50,51] and at 12 months in postmenopausal women with osteoporosis who were pre treated with TPTD.[46] However, there is evidence from a single study that the between-group difference between RLX and placebo is not statistically significantly different at 12 months in postmenopausal women with osteoporosis[46] or at 12 months in postmenopausal women receiving long-term glucocorticoids (data estimated from graph).[53]

There is evidence from two studies that ROMO is statistically more effective than placebo at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis.[54,55] and at 12 months in men with osteoporosis.[56]

The evidence is mixed for TPTD increasing femoral neck BMD, compared with placebo. There is evidence from a single study that TPTD is statistically more effective than placebo at 6,[61] 12[58] and 18 months[95] in postmenopausal women with osteoporosis. However, there is evidence from a single study that the between-group difference in TPTD compared with placebo,[59] or TPTD plus calcium and vitamin D compared with calcium or vitamin D alone,[63] is not statistically significantly different at 6 months in postmenopausal women with osteoporosis.

There is evidence from a single study that, although TPTD is not statistically more effective than placebo at increasing femoral neck BMD at 12 or 24 months in postmenopausal women with osteoporosis, treatment-switching from TPTD to DEN is significantly more effective than continued DEN at a further 24 and 48 months (open label).[65]

There is evidence from a single study that ROMO is statistically more effective than TPTD at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis who were pre treated with ALN.[67]

There is evidence from a single study that DEN is statistically more effective than ALN at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis[69] and at 12 months in postmenopausal women with osteoporosis already receiving ALN.[70] There is also evidence from a single study that DEN is statistically more effective than oral IBN at 12 months in postmenopausal women with osteoporosis,[73] that DEN is statistically more effective than RIS at 12 months in women and men with osteoporosis continuing or initiating glucocorticoids,[74] and that DEN is statistically more effective than ZOL at 12 months in postmenopausal women with osteoporosis who were previously treated with bisphosphonates.[75]

The evidence for RLX compared with ALN is mixed. There is evidence from a single study that RLX is statistically more effective than ALN at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis.[76] However, there is evidence that the between-group difference between RLX and placebo is not statistically significantly different at 12 months in postmenopausal women with osteoporosis (two studies).[77,82] There is also evidence that ALN is statistically more effective than RLX at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis (two studies).[78,82]

There is evidence from a single study that ROMO is statistically more effective than ALN at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis and that switching from ROMO to ALN is statistically more effective than continued ALN at 24 and 36 months (open label).[83]

The evidence is mixed for TPTD increasing femoral neck BMD, compared with placebo. There is evidence that TPTD is statistically more effective than RIS at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis (two studies). There is also evidence from a single study that TPTD is statistically more effective than RIS at increasing femoral neck BMD at 18 months in women and men with osteoporosis receiving glucocorticoids, in men with osteoporosis receiving glucocorticoids and in women and men with low BMD following hip fracture surgery. However, there is evidence from a single study that the between-group difference for TPTD and RIS is not statistically significantly different at 18 months in men with osteoporosis.

There is evidence from a single study that ZOL without placebo is statistically more effective than TPTD with placebo at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis.[93]

Lumbar spine bone mineral density

Six RCTs did not report femoral neck BMD, but did report lumbar spine BMD (see *Appendix 5*, *Table 23*). One RCT reported a significant increase in lumbar spine BMD for DEN, compared with placebo.[44] A placebo-controlled trial reported a significant increase in lumbar spine BMD for RLX,[47] and a small RCT reported an advantage for RLX plus alfacalcidol ($n = 31$), compared with alfacalcidol alone ($n = 34$),[49] whereas another small trial found no significant difference for RLX ($n = 48$) compared with a non-active treatment control ($n = 48$).[52] One RCT of RLX versus bisphosphonates reported that ALN and RIS had a higher percentage increase in lumbar spine BMD at 24 months than RLX (estimated in RevMan as $p < 0.001$).[79] One small RCT did not find a significant difference between TPTD ($n = 22$) and RIS ($n = 22$) in the improvement of lumbar spine BMD.[88]

Assessment of effectiveness: adverse events

Mortality

Mortality across the included studies is presented in *Appendix 5*, *Table 21*, for the non-bisphosphonate treatments compared with placebo, non-bisphosphonate treatments compared head to head and non-bisphosphonate treatments compared with bisphosphonates. None of the included studies reported on mortality following hip fracture, mortality following vertebral fracture or mortality following any other type of fracture.

Non-bisphosphonates versus placebo: mortality

Of the studies comparing DEN with placebo, six reported on mortality;[41–43,45,106,111] of the studies comparing RLX with placebo, two reported on mortality;[48,50] and of studies comparing ROMO with placebo, three reported on mortality.[54–56] Six studies comparing TPTD with placebo reported on numbers of mortality;[57–59,61,63,95] one reported that there was no statistically significant between-group difference (data were not reported).[62]

When mortality was reported in studies comparing non-bisphosphonates with placebo, event rates were low with active treatment (0.0–1.8%). Only one study reported a between-group difference,[41] which was not statistically significant ($p = 0.08$). For the studies for which between-group differences were not reported, the estimated between-group differences were not statistically significant ($p > 0.05$).

Non-bisphosphonates compared head to head: mortality

The Denosumab and Teriparatide Administration (DATA)[64] and DATA-Switch studies,[65] that compared DEN with TPTD, did not report on mortality; neither did the EUROFORS,[66] which compared TPTD with RLX. In the two studies that compared ROMO with TPTD and reported on mortality,[67,68] event rates for mortality were low with either treatment (0–2%). The estimated between-group differences were not statistically significant ($p > 0.05$).

Non-bisphosphonates versus bisphosphonates: mortality

Of the studies comparing DEN with bisphosphonates and reporting on mortality, three studies compared DEN with ALN;[69,70,72] one compared DEN with oral IBN,[73] one compared DEN with RIS[74] and one compared DEN with ZOL.[75] Across these studies event rates for mortality were low across treatments (< 1%) and the estimated between-group differences were not statistically significant ($p > 0.05$).

Of the studies comparing RLX with bisphosphonates, two studies comparing RLX with ALN reported on mortality.[76,80] Of these two studies,[76,80] event rates for mortality were low across treatments (< 1%) and the estimated between-group differences were not statistically significant ($p > 0.05$).

One study comparing ROMO with ALN reported mortality rates of < 2% with either treatment at 12 months prior to treatment-switching and of < 5% at 24 months following treatment-switching.[83] The estimated between-group differences were not statistically significant ($p > 0.05$).

Of the studies of TPTD compared with bisphosphonates, one study comparing TPTD with ALN;[74] four comparing TPTD with RIS,[87,91,99,101] and one comparing TPTD with ZOL[93] reported on mortality. Across these studies, event rates ranged from 0% to 4.4% with TPTD and from < 1% to 6.4% with bisphosphonates. The estimated between-group differences were not statistically significant ($p > 0.05$).

Adverse events and serious adverse events

Adverse events and serious adverse events (SAEs) reported across the included studies are presented in *Appendix 5*, *Table 22*, for the non-bisphosphonate treatments compared with placebo, non-bisphosphonate treatments compared head to head and non-bisphosphonate treatments compared with bisphosphonates.

Non-bisphosphonates versus placebo: adverse events

Five studies comparing DEN with placebo,[41–45,106,111] three studies comparing RLX with placebo,[47,50,94] three studies comparing ROMO with placebo[54–56] and five studies comparing TPTD with placebo,[57–59,61,63,95] reported on AEs. Event rates ranged from 37% to 94.3% with DEN, from 27.1% to 96% with RLX, from 12.9% to 78.4% with ROMO and from 21.9% to 91.9% with TPTD. The between-group differences that were reported were not statistically significant, nor were those that were estimated by ScHARR ($p > 0.05$).

Non-bisphosphonates versus placebo: serious adverse events

Five studies comparing DEN with placebo,[41–45,106,111] three studies comparing RLX with placebo,[47,48,50,94] three studies comparing ROMO with placebo[54–56] and six studies comparing TPTD with placebo[57–59,61–63,95] reported on SAEs. Event rates ranged from 2.0% to 25.8% with DEN, from 2.0% to 18.6% with RLX, from 3.2% to 12.9% with ROMO and from 0% to 10.0% with TPTD. The between-group differences that were reported were not statistically significant, nor were those that were estimated ($p > 0.05$).

Non-bisphosphonates compared head to head: adverse events

One study that compared TPTD with DEN,[64] one study that compared TPTD with RLX[66] and two studies that compared TPTD with ROMO[67,68] reported on AEs. Across these studies, event rates for TPTD ranged from 16.1%[64] to 90%,[68] and from 75.0%[67] to 82.0%[68] for ROMO; event rates were 12.1%[64] for DEN and 54.6%[66] for RLX. The reported and estimated between-group differences were not statistically significant ($p > 0.05$).

Non-bisphosphonates compared head to head: serious adverse events

The DATA[64] and DATA-Switch[65] studies, which compared TPTD with DEN before and after treatment-switching,[64] and two studies that compared TPTD with ROMO,[67,68] reported on SAEs. Across these studies, event rates for TPTD ranged from 6.5%[64] to 11.0%[95] (22.0% following treatment-switching to DEN[64]) and from 8.0%[67] to 10.0%[68] for ROMO; the event rate for DEN was 3%.[64] The estimated between-group differences were not statistically significant ($p > 0.05$).

Non-bisphosphonates versus bisphosphonates: adverse events

Of the studies of DEN compared with bisphosphonates, three studies comparing DEN with ALN,[69,71,72,109] one comparing DEN with oral IBN,[73] one comparing DEN with RIS[74] and one comparing DEN with ZOL[75] reported on AEs. Across these studies, event rates for DEN ranged from 59.6%[73] to 80.9%;[69] event rates for bisphosphonates ranged from 64.1%[71] to 91.3%[72] for ALN, and were 56.1%[73] for IBN, 69.0%[74] for RIS and 62.2%[75] for ZOL. Across these studies, both the reported and estimated between-group differences were not statistically significant ($p > 0.05$).

Of the studies of RLX compared with bisphosphonates, four studies comparing RLX with ALN reported on AEs.[76,77,80,82] Across these studies,[76,77,80,82] event rates ranged from 24% to 75.2% for RLX and from 12.0% to 74.2% for ALN. Across these studies, both the reported and estimated between-group differences were not statistically significant ($p > 0.05$).

One study comparing ROMO with ALN reported AEs at 12 months prior to treatment-switching (75.7% vs. 78.6%) and at 24 months following treatment-switching to ALN (86.6% vs. 88.6%).[83] The estimated between-group difference was $p = 0.02$ at 12 months in favour of ROMO and was $p = 0.05$ at 24 months in favour of switching from ROMO to ALN.

Of the studies comparing TPTD with bisphosphonates, one study comparing TPTD with ALN,[74] six comparing TPTD with RIS[87,88,91,92,99,101] and one comparing TPTD with ZOL[93] reported on AEs. Across these studies, event rates ranged from 31.9% to 79.1% for TPTD and from 33.3% to 81.4% for RIS; the event rate was 86% for ALN and 70.1% for ZOL.[93] The estimated between-group difference for the study comparing TPTD with ZOL[93] was statistically significantly in favour of TPTD ($p = 0.006$). All other reported or estimated between-group differences were not statistically significant ($p > 0.05$).

Non-bisphosphonates versus bisphosphonates: serious adverse events

Of the studies comparing DEN with bisphosphonates, three studies comparing DEN with ALN,[69,71,72,109] one comparing DEN with oral IBN,[73] one comparing DEN with RIS[74] and one comparing DEN with ZOL[75] reported on SAEs. Across these studies, event rates for DEN ranged from 2.4% to 16.0%. Event rates for bisphosphonates ranged from 2.2% to 6.4% for ALN, and were 5.4% for IBN, 17% for RIS and 9.1% for ZOL. The study comparing DEN with IBN[73] reported a between-group difference in favour of IBN of $p = 0.046$. Across all other studies, both the reported and estimated between-group differences were not statistically significant ($p > 0.05$).

Of the studies comparing RLX with bisphosphonates, four studies comparing RLX with ALN reported on SAEs.[76,77,82] Across these studies, event rates ranged from 24% to 75.2% for RLX and from 12% to 74.2% for ALN. Across these studies, both the reported and estimated between-group differences were not statistically significant ($p > 0.05$).

One study comparing ROMO with ALN reported on SAEs at 12 months prior to treatment-switching (ROMO, 12.8% vs. ALN, 13.8%) and 24 months following treatment-switching to ALN (ROMO switched to ALN, 28.7% vs. continued ALN, 30.0%).[83] The estimated between-group differences were not statistically significant ($p > 0.05$).

Of the studies comparing TPTD with bisphosphonates, one study comparing TPTD with ALN[74] four comparing TPTD with RIS[87,91,92,99,101] and one comparing TPTD with ZOL[93] reported on SAEs. Across these studies, event rates ranged from 11% to 28.9% for TPTD and from 16.6% to 46.8% for RIS, and were 30% for ALN and 14.6% for ZOL. The estimated between-group difference for the study comparing TPTD with ZOL[93] was statistically in favour of TPTD ($p = 0.006$). All other reported or estimated between-group differences were not statistically significant ($p > 0.05$).

Specific adverse events

Details of VTE, stroke, ONJ and atypical femoral fractures reported by the included studies are presented in *Appendix 7*.

Other evidence on adverse events

Denosumab: National Institute for Health and Care Excellence Technology Appraisal – summary of adverse events evidence The NICE TA204[10] found that, although the SmPC indicates that conditions associated with DEN include urinary tract infection, upper respiratory tract infection, sciatica, cataracts, constipation, rash, pain in extremity and skin infections, there is no evidence of increased incidence of cataracts or diverticulitis in postmenopausal women with osteoporosis and that cataracts and diverticulitis occur only in patients with prostate cancer.[21] The SmPC also states that ONJ has been reported in patients receiving DEN or bisphosphonates, with most cases occurring in people with cancer, but that some occurred in people with osteoporosis.[21]

The NICE TA204[10] for DEN also found that studies of DEN for other indications have shown that treatment may be associated with ONJ, but that there is no evidence of this from the clinical studies of DEN in women with osteoporosis and that that the available clinical evidence indicates that DEN is a well-tolerated treatment for the prevention of osteoporotic fragility fractures in postmenopausal women.

Denosumab: European Medicines Agency assessment report – summary of adverse events evidence
The European Medicines Agency assessment report for DEN[112] found that no cases of ONJ were seen in the clinical studies it summarised and that there was no increased frequency of cardiovascular events or abnormal electrocardiographs in DEN-treated patients. The report[112] found that, in one study in postmenopausal women, more subjects receiving DEN than those receiving placebo developed an infection that necessitated hospitalisation. The report[112] found that infections reported among DEN-treated subjects were characterised by common infections (e.g. pneumonia, urinary tract infection,

cellulitis, appendicitis and diverticulitis) and were not distinguishable as opportunistic infections, and that serious infection events tended to occur 6–12 months after the initial administration of DEN.

The report[112] found that, in the combined safety analysis across the four pivotal trials, the small differences noted in individual studies in the number of certain SAEs were not evident across the postmenopausal women and hormone ablation therapy populations. For other SAEs, the report found that fatalities in DEN and placebo groups occurred with the same frequencies. In one study of postmenopausal women, the report observed that significantly more patients in the DEN group than in the placebo group reported SAEs, particularly osteoarthritis and pneumonia. However, in another study of postmenopausal women, the report observed that there were no significant differences in SAEs between treatment groups.

The report[112] also found that no single type of malignancy was reported at an increased frequency in any trial of DEN. However, a significantly greater incidence of cataracts was evident in males receiving hormone ablation therapy treated with DEN than in males receiving the control.

Raloxifene: National Institute for Health and Care Excellence Technology Appraisal – summary of adverse events evidence The NICE TA161,[11] which included RLX for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, found that VTE is the most SAE reported with RLX, with an approximate threefold increased risk of VTE. The incidence of hot flushes, arthralgia, dizziness, leg cramps, influenza-like symptoms, endometrial cavity fluid, peripheral oedema and worsening diabetes is also statistically significantly greater with RLX than with placebo. The report also found that, although the impact that RLX had on cardiovascular disease is unclear, there is evidence that it lowers serum concentrations of fibrinogen, as well as total and low-density lipoprotein cholesterol levels, without increasing high-density lipoprotein cholesterol.

Raloxifene: European Medicines Agency assessment report – summary of adverse events evidence The European Medicines Agency SmPC for RLX[24] states that RLX is associated with an increased risk of venous thromboembolic events in postmenopausal women, which occurred in $< 1.1\%$ of treated patients.

Raloxifene: European Medicines Agency Summary of Product Characteristics – summary of adverse events evidence The European Medicines Agency public assessment report for RLX[113] states that the most common side effects (seen in more than one patient in 10) are vasodilation and influenza-like symptoms.

Romosozumab: draft Summary of Product Characteristics The draft SmPC for ROMO[12] notes under special precautions that (confidential information has been removed).

Teriparatide: National Institute for Health and Care Excellence Technology Appraisal – summary of adverse events evidence The NICE TA161,[11] which included TPTD for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, reported only on AEs associated with TPTD administered at 40 µg per day compared with placebo, which were nausea and headache.

Teriparatide: European Medicines Agency scientific discussion – summary of adverse events evidence The European Medicines Agency's initial marketing scientific discussion for TPTD[114] reported that, in the clinical pharmacology studies, orthostatic hypotension was observed in healthy subjects following administration of TPTD at doses of more than 20 µg per day; at the proposed therapeutic dose of 20 µg per day, the most frequently reported AEs were leg cramps, nausea and headache. The more recent European Medicines Agency variation on the scientific discussion[115] concluded that no further safety issues had been identified from further studies. The European Medicines Agency SmPC[115] states that the most commonly reported adverse reactions in patients treated with TPTD are nausea, pain in limb, headache and dizziness.

Health-related quality of life

Five studies[86,90,101,116,117] published results of reported HRQoL, measured by a validated assessment tool (see *Appendix 6*).

Non-bisphosphonates versus placebo: health-related quality of life

Health-related quality of life was reported as part of the FREEDOM trial.[116,118] At 3 years' follow-up, there were no significant differences between DEN and placebo groups on the physical function, emotional status or back-pain dimension of the Osteoporosis Assessment Questionnaire-Short Version (OPAQ-SV) (see *Appendix 6*).[116]

The HRQoL of the RLX and placebo groups did not change significantly from baseline, as measured by the Women's Health Questionnaire, the Quality of Life Questionnaire of the European Foundation for Osteoporosis-41 items (QUALEFFO-41), the EuroQol - Visual Analogue Scale (EQ-VAS) or the EuroQol-5 Dimensions (EQ-5D) Health State Profile Utility Score (see *Appendix 6*) at 36 months' follow-up in the Silverman *et al.*[50] RCT.

Non-bisphosphonates versus bisphosphonates: health-related quality of life

In the Panico *et al.*[86] RCT, both the ALN and TPTD groups improved significantly at 18 months on the QUALEFFO-41 domains of pain, everyday activities, domestic job, locomotor function, social activities and health perception, with more improvement (*p*-value not reported) for TPTD. In the mood domain, only the TPTD group improved significantly (see *Appendix 6*).

In the VERO RCT,[90] there was no significant difference between the TPTD and RIS groups: both showed significant improvement in the EQ-VAS. The MOVE RCT[101] also reported no significant difference between the TPTD and RIS groups, which both showed significant improvement in the physical component of the Short Form questionnaire-36 items.

Network meta-analysis

Methods for the network meta-analysis

A network meta-analysis was conducted for each of the five main fracture types (vertebral, non-vertebral, hip, wrist and proximal humerus) and for femoral neck BMD.

For consistency with NICE TA464,[34] the model for the NMA assumed exchangeable treatment effects (i.e. a class effect) for bisphosphonate treatments, whereby individual treatment effects are estimated for each bisphosphonate treatment, but these are assumed to arise from a common distribution (or class). Unrelated treatment effects were assumed for all non-bisphosphonate interventions. For comparison, sensitivity analyses were also conducted using a standard random effects model with unrelated treatment effects for all interventions. Further details of the statistical models are provided in *Appendix 8*.

For fracture outcomes, treatment effects are presented as hazard ratios (HRs) relative to placebo, with a HR of < 1 reflecting a reduced risk of fracture relative to the comparator treatment. To account for different durations of follow-up across the trials, the model assumed an underlying Poisson process for each trial arm, with constant event rate.[119] For femoral neck BMD, the model for the NMA included a covariate for the duration of follow-up in each study, and treatment effects are presented as the difference in mean percentage change from baseline in BMD relative to placebo after 1.6 years of follow-up (which was the average duration of follow-up in these studies).

For fracture outcomes (i.e. binomial data), heterogeneity in treatments effects was characterised as being mild (SD < 0.1), moderate ($0.1 \leq$ SD < 0.5), high ($0.5 \leq$ SD < 1) or extremely high (SD ≥ 1); for femoral neck BMD, characterisation was based on a conversion as described in Ren *et al.*[120] When appropriate, heterogeneity in treatment effects was explored by considering potential treatment effect modifiers using meta-regression.[121] Baseline risk/response can be used as a proxy for differences in participant characteristics across trials that may be modifiers of treatment effect. Adjustment for baseline risk/response was assessed using the method of Achana *et al.*[122]

Potential inconsistency between direct and indirect evidence was assessed using node-splitting.[123]

All analyses were conducted in the freely available software package WinBUGS (MRC Biostatistics Unit, Cambridge, UK)[124] and R (The R Foundation for Statistical Computing, Vienna, Austria), using the R2Winbugs[125] interface package. Convergence to the target posterior distributions was assessed using the Gelman–Rubin statistic, as modified by Brooks and Gelman,[126] for two chains with different initial values. For all outcomes, a burn-in of 75,000 iterations of the Markov chain was used, with a further 20,000 iterations retained to estimate parameters. Samples from the posterior distributions exhibited moderate correlation between successive iterations of the Markov chain, so were thinned by retaining every 15th sample.

The absolute goodness of fit was checked by comparing the total residual deviance with the total number of data points included in an analysis. The deviance information criterion (DIC) provides a relative measure of goodness of fit that penalises complexity and was used to compare different models for the same likelihood and data.[127] Lower values of DIC are favourable, suggesting a more parsimonious model.

Results are presented using the posterior median treatment effects, 95% credible intervals (CrIs) and 95% prediction intervals (PrIs). The probability of each intervention ranking was computed by counting the proportion of iterations of the Markov chain in which each intervention had each rank. The treatment effects of each intervention compared with placebo, together with the median rank and the probability of being the highest-ranking treatment, are displayed in forest plots (see *Figures 6*, *8*, *13* and *14*).

Selection of evidence contributing to the network meta-analysis

Studies included in the systematic literature review were eligible to be included in the NMA. Characteristics of the studies are summarised in *Appendix 4*, *Table 15*, and vertebral fractures are summarised in *Appendix 5*, *Table 17*.

Vertebral fractures may be assessed using either clinical methods or radiographic techniques. For studies that reported outcomes using multiple methods/definitions, radiographical assessment was selected for the main analysis, as this was the most widely reported outcome. If radiographical assessment was not available for a given study, then clinically assessed outcomes were included. Studies that did not state the assessment method were also included. A sensitivity analysis was performed (SA2) to assess the impact of including only those RCTs with clinical assessment of fractures.

Outcomes may be reported at different time points across studies. For the primary analysis data set, the longest reported time point was selected for each study and the difference in trial durations is accounted for in the statistical model, under the assumption that the fracture event rate in each study arm is constant over time. To assess this assumption, a sensitivity analysis (SA1) was conducted that restricted the analysis to studies that reported outcomes at 12 months.

To contribute to the NMA, studies were required to provide the number of events and the analysed sample size in each arm. When not reported, these quantities were estimated from other information (e.g. reported percentages, figures); however, the exact numbers are subject to uncertainty. Sensitivity was therefore assessed (SA3) by excluding these studies, along with other studies that raised concerns regarding risk of bias due to blinding issues and early study termination.

A sensitivity analysis was also conducted that excluded studies for which prior treatment with bisphosphonates was permitted (SA4).

In summary, the following four sensitivity analyses were conducted for vertebral fracture outcomes:

1. SA1 – 12-month data
2. SA2 – clinical assessment
3. SA3 – exclusion for quality issues
4. SA4 – exclusion for prior bisphosphonate treatment.

For each of the sensitivity analyses, results were compared with the main analysis to assess the impact of the NMA inclusion criteria.

Data for femoral neck BMD outcomes were presented in two different formats: as the percentage change in femoral neck BMD for each treatment group or as the MD in the percentage change between treatment groups. In addition, data were presented either numerically or in graphical format.

When available, numerical estimates for each treatment group were selected as the most accurate summaries of means and variances. For RCTs that presented results for each treatment group in graphical format, although presenting MDs numerically in the text, MDs were selected. Six RCTs[51,81,82,86,92,104] that did not provide variance estimates (in any format) were excluded.

Results of the network meta-analysis

Network diagrams for fracture outcomes and femoral neck BMD are presented in *Figures 5* and *6*, respectively.

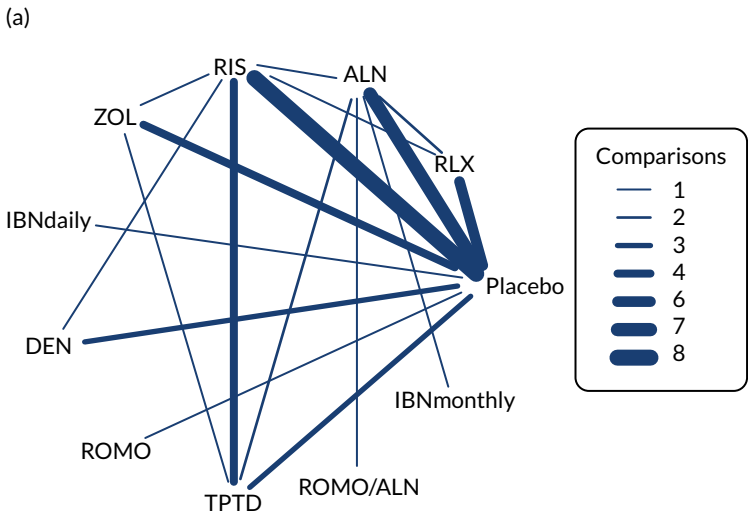

FIGURE 5 Network diagrams for fracture outcomes. (a) Vertebral; (b) non-vertebral; (c) hip; (d) wrist; and (e) proximal humerus fracture outcomes. (*continued*)

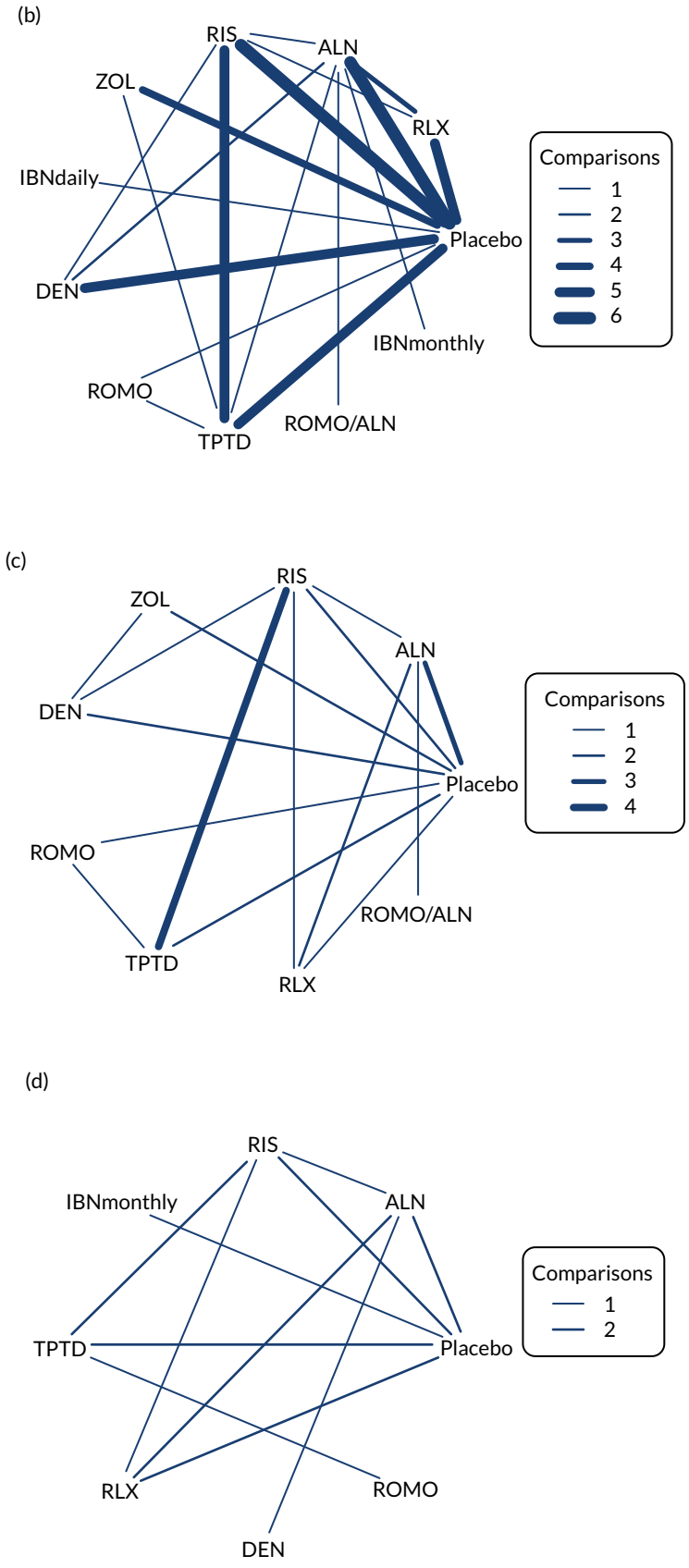

FIGURE 5 Network diagrams for fracture outcomes. (a) Vertebral; (b) non-vertebral; (c) hip; (d) wrist; and (e) proximal humerus fracture outcomes. (*continued*)

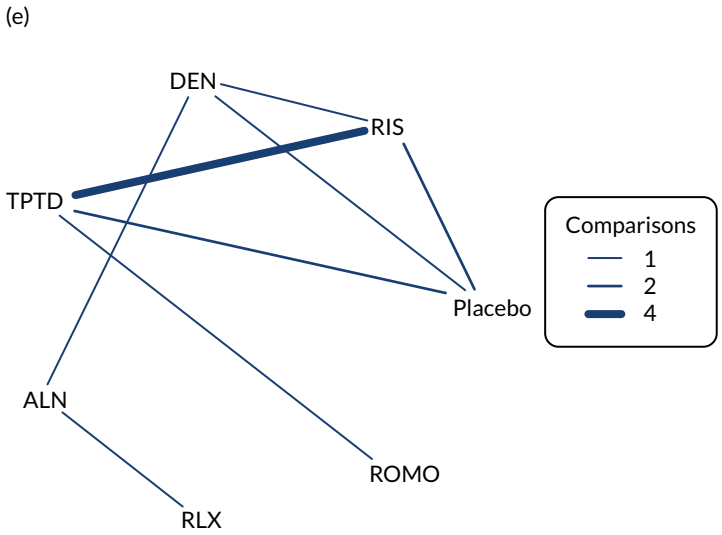

FIGURE 5 Network diagrams for fracture outcomes. (a) Vertebral; (b) non-vertebral; (c) hip; (d) wrist; and (e) proximal humerus fracture outcomes.

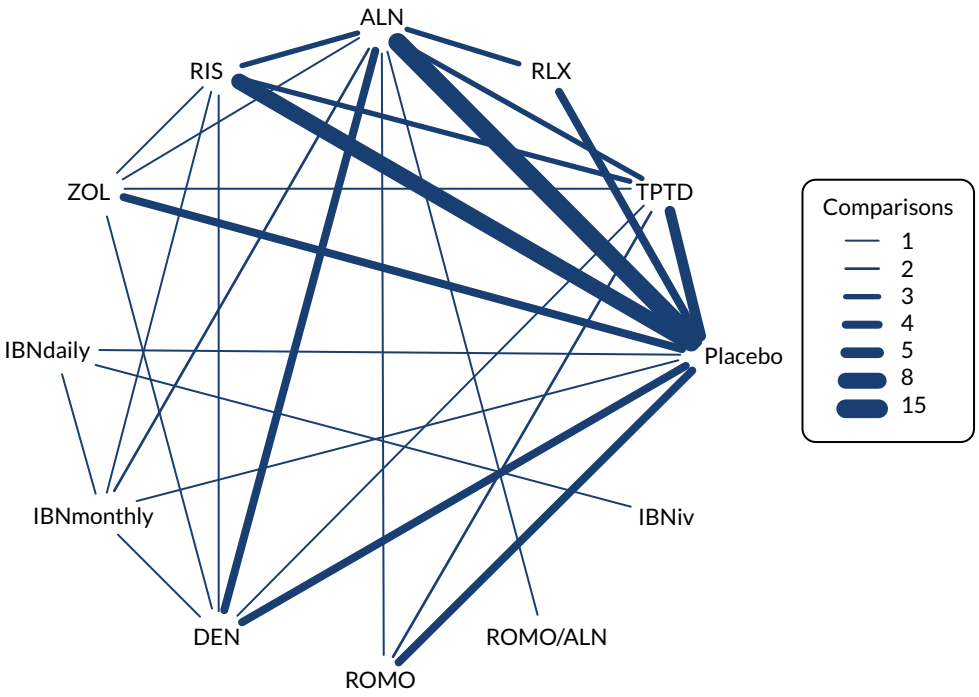

FIGURE 6 Network diagram for percentage change in femoral neck BMD.

The effects of each treatment relative to placebo are presented in *Figure 7* for all fracture outcomes based on the primary model, with class effect for bisphosphonate treatments, and unrelated treatment effects for all other interventions. Model fit is summarised in *Table 4*. For all outcomes, the model fitted the data well, with total residual deviance close to the number of data points in the network.

For comparison, results using a standard random effects model with unrelated treatment effects for all interventions are provided in *Appendix 10*. Results from the two models were found to be consistent, with a better fit (as indicated by a lower DIC) provided by the primary model.

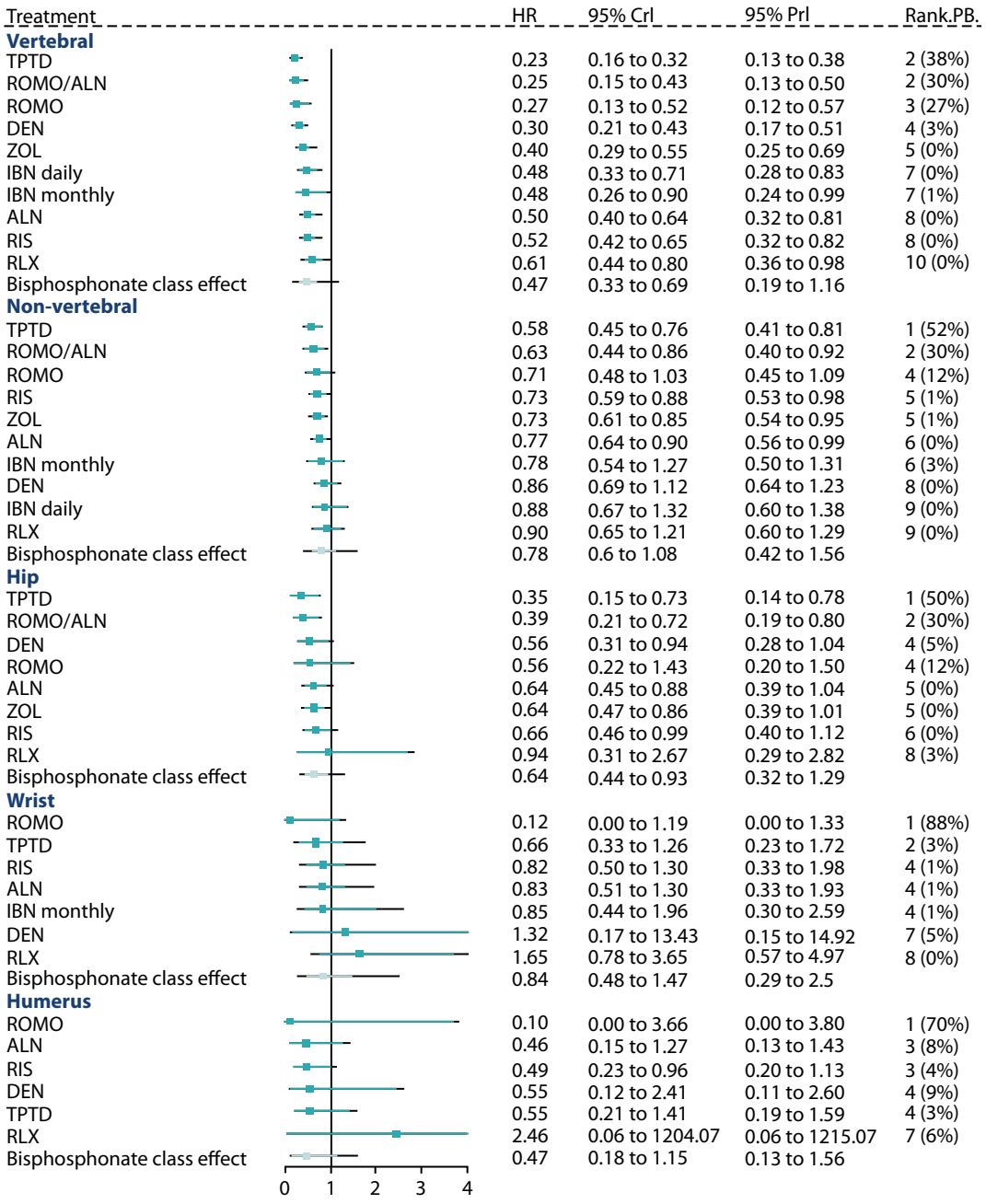

FIGURE 7 Forest plot for all fracture outcomes, main analysis. PB, probability of being the best-ranking treatment.

Vertebral fractures

Vertebral fracture data were available from 46 RCTs; 45 of these compared two treatments and one was a three-arm study.[79] Nineteen of these studies were included in TA464[34] (including one study[79] for which an additional non-bisphosphonate treatment arm was added for the current review). Two further bisphosphonate studies[129,130] not already in TA464,[34] and 24 non-bisphosphonate studies were included from the current review. A total of 11 interventions were assessed, including five non-bisphosphonate treatments.

The effects of each treatment relative to placebo are presented in *Figure 7*, and pairwise comparisons between treatments are provided in *Appendix 12*, *Table 34*. All treatments were associated with statistically significant beneficial treatment effects relative to placebo. TPTD was associated with the greatest effect (HR 0.23, 95% CrI 0.16 to 0.32), with the highest probability of being the best-ranking

TABLE 4 Summary of model fit and heterogeneity between studies and between bisphosphonate treatments, all outcomes

	Absolute model fit			Heterogeneity	
Outcome	D_{res}	Data points (*n*)	DIC	SD[a] (95% CrI)	SDt[b] (95% CrI)
Vertebral	91.21	93	153.31	0.17 (0.02 to 0.37)	0.21 (0.01 to 0.90)
Non-vertebral	74.05	86	128.40	0.08 (0 to 0.24)	0.15 (0.01 to 0.73)
Hip[c]	38.63	47	70.23	0.12 (0.01 to 0.4)	0.13 (0.01 to 0.53)
Wrist[c]	30.38	31	54.64	0.32 (0.04 to 0.67)	0.17 (0.01 to 0.62)
Proximal humerus[c]	21.99	26	41.83	0.17 (0.01 to 0.57)	0.21 (0.01 to 0.7)
Femoral neck BMD	144.70	137	258.86	0.85 (0.64 to 1.12)	0.74 (0.25 to 2.26)

D_{res},total residual deviance; SDt, standard deviation – treatment.
a Between-study SD.
b Between-bisphosphonate treatment SD.
c For hip, wrist and humerus fractures, weakly informative priors were used for the between-study and between-treatment SDs, such that SD, SDt ~half-normal(0, 0.32^2).

treatment (PB) (0.38), and was statistically significantly more effective than all active treatments apart from DEN, ROMO and ROMO/ALN (see *Appendix 12*, *Table 34*). The HR for a randomly chosen study for a new bisphosphonate is 0.47 (95% PrI 0.19 to 1.16), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

In the network, both direct and indirect comparisons were available for 12 treatment pairs. None of the comparisons showed significant evidence of inconsistency (see *Appendix 13*, *Table 40*).

Four sensitivity analyses were conducted for the main vertebral fracture network. Treatment effects are provided in *Appendix 11*, *Figure 14*, and a summary of model fit and heterogeneity is shown in *Appendix 11*, *Table 33*.

Sensitivity analysis 1 included data reported at 12 months only. Data were available from 29 RCTs, which assessed a total of 10 interventions, including four non-bisphosphonate treatments. The main difference in the results is that RIS has a more beneficial treatment effect in the 12-month sensitivity (HR 0.44, 95% CrI 0.32 to 0.60) than in the primary analysis (HR 0.52, 95% CrI 0.42 to 0.65). In both analyses, RIS has zero probability of being the best-ranking treatment. It was concluded that the results are generally consistent with those of the primary analysis, which included the longest duration of follow-up for each study, and therefore supports the use of a constant HR.

Sensitivity analysis 2 included outcomes assessed by clinical methods only. Data were available from 20 RCTs, which assessed a total of 11 interventions, including five non-bisphosphonate treatments. It was concluded that the results are generally consistent with those of the primary analysis, which includes both clinical and morphometric/radiographic outcomes. This supports the assumption that the treatment effect is not highly influenced by assessment method.

Sensitivity analysis 3 excluded studies for which there was a risk of bias in the reported outcomes. Four studies[86,92,93,95] were excluded owing to blinding issues, two studies[62,80] were terminated early and, for 10 studies,[42,43,50,129,131–136] the number of events or analysis sample size was estimated from other information. Data were available from 30 RCTs, which assessed a total of 10 interventions, including five non-bisphosphonate treatments. It was concluded that the results are consistent with those of the primary analysis, which includes all studies, and therefore supports the use of the full network of 46 studies to improve the strength of the network.

Sensitivity analysis 4 excluded studies for which prior treatment with bisphosphonates was permitted. The proportion of individuals receiving prior treatment ranged from 8–73% across the studies. Data were available from 36 RCTs, which assessed a total of 11 interventions, including five non-bisphosphonate treatments. It was concluded that the results were consistent with those of the primary analysis.

Non-vertebral fractures

Non-vertebral fracture data were available from 42 RCTs; 40 of these compared two treatments, and two were three-arm studies.[79,82] Fifteen of these studies were included in TA464[34] (including one study[79] for which an additional non-bisphosphonate treatment arm was added for the current review), and 27 non-bisphosphonate studies from the current review were included. A total of 11 interventions were assessed, including four non-bisphosphonate treatments.

Pairwise comparisons between treatments are provided in *Appendix 12*, *Table 35*. All treatments were associated with beneficial treatment effects relative to placebo, although the results were not statistically significant for all treatments. TPTD was associated with the greatest effect (HR 0.58, 95% CrI 0.45 to 0.76), with the highest PB (0.52), although there was insufficient evidence to differentiate between TPTD and the other active treatments apart from IBN daily, DEN and RLX (see *Appendix 12*, *Table 35*). The HR for a randomly chosen study for a new bisphosphonate is 0.78 (95% CrI 0.60 to 1.08), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

In the network, both direct and indirect comparisons were available for 14 treatment pairs. None of the comparisons showed significant evidence of inconsistency (see *Appendix 12*, *Table 35*).

Hip fractures

Hip fracture data were available from 23 RCTs; 22 of these studies compared two treatments and one was a three-arm study.[79] Eight of these studies were included in TA464[34] (including one study[79] for which an additional non-bisphosphonate treatment arm was added for the current review), and 15 non-bisphosphonate studies from the current review were included. A total of nine interventions were assessed, including five non-bisphosphonate treatments.

Pairwise comparisons between treatments are provided in *Appendix 12*, *Table 36*. All treatments were associated with beneficial treatment effects relative to placebo, although the comparison with placebo was not statistically significant for RLX. TPTD was associated with the greatest effect (HR 0.35, 95% CrI 0.15 to 0.73), with the highest PB (0.50), although there was insufficient evidence to differentiate between TPTD and the other active treatments (see *Appendix 12*, *Table 36*). The HR for a randomly chosen study for a new bisphosphonate is 0.64 (95% PrI 0.32 to 1.29), with the reported PrI allowing for both between-study and between-treatment heterogeneity.

In the network, both direct and indirect comparisons were available for 14 treatment pairs. None of the comparisons showed significant evidence of inconsistency (see *Appendix 13*, *Table 42*).

Wrist fractures

Wrist fracture data were available from 15 RCTs; 14 of these compared two treatments and one was a three-arm study.[79] Six of these studies were included in TA464[34] (including one study[79] for which an additional non-bisphosphonate treatment arm was added for the current review), and eight non-bisphosphonate studies from the current review were included. A total of eight interventions were assessed, including four non-bisphosphonate treatments.

Pairwise comparisons between treatments are provided in *Appendix 12*, *Table 37*. All treatments were associated with beneficial treatment effects relative to placebo, apart from DEN and RLX. Treatment

effects for DEN are based only on one small study with two events in the ALN arm and three events in the DEN arm.[70] Treatment effects for these interventions are therefore highly uncertain.

Romosozumab was associated with the greatest effect (HR 0.12, 95% CrI 0.00 to 1.19), with the highest PB (0.88), although there was insufficient evidence to differentiate between ROMO and the other active treatments (see *Appendix 12*, *Table 37*). The HR for a randomly chosen study for a new bisphosphonate is 0.84 (95% PrI 0.29 to 2.50), with the reported PrI allowing for both between-study and between-treatment heterogeneity.

In the network, both direct and indirect comparisons were available for eight treatment pairs. None of the comparisons showed significant evidence of inconsistency (see *Appendix 13*, *Table 43*).

Proximal humerus fractures

Proximal humerus fracture data were available from 13 RCTs, each comparing two treatments. Two of these studies were included in TA464[34] and 11 non-bisphosphonate studies from the current review were included. A total of eight interventions were assessed, including two bisphosphonate treatments.

Pairwise comparisons between treatments are provided in *Appendix 12*, *Table 38*. All treatments were associated with beneficial treatment effects relative to placebo, apart from RLX. Treatment effects for RLX are based on one small study[77] only, with zero events in the ALN arm and one event in the RLX arm, and so treatment effects are highly uncertain. Event numbers were generally low in this network and five of the 13 included RCTs had zero counts in one of the treatments arms.

Romosozumab was associated with the greatest effect (HR 0.10, 95% CrI 0.0 to 3.66), with the highest PB (0.77), although the treatment effect was highly uncertain and there was insufficient evidence to differentiate between ROMO and the other active treatments (see *Appendix 12*, *Table 38*). Only RIS was associated with a HR that was statistically significant compared with placebo (HR 0.49, 95% CrI 0.23 to 0.96). The HR for a randomly chosen study for a new bisphosphonate is 0.47 (95% CrI 0.18 to 1.15), with the reported PrI allowing for both between-study and between-treatment heterogeneity.

In the network, both direct and indirect comparisons were available for five treatment pairs. None of the comparisons showed significant evidence of inconsistency (see *Appendix 12*, *Table 38*).

Heterogeneity in treatment effects between studies, and between bisphosphonates, is summarised in *Table 4*. The estimates of between-study SD suggest mild (non-vertebral) and moderate (vertebral, hip, wrist, proximal humerus, femoral neck BMD) heterogeneity in treatment effects between RCTs. The estimates of between-treatment SD indicate moderate heterogeneity in effects between treatments for all outcomes (i.e. the effects of the bisphosphonates are relatively similar).

Meta-regressions were conducted to test for different treatment effects separately, according to the mean age of participants in each study and the proportion of female participants. A common meta-regression coefficient was assumed for all treatments.[121] Based on comparison of models with and without a covariate for mean age or mean percentage of females, there was no evidence that treatment effect varied with age or sex. Meta-regression coefficients were not statistically significantly different from zero, and DIC estimates were higher, implying a less favourable model. A summary of the results is provided in *Appendix 14*, *Table 45*.

Baseline fracture risk can be used as a proxy for differences in participant characteristics across trials that may be modifiers of treatment effect, and so introduce a potential source of heterogeneity in the NMA. The effect of baseline fracture risk as a potential treatment-effect modifier was explored using the method of Achana *et al.*,[122] assuming a common meta-regression coefficient for all treatments

(as for age and sex), and assuming that the baselines of each study follow a normal distribution with common mean and between-study variance. Based on a comparison of models with and without an adjustment for baseline risk, and inspection of the regression coefficients, there was no evidence that treatment effect varied with baseline risk for any of the fracture outcomes (see *Appendix 14*, *Table 45*).

Femoral neck bone mineral density

Femoral neck BMD data were available from 73 RCTs; 69 of these each compared two treatments, one was a four-arm study[68] and three were three-arm studies.[72,78,137] Thirty-two of these studies were included in TA464.[34] Three further bisphosphonate studies[129,137,138] not already in TA464,[34] and 38 non-bisphosphonate studies, were included from the current review. A total of 12 interventions were assessed, including five non-bisphosphonate treatments. The network is shown in *Figure 6*.

The effects of each treatment relative to placebo are presented in *Figure 8*. Pairwise comparisons between treatments are provided in *Appendix 12*, *Table 39*. All treatments were associated with statistically significant beneficial treatment effects relative to placebo. ROMO/ALN was associated with the greatest treatment effect (MD 6.08, 95% CrI 4.25 to 7.91), with the highest PB (0.96), and was statistically significantly more effective than all active treatments apart from ROMO (see *Appendix 12*, *Table 39*). The treatment effect for a randomly chosen study for a new bisphosphonate is 2.34 (95% PrI 1.26 to 3.28), with the reported PrI allowing for both between-study and between-treatment heterogeneity.

To account for differing trial durations, study duration was included as a trial-level covariate. The estimated impact on treatment effect of study duration, assuming a common relationship for each treatment, was 1.09 (95% CrI 0.73 to 1.45), indicating an increase in treatment effect with increasing duration of study, as expected.

As for fracture outcomes, there was no evidence that treatment effect varied with age, sex or baseline response (see *Appendix 14*, *Table 45*).

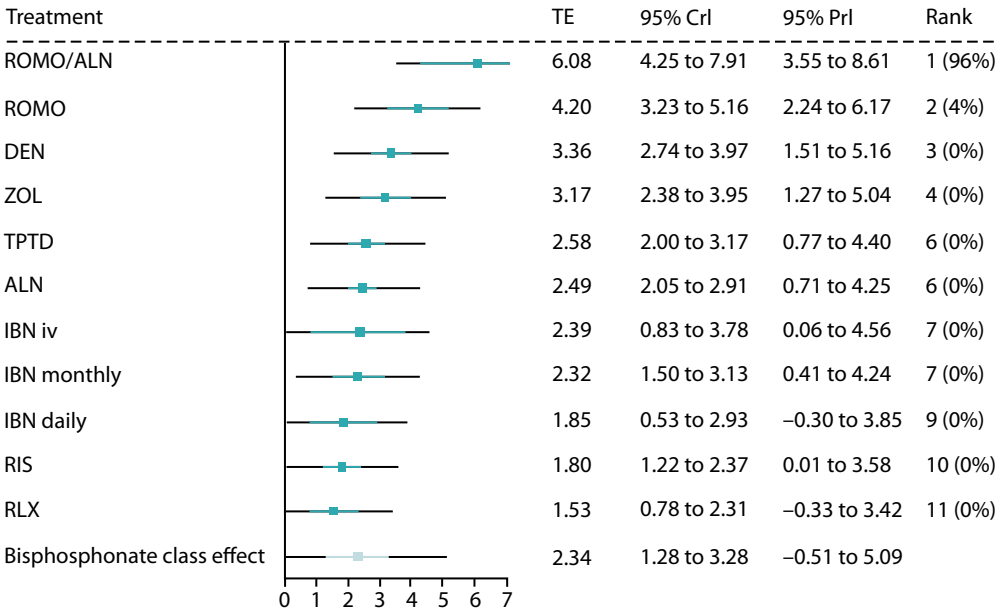

FIGURE 8 Forest plot for percentage change in femoral neck BMD.

Discussion

Quantity and quality of randomised controlled trial evidence

A systematic literature search identified 7898 records. Fifty-two RCTs of non-bisphosphonates were included (published in 69 references). Of the 52 RCTs included, 23 were RCTs comparing non-bisphosphonates with placebo, four were head-to-head comparisons of non-bisphosphonates (of which one RCT also included a bisphosphonate arm) and 25 were RCTs comparing a non-bisphosphonate with a bisphosphonate.

Studies varied in quality according to blinding and attrition. However, a sensitivity analysis removing lower-quality studies from the NMA gave results consistent with those of the main analysis. Most of the included RCTs were conducted with postmenopausal women, although there were some trials of men and steroid-induced osteoporosis for interventions for which these were licensed indications. The majority of included trials typically excluded people with underlying conditions that influence bone metabolism or people taking medications that influence bone metabolism.

Quality assessment of other domains, particularly methods for randomisation and allocation concealment, indicated a lack of reporting of the methods used by the included studies to minimise selection bias, detection bias, attrition bias and reporting bias, resulting in a judgement of 'unclear risk of bias' for many of the domains across the included studies. As a result, we were unable to identify those studies that were deemed to be at either high or low risk for all quality assessment domains. Therefore, the degree that methodological biases contributed to study results, and thus the findings of this assessment report, is unknown for some studies, meaning that the findings of this assessment report should be interpreted with caution.

Adverse events and health-related quality of life

Across studies reporting on overall mortality, event rates ranged from 0% to 6.4% across non-bisphosphonates and comparators, and between-group differences were not statistically significant. None of the included studies reported on mortality following hip fracture, mortality following vertebral fracture or mortality following any other type of fracture.

Adverse event rates ranged from 12.1% to 94.3% for DEN, from 24.0% to 96% for RLX and from 74.6% to 82% for ROMO across non-treatment-switch studies; AE rates were 86.6% in one study in which ROMO was switched to ALN, and ranged from 16.1% to 91.9% for TPTD. The majority of reported and estimated between-group differences were not statistically significant for comparisons with placebo/no active treatment, head-to-head non-bisphosphonate comparisons or comparisons with bisphosphonates. This was with the exception of one study reporting a comparison of ROMO with ALN, for which the estimated between-group difference was $p = 0.02$ at 12 months in favour of ROMO and $p = 0.05$ at 24 months in favour of ROMO switched to ALN, and one study comparing TPTD with ZOL for which the between-group difference was statistically in favour of TPTD ($p = 0.006$).

Serious adverse event rates ranged from 2% to 25.8% for DEN, from 2% to 18.6% for RLX, from 3.2% to 12.9% for ROMO and from 0% to 33% for TPTD. The majority of reported and estimated between-group differences were not statistically significant for comparisons with placebo/no active treatment, head-to-head non-bisphosphonate comparisons or comparisons with bisphosphonates. This was with the exception of one study that compared DEN with oral IBN, for which the between-group difference was statistically in favour of IBN ($p = 0.046$).

Disease-specific measures of HRQoL were reported as showing no treatment difference between DEN and placebo, or between RLX and placebo, but more improvement with TPTD than with ALN, suggested by one RCT for each comparison. On generic measures of HRQoL, there was similarity for RLX and placebo (one RCT), and TPTD and RIS (two RCTs).

Discussion of network meta-analysis results

Network meta-analyses were conducted for vertebral fractures (46 RCTs, 11 interventions), non-vertebral fractures (42 RCTs, 11 interventions), hip fractures (23 RCTs, nine interventions), wrist fractures (15 RCTs, eight interventions), proximal humerus fractures (13 RCTs, eight interventions) and femoral neck BMD (73 RCTs, 12 interventions).

For vertebral, non-vertebral and hip fractures and for femoral neck BMD, all treatments were associated with beneficial effects, relative to placebo. For both vertebral fractures and percentage change in femoral neck BMD, the treatment effects were statistically significant at a conventional 5% level for all treatments. TPTD was associated with the greatest effect for vertebral (HR 0.23, 95% CrI 0.16 to 0.32, PB 0.38), non-vertebral (HR 0.58, 95% CrI 0.45 to 0.76, PB 0.52) and hip fractures (HR 0.35, 95% CrI 0.15 to 0.73, PB 0.50), whereas ROMO was the most effective for wrist (HR 0.12, 95% CrI 0.00 to 1.19) and proximal humerus fractures (HR 0.10, 95% CrI 0.00 to 3.66), and ROMO/ALN (HR 0.10, 95% CrI 0 to 3.66, PB 0.77) was the most effective for percentage change in femoral neck BMD. For wrist and proximal humerus fractures networks, there was less RCT evidence, with treatment effects for non-bisphosphonate treatments often contributed by single studies with low event numbers, and so there is considerable uncertainty in treatment effects for certain interventions in these networks.

The reported primary analyses used outcomes reported at the longest available time point for each study and assume that the fracture event rate is constant over time. Inclusion of studies reporting vertebral fractures at 12 months only did not provide any evidence to suggest different treatment effects when the analysis is limited to specific outcome measurement times. Assessment within the studies of vertebral fractures was based on both clinical and morphometric fractures. Consideration of the studies reporting clinical fractures did not provide any evidence to suggest different treatment effects according to assessment method. Similarly, sensitivity analyses conducted to assess the impact of study quality and prior bisphosphonate treatment did not suggest different treatment effects when the affected studies were excluded.

The primary analysis model for the NMA assumed exchangeable treatment effects (i.e. a class effect) for bisphosphonate treatments and unrelated treatment effects are assumed for all non-bisphosphonate interventions. The treatment effects estimated using the primary model were broadly similar qualitatively (i.e. direction of effect) and quantitatively (i.e. magnitude of effect) to those estimated using the standard random-effects model with unrelated treatment effects for all interventions. The estimates of treatment effects for bisphosphonate interventions from the primary model are slightly closer together than those from the unrelated treatment effect model (as would be expected); however, the difference is small.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Methods

A comprehensive search was undertaken, with a cut-off date of 16 July 2018, to identify papers published in 2006 or later that evaluated the cost-effectiveness of DEN, RLX, ROMO or TPTD in any of the patient groups eligible for risk assessment within CG146.[8] Subject headings and keywords for 'osteoporosis' were combined with an economic filter without named interventions from 2014 to 2018 to update the searches conducted for TA464.[34] In addition, for records between 2006 and 2013, each of the named non-bisphosphonate interventions (RLX, DEN, ROMO and TPTD) was combined with an economics search filter to cover the years between 2006 and 2013, as studies for interventions would not have been retrieved in the review for TA464. The search strategy is provided in *Appendix 1*. The searches were limited to those published since the start of 2006 because studies reporting cost-effectiveness estimates for RLX, DEN and TPTD are assumed to have been captured in the searches and reviews that informed TA160,[12] TA161[11] and TA204[10] and studies reporting the cost-effectiveness of ROMO are not expected prior to 2006. However, any relevant studies published prior to 2006 that were identified in these previous appraisals or in published systematic reviews were included.

The following databases were searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (via Ovid), 1946–2018
- EMBASE (via Ovid), 1974–2018
- Database of Abstract of Reviews of Effects [via Centre for Reviews and Dissemination (CRD) database], 1995–2015
- Health Technology Assessment Database (via CRD database), 1995–2016
- NHS Economic Evaluation Database (via CRD database), 1995–2015.

Published economic evaluations cited in the consultee submissions were cross-checked with those identified from the search. Searches of key included studies were undertaken using the Web of Science.

Inclusion/exclusion criteria

Studies were included in the review if they reported full economic evaluations comparing DEN, RLX, ROMO or TPTD with each other, with bisphosphonates or with no treatment. Studies were included if any of the population considered would be eligible for risk assessment as per CG146.[8] For example, studies of postmenopausal women were included whether or not they specified that the women had risk factors, as those aged > 65 years would be eligible for risk assessment under CG146[8] even without risk factors being present.[8] Studies that did not assess outcomes using QALYs or that did not report the incremental cost per QALY of alternative treatment strategies were excluded. Studies that did not assess the cost-effectiveness in a UK setting were excluded, to ensure consistency with the NICE reference case.[139] Studies that assessed the cost-effectiveness of treatment at non-licensed doses were also excluded, as were studies that used treatments for other indications such as the treatment of Paget's disease or metastatic bone disease. Studies published prior to 2006 were included when identified in existing NICE appraisals or published systematic reviews, as described previously. Studies were included only if they were reported as full papers; conference abstracts were excluded from the review as they present insufficient detail to allow for a rigorous assessment of study quality. Studies not reported in the English language were also excluded. De novo economic analyses reported in the consultee submissions were included if they met the inclusion criteria of the review.

Review methods

The results of the economic searches described above were combined with the results of the searches conducted for the HRQoL review (see *Appendix 11*) and a combined sift was conducted to pick up any cross-relevant papers. The combined database was sifted by title and abstract by one reviewer. The full papers of studies that potentially met the inclusion criteria were retrieved for further inspection by the same reviewer. Studies included in the systematic review were examined to determine whether or not they met the NICE reference case.[139] We stated in our protocol that we would critically appraise the included cost-effectiveness analyses using the checklist published by Philips *et al.*,[140] but this was not done owing to time constraints.

Results

The study selection process is summarised in the form of a PRISMA flow diagram[32] in *Figure 9*, with the most common reason for exclusion being that they were non-UK studies.

Quantity of evidence identified

The database search identified 3853 citations across the combined cost-effectiveness and HRQoL searches. Three additional articles[141–143] were identified from the reference list of published reviews. None of the consultee submissions identified any published analyses not already picked up by the systematic search, but two reported de novo economic analyses, which were included, giving a total of 3858 citations. Of these, 3837 were excluded at the title and abstract stage and a further 11 were excluded at the full-paper stage; the most common reasons for exclusion were that they were non-UK

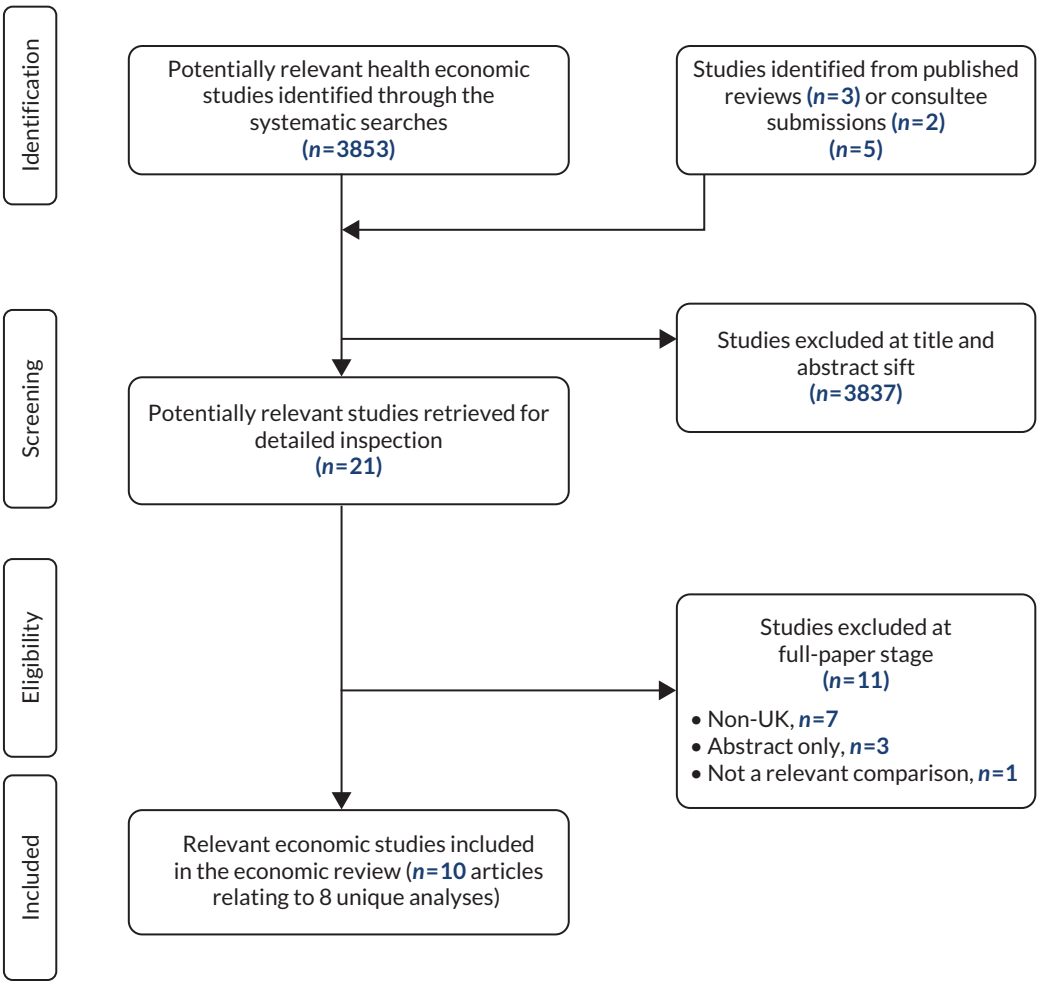

FIGURE 9 The PRISMA flow diagram of the study selection process: cost-effectiveness review.

studies or conference abstracts with limited data presented. *Appendix 15* provides the reasons for exclusion for those papers that were included during the title and abstract sift, but were later excluded after considering the full paper.

A total of 10 articles[20,34,100,141–147] were included; however, one paper, Kanis *et al.*,[142] reported a previous version of the model reported by Stevenson *et al.*,[143] and was therefore not separately extracted, and two articles provided the Evidence Review Group's summary of the company submission for TA204.[145,147] Therefore, the review included eight unique cost-effectiveness analyses. Additional documents related to TA204[10] were downloaded from the NICE website to allow a full examination of this model [note that this model is referred to as 'Waugh *et al.*[147]' to avoid confusion with the Amgen submission for the current multiple technology appraisal (MTA)]. The model described in the Amgen submission for the current MTA[100] was an adaptation of the model described in the company submission for TA204,[145,147] but these were separately extracted owing to differences between the decision problems.

Although the assessment report for TA464 by Davis *et al.*[34] did not strictly meet the inclusion criteria for this review, as it did not include any non-bisphosphonate interventions, it has been included as it was stated in the protocol for this MTA that, to ensure consistency across related appraisals, the economic analysis conducted to inform TA464 was intended to be used as the starting point for any cost-effectiveness analysis conducted by the assessment group (AG). Therefore, it was necessary to compare this model with the relevant published analyses to identify any significant areas of difference.

Study characteristics

The characteristics of the included studies are summarised in *Table 5*. Here we describe the key differences between the models in terms of their population, structure and assumptions.

Population and subgroups

Six of the included studies[20,141,143,144,146,147] were of postmenopausal women. The company submission by UCB S.A. restricted the population modelled to postmenopausal women at imminent risk of fracture, which it characterised as those with a recent major osteoporotic fracture.[20] Although no results were presented for men, UCB S.A.[20] argued that the results would also be applicable to men, as it is assumed that men will not respond differently to postmenopausal women. The AG model for TA464 (Davis *et al.*[34]) included all patients eligible for risk assessment under CG146,[8] thereby including both men and women, those with steroid-induced osteoporosis and those with and those without a prior fracture. However, Davis *et al.*[34] examined subgroups according to absolute fracture risk rather than according to any of these specific patient characteristics. The submission by Amgen Inc.[100] did not restrict the population to postmenopausal women; instead, it included people eligible for risk assessment under CG146[8] at varying levels of absolute fracture risk. This was similar to the approach taken in TA464,[34] except that the only risk cut-off points examined in the Amgen Inc.[100] submission were 10-year risks of 10% and 20%, whereas Davis *et al.*[34] reported outcomes for 10 risk deciles and also used regression to estimate thresholds for cost-effective intervention when treating risk as a continuous variable.

Several of the analyses presented results separately for those with and those without a prior fracture[141,143,144,147] or presented separate estimates for subgroups defined by combinations of age and *T*-Score,[147] age and number of risk factors[146] or *T*-Score and risk factors.[147] Two studies[34,146] estimated the threshold for cost-effective intervention and expressed this using 10-year risk of fracture. Two studies[20,100] provided results for patients with a specific level of absolute fracture risk, but explored alternative specified levels of absolute fracture risk in scenario analyses.

None of the included economic evaluations provided an incremental analysis across all of the interventions and comparators identified in the scope of this appraisal. Two[141,144] provided comparisons of RLX versus no treatment. Strom *et al.*[146] compared DEN with bisphosphonates (ALN and RIS) and no treatment. Stevenson *et al.*[143] conducted an incremental analysis across multiple technologies, but did not include DEN or ROMO. The submission by UCB S.A.[20] did not provide a comparison with oral

TABLE 5 Characteristics of included studies: cost-effectiveness review

First author	Population and interventions	Type of evaluation	Perspective	Time horizon	Cost year and cost discount rate	Cost source	Benefits population and benefits discount rate	Benefits source and benefits instrument	Effectiveness data
Kanis 2005[141] (MORE)	• Postmenopausal women – subgroups for those with and those without prior fracture • RLX, no treatment	Cohort Markov model	UK NHS	Not stated	• 2002 • 6%	Published estimates and reference costs	• Patient only • 1.5%	EQ-5D in Swedish patients using UK valuation set	Single study estimate (MORE). In addition to fracture outcomes, includes beneficial effect on breast cancer and heart disease and adverse effect on VTE
Stevenson 2005[143]	• Postmenopausal women • Bisphosphonates, RLX; TPTD; no treatment[a]	Patient-level Markov model	UK NHS and PSS	Lifetime	• 2001/2 • 6%	Fracture costs were based on published estimates that were uplifted	• Patient only • 1.5%	• Observational data • EQ-5D	Systematic review and meta-analysis conducted by authors
Kanis 2008[144] (BONE)	• Postmenopausal women • Bisphosphonates, RLX,[a] no treatment	Cohort Markov model	UK NHS (includes nursing home admission)	Lifetime	• 2004/5 • 3.5%	Published literature (UK estimates of length of stay and cost per bed-day and Swedish estimates of ratio of outpatient to inpatient costs)	3.5%	EQ-5D in Swedish patients using UK tariff	Published systematic review and meta-analysis including breast cancer reduction for RLX
Scotland[145]/Waugh 2011[147]/Amgen submission for TA204[147]	• Postmenopausal women unable to take, comply with or tolerate bisphosphonates – 70 years, *T*-score of –2.5; subgroups of those with and those without prior fracture • DEN, RLX, i.v. bisphosphonates, TPTD, oral bisphosphonates, no treatment[a]	Cohort Markov model	UK NHS and PSS	Lifetime	• 2009 • 3.5%	HRG costs and BNF drug prices	• Patients • 3.5%	EQ-5D using UK tariff	Company's systematic review and meta-analysis with indirect comparison (Bucher method[148])

First author	Population and interventions	Type of evaluation	Perspective	Time horizon	Cost year and cost discount rate	Cost source	Benefits population and benefits discount rate	Benefits source and benefits instrument	Effectiveness data
Strom 2013[146]	• Postmenopausal women – subgroups by fracture risk • DEN, ALN, RIS, no treatment[a]	Cohort Markov model	UK NHS	Lifetime	• 2010 • 3.5%	Published literature (UK estimates of length of stay and cost per bed-day and Swedish estimates of ratio of outpatient to inpatient costs)	• Patient only • 3.5%	EQ-5D in Swedish patients using UK tariff	Systematic review and meta-analysis
Davis 2016[34]	• People eligible for risk assessment as per CG146[8] • Bisphosphonates, no treatment	Discrete event simulation (patient-level model to capture individual's history)	UK NHS and PSS	Lifetime	• 2014 • 3.5%	NHS reference costs, PSSRU unit costs, national drug tariff and database of generic drug costs	• Patient only • 3.5%	EQ-5D using UK tariff from published studies identified by systematic review	Author's systematic review and NMA
UCB S.A. 2018[20]	• Women at imminent risk of fracture (recent major fracture, 10-year risk of 30%) • ROMO, ALN, RIS, i.v. ZOL, TPTD, DEN	Patient-level Markov model	UK NHS and PSS	Lifetime	• 2017/18 • 3.5%	NHS reference costs, PSSRU unit costs, national drug tariff (same source cited for fracture costs but different figures provided)	• Patient only • 3.5%	• Observational study • EQ-5D using UK tariff	Company's systematic review and NMA
Amgen Inc. 2018[100]	• People eligible for risk assessment as per CG146[8] who cannot take oral bisphosphonates • DEN, RLX, no treatment (i.v. ZOL and oral bisphosphonates in secondary analysis)	Cohort Markov model	UK NHS and PSS	Lifetime	• 2016/17 • 3.5%	NHS reference costs, PSSRU unit costs, national drug tariff and database of generic drug costs (costs as for TA464[34] except changes in monitoring and administration costs)	• Patient only • 3.5%	• Systematic review in TA464[34] • EQ-5D using UK tariff	Company's review and NMA

BNF, *British National Formulary*; HRG, Healthcare Resource Group; PSS, Personal Social Services.
a Other non-relevant interventions were also modelled, for example oestrogen, strontium ranelate.

or i.v. IBN, but included all other comparators. The Amgen Inc. submission[100] stated that DEN was primarily used in primary care by patients unable to take an oral bisphosphonate; therefore, the main comparator was RLX or no treatment. However, secondary analyses were provided comparing DEN with i.v. ZOL and oral bisphosphonates. The company submission for TA204, described by Waugh *et al.*,[147] also restricted the decision problem to patients unable to take bisphosphonates. Their primary analysis compared DEN with RLX and no treatment, but they also included comparisons with i.v. IBN, i.v. ZOL, TPTD and oral bisphosphonates in secondary analyses. Davis *et al.* included only bisphosphonates and no treatment in their incremental analysis, which was consistent with the scope of TA464.[34]

Model structure and outcomes modelled

Seven studies[20,100,141,143,144,146,147] used a Markov model framework: five used a cohort-level modelling approach and two[20,143] used a patient-level Markov simulation. Four[20,100,146,147] of the Markov models employed a 6-monthly cycle length, whereas the other three[141,143,144] used an annual cycle length. The AG for TA464 used a discrete event framework, which is a patient-level simulation that does not require the use of fixed time cycles. All of the studies included separate health states for hip fracture and vertebral fracture, and all of the studies incorporated long-term consequences for these two fracture sites either by incorporating post-hip and post-vertebral fracture health states in a cohort-level model or by tracking patient's prior fracture status in a patient-level simulation. All studies included wrist fracture. All but one study[141] included fractures at sites other than the hip, wrist and vertebrae, but some[34,100,141,143,147] modelled wrist fractures separately to other fracture sites. One study[20] bundled wrist fracture together in a health state with fractures at other sites. Davis *et al.*[34] incorporated separate health states for wrist and proximal humerus fracture; fractures at additional sites (femoral shaft, humeral shaft, pelvis, scapula, clavicle, sternum, ribs, tibia and fibula) were incorporated by increasing the incidence of fractures at the four main sites (hip, wrist, vertebral and proximal humerus), with the allocation of these additional fractures to the main fracture type expected to have similar costs and utilities. The majority of the other studies included fractures at additional sites in a single health state, with the costs, mortality and utility estimates being based on either a weighted mean across the included sites or an assumption that the consequences would be consistent with those for a known fracture site such as the wrist.

The use of a cohort-level approach meant that, in four models,[141,144,146,147] future fractures were restricted for a patient experiencing a hip or vertebral fracture to ensure that patients did not transition to a health state with lower costs or better quality of life when experiencing a subsequent fracture that was less severe than the initial fracture experienced. In general, the approach taken was that patients experiencing a hip fracture were only at risk of subsequent hip fractures and patients experiencing a vertebral fracture were only at risk of hip or subsequent vertebral fractures. One model,[100] which used a similar hierarchical Markov structure, adjusted for the missing fracture outcomes in patients having hip and vertebral fractures by estimating the 'downstream' costs of subsequent fractures that were prevented by the hierarchical Markov structure. It was not necessary to restrict the sequence of fractures experienced in either of the patient-level simulations, as costs and utilities can be made dependent on an individual's entire history. However, Davis *et al.*[34] restricted the number of fractures possible for each fracture type to one per bone, with an additional limit of four vertebral fractures, four rib fractures and two pelvic fractures.

Three studies included non-skeletal health outcomes, with three[141,143,144] including breast cancer, two[141,144] including coronary heart disease (CHD) and two[141,144] including either stroke or VTE. All except one study[141] reported including an increased risk of nursing home admission after hip fracture.[20,34,100,143,144,146,147] None of the studies included an increased risk of nursing home admission following fractures at other sites, but Davis *et al.*[34] presented a sensitivity analysis in which an equivalent rate of nursing home admission occurred for both vertebral fracture and hip fracture.

Treatment duration

Four of the studies modelled a maximum treatment duration of 5 years for all treatments.[141,144,146,147] Davis *et al.*[34] assumed a 5-year intended treatment duration for all bisphosphonates except i.v. ZOL, for which a 3-year intended treatment duration was assumed. Stevenson *et al.*[143] assumed a 5-year treatment duration for all treatments except TPTD, for which the treatment duration was assumed to be 18 months. One study (Amgen Inc.[100]) assumed a treatment duration of 10 years for DEN, 3 years for ZOL and 5 years for RLX. Another study assumed a 4-year treatment duration for all interventions except DEN, which was assumed to be given lifelong (UCB S.A.[20]) (although it was noted that, in the actual model, persistence data were set to zero from 5 years, so it is unclear what treatment duration was actually implemented).

Treatment initiation, monitoring, and administration

All but one of the studies (Davis *et al.*[34]) incorporated resource use for the monitoring of treatment. None of the studies included any costs for the administration of oral therapies. However, there was inconsistency across the studies for the administration costs for s.c. and i.v. therapies. The exact costs for administration and monitoring are discussed further in *Treatment initiation, administration and monitoring*, where we also describe the approach taken in the AG analysis.

Persistence

Persistence was included in either the base-case or sensitivity analysis in six of the models.[20,34,100,144,146,147] In Davis *et al.*,[34] the persistence data applied in the model were identified from a review of systematic reviews. In the other models, one[146] used published estimates but did not describe how they were identified, one[20] used a mixture of published and unpublished data, two[100,147] used data on file from an unpublished study and one applied the assumption made in the model that informed TA160 and TA161.[149] Many of the estimates came from analyses of real-world data sources, such as administrative databases, with three models incorporating estimates from a large UK primary care database [Clinical Practice Research Datalink (CPRD)/General Practice Research Database (GPRD)].[20,100,147] A full discussion of the data sources used in these models and the choice of data source for the AG model is provided in *Treatment persistence*.

Treatment effectiveness beyond the treatment period

All of the studies assumed that treatment effectiveness falls linearly over time after patients discontinue treatment. The period between treatment discontinuation and when the treatment effect has fallen to zero is known as the offset period. Three studies assumed an offset period equal to the treatment duration for all interventions.[141,144,146] Davis *et al.*[34] and Stevenson *et al.*[143] made the same assumption for all but one intervention. Owing to the shorter treatment period for TPTD (18 months), Stevenson *et al.*[143] applied the full treatment effect for 3.5 years after the end of treatment, and this was noted as a very favourable assumption. Davis *et al.*[34] assumed a longer offset (7 years) for ZOL, such that the treatment effect fell to zero by 10 years, despite the shorter treatment duration of 3 years. In the base-case analysis, in which the treatment persistence was < 3 years, the same ratio of offset period to treatment duration was applied by Davis *et al.*[34] (i.e. offset $= 7/3 \times$ treatment persistence). Two studies assumed a 1-year offset for all treatments,[100,147] and one study[20] assumed an offset equal to treatment duration for all interventions except DEN, for which it was set to 1 year. The evidence regarding offset periods and the choice of offset period assumed in the AG model is discussed further in *Offset period*.

Adverse events

All of the studies included some AEs in either their base-case or their sensitivity analyses, but there was considerable inconsistency between the studies in terms of the AEs included. Three papers included gastrointestinal (GI) AEs in their base-case analysis[20,34,147] and two included them in a sensitivity analysis.[144,146] The model reported in the company submission by Amgen Inc. for TA204 (Waugh *et al.*[147]), included GI AEs for oral bisphosphonates, but these were not included in the updated version of this model reported in the company submission by Amgen Inc. for the current appraisal.[100] Stevenson *et al.*[143]

did not include any GI AEs for bisphosphonates in their analysis, but their model was later adapted to include GI AEs for bisphosphonates in an analysis by Stevenson and Davis[149] conducted to inform TA160 and TA161. There was some consistency in the assumptions regarding GI AEs across the various models, with three models[144,146,147] using the assumptions from TA160 and TA161 and one[20] using assumptions consistent with those applied in TA464 (Davis *et al.*[34]), which themselves were very similar to those applied by Stevenson and Davis.[149] Davis *et al.*[34] included a one-off QALY loss to account for influenza-like symptoms following administration of i.v. bisphosphonates. None of the other studies included any AEs for i.v. bisphosphonates. Two studies included VTE as a side effect of RLX.[141,144] Amgen Inc. included cellulitis (a common bacterial skin infection) as an AE of DEN in the model reported in the company submission for TA204,[147] but did not include any AEs for DEN in the model reported in the company submission for the current appraisal.[100] Strom *et al.*[146] did note that skin infections are more frequently reported for DEN, but did not include cellulitis in their model. No studies reported including AEs for ROMO or TPTD. None of the studies included atypical femoral fracture or ONJ as AEs.

Mortality following fracture

Davis *et al.*[34] incorporated post-hip fracture mortality by assuming that a fixed proportion (which was sex and age specific) of patients experiencing hip fracture would die 3 months after fracture. This was based on evidence from a study by Tosteson *et al.*,[150] which found that the excess risk of mortality was limited to the first 6 months after fracture when adjusting for a number of prognostic factors including pre-fracture health status, and evidence from a study by Abrahamsen *et al.*,[151] which found that approximately half of all excess mortality had occurred at 3 months. Davis *et al.*[34] incorporated an increased risk of death following hip and vertebral fracture and assumed no increased risk for fractures at other sites. The same temporal pattern of risk was assumed for vertebral fractures.

Four of the other models identified in the review[20,100,146,147] applied HRs to the general population mortality rate, with the HRs for hip and vertebral fracture applied for 8 years following fracture and the HRs for non-hip non-vertebral fractures applied for 1 year following fracture. The data inputs appear to be consistent across these four models, with the primary source cited being Johnell *et al.*[152] for clinical vertebral fractures, Jönsson *et al.*[153] for hip fractures and Barrett *et al.*[154] for 'other fractures'. These four models all assumed that only 30% of the increased risk was attributable to the fracture itself and downweighted the additional mortality risks accordingly. Kanis *et al.*[141] cited the same data source[152] for mortality after vertebral fracture, but details are not provided on the duration over which the HR is applied or the proportion of excess risk that is considered attributable to fracture. Kanis *et al.*[144] cited alternative sources[155–157] and stated that 30% was assumed to be causally related, but does not describe the duration over which the HRs are applied. Stevenson *et al.*[143] used unpublished estimates from the Anglian audit of hip fracture,[158] which reported mortality risk for several different age bands, and adjusted these to remove those deaths not causally related to hip fracture using the data from Parker and Anand.[157] Stevenson *et al.*[143] based their risk of death following vertebral fracture on a study by Center *et al.*[159] Stevenson *et al.*[143] included a twofold increase in mortality following proximal humerus fracture, citing Johnell *et al.*,[152] but assumed no increased risk of mortality following wrist fractures. None of the published models identified sources of data that were more recent than those identified by the AG during TA464.[34]

Consistency with the National Institute for Health and Care Excellence reference case

All of the included studies measured direct health effects for patients, and none included any benefits for carers. All of the studies reported using published estimates of utility following fracture from studies that had measured utility using the EQ-5D using the UK general population valuation set. There was some inconsistency in the approach taken to estimating utility following nursing home admission, with one study[147] reporting no additional disutility, one study[143] reporting using a value based on an expert panel, one study[34] reporting a value based on the EQ-5D and several studies not reporting the approach taken to estimating utility values for nursing home admission.[20,100,141,144,146]

One study[141] based its effectiveness estimate on a single RCT and reported a comparison only between the interventions included in the RCT (RLX vs. no treatment). The other studies all sourced their effectiveness estimates from a systematic review and meta-analysis, although only the three most recent models[20,34,100] used NMA to estimate the relative treatment between active comparators. One study[147] used the method published by Bucher *et al.*[148] to conduct an indirect comparison. Two studies[143,146] present incremental analyses that appear to be based on naive indirect comparisons based on equivalent outcomes for patients receiving placebo. The remaining study[144] provided comparisons only against no treatment.

Five studies explicitly reported using an NHS and Personal Social Services (PSS) perspective.[20,34,100,143,147] Three studies reported taking a health-care perspective,[141,144,146] but two of these[144,146] also included nursing home costs, which are likely to fall under PSS rather than NHS in a UK context, although some may also fall under societal costs if families pay privately for nursing home care. Discounting consistent with the current NICE reference case (3.5% for both costs and QALYs)[139] was applied in all but two studies,[141,143] in which discounting was applied at rates consistent with previous NICE methods guidance (6% for costs and 1.5% for QALYs). The time horizon is not explicitly stated for the 2005 publication by Kanis *et al.*,[141] but, otherwise, all of the included economic evaluations incorporated a lifetime horizon, although, in the analysis by Stevenson *et al.*,[143] the Markov model was used for the first 10 years and then additional calculations were used to estimate QALYs gained over the remaining lifetime.

Quality and applicability of studies

The only analyses considered to be broadly consistent with the NICE reference case were the models described in the submissions by UCB S.A.[20] and Amgen Inc.[100] and the analysis by Davis *et al.*,[34] which informed TA464.[9] None of the other models provided an incremental analysis informed by a systematic review and NMA, which is a significant deviation from the NICE reference case, and may be a potential source of bias. However, it is noted that the analysis by Davis *et al.*[34] was not relevant to the decision problem; it was included purely to allow comparisons to be made between the published models and the model we intended to adapt for this appraisal.

Study conclusions

Owing to the concerns regarding applicability to the decision problem and consistency with the NICE reference case, for several of the studies[34,141,144–147] included in the review, results are summarised here only for the UCB S.A.[20] and Amgen Inc.[100] submissions.

In the Amgen Inc. company submission,[100] which investigated the cost-effectiveness of DEN in a population of patients with a 10-year fracture risk of 20%, DEN was found to be associated with an incremental cost-effectiveness ratio (ICER) of £27,792 per QALY, compared with RLX, and an ICER of £27,363 per QALY compared with no treatment. At the same risk of facture, DEN was also found to dominate ZOL.

In the UCB S.A. submission,[20] which investigated the cost-effectiveness of a treatment sequence of 1 year of ROMO followed by 4 years of ALN (ROMO/ALN), in a population of postmenopausal women with a 10-year fracture risk of 30%, ROMO/ALN was found to be associated with an ICER of (confidential information has been removed) per QALY compared with ALN alone, and (confidential information has been removed) per QALY compared with no treatment. The UCB S.A. submission[20] also presented scenario analyses comparing ROMO/ALN with RIS, ZOL, RLX, DEN and TPTD (administered for 18 months and 24 months). The ICERs for ROMO/ALN when compared with these alternative comparators were (confidential information has been removed) and dominating (ROMO/ALN had more QALYs and a lower cost than TPTD for both the 18- and 24-month treatment durations), respectively, when using the Patient Access Scheme (PAS) price for ROMO.

Review conclusions

The review has identified that there are no published cost-effectiveness studies that compare all of the interventions and comparators specified in the scope of this appraisal across the broad population specified

in the scope, which is patients eligible for risk assessment under CG146.[8] Although the Amgen Inc.[100] and UCB S.A.[20] submissions provide an incremental analysis for the majority of the interventions and comparators specified in the scope (neither compared with i.v. IBN), their analyses are restricted to high-risk subgroups of the population. However, this review was useful in identifying areas where the model used in TA464[34] differed from the models included in the review. These are discussed further in *Independent economic assessment*, where we describe the changes made to the model reported by Davis *et al.*[34]

Independent economic assessment

Methods

Having considered the review of published models and the models included in the company submissions, the AG decided to adapt the model used to inform TA464 (Davis *et al.*[34]) rather than developing a de novo model for this assessment. However, based on the review of models, the AG recognised that there were several areas where it would be useful to consider whether or not the model should be updated or adapted. The areas identified for consideration were as follows:

- treatment persistence – the duration of time the patient persists with treatment
- offset period – the period between when treatment ends and the treatment effect reaches zero
- incorporation of AEs specific to non-bisphosphonates
- resource use associated with monitoring and administration of treatments
- utility values following fracture
- drug prices
- disease costs (i.e. fracture, nursing home admission).

It was not feasible to conduct a full systematic review of the literature to inform each of these updates to the model. Instead, the AG considered any additional sources of evidence provided in the company submission or cited in the published cost-effectiveness studies. This was supplemented by ad hoc searches using Google Scholar (Google Inc., Mountain View, CA, USA) to identify any recent systematic reviews. A more rigorous approach was taken to identifying updated estimates of utility following fracture. For this, we conducted a full systematic search for studies reporting utility pre and post fracture, as measured by the EQ-5D. The aim of this review was to update the review conducted for TA464 by Davis *et al.*[34]

In addition to these updates, the AG also identified that changes to the Visual Basic for Applications (VBA) code would be needed to (1) increase the number of treatment strategies that can be modelled, (2) allow for drug-specific offset periods and (3) allow for sequences of treatments to be modelled.

Unless otherwise stated, all other aspects of the model remain unchanged from the model used to inform TA464,[9] as described in the Assessment Report for TA464 (Davis *et al.*[34]), with the additional change regarding nursing and residential care home costs described in the addendum provided before the second committee meeting.[160] The other changes documented in the addendum are superseded by the updated NMA reported in *Chapter 3, Network meta-analysis*, and the need to update drug costs to reflect current prices.

Model structure

The ScHARR osteoporosis model (used in TA464[34]) is a discrete event simulation (DES), which simulates the clinical events occurring over the lifetimes of individual patients with heterogeneous characteristics. A patient-level simulation approach was chosen to allow the future events experienced by patients to be affected by prior events such as incident fractures. We chose to model a heterogeneous population because we anticipated that certain patient characteristics, such as age, would be non-linearly related to cost-effectiveness. For example, older patients are more likely to have experienced a prior fracture, and may therefore have a lower quality of life at baseline, and they are also more likely than younger patients to be admitted to a long-term nursing or residential care home following a hip fracture. Both of these

factors will influence the costs and QALYs that can be gained from avoiding a fracture. In this situation, the cost-effectiveness for a patient with average characteristics is not the same as the average cost-effectiveness when taking into account the distribution of that characteristic across the population.

In general, in a DES model, a patient's progression through the model is determined by the events that occur, rather than by the health states they occupy. *Figure 10* shows the clinical events that can occur during a patient's lifetime, with the arrows showing which events can occur following other events (note that this is not a state-transition diagram, as patients do not reside in the state defined by the most recent event until the next event is experienced). In the ScHARR osteoporosis model, the main clinical events were fracture, death and new admission to residential care. Fractures at different sites were processed using separate fracture events for hip; wrist; vertebral and proximal humerus. These are the sites most strongly associated with osteoporosis and these are the fracture sites included by both the QFracture and FRAX risk calculators. Fractures at additional sites (e.g. femoral shaft, humeral shaft, pelvis, scapula, clavicle, sternum, ribs, tibia and fibula) have been incorporated by increasing the incidence of these four event types, rather than by adding additional competing events.

In a DES, no changes are made to a patient's attributes between events, but the event list that determines the future events experienced can be resampled each time an event occurs to incorporate any changes in patient characteristics. Dummy events were included in the model to ensure that patient attributes were updated at 1 year after the start of the model, at the end of treatment, at the end of the offset period, at 5 years, at 10 years and 1 year after each incident fracture. Linear approximation is used to adjust for age-related changes in utilty between events.

Utility in the model is based on a combination of sex, age, fracture history and residential status (community dwelling or institutionalised). Separate utility multipliers and costs are applied to the first and subsequent years after fracture to reflect the differences between the acute and chronic impact of

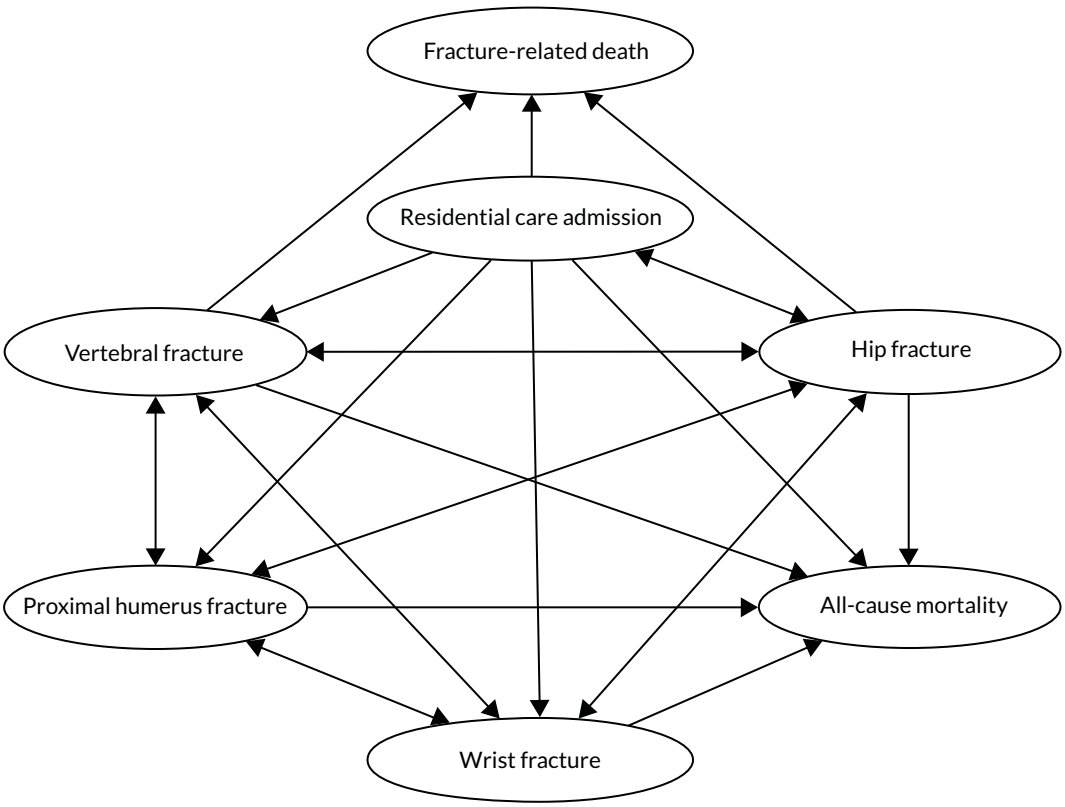

FIGURE 10 Clinical events that can occur during a patient's lifetime in the DES.

fracture. The chronic cost is set to the maximum chronic cost for all fracture events experienced so far. Therefore, the maximum chronic cost for any individual is the cost for institutionalised patients. Drug costs are applied from the start of the simulation until the end of the treatment period and are assumed to accrue at a constant rate across time. Death does not incur any additional costs in the model, but the acute cost of fracture is incurred for both fatal and non-fatal fractures.

The model also incorporates the following structural assumptions:

- There are no restrictions on the sequence of fractures that can be experienced.
- The maximum number of fractures that can be experienced is limited to one per bone (i.e. two hip fractures), with an additional limit of four vertebral fractures, four rib fractures and two pelvic fractures.
- Death attributable to fracture occurs 3 months after fracture, with other fracture events possible during this period, but no mortality from non-fracture-related causes.
- Incident fractures increase the risk of future fractures.
- A fracture event occurring < 1 year after a previous event supersedes the dummy event used to update patient attributes 1 year after fracture, thus reducing the acute period for the earlier fracture.
- Nursing home admission can occur only following fracture; therefore, patients who are community dwelling at the start of the simulation do not transfer to nursing home care as they age unless this is simulated to occur following a fracture.

A brief overview of the key features of the ScHARR osteoporosis model used in TA464[34] is provided in *Table 6*, alongside a description of the key changes to the model since TA464. The only deviation from the NICE reference case to note is that the utility estimates for ONJ have been valued using the US rather than the UK valuation set for the EQ-5D.

Population

The population is patients eligible for risk assessment under CG146,[8] as per the final NICE scope (see *Chapter 1*, *Measurement of disease*). It should be noted that this includes both men and women, those with and those without a prior fracture, those with steroid-induced osteoporosis, those with secondary osteoporosis and those with other risk factors for fragility fracture. CG146 recommends that either FRAX[30] or QFracture[31,163,164] be used to assess the absolute risk of fracture. To explore whether or not the most cost-effective treatment varies for patients at different levels of absolute fracture risk, we report the variation in incremental net monetary benefit (INMB) across risk using

TABLE 6 Overview of the modelling methodology and key data sources

Model feature	Description of model in TA464[34]	Description of revised model
Decision problem	To assess the cost-effectiveness of bisphosphonates compared with no treatment at varying levels of absolute fracture risk as defined by the FRAX and QFracture risk assessment tools	To assess the cost-effectiveness of non-bisphosphonates compared with bisphosphonates and no treatment at varying levels of absolute fracture risk as defined by the FRAX and QFracture risk assessment tools
Type of economic evaluation	Cost-effectiveness analysis with benefits expressed as QALYs	No change
Population/subgroups	• The model simulates the heterogeneous patient population eligible for risk assessment under CG146[8] • The population is stratified into 10 risk categories and results are presented for each risk category. This is done once using FRAX and once using QFracture	No change (see *Population*)

TABLE 6 Overview of the modelling methodology and key data sources (*continued*)

Model feature	Description of model in TA464[34]	Description of revised model
Interventions	• ALN • RIS • Oral IBN • i.v. IBN • i.v. ZOL	• DEN • RLX • ROMO • TPTD • (see *Interventions and comparators*)
Comparators	No treatment	No treatment and the bisphosphonates listed as comparators for TA464 (see *Interventions and comparators*)
Perspective	NHS and PSS	No change
Model type	DES with heterogeneous patient population	No change
Model events	Clinical events are fracture, death (all-cause mortality and fracture-related mortality) and nursing home admission. There are four possible fracture events (hip, wrist, vertebral and proximal humerus), with fracture at other sites included by increasing the incidence of these events Dummy events are used to update attributes 1 year after fracture and to update the fracture risks once treatment finishes	No change (see description of model events in *Model structure*)
Time horizon	Lifetime (up to the age of 100 years)	No change
Duration of treatment	Mean duration of persistence with treatment from observational studies	Data sources for persistence with oral bisphosphonates have been updated. Additional persistence data have been identified for non-bisphosphonates (see *Treatment persistence*)
Natural history	Time to fracture is based on the estimate of absolute fracture risk for major osteoporotic fractures (hip, wrist, proximal humerus and vertebral) provided by either QFracture or FRAX, which is uplifted to include fractures at additional sites. The distribution of fractures across different sites is based on incidence data from Sweden. The increased risks of fracture following incident fracture are based on a published systematic review	No change
Effectiveness	The HRs from the systematic review and NMA are applied for the duration of treatment. Some effectiveness is assumed to persist beyond treatment during the 'offset period'. A linear decline in treatment effect is assumed during this time	• The NMA has been updated to include studies for non-bisphosphonates and any new bisphosphonates studies published since TA464 (see *Effectiveness data*) • Data have been identified on the duration of treatment effect after treatment cessation for the non-bisphosphonates (see *Offset period*) • No changes were made to offset assumptions for bisphosphonates (see *Offset period*)
AEs	Upper GI side effects for oral bisphosphonates and influenza-like symptoms for i.v. bisphosphonates are included by applying one-off cost and QALY deductions in the first month of treatment	Additional AEs have been incorporated for the following (see *Adverse events*): • ONJ • VTE • Cellulitis

continued

TABLE 6 Overview of the modelling methodology and key data sources (*continued*)

Model feature	Description of model in TA464[34]	Description of revised model
Mortality	• All-cause mortality is based on UK lifetables[161] • Fracture-related mortality is based on estimates of excess mortality attributable to hip and vertebral fractures from a case–control study[162] using routine data from UK general practice	No change
Utility data	Utility decrements based on EQ-5D scores pre and post fracture were obtained from a systematic review. Utility decrement for nursing home admission was based on a single study, identified from the literature, that used EQ-5D. Variation in baseline utility by age and sex was based on UK EQ-5D population estimates	• The utility decrements for fracture have been updated to reflect new evidence identified in an updated systematic review (see *Health-related quality of life*) • Utility estimates have been identified and incorpated for the AEs of ONJ, VTE and cellulitis (see *Adverse events*) • The incorporated utility estimates are all based on EQ-5D with valuation using the UK time trade-off data set, with the exception of ONJ for which the estimates are based on the US valuation set for the EQ-5D
Resource use and unit costs	• The analysis includes drug costs, administration costs and costs of fracture, including costs on primary care, secondary care and PSS • Post-fracture costs were based on a case–control study that used routine data from UK general practice. Nursing home admission following hip fracture was based on a UK observational study of discharge destinations • Unit costs are taken from NHS reference costs, PSSRU unit costs, the primary care National Drug Tariff and the eMIT database of generic drug costs in secondary care • Costs are reported in Great British pounds (£) • Cost year is 2014	• Drug costs have been updated using the latest National Drug Tariff and eMIT database (see *Drug costs*) • Costs for monitoring (DXA scanning and annual physican review) have been incorporated. (see *Drug costs*) • Administration costs for i.v. bisphosphonates have been updated and administration costs for non-bisphosphonates have been incorporated. (see *Treatment initiation, administration and monitoring*) • Other costs have been inflated using standard inflation indicies (see *Disease costs*) • Costs are reported in Great British pounds (£) • Cost year is 2018
Discounting	3.5% per annum for both costs and QALYs	No change
Sensitivity analysis	Probabilistic sensitivity analysis was undertaken for the base-case scenario to estimate the mean costs and benefits when taking into account parameter uncertainty Structural uncertainty was assessed through scenario analysis in which parameters were set to their mid-point values	No change

eMIT, electronic market information tool.

two approaches. First, we report outcomes for 10 risk categories, based on deciles of absolute fracture risk. Second, we use regression to determine the relationship between INMB and absolute risk as a continuous variable. These steps are undertaken for absolute risk assessed by FRAX and for absolute risk assessed by QFracture.

Interventions and comparators

The treatment strategies modelled (and the intended treatment durations) were as follows:

- oral ALN (5 years)
- oral RIS (5 years)
- oral IBN (5 years)
- i.v. IBN (5 years)
- i.v. ZOL (3 years)
- RLX (5 years)
- DEN (10 years)
- TPTD (2 years)
- ROMO (1 year) followed by ALN (4 years).

These were all compared with a strategy of no treatment to estimate the incremental costs, incremental QALYs and INMB relative to no treatment. We note that, in the base-case analysis, the actual treatment duration modelled is determined by the duration of treatment persistence rather than the intended treatment duration, but it is necessary to specify the intended treatment duration for the scenario analysis assuming full persistence.

The intended treatment durations for bisphosphonates (3 years for ZOL and 5 years for all others) are based on the assumption made in TA464.[34] For the sequence of ROMO followed by ALN, the 1-year treatment duration for ROMO is based on the anticipated marketing authorisation. However, the anticipated marketing authorisation also states that ROMO should be followed by an anti-resorptive agent, but does not specify the duration for anti-resportive treatment. In the ARCH trial,[83] patients in both arms received open-label ALN after the 1-year double-blind phase. In the clinical study report[20] for the ARCH trial, the mean duration of ALN exposure after the 1-year double-blind phase is (confidential information has been removed) in both arms, but the maximum treatment exposure is between (confidential information has been removed) years across the two trial arms. To have the same overall intended treatment duration as the ALN strategy, we decided to model the ROMO/ALN strategy as including 4 years of ALN. For DEN, we have assumed an intended treatment duration of 10 years, as this is what was assumed in the Amgen Inc. submission,[100] in which it was argued that there are data from the FREEDOM study[104] on the efficacy and safety of up to 10 years of DEN treatment.

Treatment persistence

In the AG model, we have assumed that costs and benefits are linearly related to the duration of treatment persistence; therefore, the individual-level variation in persistence does not need to be modelled. The assumption was found to be reasonable in sensitivity anslyses reported by Davis *et al.*[34] Therefore, the variable that needs estimating to inform the model is the mean treatment persistence and standard error of the mean, which describes the uncertainty around the mean for the probabilistic sensitivity analysis (PSA).

In the model that informed TA464, Davis *et al.*[34] used published estimates of treatment persistence from observational cohort studies, with separate estimates applied for oral bisphosphonates, based on a systematic review by Imaz *et al.*,[165] and for i.v. bisphosphonates, based on a US study of Medicare patients (Curtis *et al.*[166]). Davis *et al.*[34] applied the mean persistence reported in these studies to all patients receiving treatment, rather than modelling individual-level heterogeneity in treatment persistence. The model in the Amgen Inc. submission[100] used persistence data from a retrospective analysis of a large UK primary care database (the CPRD) (Amgen Inc.,[100] data on file). The proportion persisting with treatment over 5 years was estimated from these data and extrapolated beyond 5 years in the model based on the last year of data. The model in the UCB S.A. submission[20] used published estimates for treatment persistence for bisphosphonates and RLX from a UK GPRD study and data from a non-UK registry study for DEN. Unpublished data were cited by UCB S.A.[20] as the

source for TPTD and ZOL persistence. For the sequence of ROMO followed by ALN, the model submitted by UCB S.A.[20] assumed that 90% of patients would persist with ROMO up to 1 year, based on experience from clinical trials, and that, once patients switched to ALN, the treatment persistence would be 85% of that observed for DEN – the treatment with the highest persistence rate, based on the published estimates. Strom *et al.*[146] used persistence data for oral bisphosphonates from a UK CPRD study (Li *et al.*;[167] similarities suggest that this is the same study cited by UCB S.A.) to model persistence over time for the first 3 years and then assumed that all patients reaching 3 years would continue on oral bisphosphonates. Strom *et al.*[146] used a non-UK randomised crossover comparison study[109] to model treatment persistence with DEN. Kanis *et al.*[144] assumed that 50% of patients receiving oral bisphosphonates persist up to 3 months and the rest persist up to the intended treatment duration, based on the assumption used in the analysis that informed TA160 and TA161. It is not clear what assumption was made by Kanis *et al.*[144] regarding treatment persistence for RLX. In the model based on the MORE study,[141] patient compliance was not taken into account, but it was noted in the discussion that 92% of patients took > 80% of their study medication. In the model submitted by Amgen Inc. for TA204,[147] treatment persistence was assumed to be 100% for all treatments in the base-case analysis, but a lower rate of treatment persistence for oral bisphosphonates was applied in a sensitivity analysis based on data from the GPRD (GPRD is the previous name of the CPRD, but the data used here appear to be from a different study to that used in the current Amgen Inc. submission[100]).

Both of the company submissions used data from the same large UK primary care database (GPRD/CPRD). The published analysis by Li *et al.*[168] gave median durations of persistence for oral bisphosphonates ranging from 5 to 7 months across the more commonly used weekly and monthly preparations, whereas the more recent, but unpublished, analysis cited in the Amgen Inc. submission[100] had a lower median persistence of (confidential information has been removed) months for all oral bisphoshonates. However, the AG notes that the data from Li *et al.*[168] suggest that the time-to-discontinuation curve has a long tail, so mean persistence will be longer than median persistence.

The AG estimated mean time on treatment from the Kaplan–Meier estimates published by Li *et al.*[168] by crudely estimating the area under tha Kaplan–Meier curve, assuming linear changes between the estimates reported. The data from the more recent analysis presented in the Amgen Inc. submission[100] were considered less mature than the data presented by Li *et al.*[168] Mean durations of persistence in the first 5 years after starting treatment were estimated to be 1.7 years, 1.5 years and 1.4 years for ALN, RIS and RLX, respectively. Estimates for oral IBN were not possible owing to missing data at 5 years. Although separate estimates of persistence are provided for ALN and RIS, in the absence of any data demonstrating that treatment persistence differs significantly between different oral bisphosphonates, we decided to apply the average persistence data from ALN and RIS to all oral bisphosphonates. We note that mean treatment persistence is approximately three times longer under this assumption than assumed previously in the model that informed TA464.[34]

The AG was not convinced that data from a primary care database, as used in the Amgen Inc. model,[100] would be generalisable to i.v. bisphosphonates (and likewise TPTD) as these are usually prescribed in secondary care. Given this concern, and in the absence of any other alternative data sources, the AG decided to use the same estimates of treatment persistence for i.v. bisphosphonates as assumed in the model that informed TA464.[34]

The evidence on the long-term persistence with DEN appears to be very limited, with most studies reporting a maximum of 24 months' follow-up.[109,169–171] It is difficult to estimate the mean or median duration of treatment from studies that are limited to 2 years when persistence is high at 2 years and it is possible for DEN to be given long term. The analysis of CPRD data presented in the Amgen Inc. submission[100] presents data beyond 2 years, but these were described as exploratory analyses only. The AG were concerned about whether or not the analysis of CPRD data presented by Amgen Inc. would accurately capture DEN persistence as, although DEN may sometimes be administered in primary care, treatment is usually initiated in secondary care. Therefore, any estimate of persistence derived solely

from primary care records may fail to accurately capture treatment discontinuation in the transition between secondary and primary care. The persistence data used for DEN in the UCB S.A. submission[20] match the cited source (Karlsson *et al.*[170]) up to 24 months, but beyond that they have simply assumed a fixed proportional decrease in the numbers that are persistent, based on a comparison between the 18-month and 24-month persistence rates. The AG decided to estimate the mean treatment persistence from the CRPD data presented by Amgen Inc. in their model. The estimates of persistence appear to be very uncertain beyond 4 years, but there appears to be a constant risk of discontinuation from years 2 to 4. The AG decided to use the rate of discontinuation between years 2 and 4 to estimate the proportionate decrease in persistence experienced thereafter. From this, the mean treatment persistence over 10 years was estimated to be (confidential information has been removed). The AG notes that these estimates are uncertain owing to the exclusive use of primary care records and the need for an assumption to be made to extrapolate persistence up to 10 years because of the low proportion of patients captured in the analysis beyond 2 years (confidential information has been removed).

Several sources of persistence data were identified for TPTD. As stated above, the estimates based on UK primary care databases were discounted based on the fact that TPTD is usually prescribed in secondary care. However, two published articles[172,173] were identified from ad hoc literature searches that described persistence in UK patients in real clinical practice based on data from the main home care provider of TPTD in the UK. Both these studies were conducted before the maximum duration of treatment in the marketing authorisation was extended from 18 to 24 months, but they show high levels of persistence at 18 months of 79%[172] and 74%[173] for women and men, respectively. However, these estimates were based on Kaplan–Meier data taking into account the censoring of patients who were still on treatment at the longest follow-up. Data from the European Extended Forsteo Observational Study (ExFOS),[174] which was a large European real-life clinical practice study of TPTD use after the licence was extended to 24 months, showed a mean treatment duration of 20.7 months, despite 29% of patients residing in countries where the licence remained restricted to 18 months. All three papers show a fairly linear fall-off in persistence, although a more rapid fall in persistence was seen in the ExFOS study at 18 months in the countries with 24-month reimbursement, which could be explained by a lack of uptake of the longer dosing schedule. We decided to use the data from UK women to estimate the average duration of treatment. To do this, we assumed a constant rate of discontinuation from 0 to 24 months, based on the rate observed over 18 months by Arden *et al.*,[172] giving an estimated mean persistence time of 1.72 years (20.6 months), which is reasonably consistent with the estimate from ExFOS, which had a mean treatment duration of 20.7 months. We decided to take the standard error of the mean (0.14 months) from the ExFOS study as the measure of uncertainty for the estimate applied in the model. When sampling this parameter in the PSA, the maximum number of doses was capped at 24, as per the SmPC for TPTD.[25]

For ROMO, the manufacturer claimed that 90% of patients persisted to 12 months, based on data from the clinical trials. The AG used data on doses received in the ARCH study[83] to estimate mean persistence with treatment, and found that this agreed with patients being treated for a mean of (confidential information has been removed), although it noted that only (confidential information has been removed) of patients received all 12 doses of ROMO. When sampling this parameter in the PSA, the maximum number of doses was capped at 12, as per the draft SmPC for ROMO provided in the UCB S.A. submission.[12] For the sequence of ROMO followed by ALN, we have assumed that treatment persistence with ALN is the same as for the ALN-only strategy.

Effectiveness data

The HRs estimated in the NMA (see *Figure 6*) were applied in the model for the duration of treatment, with a linear increase to a HR of 1 (i.e. no treatment effect) during the offset period. For the treatment sequence of ROMO followed by ALN, the HR for ROMO followed by ALN was applied during both the ROMO and the ALN treatment periods, as the HR estimate in the NMA was based on fractures occurring during both treatment phases. The NMA requires a single estimate of treatment effect for

each study; therefore, it would not have been possible to generate separate estimates of treatment efficacy for the ROMO and ALN parts of the treatment sequence.

When data on fracture outcomes were lacking for i.v. IBN, the AG used the NMA estimate for daily oral IBN, as the marketing authorisation for i.v. IBN was based on studies demonstrating that i.v. IBN had superior BMD outcomes compared with daily oral IBN. It is noted that this is potentially unfavourable to i.v. IBN if superior BMD outcomes translate into superior fracture prevention outcomes. However, this is consistent with the approach taken in TA464.[34]

For vertebral fracture, we have used the outputs of the base-case NMA, which included studies reporting morphometric fractures. This is because the outcome of morphometric fracture was more widely reported, and the NMA sensitivity analysis that excluded studies that reported only morphometric fractures, leaving just those studies reporting clinical vertebral fracture, was found to produce results that were consistent with the base-case analysis.

In the model that informed TA464,[34] it was possible to use the bisphosphonate class effect estimate when data on individual bisphosphonates were lacking. In the updated networks described in *Chapter 3*, *Network meta-analysis*, no hip fracture data were available for i.v. IBN and monthly oral IBN, but data were available for all non-bisphosphonates. We decided to apply the bisphosphonate class effect estimate for i.v. IBN and monthly oral IBN when data were lacking for hip fracture. We note that the class effect for bisphosphonates was very similar to the estimates for ALN, RIS and ZOL, and so this was not considered to unfairly bias the cost-effectiveness analysis.

In the analysis that informed TA464,[34] the data were considered too sparse for the outcome of proximal humerus fracture, so the non-vertebral NMA estimates were used instead. In the NMAs conducted for the current MTA, the networks were sparsely populated for non-bisphosphonates for the outcomes of both wrist fracture and proximal humerus fracture. The AG decided to use the NMA estimates from the non-vertebral fracture NMA for both wrist and proximal humerus fractures as this allowed a single network to be used to estimate HRs for all interventions. This was considered preferable to using data from different networks for bisphosphonates and non-bisphosphonates, as the wrist and proximal humerus fracture estimates would be more uncertain than the non-vertebral fracture estimates.

In the base-case analysis, the convergence diagnosis and output analysis (CODA) samples from the NMA were used, as these preserve the underlying joint distribution of the HRs, but, in the deterministic analyses, the median HR was used.

Offset period

The AG used a review by Idolazzi *et al.*[175] and papers cited in the company submission to identify relevant studies that could be used to inform the assumptions regarding the appropriate offset periods for the different treatments modelled.

For ALN, the key study was considered to be the Fracture Intervention Trial Long-term Extension (FLEX),[176,177] as this provided comparative data on both fracture risk and BMD for patients remaining on, or stopping treatment with, ALN after 5 years of treatment. This study found that it took 5 years for total hip BMD to return to pre-treatment levels when treatment with ALN was discontinued after 5 years. This was supported by no separation of the time-to-event curves for non-vertebral fractures for patients remaining on treatment compared with those stopping treatment. There was some evidence of a continued treatment effect for lumbar spine BMD, and a continued reduction in vertebral fracture risk was observed (RR 0.45, 95% CI 0.24 to 0.88) for patients who continued ALN compared with those who discontinued ALN.

For RIS, two studies were identified.[178,179] Watts *et al.*[179] reported the outcomes of patients randomised to either placebo or RIS in the year after discontinuing the study drug. Eastell *et al.*[178] reported the outcomes of patients in the year after completing the Vertebral Efficacy with Risedronate Therapy-Multinational (VERT-MN) study, in which patients were randomised to either RIS or placebo for 3 years, followed by a 2-year open-label extension on the allocated study drug, followed by 2 years of open-label RIS in both groups. Both studies reported that BMD gains at the hip were lost in the 1 year following treatment discontinuation, although Watts *et al.*[179] observed smaller losses in lumbar spine BMD and reported a statistically significant reduction in vertebral fracture incidence between those previously treated with RIS and those previously treated with placebo, in the year after treatment discontinuation.

The data identified for oral IBN were limited to those from 1-year post-trial follow-up from an early dose-finding study,[180] which included the 2.5-mg daily dose that has been shown in non-inferiority bridging studies to be equivalent to the 150-mg monthly dose that is now licensed.[181] This study[180] appears to show a similar pattern to that seen for RIS, in that hip BMD appears to return to pre-treatment levels in the year after treatment, with a slightly slower return for lumbar spine BMD. However, as the duration of treatment was only 1 year, it is not clear whether the offset time is 1 year regardless of treatment duration, or whether it would increase in proportion to treatment duration.

For oral bisphosphonates, the AG decided to keep the assumption made previously in the model that informed TA464,[34] which was that treatment effect falls to zero over a period equal to the initial treatment duration for all oral bisphosphonates, as this was accepted previously by the NICE Appraisal Committee. However, in a sensitivity analysis, we have also explored the possibility of a fixed 1-year offset time for RIS and oral IBN.

For i.v IBN, no studies were identified that explored BMD or fracture outcomes following treatment discontinuation. Therefore, we assumed that the offset period would be the same as for oral IBN and set it equal to treatment duration, with a fixed 1-year offset explored in a sensitivity analysis.

For i.v. ZOL, data from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) – Pivotal Fracture Trial extension study are provided by Black *et al.*[182] In the extension study, patients who had received 3 years of ZOL were randomised to receive either ZOL or placebo for a further 3 years. At the end of the study, femoral neck BMD had declined in those who switched to placebo, but not to baseline levels, suggesting an offset period that is longer than the treatment duration when measured based on BMD changes. This suggests a slightly longer tailing-off of treatment effect than observed for ALN in the FLEX study. There was, however, no statistically significant difference in non-vertebral fractures between placebo and ZOL in the extension phase. Similar to the results from the FLEX study, further gains were made in lumbar spine BMD after discontinuation, and there was a statistically significant difference in new vertebral fractures in the extension stage of HORIZON.

For i.v. ZOL, the AG decided to keep the assumption made previously in the model that informed TA464,[34] which was that treatment effect falls to zero 10 years after the start of a 3-year treatment period. For patients stopping treatment early, the offset duration was assumed to decrease proportionately. A sensitivity analysis assuming an offset period equal to treatment duration was also conducted.

For TPTD, data on treatment in women were identified from the FPT follow-up study,[183,184] which followed up patients for a median duration of 30 months after the RCT phase of the study. The RCT phase was terminated early (owing to concerns regarding the safety of long-term use); the median treatment duration was 20 months. During the follow-up study, patients were treated according to local standards and a high proportion (i.e. 56.9% of those randomised to the licensed dose of TPTD in the RCT phase) received other osteoporosis interventions. To account for this, results were presented

for the subgroup with no further osteoporosis intervention, in addition to the analysis for all patients. Statistically significant reductions in vertebral fractures were reported by Lindsay *et al.*[183] in the 18 months following discontinuations, and not all of the lumbar spine BMD gained during treatment had been lost by 18 months. For non-vertebral fractures, statistically significant differences were not found for the licensed dose compared with placebo at the longer follow-up point of 30 months post discontinuation when adjusting for usage of other osteoporosis medications. Furthermore, the gains in femoral neck and total hip BMD appeared to be lost by 18 months in the group not receiving other osteoporosis interventions. A second smaller study[185] in men with a shorter follow-up time had similar findings. Based on these two studies, we decided to assume an offset period equal to the treatment duration.

For RLX, two relevant studies were identified. One compared continuation with RLX with discontinuation in patients previously treated for 96 weeks.[186] Although there were some baseline differences in BMD, the percentage change in lumbar spine BMD from baseline was no longer statistically significant at 144 weeks in the group that had discontinued at 96 weeks, whereas the benefit in lumbar spine BMD was maintained in those continuing RLX up to 192 weeks from baseline. A second RCT extension study,[187] which examined 1-year outcomes in patients discontinuing after 5 years of RLX, oestrogen or placebo, found that BMD values were significantly lower 1 year after discontinuing than at the end of treatment therapy for both lumbar spine and femoral neck BMD. Although these data are from a small study, they support a rapid loss of efficacy in the year after treatment even for patients treated for > 2 years. Based on these two studies,[186,187] we decided to apply a 1-year offset period for RLX.

For DEN, two papers[188,189] reporting outcomes from a single study were identified. The paper reporting 2 years' follow-up post discontinuation in patients allocated to either 2 years of DEN or 2 years of placebo found that gains in both lumbar spine BMD and total hip BMD were lost in the first year after discontinuation, suggesting that an offset period of 1 year would be reasonable for DEN. A third paper,[190] presenting an analysis of post-trial outcomes of patients from the FREEDOM study, was also identified, which described a rapid fall in BMD in the first year after discontinuation, even after treatment lasting 10 years. Although this analysis was limited to 12 women from a single site, and can therefore be considered as only weak evidence, this analysis is supportive of a fixed offset period of 1 year, rather than one that varies with treatment duration. Therefore, for DEN we have assumed a fixed offset period equal to 1 year (or, when this is < 1 year, the treatment duration).

For ROMO, no data were identified in the published literature on the treatment effect following discontinuation. In sequences in which ROMO is followed by ALN, we have assumed an offset period equal to the total duration of the treatment sequence, with efficacy during the offset linearly declining from the efficacy observed across the treatment sequence. This is consistent with the assumption applied by UCB S.A.[20]

Drug costs

For drugs with multiple preparations, the cost was based on the lowest cost preparation available. For drugs administered in primary care, the costs were taken from the NHS drug tariff.[191] For drugs administered in secondary care, the electronic market information tool (eMIT) database[192] was used for generic preparations (i.v. bisphosphonates) and the NHS drug tariff[191] price was used when no generic preparation was listed as being available (i.e. for TPTD and DEN). For ROMO, the annual costs for both the list price and the PAS price were taken from the company submission. The PAS price was used in the AG's base-case analysis. The price used for TPTD was based on the branded formulation (Forsteo), as no prices were available for the biosimilar versions (Movymia and Terrosa)[22,23] when this report was prepared.

The dosing, cost per item and annual cost for each treatment strategy are summarised in *Table 7*.

TABLE 7 Treatment-specific model inputs

	ALN/RIS/IBN (oral)	IBN i.v.	ZOL i.v.	RLX	DEN	TPTD	ROMO/ALN[a]
Intended treatment duration (years)	5	5	3	5	10	2	1
Mean persistence (years)	1.60	1.1	1.7	1.38	Confidential information has been removed	1.72	Confidential information has been removed
Offset	1.60	1.10	3.96	1.00	1.00	1.72	N/A[b]
Drug acquisition costs							
Dosing unit	70 mg/35 mg/ 150 mg	3 mg in 3 ml	5 mg/100 ml	60 mg	60 mg	20 µg	210 mg
Dosing frequency	Weekly/weekly/ monthly	Quarterly	Annual	Daily	Biannual	Daily	Monthly
Unit cost	£0.76 per 4/ £0.76 per 4/ £0.99 per 1	£7.89 per 1	£13.24 per 1	£3.27 per 28	£183.00 per 1	£271.88 per 30	Not provided
Total cost per year (£)	9.91/9.91/11.88	31.56	13.24	42.63	366.00	3307.87	Confidential information has been removed
Administration costs							
Route of administration	Oral	i.v.	i.v.	Oral	s.c. injection	s.c. injection	s.c. injection
Resource use for administrations	N/A	Outpatient	Day case	N/A	Two as outpatient, then general practice nurse	Self-administered	Self-administered
Cost per administration (£)	N/A	150.38	253.32	N/A	10.85 (150.38 first year)	N/A	0.00
Number of administrations per year	N/A	4	1	N/A	2	N/A	12
Total cost per year (£)	0.00	601.52	253.32	0.00	21.70 (300.76 first year)	N/A	0.00

continued

TABLE 7 Treatment-specific model inputs (*continued*)

	ALN/RIS/IBN (oral)	IBN i.v.	ZOL i.v.	RLX	DEN	TPTD	ROMO/ALN[a]
Monitoring costs							
Type of follow-up visit	GP	Outpatient	Outpatient	GP	GP, with one in four as outpatient	Outpatient	Outpatient
Cost (£) per follow-up visit (one per annum)	38.00	150.38	150.38	38.00	66.09 (average)	150.38	150.38
Years between DXA	5	5	3	5	5	2	1
Annualised BMD measurement costs (£)	13.66	13.66	13.66	13.66	13.66	34.14	68.29
Total monitoring costs per year (£)	51.66	165.04	173.14	51.66	79.75	184.52	218.67
Total annual costs (£)	61.57/61.57/ 63.54	797.11	439.71	94.29	467.45 (746.51 in first year)	3492.40	Confidential information has been removed

GP, general practitioner; N/A, not applicable.
a Data here relate to the ROMO part of the ROMO/ALN sequence. Data for the ALN part of the sequence are as for ALN used first-line, with the exception that treatment duration with ALN is 4 years, not 5 years, and DXA is assumed to occur at the end of the 4 years rather than after 5 years.
b Total offset time for sequence is (confidential information has been removed) years.

Treatment initiation, administration and monitoring

Six of the studies assumed that patients would undergo DXA every other year while on treatment.[20,100,141,144,146,147] Stevenson *et al.*[143] assumed that patients would undergo DXA at years 2 and 5. Davis *et al.*[34] did not include any DXA to monitor treatment with bisphosphonates. Not all of the papers were explicit about whether or not patients were assumed to have undergone DXA before starting treatment, but, in Davis *et al.*,[34] all costs that related to risk assessment, which may include DXA for some patients, were considered to have been already inccurred prior to treatment choice, as these were included in the cost-effectiveness analysis for risk assessment in CG146.[8] The AG considered that the inclusion of routine DXA in the model was problematic as the approach taken may differ depending on the baseline risk of the patient and the treatment being administered. For example, CG146 does not recommend that DXA is performed routinely as part of the risk assessment of patients.[8] Therefore, it is reasonable to assume that many patients may be started on the current first-line therapy, which is oral bisphosphonates, without DXA, and this is consistent with the approach recommended in the NICE-accredited NOGG guideline.[14] However, the NOGG also recommends that FRAX with BMD is used to reassess patients at the end of 5 years of bisphosphonate therapy (3 years for ZOL). On this basis, we decided to assume that patients undergo DXA when they reach the end of the intended treatment duration. We made an exception for DEN, as the intended treatment duration is much longer than for other therapies, so we assumed that DXA is undertaken every 5 years. This was based on advice from one of our clinical experts that patients receiving DEN in primary care would be likely to be reviewed in specialist care at 3 or 5 years. For the treatment sequence of ROMO followed by ALN, we assumed that a patient would undergo DXA once at the end of the 1 year of ROMO and once at the end of the 4 years of ALN. Because treatment duration in the model is based on average treatment persistence rather than the distribution of persistence across the population, the AG incorporated the cost of DXA as an annualised cost; otherwise, no DXA costs would be applied, as the average patient never reaches the intended treatment duration. This is consistent with the assumption that costs and benefits are linearly related to the duration of treatment persistence and, therefore, the individual-level variation in persistence does not need to be modelled. The cost applied for DXA is based on the NHS reference cost for direct-access DXA (£68.29 for RD50Z).[193]

Four of the studies assumed that patients would attend annual general practitioner (GP) appointments to monitor treatment.[20,141,146,147] Amgen Inc.[100] assumed the same for treatments given in primary care (which included oral bisphosphonates and DEN), but assumed secondary care follow-up appointments for i.v. bisphosphonates. Kanis *et al.*[144] assumed one GP appointment to initiate treatment. Stevenson *et al.*[143] assumed two GP appointments per annum, whereas Davis *et al.*[34] did not include any GP appointments for monitoring. There is now a NICE QS[13] that states that patients having bone-sparing treatments should have medication reviews to discuss AEs and adherence, but the frequency of the reviews is not specified. We have assumed that patients will have annual reviews and that those reviews will occur in primary care for oral bisphosphonates and RLX. For this, we applied the cost per average GP patient contact (£38.00 per 9.22 minutes).[16] For DEN, we were advised that patients would be reviewed in secondary care every 3–5 years, so we have assumed that one in four annual reviews will occur in secondary care. For i.v. bisphosphonates, ROMO and TPTD, we have assumed that the annual review occurs in secondary care as an outpatient endocrinology appointment. The cost (£150.38) for a consultant-led, non-admitted, face-to-face follow-up attendance at endocrinology outpatient has been applied [Healthcare Resource Group (HRG) currency code WF01A, service code 302].[193]

As noted previously, none of the studies identified in the review included any costs for the administration of oral therapies; this was the assumption applied in our model. UCB S.A.[20] also assumed no administration costs for s.c. therapies (i.e. DEN, TPTD and ROMO). In the Amgen Inc. submission for this MTA,[100] it was assumed that DEN would be given by a general practice nurse, whereas, in the Amgen Inc. submission for TA204,[147] they assumed that one injection would be administered during the annual GP visit, and therefore one additional GP appointment was required per annum for the second injection. For DEN, we assumed that patients would initiate treatment in

secondary care, with the first two doses being given as an outpatient procedure using the same HRG codes as applied for i.v. IBN. Thereafter, it was assumed that DEN would be administered under a shared care agreement, with a primary care nurse providing future doses during a 15.5-minute appointment at a cost of £10.85 (based on £42.00 per hour for general practice nurse contact time).[16] This was based on advice from our clinical experts that, ideally, only the first one or two doses would be given in secondary care, although they also noted that there is significant variation in practice surrounding shared care agreements, with some local areas having a poor uptake of primary care administration.

Stevenson *et al.*[143] do not describe any additional administration costs for TPTD. Waugh *et al.*[147] included one additional GP appointment for initiation of TPTD. The AG did not consider that any additional costs were necessary for the administration of TPTD, given that it is self-administered, and an annual secondary care review has already been included for TPTD, as described previously.

Davis *et al.*[34] assumed that i.v. IBN is delivered during an outpatient endocrinology appointment and that i.v. ZOL is delivered as a day-case procedure using the HRG code for administration of a simple parenteral chemotherapy (SB12Z). UCB S.A.[20] assumed that administration of i.v. ZOL occurred in secondary care, but the exact source of the cost applied is unclear. In the Amgen Inc. submission for TA204, administration of i.v. bisphosphonates was assumed to occur in secondary care under the same HRG code as used by Davis *et al.*[34] for i.v. ZOL. However, in the Amgen Inc. submission for the current MTA,[100] it was argued that the use of an oncology HRG was inappropriate; instead, the cost was based on day case and elective inpatient spells averaged over nine HRG codes related to non-inflammatory bone and joint disorders and pathological fractures. The AG was already aware of a study that compared the cost of secondary care infusion of ZOL with a home-care delivery model in a UK NHS setting.[194] In correspondence with the study author (Opinder Sahota, Nottingham University Hospitals NHS Trust, 2018, personal communication), it was stated that the reference cost, including the drug costs, for this activity was £300 per patient (£14,980 per 50 patients), and this included acquisition of the drug at a discounted (undisclosed) cost from the manufacturer. However, the income for the activity based on the tariff was much lower, at £143 per patient, which also includes the cost of drug acquisition. Based on these figures, we felt that the estimates provided by Amgen Inc. were probably too high and we decided to use the HRG codes applied in the model that informed TA464,[34] but updated to the latest reference costs,[193] giving a cost of £253 for day-case infusion of i.v. ZOL (day case, SB12Z delivery of simple parenteral chemotherapy at first attendance).

For i.v. IBN, no alternative estimates of administration costs were identified from the studies included in the review. Therefore, we decided to assume the same resource use as in the model used to inform TA464[34] (one outpatient endocrinology follow-up appointment), but we updated the unit cost to reflect the latest reference costs,[193] giving a cost of £150.

Adverse events

For oral and i.v. bisphosphonates, the AG decided not to change the approach to modelling AEs that was adopted in TA464,[34] as there was no new evidence on which to base alternative assumptions identified from the review of cost-effectiveness studies.

The AG decided to include serious (i.e. leading to hospitalisation) cellulitis as an AE for DEN because it had been included in the model that informed TA204,[147] although it was noted that the 10-year results of the FREEDOM study[41,104] suggest that the incidence rate of cellulitis is low, at $\leq 0.2\%$ in each of the study years. The HRG cost for a non-elective inpatient spell for minor skin conditions with interventions ranges from £2588 to £7764, depending on the level of complications and comorbidities, with a weighted average of £4467.[193] Assuming an incidence rate of 0.2% per annum and applying this weighted cost to the incident population would increase the cost of DEN by £8.93 per annum. The AG identified a paper that had estimated the QALY loss of cellulitis as 0.005 QALYs (reduction in EQ-5D score by 26.3% for 7 days), based on a comparison of EQ-5D scores in a prospective RCT of antibiotics versus placebo to

prevent recurrent cellulitis.[195] This is equivalent to a loss in INMB of £0.20 per annum. As the duration of treatment persistence with DEN in the model is (confidential information has been removed) years, this would suggest that the total impact of cellulitis is a reduction in INMB for DEN of the order of (confidential information has been removed). Costs and QALY losses for cellulitis per year of exposure to DEN have been included in the base-case model.

The AG notes that the Medicines and Healthcare products Regulatory Agency (MHRA)/Commission on Human Medicines (CHM) has issued advice regarding the risk of atypical femoral fractures for both DEN and bisphosphonates,[28] but this advice states that these events are rare and that they are primarily related to long-term use. The AG decided not to include atypical femoral fractures as a separate AE in the model. This was, first, because the HRs for fractures estimated from the clinical trials would already include any impact of the drug on atypical femoral fractures, and including them as a separate event may result in these outcomes being double-counted in the model. The AG accepts that atypical femoral fractures may not have been captured in the trials if they occur only after long-term use of osteoporosis treatment. However, the AG notes that the base-case scenario incorporates real-world treatment persistence, which is much shorter than the intended treatment duration for both bisphosphonates and DEN, making these AEs that occur with long-term use less relevant to these treatments as they are modelled.

The AG notes the MHRA/CHM advice regarding the risk of ONJ in patients receiving bisphosphonates.[28] The advice states that the risk is considered to be substantially higher in those receiving i.v. bisphosphonates in the treatment of cancer than in those receiving i.v. bisphosphonates for the treatment of osteoporosis, and the risk is said to be related to cumulative dose. Similarly, the MHRA/CHM advice on DEN states that it is a common side effect for those patients receiving DEN for the treatment of cancer and recommends dental examination and preventative dentistry treatment in all patients starting DEN for cancer.[28] It should be noted that the dose for cancer is 120 mg monthly, rather than 60 mg every 6 months, and, in the context of using DEN to prevent osteoporotic fracture, such precautions are recommended by the MHRA/CHM only for those with risk factors.[28] The AG also notes that a systematic review by Boquete-Castro *et al.*[196] states 'it should be stressed that most of the adverse effects of DEN appear with doses of 120 mg. Adverse effects with doses of 60 mg are directly related to the duration of treatment.'. Although there appears to be less concern regarding ONJ in patients receiving anti-resportive agents for osteoporosis than for ONJ in patients receiving anti-resportive agents for cancer, the AG decided to incorporate this AE in the model to establish the likely impact on the cost-effectiveness estimates.

The AG examined a systematic review reported by Khan *et al.*,[197] which was conducted to inform an international consensus statement on ONJ. Khan *et al.*[197] conclude from their review that 'the incidence of ONJ in the osteoporosis patient population appears to be very low, ranging from 0.15% to < 0.001% person-years of exposure and may be only slightly higher than the frequency observed in the general population'. For oral bisphosphonates, the review by Khan *et al.*[197] identified a UK (Scottish) prospective case series that reported an incidence for ONJ of one case per 4545 drug patient-years (0.022%) for patients exposed to ALN.[198] This was within the incidence range of 1.04–69 cases per 100,000 patient-years reported by the other studies identified in the review by Khan *et al.*[197] It should be noted that Lo *et al.*[199] found, in a cross-sectional survey conducted in the USA, that prevalence of ONJ was related to duration of exposure, with estimated prevalences of 0%, 0.05% and 0.21% in patients exposed for < 2 years, 2 to just under 4 years and ≥ 4 years. For i.v. bisphosphonates, Khan *et al.*[197] reported an incidence range of 0–90 per 100,000 patient-years. The incidence estimated across five RCTs is given by Khan *et al.*[197] as < 1 in 14,200 patient-years of exposure (< 0.007%). For DEN, Khan *et al.*[197] reported that the estimates of incidence ranged from 0 to 30.2 per 100,000 patient-years. However, more recent data from the 10-year follow-up of the FREEDOM trial[41,104] gave an exposure-adjusted incidence of ONJ of 5.2 per 10,000 participant-years (0.052%). The SmPC for DEN states that the incidence is related to the duration of exposure.[200] Given that there is a lack of comparative data on the incidence of ONJ across the different forms of anti-resportives, and that the estimates for

the different anti-resportive drugs all relate to different periods of exposure, we have decided to assume the same incidence per year of drug exposure across all anti-resportives. This was based on the estimate from the prospective case series in Scotland.[198] This was because this estimate fell within the range provided by Kahn *et al.*[197] for each type of anti-resportive (oral bisphosphonates, i.v. bisphosphonates and DEN) and was based on the average duration of use in clinical practice; therefore, it would be more applicable to the duration of treatment persistence modelled in this analysis.

A paper[201] measuring health utility in patients with ONJ was identied using ad hoc searches of Google Scholar. It reported utility measured by the EQ-5D in 34 cancer patients with bisphosphonate-associated ONJ. However, it should be noted that it was not compliant with the reference case in several ways. First, although the pateints had all themselves experienced ONJ, they were asked to value clinical vignettes describing different stages of ONJ in patients who also have cancer, rather than being asked to value their own health state. Second, the utilty weights applied were from the US, rather than the UK, valuation set. However, given the lack of alternative estimates, we calculated the average utility decrement based on the utility decrements (relative to patients with cancer but without ONJ) for stages 2 and 3 (–0.33 and –0.61, respectively) and the distribution of ONJ stages (two were stage 3 and nine were stage 2) across the UK prospective case series reported by Malden and Lopes.[198] This gave an average utility decrement of –0.38. The mean time from diagnosis to healing (6.5 months) was taken from the same study[198] to give an average QALY loss of 0.206 per case of ONJ. The NHS reference cost for a minor outpatient oral surgical procedure was applied (HRG code CD03A, £166)[193] to account for the cost of surgical management, as most patients in the Malden and Lopes[198] case series had some form of surgical management, with debridement being the most common procedure. We note that the Malden and Lopes[198] case series may have missed less severe cases of ONJ, which would be classed as stage 1. However, as cancer pateints with stage 1 ONJ were found not to have EQ-5D values significantly different from those of cancer patients without ONJ (Miksad *et al.*[201]), and patients with stage 1 would be more likely to be managed conservatively,[197] we felt that exclusion of this group was unlikely to significantly bias the estimates of costs and QALYs resulting from ONJ, provided they are excluded from both the incidence estimates and the estimates of costs and QALYs per case. Costs and QALY losses per year of exposure to DEN, oral bisphosphoantes and i.v. bisphosphonates have been included in the base-case analysis, but we note that their impact is very small owing to the extremely low incidence.

Kanis *et al.*[141] applied HRG costs and a utility loss in the year after VTE, but not beyond. The utility decrement was based on an assumption, as no estimate was identified from the literature. No other models identified in the literature review included VTE as an adverse outcome. Rather than extend the AG model to incorporate the competing risk of VTE in patients at risk of fracture, the AG decided to estimate the average discounted lifetime cost and QALY loss attributable to VTE using a published model (Pandor *et al.*[202]). As this model was constructed to estimate the costs and benefits of thromboprophylaxis, the AG removed all costs and QALY losses attributable to the thromboprophylaxis itself, including the increased risks of bleeding during the prophylaxis, thereby reducing the model to a comparison of two groups whereby the only difference between them is their risk of VTE. All conseqeunces related to asymptomatic VTE were removed from the model as these were not considered relevant, as it is only symptomatic VTE that has been recorded as an adverse outcome. The AG then compared costs, QALYs and the number of symptomatic VTEs for the strategies of prophyalixs for all and prophyalixs for none. These figures were used to estimate the average discounted lifetime cost and QALY loss per symptomatic VTE, which were estimated to be £1890 and 0.77 QALYs for a patient with a starting age of 50 years.

The largest RCT reporting VTE as an adverse outcome for RLX was the MORE study,[51,102] which reported that 25 out of 2557 patients receiving RLX experienced VTE, whereas eight out of 2576 patients receiving placebo experienced VTE. Based on the increased incidence observed in the MORE study, the excess rate of VTE attributable to RLX was estimated to be 0.67% over the 3-year study period. Ettinger *et al.*[51] did not report the proportion of these events that were PEs, but did say that a

mixture of PE and DVT events were observed. The study by Silverman *et al.*[50] did report the breakdown by type of VTE: four of the 12 VTE events in the RLX-treated arm were PEs. It should be noted that, in the model by Pandor *et al.*,[202] 30% of symptomatic VTE events are PEs, which is reasonably consistent with the ratio of PE to DVT observed in the RLX arm of the study by Silverman *et al.*[50]

By applying the estimates of costs and QALYs per symptomatic VTE derived from Pandor *et al.*[202] to the excess incidence observed in the MORE study, we estimated a reduction in INMB of £116 per patient enrolled in the MORE study when valuing a QALY at £20,000 (and assuming that VTE occurred at 50 years of age). Given that the average duration of persistence in the model for treatment with RLX is 1.38 years, if we assume that the absolute risk is proportional to the time spent on treatment, the INMB loss attributable to VTE would be of the order of £53 per patient started on treatment (cost of £5.80, QALY loss of 0.00237). It should be noted that the QALY losses would be fewer for older patients experiencing VTE, as much of the QALY loss is attributed to long-term sequelae that have a greater impact on patients with a higher life expectancy. However, when assuming a start age of 75 years, the INMB loss attributable to VTE per patient started on RLX was estimated to be £47 (compared with £53 for patients aged 50 years), so the error associated with applying costs and QALYs as estimated for a patient aged 50 years was not considered likely to have resulted in a large bias. The average cost and QALY loss attributable to excess VTE were applied to each patient initiating treatment with RLX, with the risk proportional to time spent on treatment, such that they have a bigger impact in the sensitivity analysis assuming full treatment persistence.

Disease costs

The costs of fracture in the TA464[34] model were based on a UK resource use study reported in two papers by Gutiérrez *et al.*,[203,204] which used a general practice database (The Health Improvement Network) to estimate resource use for those who fractured compared with matched controls. Unit costs from the 2013/14 reference costs[205] and the 2014 PSSRU unit costs[206] were then applied to this resource use to estimate the total cost in the year of fracture and in the subsequent years following fracture. None of the studies included in the review provided a more recent source of resource use. Two studies[20,100] reported using costs based on Gutiérrez *et al.*,[203,204] and five[141,143,144,146,147] used estimates from the literature from less recent publications.

The AG identified two additional relevant UK studies in the systematic database search conducted to identify published cost-effectiveness analyses. Lambrelli *et al.*[207] used a methodology similar to that employed by Gutiérrez *et al.*, but using an alternative primary care database (the CPRD), with linkage to a secondary care database [Hospital Episode Statistics (HES)]. Lambrelli *et al.*[207] reported costs in the year following hip fracture of £7359. Leal *et al.*[208] reported higher costs, of £14,163, based on an analysis of HES data alone. This analysis excluded activity in primary care and was focused solely on patients admitted to hospital following fracture. For comparison, the estimate used in TA464,[34] based on the data from Gutiérrez *et al.*,[203,204] when excluding the costs of home help, was £6274. The AG decided to use the data from TA464,[34] and to adjust it using 2017 PSSRU inflation indices,[16] as the two studies by Gutiérrez *et al.*[203,204] provided a consistent methodology for estimating both hip and non-hip fractures, included activity in both primary and secondary care settings and incorporated prescription costs.

Costs for home help and residential care/nursing home admission were estimated by uplifting the estimates used in TA464[34] using PSSRU inflation indices.[16]

The costs applied in the first and subsequent years following fracture are summarised in *Table 8*.

Health-related quality of life

We conducted a rapid update of the systematic review of HRQoL studies conducted for TA464.[34] This comprised a systematic serach for studies reporting EQ-5D utility data for the year post fracture. Further details on the review methods and findings can be found in *Appendix 16*. In summary, the

TABLE 8 Costs and utility values applied in the first and subsequent years following fracture

Parameter	Fracture				New admission to residential care
	Hip	Vertebrae	Proximal humerus	Wrist	
Costs in year of fracture[a] (£)	8568	4342	1358	896	24,519
Costs in subsequent years[a] (£)	110	345	73	73	24,519
Utility multiplier in year of fracture	0.55[b]	0.68[b]	0.78[c]	0.83[b]	0.625[d]
Utility in subsequent years	0.86[b]	0.85[b]	1.00[c]	0.99[b]	0.625[d]

ICUROS, International Costs and Utilities Related to Osteoporotic Fractures Study.
a Data applied in TA464,[34] but inflated using PSSRU inflation indices.[16]
b ICUROS data reported by Svedbom *et al.*[209]
c Calculated from the Australian ICUROS subgroup data reported by Abimanyi-Ochom *et al.*[210] and assumed fixed in the PSA.
d Data from Tidermark *et al.*[211] previously applied in TA464.[34]

review identified four papers all reporting outcomes from the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS).[209,210,212,213] This study was previously identified in the review conducted for TA464.[34] However, the four new papers identified reported additional data. ICUROS was an international multicentre study; two of the papers[210,212] reported outcomes from specific countries that formed subgroups of the overall ICUROS population. The other two papers reported longer-term follow-up from the overall international data set. One of these papers[213] restricted its analysis to those patients with complete follow-up on both the EQ-5D and the EQ-VAS, which resulted in a smaller population available for analysis. The paper reporting outcomes from the international cohort without restricting to patients who also reported EQ-VAS was chosen, as it was the larger data set.[209] This paper reported utility multipliers for the year following fracture and subsequent years for hip, wrist and vertebral fractures. The multipliers presented in the paper were applied directly in the model. However, no data were presented in this paper for proximal humerus fractures. The only paper reporting outcomes following proximal humerus fracture was the one reporting outcomes for the Australian subpopulation of ICUROS.[210] Although these data were specific to a different country, results were presented in an appendix using the UK time trade-off tariff for the EQ-5D. From these data, we calculated utility multipliers for the year following humerus fracture and subsequent years, using the same methodology as employed in the international paper for the other fracture types. The utility values applied are summarised in *Table 8*.

Model validation

The model is designed to operate in several different modes, which facilitates debugging and validation. A description of the general validation methods used, and the specific methods used to validate each structural change to the model, is provided in *Appendix 17*.

Approach to sensitivity analysis

A PSA has been conducted to estimate the mean costs and QALYs gained when taking into account the uncertainty in the parameter values used in the model. In general, parameters were estimated using the following distributions: gamma distributions for costs, log-normal distributions for HRs (except the efficacy estimates, which were based on the CODA samples from the NMA) and beta distributions for utility values and probabilities. The treatment persistence estimates were assumed to be normally distributed, but maximum and minimum values were applied to ensure that they did not fall below zero or exceed the intended treatment duration. None of the parameters used to estimate fracture risk, in the absence of treatment, was varied in the PSA. This was to ensure that a specific set of patient characteristics was consistently mapped to the same survival curve for fracture-free survival without any parameter uncertainty. The following additional parameters were not varied in the PSA: drug prices; discount rates; unit costs sourced from the PSSRU; utility in the second year after proximal

humerus fracture; life expectancy after fracture associated with excess mortality; unit costs for prescriptions after fracture; the proportion of self-funders for residential care; and costs and QALY decrements for AEs.

Structural sensitivity analyses were conducted to explore whether or not the results were sensitive to different model assumptions. To reduce model computation time, the structural sensitivity analyses were conducted using mid-point parameter inputs, rather than using the full PSA version of the model. Any structural sensitivity analyses conducted during TA464 that showed minimal impact were not repeated here. The structural sensitivity analyses that were found to have the biggest impact in TA464 were those related to treatment perisistence and AEs.

We conducted the following structural sensitivity analyses:

- assuming full persistence with treatment up to the intended treatment duration
- alternative assumptions for offset periods [1-year offset periods for RIS, IBN (oral and i.v.) and TPTD, and an offset period equal to treatment duration for ZOL, DEN and RLX]
- HRs for bisphosphonates based on class effect estimate (the predicted HR for a new drug in the same class).

We noted that both the Amgen Inc.[100] and UCB S.A.[20] submissions focused on high-risk subgroups. To generate some comparable results, we conducted an exploratory scenario analysis in which we fixed the patient characteristics to obtain an estimate of the cost-effectiveness for an example high-risk patient. The patient characteristics were chosen to match those used in the UCB S.A. model[20] as closely as possible, although an exact match was not possible as the AG model uses FRAX for unknown BMD whereas the UCB S.A. model[20] specifies the *T*-score of the patient. The patient characteristics selected were female, aged 75 years, had a history of fracture, a body mass index of 21 kg/m^2 and one additional risk factor, which was chosen to be moderate alcohol consumption (3–6 units per day) to give a FRAX risk that was similar to the FRAX risk of 30% reported for the patient population in the UCB S.A. economic model. This example patient had a FRAX score of 31.6%. The model was then run for 500,000 PSA samples with these patient characteristics fixed, but allowing life expectancy to be sampled.

Base-case results

The base-case results are based on model outcomes for 2 million patients from the PSA version of the model. For each individual patient, a unique set of PSA parameter inputs was sampled (see *Approach to the sensitivity analysis*). As the cost-effectivenss is dependent on absolute risk of fracture, results are provided for 10 risk categories, each containing approximately 200,000 patients. The results presented for each risk category are based on the average costs and QALYs across the simulated patients falling into that risk category. It should be noted that the patients in the risk categories differ for QFracture and FRAX, as each risk category is based on a decile of risk scores across the population modelled to ensure that each risk category contains approximately the same number of patients and is not underpowered relative to the other risk categories.

The adverse clinical outcomes avoided (i.e. fractures, fatal fractures and new admissions to nursing/residential care) compared with no treatment, when using QFracture to estimate fracture risk, are summarised in *Table 9*, along with the life-years gained (the equivalent data when using FRAX to estimate fracture risk can be found in *Appendix 18*). It should be noted that, as these are based on the mean outcomes from the PSA, which incorporates estimates of efficacy based on the CODA samples from the NMA, it is possible for a drug with a mid-point HR close to 1 and a broad CrI to have an adverse impact on fracture, on average, across the PSA samples. This is the case for RLX, for which the HR for hip fracture was 0.93 (95% CrI 0.30 to 2.76), resulting in a predicted small increase in hip fractures, on average, across the PSA samples. This was not observed when running the model using the mid-point HRs; therefore, it clear that it is being caused by the distribution of CODA samples for the hip fracture HR for RLX.

TABLE 9 Clinical outcomes across the whole population eligible for fracture risk assessment when using QFracture to estimate fracture risk

Drug	Number of adverse clinical outcomes avoided per 100,000 patients treated, when compared with no treatment							Total life-years gained per patient vs. no treatment
	Total fractures	Hip fracture	Vertebral fracture	Proximal humerus fracture	Wrist fracture	Nursing home/ residential care admission	Fatal fracture	
ALN	353	93	85	45	130	16	14	0.0011
RIS	366	83	85	52	147	15	13	0.0010
IBN (oral)	295	81	85	35	94	13	13	0.0010
IBN (i.v.)	147	52	55	9	31	8	9	0.0007
ZOL	617	145	161	80	231	25	26	0.0020
RLX	37	−16	27	17	9	5	−1	0.0005
DEN	507	172	182	42	110	41	30	0.0029
TPTD	660	176	147	91	247	31	27	0.0020
ROMO/ ALN	833	248	158	129	298	56	34	0.0030

It can be seen from *Table 9* that ROMO/ALN results in the largest number of fractures avoided, followed by TPTD. DEN has fewer fractures avoided in total than TPTD, but a higher number of life-years gained. This is because the life-years gained are dependent on both the number and the type of fractures avoided, as only hip and vertebral fractures have an excess mortality risk. It can be seen that DEN avoids a similar number of hip fractures as TPTD, but DEN avoids more vertebral fractures than TPTD, meaning that there are fewer fatal fractures for DEN, which results in a greater number of life-years gained.

The ICERs for non-bisphosphonates versus no treatment and the treatment with maximum INMB (when valuing a QALY at either £20,000 or £30,000) for each risk category are summarised in *Table 10*. We used a regression using a generalised additive model to estimate the relationship between INMB and absolute risk as a continuous variable for both QFracture and FRAX. Plots of the predicted INMBs when valuing a QALY at £20,000 for each non-bisphosphonate treatment are summarised in *Figure 11* for QFracture and in *Figure 12* for FRAX (results for ROMO/ALN are confidential and have been removed). A negative INMB in *Figures 11* and *12* indicates an ICER of > £20,000 per QALY compared with no treatment. It can be seen that the INMB relative to no treatment increases with increasing baseline risk for both QFracture and FRAX for DEN, TPTD and ROMO/ALN, but the INMBs remain under zero across the range of fracture risk observed in the population eligible for risk assessment. For RLX, the relationship between fracture risk and INMB is less clear, particularly when using FRAX to estimate fracture risk. The INMB of RLX versus no treatment predicted by the regression does go above zero from a FRAX score of 32.6–37.8%, but it should be noted that the predictions become more uncertain as the risk scores increase, as they are informed by estimates from fewer simulated patients. For example, only 2% of patients have a FRAX score of > 30% and 0.2% of patients have a FRAX score of > 40%, which is why we do not present the INMB plots for FRAX scores of > 40%. The risks of fracture predicted by QFracture are generally lower than the risks predicted by FRAX, meaning that only 0.3% have a risk score of > 30% when using QFracture. The plot of INMB versus risk for RLX may also be less well defined for RLX than for the other non-bisphosphonates, as RLX resulted in the fewest number of fractures being prevented, making the estimates of average INMB gains from prevented fractures more uncertain.

TABLE 10 The ICERs vs. no treatment and treatment with maximum INMB by risk deciles for QFracture and FRAX

	ICERs by risk decile										
Drug	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**All**
Qfracture score (%)	***0.5***	***0.7***	***1.0***	***1.4***	***2.0***	***2.7***	***3.9***	***5.5***	***8.4***	***16.0***	***NA***
ALN	£675,004	£290,229	£125,805	£126,025	£77,059	£65,281	£30,452	£14,820	£5622	Dominates	£31,200
RIS	£829,832	£319,027	£129,889	£100,618	£81,404	£64,979	£32,482	£17,119	£7235	Dominates	£33,840
IBN (oral)	£948,571	£301,165	£119,370	£137,375	£93,736	£68,805	£34,713	£21,840	£9443	Dominates	£38,321
IBN (i.v.)	Dominated	Dominated	Dominated	Dominated	Dominated	£4,373,315	£1,250,818	£564,407	£398,475	£266,492	£1,442,071
ZOL	Dominated	£2,984,339	£808,583	£723,860	£442,296	£353,780	£210,441	£127,491	£93,903	£60,300	£236,247
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
DEN	£1,794,421	£1,092,301	£1,868,896	£632,830	£523,142	£502,655	£462,072	£250,729	£166,441	£126,392	£388,796
TPTD	£8,610,782	£5,871,874	£3,731,997	£3,083,847	£2,356,350	£1,964,475	£1,366,400	£971,695	£671,001	£457,894	£1,419,377
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Which treatment has maximum INMB at £20,000 per QALY	No treatment	No treatment	No treatment	No treatment	No treatment	No treatment	No treatment	ALN	ALN	ALN	No treatment
Which treatment has maximum INMB at £30,000 per QALY	No treatment	No treatment	No treatment	No treatment	No treatment	No treatment	No treatment	ALN	ALN	ALN	No treatment

continued

TABLE 10 The ICERs vs. no treatment and treatment with maximum INMB by risk deciles for QFracture and FRAX (*continued*)

	ICERs by risk decile										
Drug	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**All**
FRAX score (%)	***3.1***	***4.3***	***5.0***	***5.6***	***6.2***	***7.3***	***8.8***	***10.7***	***14.9***	***25.1***	***NA***
ALN	£28,541	£27,325	£16,808	£15,524	£11,362	£8951	£3791	Dominates	Dominates	Dominates	£3659
RIS	£32,429	£27,654	£15,575	£17,389	£11,265	£8736	£4572	Dominates	Dominates	Dominates	£4181
IBN (oral)	£34,519	£27,349	£17,728	£16,459	£12,209	£12,389	£6035	£734	Dominates	Dominates	£5333
IBN (i.v.)	£1,214,068	£853,480	£443,563	£430,771	£342,182	£362,332	£367,423	£215,680	£163,225	£111,944	£299,662
ZOL	£170,998	£145,587	£110,846	£96,012	£82,355	£82,446	£63,432	£51,057	£37,737	£20,257	£68,512
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	£57,050	Dominated	Dominated	Dominated
DEN	£398,751	£250,782	£195,106	£220,601	£184,386	£193,385	£140,582	£95,158	£89,300	£58,730	£145,830
TPTD	£1,254,448	£1,115,769	£832,835	£745,024	£632,511	£622,664	£542,248	£439,478	£343,693	£244,558	£549,324
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Which treatment has maximum INMB at £20,000 per QALY	No treatment	No treatment	RIS	ALN	RIS	ALN	ALN	ALN	ALN	ALN	ALN
Which treatment has maximum INMB at £30,000 per QALY	ALN	ALN	RIS	ALN	RIS	ALN	ALN	ALN	ALN	ALN	ALN

NA, not applicable.

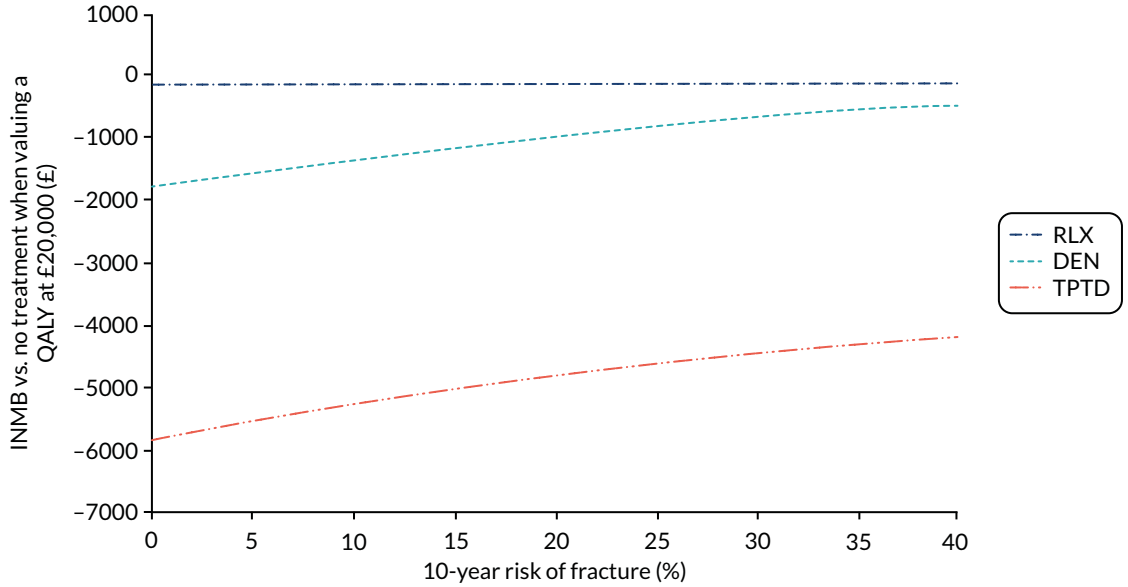

FIGURE 11 The INMB as a function of absolute fracture risk, as determined by QFracture.

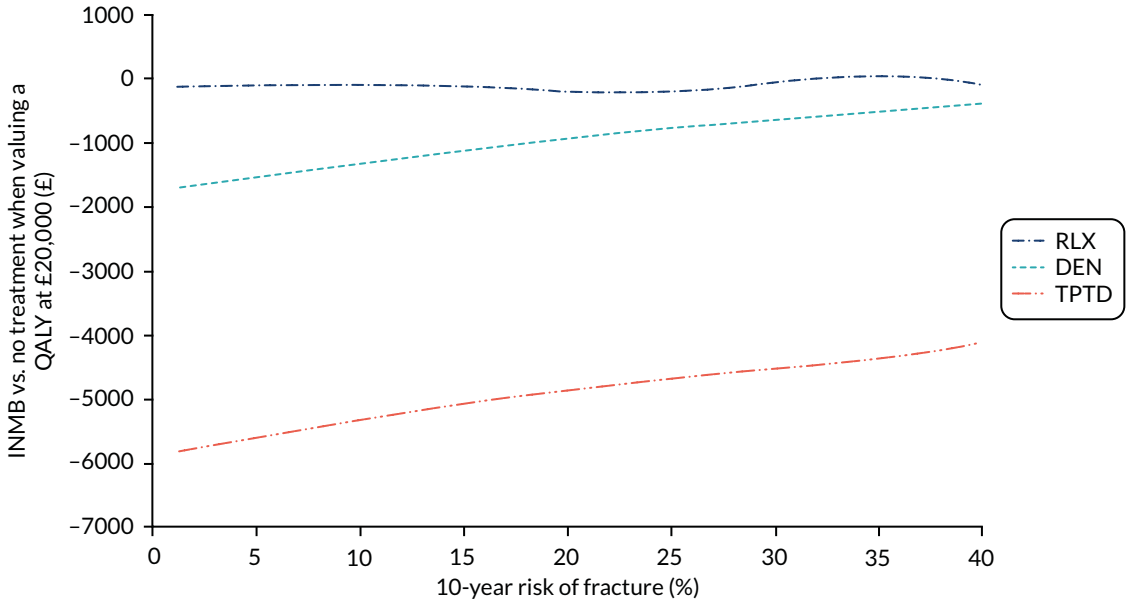

FIGURE 12 The INMB as a function of absolute fracture risk, as determined by FRAX.

The AG also ran the regression of INMB against QFracture and FRAX when assuming that a QALY is valued at £30,000. The predicted INMBs remained under zero across the full range of risk scores observed for RLX, TPTD and ROMO/ALN for both QFracture and FRAX. For DEN, the predicted INMB was above zero, indicating that DEN has an ICER of < £30,000 compared with no treatment for FRAX scores of > 45%; it remained under zero for the full range of QFracture scores. However, the AG notes that the estimates of INMB at these very high levels of risk are uncertain as they are informed by < 0.05% of the simulated population.

A full incremental analysis for each risk category is presented in *Appendix 19* for QFracture and in *Appendix 20* for FRAX. The optimal treatment (i.e. the one with the maximum INMB) when valuing a QALY at either £20,000 or £30,000 is summarised in *Table 10* for easy reference. It can be seen that the optimal treatment when valuing a QALY at £20,000 is no treatment for patients in the lower-risk categories and oral bisphosphonates for patients in the higher-risk categories. When valuing a QALY at

£30,000, oral bisphosphonates have the maximum INMB even in the lowest-risk category when using FRAX to estimate fracture risk (average risk of 3.1%), but no treatment is still the optimal strategy in the lowest-risk category when using QFracture to estimate fracture risk. Using the predicted INMBs from the regression we can say that oral bisphosphonates have maximum INMB from a FRAX score of 4.5% and from a QFracture score of 5.2% when valuing a QALY at £20,000.

The i.v. bisphosphonates never have a higher INMB than the oral bisphosphonates. However, ZOL has a positive INMB compared with no treatment for a fracture risk of 31.1% for Qfracture and of 22.5% for FRAX. Conversely, i.v. IBN is always dominated by i.v. ZOL because of the higher costs associated with quarterly administration and the poorer efficacy estimates.

Raloxifene is dominated by no treatment (higher costs and fewer QALYs gained) across all QFracture risk categories and across all but one FRAX risk category (category 8, with an average risk of 10.7%). This is explained by the few numbers of fracture prevented and the VTE risk associated with RLX.

Teriparatide is consistently dominated by ROMO/ALN across all risk categories for both QFracture and FRAX, despite having similar efficacy estiamtes. This is because the treatment duration and offset period for the ROMO/ALN sequence, which determine how long the efficacy estimates are appied in the model, are based on the combined duration of the treatment sequence but the cost for the ALN part of the sequence is much lower than the cost of TPTD.

Sensitivity analyses results

The results for the structural sensitivity analyses (conducted using mid-point parameter estimates) are presented in *Appendix 21*. In broad terms, the results for non-bisphosphonates were consistent with the base-case analysis in that none of the non-bisphosphonates had an ICER of < £30,000 per QALY when compared with no treatment in any of the QFracture or FRAX risk categories across any of the sensitivity analyses examined.

The exploratory scenario analysis examining a population with fixed patient characteristics, chosen to give a FRAX score of approximately 30%, resulted in an ICER of £13,544 for DEN compared with no treatment (see *Appendix 21*, *Table 74*). The ICER for ZOL compared with no treatment was £11,427, but ZOL was extendedly dominated, leaving ALN, DEN and ROMO/ALN on the cost-effectiveness frontier. ALN remained the optimal treatment when valuing a QALY at £20,000, as DEN compared with ALN had an ICER of £26,977. However, this scenario analysis shows that the results may be more favourable when considering specific high-risk groups, even though the ICER for DEN compared with no treatment in the highest decile of FRAX risk scores, in which the average risk score was 25%, was > £30,000 per QALY. However, the AG believes that this exploratory scenario analysis should be interpreted cautiously, given that it is based on a single example set of patient characteristics and the cost-effectiveness may differ for patients with different characteristics but the same FRAX score. It is also noted that the results for the same patient were qualitatively different when using QFracture to estimate fracture risk, as the risk was much lower (13.3%) than the fracture risk obtained when using FRAX. In this scenario, none of the non-bisphosphonates had an ICER of < £30,000 when compared with no treatment (see *Appendix 21*, *Table 75*) and using QFracture to estimate absolute fracture risk.

Discussion

A key strength of the approach we have taken is that we have been able to adapt the model used in TA464 to allow the cost-effectiveness of non-bisphosphonates to be assessed in a manner consistent with the approach used previously to assess the cost-effectiveness of bisphosphonates. However, although the overall model structure and many of the data inputs have remained unchanged to maintain consistency, there are several differences that should be noted. We have updated the estimates of treatment persistence used for oral bisphosphonates to incorporate a new data source identified in the UCB S.A. company submission.[20] This has increased the duration of treatment persistence for oral bisphosphonates threefold. We have incorporated monitoring costs for bisphosphonates consisting of

annual follow-up appointments to encourage persistence and manage AEs and DXA when completing treatment to assess the need for continued treatment. We have applied the HRs from the NMA for each individual bisphosphonate, as per the original AG report for TA464,[34] rather than the estimates based on the bisphosphonate class effect as presented in the addendum[160] that followed the original assessment report. However, this only affects the incremental cost-effectiveness of non-bisphosphonates relative to bisphosphonates. We have incorporated ONJ, VTE and cellulitis as AEs in the model. The utility values applied following fracture in the revised model are based on an updated systematic review of utility estimates. The costs following fracture have been uplifted to reflect price changes over time, and the drug costs were updated to reflect current prices. For consistency, we have used non-vertebral fracture HRs for wrist fractures for all interventions owing to few data on this outcome for non-bisphosphonates, whereas previously we used wrist fracture-specific outcomes for the bisphosphonates, as the data were less sparse when considering only the bisphosphonate interventions.

Although assessing the cost-effectiveness of non-bisphosphonates was the objective of this analysis, it is noted that the level of fracture risk at which the oral and i.v. bisphosphonates become cost-effective is higher than in the analysis that informed TA464.[34] This is due to the inclusion of monitoring costs, which add an additional £52 per annum to the drug costs, which are around £10 per annum. However, these revised estimates of cost-effectiveness for oral bisphosphonates appear to be reasonably consistent with the intervention thresholds specified in the NICE QS149,[13] which provide age-related intervention thresholds varying from a 10-year absolute risk level of 5.9% in patients aged 40 years to 20% in patients aged $\geq$ 70 years. In addition, it is noted that TA464[9] recommends i.v. bisphosphonates for patients with a fracture risk of $\geq$ 10%, but i.v. IBN and ZOL had ICERs of > £30,000 at this risk level in the revised analysis. Again, this is likely to be as a result of the incorporation of additional costs for monitoring in secondary care and the correction to the administration costs for i.v. IBN.

The models in the UCB S.A.[20] and Amgen Inc.[100] submissions both focused their analysis only on higher-risk subgroups of the population specified in the scope, whereas the AG model provides cost-effectiveness estimates for 10 risk categories covering the whole population eligible for risk assessment under CG146.[8] It is therefore difficult to compare the results directly. However, the AG model provides much higher ICERs than those provided by the analyses described in the UCB S.A.[20] and Amgen Inc.[100] submissions, even for the highest FRAX and QFracture risk categories, although an exploratory scenario analysis examining an example high-risk patient with a FRAX score of approximately 30% resulted in an ICER for DEN compared with no treatment that was < £30,000 per QALY. This finding suggests that the cost-effectiveness estimates for some non-bisphosphonates may be more favourable for specific high-risk patients, although the AG notes that this scenario analysis should be interpreted somewhat cautiously, as cost-effectiveness may differ for patients with a similar FRAX score.

There are several key differences between the AG analysis and the analyses presented in the UCB S.A.[20] and Amgen Inc.[100] submissions that should also be noted when interpreting these differences. The model in the Amgen Inc. submission[100] incorporated a much higher cost of administration for i.v. ZOL than the AG model (£559 vs. £253), which resulted in a more favourable comparison of DEN with ZOL. The model in the Amgen Inc. submission[100] assumed that all DEN treatments would be administered in primary care, whereas the AG model assumed that the first two DEN treatments would be given in secondary care, which substantially increases the administration costs for DEN. The model in the Amgen Inc. submission[100] applied a 1-year offset to all drugs, which is unfavourable compared with what the AG assumed for all drugs except DEN and RLX. The approach taken to model mortality following fracture differed in the models in the Amgen Inc.[100] and UCB S.A.[20] submissions, which allowed for an increased risk of mortality that persisted beyond the 6-month time frame assumed by the AG for excess mortality attributable to fracture. However, it was not possible to assess the impact of the different assumptions on mortality attributable to fracture in the AG model because of the different model structures employed. The model in the UCB S.A. submission[20] applied different efficacy estimates at different time points (different estimates every 6 months, up to 4 years). The AG found that restricting the NMA to studies

reporting vertebral fractures at 12 months did not provide any evidence to suggest different treatment effects when the analysis is limited to specific outcome measurement times. Based on this, the NMA used to inform the AG model incorporated outcomes reported at the longest available time point for each study, and assumed that the fracture event rate is constant over time. UCB S.A. applied the maximum of a time-dependent RR for recent fracture and the RR of having had a prior fracture according to FRAX. In contrast to this, the AG model included HRs that increase the risk of fracture following an incident fracture, which are applied for the remainder of the model. However, in the AG model, the increased risk incoporated in the QFracture and FRAX scores is removed at the time of the incident fracture. It is unclear what effect these different approaches have had on the estimates of future fracture risk following an incident fracture. UCB S.A. applied different persistence assumptions for patients receiving ALN following ROMO than for patients receiving ALN from the start of the model, whereas the AG assumed that a patient's persistence with ALN treatment woud be independent of whether or not they had previously received ROMO.

One of the key limitations of the AG analysis is that we have assumed that all of the treatment strategies modelled are viable options for all patients in the population. This allowed us to run the model once for the whole population eligible for risk assessment and to determine a single absolute risk threshold for cost-effective intervention for each treatment. Applying a strict interpretation of the licensed indications for each treatment would have required running the analysis multiple times for different groups that have different treatment options, which was not feasible. Although incremental analyses are usually conducted over a set of potentially interchangeable treatments, in reality, it is often the case that some of the cohort of patients who are eligible for one treatment would be contraindicated for another, and allowances are made for this when interpreting the cost-effectiveness results. For example, it is possible to rank the treatments in order of decreasing INMB and treat with the next most cost-effective treatment when the optimal treatment is contraindicated.

Similarly, although we have not explicitly conducted separate analyses within and between particular drug classes, it is possible to use the INMB estimates provided to identify the optimal treatment in a particular class. For example, deleting the RLX, TPTD and ROMO/ALN rows from the results tables shown in *Appendices 14* and *15* and examining the INMBs estimates for the remaining interventions would allow the optimal treatment to be identified within the class of anti-resportives (ALN, RIS, IBN, ZOL and DEN). Alternatively, deleting the bisphosphonate rows from the tables would allow the optimal treatment to be identified for patients for whom bisphosphonates are contraindicated.

The AG economic model assumes that the relative treatment effect (i.e. HR) is consistent across all populations included in the scope, despite there being heterogeneity in terms of sex, risk factors (e.g. prior fracture and steroid use) and baseline risk across studies included in the NMA. However, there was no evidence that treatment effect varied with age, sex or baseline risk, based on the meta-regression conducted for the NMA outcomes of fracture and BMD.

We note that there are limited data on the long-term persistence for all treatments, but particularly for the non-bisphosphonates, and the estimates of treatment persistence for TPTD and DEN, in particular, are based on a fairly crude extrapolation of Kaplan–Meier plots for treatment discontinuation. However, the sensitivity analyses in which patients were assumed to persist for the full intended treatment duration did not result in ICERs falling under £30,000 per QALY for any of the non-bisphosphonate treatments.

The economic analysis of ROMO is based on the assumption that it will be used in sequence with 4 years of ALN and that the efficacy observed during the 24 months of the ARCH[83] RCT will continue during the full 4 years of ALN. This results in the treatment effect being extrapolated beyond the trial period in the analysis, assuming full persistence with treatment. However, the overall duration of treatment is < 4 years in the base-case model because of the application of real-world persistence data for ALN; therefore, the need for extrapolation is minimised.

Adverse events have been incorporated in a fairly crude manner by applying an average cost and QALY decrement to every individual treated, based on the average incidence, rather than including the AEs as separate competing events in the model. The benefit of doing this is that it avoids the impact of very rare AEs, such as ONJ, being missed because they do not occur often in the simulated population. The estimates of costs and QALY decrements attributable to AEs were also not included in the PSA, which may mean that the decision uncertainty associted with AEs will be underestimated. However, this is unlikely to be a significant limitation for cellulitis and ONJ, for which the AE event rates were very low and the average costs and QALY decrements per treated patient were small and are therefore unlikely to be significant drivers of cost-effectiveness. However, the average loss of INMB attributable to the AE of VTE for RLX was relatively large in comparison to the cost of treatment (discounted INMB decrement of £53 per patient started on treatment vs. an annual drug cost of £43), meaning that this is likely to be a significant driver of cost-effectiveness for RLX. (Although an explicit scenario analysis has not been conducted, the AG expects that, for the majority of the risk categories, the INMBs would be unlikely to be above zero when removing the impact of VTE, based on the results presented.)

We note that the cost-effectiveness analysis is based on current prices for each intervention and, when there is more than one preparation, we have assumed that the lowest-cost preparation is used, which is often the generic form, when one is available. We also note that prices for the two biosimilar versions of TPTD (Movymia and Terrosa)[22,23] were not available when this report was prepared. It is likely that these biosimilar preparations will have a lower cost; therefore, the estimates of cost-effectiveness for TPTD may be overly pessimistic compared with what may be achieved in practice in future years if there is widespread uptake of these biosimilars and they are made available at a substantially lower cost than TPTD.

The scope[19] of the MTA stated that treatment sequences would be considered if the evidence allowed. The only treatment sequence modelled by the AG is ROMO/ALN, as no other treatment sequences were included in the NMA for fracture outcomes. The AG notes that the UCB S.A. submission[20] also contained cost-effectiveness estimates for the sequence of ALN/ROMO, but it appears that this was based on an assumption of clinical equivalence for ROMO/ALN and ALN/ROMO and assumptions regarding the appropriate offset period. Although there was RCT evidence comparing the sequence of ROMO/DEN with placebo followed by DEN from the FRAME[54] RCT, it was not possible to include this RCT in the NMAs (as neither study arm connected with any other studies included in the networks); therefore, we have not been able to estimate the cost-effectiveness of the ROMO/DEN sequence.

One of the strengths of this analysis is that we have been able to estimate the cost-effectiveness of each intervention across the broad range of absolute fracture risk observed in the population eligible for risk assessment under CG146.[8] However, the downside of the approach we have taken is that the estimates of cost-effectiveness are uncertain in patients at high risk of fracture (e.g. > 30%) as they are informed by fewer simulated patients. We tried to address this by conducting an exploratory sensitivity analysis for an example high-risk patient; however, we note that the cost-effectiveness of other patients with similar FRAX scores may differ and that the regression of INMB across the full range of risk scores observed in the population eligible for fracture risk assessment did not identify a risk at which the ICER fell under £20,000 for any of the non-bisphosphonates.

Chapter 5 Assessment of factors relevant to the NHS and other parties

The only non-bisphosphonate not currently in use in the NHS in England is ROMO. The UCB S.A. submission[20] states that 'there is likely no administration costs or initiation costs associated with romosozumab as the training of injection techniques will be provided as part of the patient support program provided by UCB'. The AG believes that the impact on NHS services of introducing ROMO to the NHS in England is anticipated to be small, as the needs of patients on ROMO are likely to be simlar to those on TPTD, which is already an established treatment.

Chapter 6 Discussion

Statement of principal findings

Fifty-two RCTs of non-bisphosphonates were included in the review. An additional 51 RCTs of bisphosphonates were included for the NMAs.

Across studies reporting overall mortality, there were no significant differences between non-bisphosphonate treatment arms and their comparators of placebo, other non-bisphosphonates or bisphosphonates. The ranges of SAE rates were as follows: DEN, 2–25.8%; RLX, 2–18.6%; ROMO, 3.2–12.9%; and TPTD, 0–33%.

In NMAs for vertebral, non-vertebral and hip fractures, and for femoral neck BMD, all treatments were associated with beneficial effects relative to placebo. For both vertebral fractures and percentage change in femoral neck BMD, the treatment effects were statistically significant at a conventional 5% level for all treatments. TPTD was associated with the greatest effect for vertebral (HR 0.23, 95% CrI 0.16 to 0.32, PB 0.38), non-vertebral (HR 0.58, 95% CrI 0.45 to 0.76, PB 0.52) and hip fractures (HR 0.35, 95% CrI 0.15 to 0.73, PB 0.50), whereas ROMO was the most effective for wrist fractures (HR 0.12, 95% CrI 0.00 to 1.19) and proximal humerus fractures (HR 0.10, 95% CrI 0.00 to 3.66), and ROMO/ALN was the most effective for percentage change in femoral neck BMD (HR 0.10, 95% CrI 0 to 3.66, PB 0.77). In general, the ranking of treatments varied for the different outcomes.

The cost-effectiveness review found that there are no published studies that compare all of the interventions and comparators specified in the scope of this appraisal across the broad population specified in the scope. The models described in the UCB S.A.[20] and Amgen Inc.[100] submissions focused on high-risk poulations and a subset of comparators.

The ICERs are > £20,000 per QALY for all non-bisphosphonate interventions compared with no treatment across the range of QFracture and FRAX scores expected in the population eligible for fracture risk assessment. The ICER for DEN was predicted by the regression analysis to fall below £30,000 at very high levels of risk (FRAX score of > 45%), but the estimates of cost-effectiveness are very uncertain at this level of risk. An exploratory scenario analysis examining an example high-risk patient also suggested that the cost-effectiveness of DEN may be more favourable for high-risk patients with specific characteristics.

The incremental analysis found that the intervention with maximum INMB (when valuing a QALY at either £20,000 or £30,000) was either no treatment or oral bisphosphonates across all 10 risk categories for both QFracture and FRAX scores.

Strengths and limitations of the assessment

Strengths

A comprehensive search for RCTs was undertaken. RCTs were available for all treatments of interest, reporting fracture data and femoral neck BMD data. NMAs were used to synthesise the evidence, permitting a coherent comparison of the efficacy of interventions in terms of fracture and femoral neck BMD. Although studies varied in quality, a sensitivity analysis removing lower-quality studies from the NMA gave results consistent with the main analysis.

A key strength of the approach we have taken in the economic evaluation is that we have been able to adapt the model used in TA464 to allow the cost-effectiveness of non-bisphosphonates to be assessed in a manner consistent with the approach used previously to assess the cost-effectiveness of bisphosphonates.

Limitations

Evidence was restricted to English-language publications. Most RCTs had a primary end point of BMD, which is a surrogate end point, rather than fractures, which are of clinical importance to patients. Studies varied in quality, particularly on the domains of blinding and attrition, and were not all well reported. For wrist and proximal humerus fractures, there was less RCT evidence. Although NMAs were conducted, there is considerable uncertainty in treatment effects for certain interventions in these networks. However, for the economic analysis, we were able to use the non-vertebral fracture NMA outcomes for wrist and proximal humerus fracture, as the evidence in this network was less sparse.

Owing to the limitations of the evidence available, we were able to model only one treatment sequence in the economic analysis. Although we were able to estimate the INMB as a function of absolute risk across the full range of risk scores expected among the population eligible for risk assessment, the estimates of INMB in patients at very high risk of fracture (e.g. > 30%) are uncertain as they are based on a small proportion of the simulated population (< 2% for FRAX and < 0.2% for QFracture).

Uncertainties

Although statistically significant treatment effects were found when comparing interventions with placebo, the effects of non-bisphosphonates were generally similar (with non-statistically significant pairwise HRs). There was evidence of moderate heterogeneity in treatment effects between studies.

Other relevant factors

Any future introduction of biosimilar treatments for TPTD or DEN would be likely to change the cost-effectiveness of these treatments. This assessment report was prepared while ROMO was still being assessed by the European Medicines Agency; therefore, it is based on the anticipated rather than the final licensed indication for ROMO.

Chapter 7 Conclusions

Randomised controlled trials, of varying quality, were available for all non-bisphosphonate treatments of interest, reporting fracture data and femoral neck BMD data. Domains regarding methodological quality were not consistently reported across trials. All treatments were associated with beneficial effects, relative to placebo. For each intervention, reported SAEs varied across trials, with the majority of between-group differences not being statistically significant for comparisons with placebo/no active treatment, head-to-head non-bisphosphonate comparisons or comparisons with bisphosphonates.

The ICERs are > £20,000 per QALY for all non-bisphosphonate interventions compared with no treatment across the range of QFracture and FRAX scores expected in the population eligible for fracture risk assessment. The ICER for DEN was predicted by the regression analysis to fall below £30,000 at very high levels of risk (FRAX score of > 45%), but the estimates of cost-effectiveness are very uncertain at this level of risk. An exploratory scenario analysis examining an example high-risk patient also suggested that the cost-effectiveness of DEN may be more favourable for high-risk patients with specific characteristics.

Implications for service provision

As the majority of the non-bisphosphonate interventions are already part of current practice, and the additional treatment of ROMO is likely to be delivered in a similar manner to TPTD, we do not anticipate any significant implications for service provision associated with these treatments.

Suggested research priorities

Additional head-to-head studies, of good methodological quality, comparing non-bisphosphonates would be beneficial, as few of the RCTs identified in the systematic review were head-to-head comparisons. In particular, it would be useful to know whether or not a treatment sequence of TPTD followed by ALN provides similar efficacy to the ROMO/ALN sequence. RCTs with a primary end point of fractures, rather than BMD, are preferable, as fractures are of clinical relevance to patients.

There were not many trials with a follow-up of > 36 months. The reporting of long-term outcomes from the ARCH[83] and FRAME[54] studies for ROMO, in particular, would be useful, to see if the treatment effectiveness persists during the following years of anti-resportive treatment.

Although there were few data on wrist and humerus fractures for non-bisphosphonates, further research to gather these is unlikely to be useful, as we were able to use the outcomes from the non-vertebral fracture network. Similarly, although there were few RCTs with men or of steroid-induced osteoporosis, these showed similar treatment effect patterns to postmenopausal women, and so further research in these populations is not considered a research priority.

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Data-sharing statement

Data can be obtained from the corresponding author, subject to their being non-confidential.

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Appendix 1 Literature search strategies

Clinical effectiveness

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R), 1946–2018

Searched: 11 July 2018.

#	Searches
1	exp osteoporosis/
2	osteoporo*.tw.
3	bone diseases, metabolic/
4	exp Bone Density/
5	(bone adj3 densit*).tw.
6	exp fractures, bone/
7	fractures, cartilage/
8	fracture*.tw.
9	(bone* adj2 fragil*).tw.
10	bone mineral densit*.tw.
11	bone loss.tw.
12	bmd.tw.
13	or/1-12
14	(alendron* or fosomax or fosavance or 121268-17-5).mp.
15	(ibandron* or boniva or bondronat or bonviva or adronil or 114084-78-5).mp.
16	(risedron* or actonel or atelvia or benet or 105462-24-6).mp.
17	(zoledron* or zometa or zomera or aclasta or reclast or 118072-93-8).mp.
18	or/14-17
19	limit 18 to yr = "2014 -Current"
20	(abaloparatide or eladynos or 247062-33-5).mp.
21	(DEN or prolia or xgeva or 615258-40-7).mp.
22	(RLX or evista or keoxifene or 84449-90-1).mp.
23	(ROMO or evenity or 909395-70-6).mp.
24	(TPTD or forsteo or 52232-67-4 or movymia or terrosa).mp.
25	or/20-24
26	13 and (19 or 25)
27	meta-analysis as topic/
28	(meta analy* or metaanaly*).tw.
29	Meta-Analysis/
30	(systematic adj (review*1 or overview*1)).tw.
31	'Review Literature as Topic'/
32	or/27-31

#	Searches
33	(cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
34	((reference adj list*) or bibliograph* or hand-search* or (relevant adj journals) or (manual adj search*)).ab.
35	((selection adj criteria) or (data adj extraction)).ab.
36	"review"/
37	35 and 36
38	comment/or editorial/or letter/
39	Animals/
40	Humans/
41	39 not (39 and 40)
42	38 or 41
43	32 or 33 or 34 or 37
44	43 not 42
45	26 and 44
46	Randomized controlled trials as Topic/
47	Randomized controlled trial/
48	Random allocation/
49	randomized controlled trial.pt.
50	Double blind method/
51	Single blind method/
52	Clinical trial/
53	exp Clinical Trials as Topic/
54	controlled clinical trial.pt.
55	clinical trial*.pt.
56	multicenter study.pt.
57	or/46-56
58	(clinic* adj25 trial*).ti,ab.
59	((singl* or doubl* or treb* or tripl*) adj (blind* or mask*)).tw.
60	Placebos/
61	Placebo*.tw.
62	(allocated adj2 random).tw.
63	or/58-62
64	57 or 63
65	Case report.tw.
66	Letter/
67	Historical article/
68	65 or 66 or 67
69	exp Animals/
70	Humans/
71	69 not (69 and 70)

#	Searches
72	68 or 71
73	64 not 72
74	26 and 73
75	45 or 74

EMBASE, 1974–2018

Searched: 11 July 2018.

#	Searches
1	exp osteoporosis/
2	osteoporo*.tw.
3	metabolic bone disease/
4	exp bone density/
5	(bone adj3 densit*).tw.
6	exp fracture/
7	cartilage fracture/
8	fracture*.ti,ab.
9	(bone* adj2 fragil*).tw.
10	bone mineral densit*.tw.
11	bone loss.tw.
12	bmd.tw.
13	or/1-12
14	(alendron* or fosomax or fosavance or 121268-17-5).mp.
15	(ibandron* or boniva or bondronat or bonviva or adronil or 114084-78-5).mp.
16	(risedron* or actonel or atelvia or benet or 105462-24-6).mp.
17	(zoledron* or zometa or zomera or aclasta or reclast or 118072-93-8).mp.
18	or/14-17
19	limit 18 to yr = "2014 -Current"
20	(abaloparatide or eladynos or 247062-33-5).mp.
21	(DEN or prolia or xgeva or 615258-40-7).mp.
22	(RLX or evista or keoxifene or 84449-90-1).mp.
23	(ROMO or evenity or 909395-70-6).mp.
24	(TPTD or forsteo or 52232-67-4 or movymia or terrosa).mp.
25	or/20-24
26	13 and (19 or 25)
27	exp Meta Analysis/
28	((meta adj analy*) or metaanalys*).tw.
29	(systematic adj (review*1 or overview*1)).tw.
30	or/27-29
31	cancerlit.ab.

#	Searches
32	cochrane.ab.
33	embase.ab.
34	(psychlit or psyclit).ab.
35	(psychinfo or psycinfo).ab.
36	(cinahl or cinhal).ab.
37	science citation index.ab.
38	bids.ab.
39	or/31-38
40	reference lists.ab.
41	bibliograph*.ab.
42	hand-search*.ab.
43	manual search*.ab.
44	relevant journals.ab.
45	or/40-44
46	data extraction.ab.
47	selection criteria.ab.
48	46 or 47
49	review.pt.
50	48 and 49
51	letter.pt.
52	editorial.pt.
53	animal/
54	human/
55	53 not (53 and 54)
56	or/51-52,55
57	30 or 39 or 45 or 50
58	57 not 56
59	26 and 58
60	Clinical trial/
61	Randomized controlled trial/
62	Randomization/
63	Single blind procedure/
64	Double blind procedure/
65	Crossover procedure/
66	Placebo/
67	Randomi?ed controlled trial*.tw.
68	Rct.tw.
69	Random allocation.tw.
70	Randomly allocated.tw.

#	Searches
71	Allocated randomly.tw.
72	(allocated adj2 random).tw.
73	Single blind*.tw.
74	Double blind*.tw.
75	((treble or triple) adj blind*).tw.
76	Placebo*.tw.
77	Prospective study/
78	or/60-77
79	Case study/
80	Case report.tw.
81	Abstract report/or letter/
82	or/79-81
83	animal/
84	human/
85	83 not (83 and 84)
86	or/79-81,85
87	78 not 86
88	26 and 87
89	59 or 88

Web of Science® Core Collection

Science Citation Index Expanded (1900–2018); Conference Proceedings Citation Index – Science (1990–2018)

Searched: 11 July 2018.

#	Searches
# 1	TOPIC: (osteoporo*)
# 2	TOPIC: ((bone NEAR/3 densit*))
# 3	TOPIC: (fracture*)
# 4	TOPIC: (bone mineral densit*)
# 5	TOPIC: (bone loss)
# 6	TOPIC: (bmd)
# 7	#6 OR #5 OR #4 OR #3 OR #2 OR #1
# 8	TOPIC: ((alendron* or fosomax or fosavance or 121268-17-5))
# 9	TOPIC: ((ibandron* or boniva or bondronat or bonviva or adronil or 114084-78-5))
# 10	TOPIC: ((risedron* or actonel or atelvia or benet or 105462-24-6))
# 11	TOPIC: ((zoledron* or zometa or zomera or aclasta or reclast or 118072-93-8))
# 12	#11 OR #10 OR #9 OR #8
	Timespan = 2014-2018
# 13	TS = ((abaloparatide or eladynos or 247062-33-5))

#	Searches
# 14	TS = ((DEN or prolia or xgeva or 615258-40-7))
# 15	TS = ((RLX or evista or keoxifene or 84449-90-1))
# 16	TS = ((ROMO or evenity or 909395-70-6))
# 17	TS = ((TPTD or forsteo or 52232-67-4 or movymia or terrosa))
# 18	#17 OR #16 OR #15 OR #14 OR #13
# 19	#7 and (#12 or #18)
# 20	TS = ((meta-analysis or meta analy* or metaanaly*)) OR TS = (("review literature" or "literature review")) OR TS = (("systematic review*" or "systematic overview*")) OR TS = ((cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit)) OR TS = (("reference list*" or bibliograph* or hand-search* or "relevant journals" or "manual search*")) OR TS = ((("selection criteria" or "data extraction") and review))
# 21	#20 AND #19
# 22	TS = (("clinic* trial*" or "randomi* controlled trial*")) OR TS = (((singl* or doubl* or treb* or tripl*) and (blind* or mask*))) OR TS = ((placebo*)) OR TS = ((allocat* and random*))
# 23	#22 AND #19

Cochrane Database of Systematic Reviews: Wiley Online Library, 1996–2018; Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Online Library, 1898–2018; Health Technology Assessment Database: Wiley Online Library, 1995–2016; Database of Abstracts of Reviews of Effects (DARE): Wiley Online Library, 1995–2015

Searched: 11 July 2018.

#	Searches
#1	MeSH descriptor: [Osteoporosis] explode all trees
#2	osteoporo*:ti,ab,kw
#3	MeSH descriptor: [Bone Diseases, Metabolic] this term only
#4	MeSH descriptor: [Bone Density] this term only
#5	(bone next/3 densit*):ti,ab,kw
#6	MeSH descriptor: [Fractures, Bone] explode all trees
#7	MeSH descriptor: [Fractures, Cartilage] explode all trees
#8	fracture*:ti,ab
#9	(bone* next/2 fragil*):ti,ab,kw
#10	bone mineral densit*:ti,ab,kw
#11	bone loss:ti,ab,kw
#12	bmd:ti,ab,kw
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14	(alendron* or fosomax or fosavance or 121268-17-5):ti,ab,kw
#15	(ibandron* or boniva or bondronat or bonviva or adronil or 114084-78-5):ti,ab,kw
#16	(risedron* or actonel or atelvia or benet or 105462-24-6):ti,ab,kw
#17	(zoledron* or zometa or zomera or aclasta or reclast or 118072-93-8):ti,ab,kw
#18	(or #14-#17)
#19	#13 and #18 Publication Year from 2014 to 2018
#20	(abaloparatide or eladynos or 247062-33-5):ti,ab,kw

#	Searches
#21	(DEN or prolia or xgeva or 615258-40-7):ti,ab,kw
#22	(RLX or evista or keoxifene or 84449-90-1):ti,ab,kw
#23	(ROMO or evenity or 909395-70-6):ti,ab,kw
#24	(TPTD or forsteo or 52232-67-4 or movymia or terrosa):ti,ab,kw
#25	(or #20-#24)
#26	#19 or #25

World Health Organization International Clinical Trials Registry Platform

Searched: 11 July 2018.

#	Searches
1	(alendron* or fosomax or fosavance or 121268-17-5).mp.
2	(ibandron* or boniva or bondronat or bonviva or adronil or 114084-78-5).mp.
3	(risedron* or actonel or atelvia or benet or 105462-24-6).mp.
4	(zoledron* or zometa or zomera or aclasta or reclast or 118072-93-8).mp.
5	(abaloparatide or eladynos or 247062-33-5).mp.
6	(DEN or prolia or xgeva or 615258-40-7).mp.
7	(RLX or evista or keoxifene or 84449-90-1).mp.
8	(ROMO or evenity or 909395-70-6).mp.
9	(TPTD or forsteo or 52232-67-4 or movymia or terrosa).mp.

Thirty-four systematic reviews were checked for RCTs meeting the inclusion criteria.[214–247]

Cost-effectiveness studies of osteoporosis

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily, and Versions(R), 1946–2018

Searched: 16 July 2018.

#	Searches
1	exp osteoporosis/
2	osteoporo*.tw.
3	bone diseases, metabolic/
4	exp Bone Density/
5	(bone adj3 densit*).tw.
6	exp fractures, bone/
7	fractures, cartilage/
8	fracture*.tw.
9	(bone* adj2 fragil*).tw.
10	bone mineral densit*.tw.
11	bone loss.tw.

#	Searches
12	bmd.tw.
13	or/1-12
14	exp "Costs and Cost Analysis"/
15	Economics/
16	exp Economics, Hospital/
17	exp Economics, Medical/
18	Economics, Nursing/
19	exp models, economic/
20	Economics, Pharmaceutical/
21	exp "Fees and Charges"/
22	exp Budgets/
23	budget*.tw.
24	ec.fs.
25	cost*.ti.
26	(cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab.
27	(economic* or pharmacoeconomic* or pharmaco-economic*).ti.
28	(price* or pricing*).tw.
29	(financial or finance or finances or financed).tw.
30	(fee or fees).tw.
31	(value adj2 (money or monetary)).tw.
32	quality-adjusted life years/
33	(qaly or qalys).af.
34	(quality adjusted life year or quality adjusted life years).af.
35	or/14-34
36	13 and 35
37	limit 36 to yr = "2014 -Current"

EMBASE, 1974–2018

Searched: 16 July 2018.

#	Searches
1	exp osteoporosis/
2	osteoporo*.tw.
3	metabolic bone disease/
4	exp bone density/
5	(bone adj3 densit*).tw.
6	exp fracture/
7	cartilage fracture/
8	fracture*.ti,ab.
9	(bone* adj2 fragil*).tw.

#	Searches
10	bone mineral densit*.tw.
11	bone loss.tw.
12	bmd.tw.
13	or/1-12
14	*economics/
15	(economic adj2 model*).mp.
16	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,hw,kw.
17	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,hw,kw.
18	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,hw,kw.
19	(cost or economic*).ti,hw,kw. and (costs or cost-effectiveness or markov).ab.
20	or/14-19
21	13 and 20
22	limit 21 to yr = "2014 -Current"

Health Technology Assessment Database: Centre for Reviews and Dissemination, 1995–2016; NHS Economic Evaluation Database: Centre for Reviews and Dissemination, 1995–2015; Database of Abstracts of Reviews of Effects: Centre for Reviews and Dissemination, 1995–2015

Searched: 16 July 2018.

#	Searches
1	MeSH DESCRIPTOR Osteoporosis EXPLODE ALL TREES
2	(osteoporo*)
3	MeSH DESCRIPTOR Bone Diseases, Metabolic
4	MeSH DESCRIPTOR Bone Diseases
5	(bone adj3 densit*)
6	MeSH DESCRIPTOR Fractures, Bone EXPLODE ALL TREES
7	MeSH DESCRIPTOR Fractures, Cartilage EXPLODE ALL TREES
8	(fracture*)
9	(bone* adj2 fragil*)
10	(bone mineral densit*)
11	(bone loss)
12	(bmd)
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	(#14) FROM 2014 TO 2018
15	(#15) IN HTA FROM 2014 TO 2018
16	(#15) IN NHSEED FROM 2014 TO 2018
17	(#15) IN DARE FROM 2014 TO 2018

The EuroQol-5 Dimensions and osteoporosis

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily, and Versions(R), 1946–2018

Searched: 19 July 2018.

#	Searches
1	exp osteoporosis/
2	bone diseases, metabolic/
3	osteoporo*.tw.
4	or/1-3
5	(bone adj6 densit*).tw.
6	bone density/
7	bmd.ti,ab.
8	(bone or bones).mp.
9	exp densitometry/
10	tomography, x-ray computed/
11	densit*.tw.
12	10 and 11
13	9 or 12
14	8 and 13
15	5 or 6 or 7 or 14
16	exp fractures, bone/
17	fractures, cartilage/
18	fracture*.ti,ab.
19	or/16-18
20	15 or 19
21	4 and 20
22	(euroqol or euro qol or eq5d or eq 5d).mp.
23	21 and 22
24	limit 23 to yr = "2014 -Current"

EMBASE, 1974–2018

Searched: 19 July 2018.

#	Searches
1	exp osteoporosis/
2	osteoporo*.tw.
3	metabolic bone disease/
4	or/1-3
5	(bone adj6 densit*).tw.
6	bone density/
7	bmd.ti,ab.

#	Searches
8	(bone or bones).mp.
9	exp densitometry/
10	tomography/
11	densit*.tw.
12	10 and 11
13	9 or 12
14	8 and 13
15	5 or 6 or 7 or 14
16	exp fracture/
17	cartilage fracture/
18	fracture*.ti,ab.
19	16 or 17 or 18
20	15 or 19
21	4 and 20
22	(euroqol or euro qol or eq5d or eq 5d).mp.
23	21 and 22
24	limit 23 to yr = "2014 -Current"

Appendix 2 Excluded studies

Thirty-four studies of non-bisphosphonates were excluded.

TABLE 11 Excluded studies

Trial	Reason for exclusion
Bone 2008[188] and extension (Bone 2011)[189]	• Population outside scope • Low BMD not osteoporosis (and mean age < 65 years)
Naylor 2010[186]	• Population outside scope • Low BMD not osteoporosis (and mean age < 65 years)
Dore 2010[248]	• Population outside scope • Low BMD not osteoporosis (and mean age < 65 years)
Cosman 2009[249]	• Comparison outside scope • Stopping study
Smith 2009[250]	• Population outside scope • Cancer treatment
Ellis 2008[251]	• Population outside scope • Cancer treatment
Gnant 2015[252]	• Population outside scope • Cancer treatment
Klotz 2014[253]	• Population outside scope • Cancer
Raje 2018[254]	• Population outside scope • Cancer
Henry 2010[255]	• Population outside scope • Cancer; conference abstract only
Fazeli 2014[256]	• Population outside scope • Anorexia nervosa
RUTH[257]	• Population outside scope • Coronary heart disease
Bonani 2012[258]	• Population outside scope • Post kidney transplant
Haghverdi 2014[259]	• Population outside scope • Chronic kidney disease
Szczepanek 2017[260]	• Population outside scope • Low BMD not osteoporosis • Intestinal failure
Zhu 2017[261]	• Conference abstract only • Insufficient details reported
Thomas 2014[262]	• Conference abstract only • Insufficient details reported
Galesanu 2015[263]	• Conference abstract only • Insufficient details reported
TOWER[264]	• Intervention outside scope • Unlicensed dose of TPTD

continued

TABLE 11 Excluded studies (*continued*)

Trial	Reason for exclusion
Cosman 2008[265]	• Intervention outside scope • Unlicensed dose of TPTD
Body 2002[266]	• Intervention outside scope • Unlicensed dose of TPTD
Finkelstein 2010[267]	• Intervention outside scope • Unlicensed dose of TPTD
Iseri 2017[268]	• Intervention outside scope • Unlicensed dose of ALN
Iwamoto 2008[269]	• Intervention outside scope • Unlicensed dose of ALN
Roux 2014[270]	• Intervention outside scope • Unlicensed dose of RIS
Mok 2014[271]	• Intervention outside scope • Pooled bisphosphonate data; doses not reported
Gonnelli 2006[272]	• Intervention outside scope • Pooled comparator data includes treatments outside scope
CORE (extension of MORE)[273]	• Intervention outside scope • Pooled unlicensed and licensed doses of RLX from MORE study[51]
Majima 2008[274]	• Comparison outside scope • RLX vs. RLX plus alfacalcidol
Seeman 2010[275]	• Outcomes outside scope • No outcomes of interest
SHOTZ[276]	• Outcomes outside scope • No outcomes of interest
Bai 2013[277]	• Outcomes outside scope • No usable outcomes
AVA osteoporosis[278]	• Outcomes outside scope • No outcomes of interest

AVA, Anabolism Versus Antiresorption; CORE, Continuing Outcomes Relevant to Evista; RUTH, Raloxifene Use for The Heart; SHOTZ, Skeletal Histomorphometry in subjects On Teriparatide or Zoledronic acid therapy; TOWER, Teriparatide Once-Weekly Efficacy Research.

Appendix 3 Bisphosphonate studies

Of 48 RCTs (reported in 59 references) included in TA464,[9,34] 38 RCTs (reported in 48 references) were included in the NMAs of fracture and/or femoral neck BMD data in this report.

Three additional bisphosphonate RCTs were identified by the searches in this report (see *Appendix 1*) to update the review of TA464. These were included in the NMAs.

Seven RCTs from TA464 were excluded for not reporting either fracture or femoral neck BMD data. In addition, three RCTs of bisphosphonates from TA464 were excluded for being conducted in a cancer population.

TABLE 12 Included bisphosphonate RCTs from TA464[34]

Trial	Population	Intervention and comparator(s)	Vertebral fracture NMA	Femoral neck BMD NMA
Adami 1995[279]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day		Yes
FIT I (Black 1996)[280]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day	Yes	Yes
FIT II (Cummings 1998)[281]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day	Yes	Yes
Bone 2000[282]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day		Yes
Carfora 1998[135]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day	Yes	
Dursun 2001[131]	Postmenopausal women with osteoporosis	• Calcium • ALN, 10 mg per day + calcium	Yes	Yes
Greenspan 2002[283]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day		Yes
Greenspan 2003[284]	Postmenopausal women aged ≥ 65 years	• Placebo • ALN, 10 mg per day		Yes
Ho 2005[285]	Postmenopausal women with osteoporosis	• Calcium • ALN, 10 mg per day + calcium		Yes
Liberman 1995[134]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day	Yes	Yes
Orwoll 2000[286]	Men with osteoporosis	• Placebo • ALN, 10 mg per day	Yes	Yes
Miller 2004[129]	Men with osteoporosis	• Placebo • ALN, 70 mg per week	Yes	
FOSIT (Pols 1999)[287]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day		Yes

continued

TABLE 12 Included bisphosphonate RCTs from TA464[34] (*continued*)

Trial	Population	Intervention and comparator(s)	Vertebral fracture NMA	Femoral neck BMD NMA
Saag 1998;[288] Adachi 2001[289]	Men and women with glucocorticoid-induced osteoporosis	• Placebo • ALN, 10 mg per day		Yes
BONE (Chesnut 2004);[136] Chesnut 2005[290]	Postmenopausal women with osteoporosis	• Placebo • IBN, 2.5 mg per day • IBN, 20 mg every other day	Yes	Yes
McClung 2009[291]	Postmenopausal women with osteoporosis	• Placebo • IBN, 150 mg per month		Yes
DIVA (Delmas 2006);[292] Eisman 2008[293]	Postmenopausal women with osteoporosis	• IBN, 2.5 mg per day • IBN, 2 mg intravenously, twice per month • IBN, 3 mg intravenously, three times per month		Yes
MOBILE (Miller 2005);[294] Reginster 2006[181]	Postmenopausal women with osteoporosis	• IBN, 2.5 mg • IBN, 50 mg, two doses per month • IBN, 100 mg per month • IBN, 150 mg per month		Yes
Boonen 2009[295]	Men with osteoporosis	• Placebo • RIS, 35 mg per week	Yes	Yes
Cohen 1999[296]	Men and women aged 18–85 years receiving glucocorticoids	• Placebo • RIS, 5 mg per day	Yes	Yes
BMD-MN (Fogelman 2000)[297]	Postmenopausal women with osteoporosis	• Placebo • RIS, 5 mg per day	Yes	Yes
Hooper 2005[132]	Postmenopausal women with osteoporosis	• Placebo • RIS, 5 mg per day	Yes	Yes
VERT-NA (Harris 1999);[298] Ste-Marie (2004)[299]	Postmenopausal women with osteoporosis	• Placebo • RIS, 5 mg per day	Yes	Yes
VERT-MN (Reginster 2000);[300] Sorensen 2003[301]	Postmenopausal women with osteoporosis	• Placebo • RIS, 5 mg per day	Yes	Yes
Leung 2005[302]	Postmenopausal women with osteoporosis	• Placebo • RIS, 5 mg per day		Yes
Reid 2000[303]	Men and women taking glucocorticoids for ≥ 6 months	• Placebo • RIS, 5 mg per day	Yes	Yes
Ringe 2006;[304] Ringe 2009[305]	Men with osteoporosis	• Placebo • RIS, 5 mg per day	Yes	
HORIZON-PFT (Black 2007);[133] Reid 2010[306]	Postmenopausal women with osteoporosis	• Placebo • ZOL, 5 mg per year	Yes	Yes
HORIZON-RFT (Lyles 2007);[307] Adachi 2011[308]	Men and women aged ≥ 50 years within 90 days after surgical repair of a hip fracture	• Placebo • ZOL, 5 mg per year	Yes	Yes

TABLE 12 Included bisphosphonate RCTs from TA464[34] (*continued*)

Trial	Population	Intervention and comparator(s)	Vertebral fracture NMA	Femoral neck BMD NMA
Boonen 2012[309]	Men with osteoporosis	• Placebo • ZOL, 5 mg per year	Yes	Yes
McClung 2009[310]	Postmenopausal women with osteoporosis	• Placebo • ZOL, 5 mg per year		Yes
MOTION (Miller 2008)[311]	Postmenopausal women with osteoporosis	• ALN, 70 mg per week • IBN, 150 mg per month	Yes	Yes
Muscoso 2004[79]	Postmenopausal women with osteoporosis	• RIS, 5 mg per day • ALN, 10 mg per day	Yes	
Sarioglu 2006[312]	Postmenopausal women with osteoporosis	• RIS, 5 mg per day • ALN, 10 mg per day		Yes
FACT (Rosen 2005);[313] Bonnick 2006[314]	Postmenopausal women with osteoporosis	• ALN, 70 mg per week • RIS, 35 mg per week		Yes
FACTS (Reid 2006;[315] Reid 2008[316])	Postmenopausal women with osteoporosis	• ALN, 70 mg per week • RIS, 35 mg per week		Yes
HORIZON (Reid 2009)[317]	Men and women taking glucocorticoids for < 3 months or ≥ 3 months	• ZOL, 5 mg per year • RIS, 5 mg per day	Yes	Yes

BMD-MN, Bone Mineral Density-Multinational; BONE, iBandronate Osteoporosis vertebral fracture trial in North America and Europe; DIVA, Dosing IntraVenous Administration; FACT, Fosamax Actonel Comparison Trial; FACTS, Fosamax Actonel Comparison Trial international study; FIT, Fracture Intervention Trial; FOSIT, FOSamax International Trial; MOBILE, Monthly Oral iBandronate In LadiEs; MOTION, Monthly Oral Therapy with Ibandronate for Osteoporosis iNtervention; PFT, Pivotal Fracture Trial; RFT, Recurrent Fracture Trial; VERT-MN, Vertebral Efficacy with Risedronate Therapy-Multinational; VERT-NA, Vertebral Efficacy with Risedronate Therapy-North American.

TABLE 13 Included bisphosphonate RCTs from updated review (additional to the NICE TA464)

Trial	Population	Intervention and comparators	Included in fracture rate NMA?	Included in femoral neck BMD NMA?
TRIO[137]	Postmenopausal women with osteoporosis	• ALN • IBN • RIS	No	Yes
Tan 2016[138]	Postmenopausal women with osteoporosis	• ALN • ZOL	No	Yes
ZONE[130]	Women and men with osteoporosis	• Placebo • ZOL	Yes	No

TRIO, Tablets, Rings, and Injectables as Options for Women; ZONE, ZOledroNate treatment in Efficacy to osteoporosis.

TABLE 14 Bisphosphonate RCTs excluded from TA464

Trial	Population	Intervention and comparators	Reason for exclusion
Chesnut 1995[318]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day	Outcome outside scope
CORAL (Klotz 2013)[319]	Men with androgen deprivation bone loss in non-metastatic prostate cancer	• Placebo • ALN, 70 mg per week	Population outside scope, cancer
Shilbayeh 2004[320]	Postmenopausal women with osteoporosis	• Placebo • ALN, 10 mg per day	Outcome outside scope
Smith 2004[321]	Men and women with asthma and/or chronic obstructive airways disease	• Placebo • ALN, 10 mg per day	Outcome outside scope
ARIBON (Lester 2008)[322]	Postmenopausal women with breast cancer	• Placebo • IBN, 150 mg per month	Outcome outside scope
Choo 2011[323]	Men with androgen deprivation bone loss in non-metastatic prostate cancer	• Placebo • RIS, 35 mg per week	Population outside scope; cancer
McClung 2001[324]	Postmenopausal women with osteoporosis	• Placebo • RIS, 5 mg per day	Outcome outside scope
Taxel 2010[325]	Men aged > 55 years and within 1 month of receiving an initial injection of androgen deprivation therapy for prostate cancer	• Placebo • RIS, 35 mg per week	Population outside scope; cancer
Atmaca 2006[326]	Postmenopausal women with osteoporosis	• RIS, 5 mg per day • ALN, 10 mg per day	Outcome outside scope
ROSE (Hadji 2010;[327] Hadji 2012[328])	Postmenopausal women with osteoporosis	• ZOL, 5 mg per year • ALN, 70 mg per day	Outcome outside scope

ARIBON, reversal of anastrozole (ARImidex) induced bone loss with oral monthly IBN (BONdronat) treatment during adjuvant therapy for breast cancer; CORAL, Cancer and Osteoporosis Research with Alendronate and Leuprolide; ROSE, Rapid Onset and Sustained Efficacy.

Appendix 4 Trial and population characteristics

TABLE 15 Trial characteristics

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
DEN vs. placebo						
FREEDOM: Cummings 2009;[41] Bone 2017[104]	International, randomised, placebo-controlled trial – 21 centres in USA and Canada	Women between the ages of 60 and 90 years with a lumbar spine or total hip *T*-score of < −2.5 Excluded if they had conditions that influence bone metabolism or had taken oral bisphosphonates for > 3 years	• Placebo, *n* = 3906 • DEN, 60 mg s.c., 3902 • Both every 6 months	All women received daily supplements containing at least 1000 mg of calcium	36 months and OLE to 84 months	New vertebral fracture
ADAMO (NCT00980174): Orwoll 2012[42]	Randomised placebo-controlled Phase III trial; international, multicentre (Belgium, Canada, Denmark, France, Poland, Sweden, the USA)	Men with low BMD, lumbar spine or femoral neck BMD *T*-score of ≤ −2.0 or ≥ −3.5, or previous major osteoporotic fracture and BMD-score of ≤ −1.0 or ≥ −3.5 Excluded if severe, or multiple, vertebral fracture(s), conditions that influence bone metabolism or prior bisphosphonate treatment (≥ 3 months in previous 2 years or ≥ 1 month in prevous year or within 3 months of randomisation	• Placebo for 1 year, then open-label DEN for 1 year, *n* = 121 • DEN: 60 mg of DEN every 6 months for 2 years (1 year blinded, then 1 year open label), *n* = 121	Daily calcium (≥ 1000 mg) and vitamin D (≥ 800 IU)	24 months	Lumbar spine BMD percentage change from baseline at 12 months

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
DIRECT (NCT00680953): Nakamura 2014[43]	Randomised placebo-controlled Phase III trial, multicentre, Japan, OLE	Postmenopausal women and men aged ≥ 50 with osteoporosis; 1–4 vertebral fractures and lumbar spine BMD *T*-score of < −1.7 (YAM in Japan 80%), or total hip BMD *T*-score of < −1.6 Excluded if severe, or two or more moderate, vertebral fractures, conditions that influence bone metabolism, or prior bisphosphonate treatment (≥ 3 years, or with 6 months of randomisation), prior hormonal treatments, calcitonin or TPTD within 6 weeks of enrolment	• Placebo for 2 years followed by open-label DEN for 1 year, *n* = 511 • DEN, 60 mg every 6 months for 2 years followed by open-label DEN for 1 year, *n* = 500	Daily calcium (≥ 600 mg) and vitamin D (≥ 400 IU)	36 months	Incidence of new or worsening vertebral fracture by X-ray at 24 months
Nakamura 2012[44]	Randomised placebo-controlled Phase II trial, multicentre, Japan	Postmenopausal women aged ≤ 80 years, ambulatory, osteoporosis, lumbar spine BMD *T*-score (for Japanese subjects) of ≤ −2.5 or ≥ −4.0 or femoral neck or total hip BMD of ≤ −2.5 or ≥ −3.5 Excluded if any severe or two or more moderate vertebral fracture, hypocalcaemia, prior bisphosphonates or parathyroid hormone within 12 months, or hormonal or calcium treatment within 3 months prior to randomisation	• Placebo, *n* = 55 • DEN, 60 mg every 6 months, *n* = 54 • For 1 year	Daily calcium (≥ 600 mg) and vitamin D (≥ 400 IU)	12 months	Lumbar spine BMD percentage change from baseline at 12 months

continued

TABLE 15 Trial characteristics (*continued*)

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Koh 2016[45] (NCT01457950)	Randomised placebo-controlled Phase III trial, multicentre, Korea, OLE	Postmenopausal women aged 60–90 years, Korean-born, lumbar spine or total hip BMD of < −2.5 or ≥ −4.0 Excluded if conditions that influence bone metabolism, increased risk of ONJ, hypo- or hypercalcaemic, vitamin D deficiency, prior treatment with bone metabolism drugs	• Placebo for 6 months, then open-label DEN for 6 months, *n* = 66 • DEN, 60 mg for 6 months then open-label DEN for 6 months, *n* = 69	Daily calcium (≥ 1000 mg) and vitamin D (≥ 400 IU)	12 months	Lumbar spine BMD percentage change from baseline at 6 months
RLX vs. placebo						
Adami 2008[46]	International, randomised-controlled trial – 32 clinical centres in seven countries (the USA, France, Germany, Spain, Italy, Canada and Australia)	Postmenopausal women aged 50–80 years, BMD *T*-score of < −2.5 at the lumbar spine Exclude if had condition or receiving treatment affecting BMD	• Placebo, *n* = 172 • RLX, 60 mg, *n* = 157 • Both daily • All pre treated for 12 months with TPTD (20 µg s.c. daily) prior to randomisation	All participants received oral supplements of at least 500 mg per day of elemental calcium and 400–800 IU per day of vitamin D	12 months from randomisation	Lumbar spine BMD
Morii 2003;[47] Japan; Clinical Trial Research Group	Randomised placebo-controlled, multicentre; Japan	Postmenopausal (≥ 2 years) women, aged ≤ 80 years, lumbar spine BMD of ≤ −2.5 YAM Excluded if conditions that influence bone metabolism, hormonal therapy, pathologic fractures or lumbar spine BMD unevaluable, bisphosphonates within 6 months	• Placebo, *n* = 100 • RLX, 60 mg daily, *n* = 100	Daily calcium (500 mg) and vitamin D (200 IU)	12 months	Lumbar spine BMD percentage change from baseline at 12 months

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Liu 2004[48]	Randomised placebo-controlled, multicentre; China	Postmenopausal (≥ 2 years) women, aged 50–80 years, lumbar spine or femoral neck BMD *T*-score of ≤ −2.5 Excluded if conditions or treatments that influence bone metabolism	• Placebo, *n* = 102 • RLX, 60 mg daily, *n* = 102	Daily calcium (500 mg) and vitamin D (200 IU)	12 months	Lumbar spine BMD percentage change from baseline at 12 months
Gorai 2012[49]	Randomised controlled trial, open-label, two centres, Japan	Postmenopausal (≥ 2 years) women, lumbar spine BMD of ≤ −2.0 YAM Excluded if conditions or treatments that influence bone metabolism, bisphosphonates within 18 months	• Alfacalcidol, 1 µg per day, *n* = 46 • RLX, 60 mg per day, *n* = 42 • RLX, 60 mg per day plus alfacalcidol, 1 µg per day, *n* = 45	NA	24 months	Lumbar spine BMD percentage change from baseline and bone turnover
Silverman 2008[50] (NCT00205777)	Randomised controlled trial, Phase III, multicentre, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Italy, Lithuania, Mexico, the Netherlands, New Zealand, Norway, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, the USA	Postmenopausal (≥ 2 years) women, aged 55–85 years, lumbar spine or femoral neck BMD *T*-score of ≤ −2.0 or ≥ −4.0, or one or more mild vertebral fracture and lumbar spine or femoral neck BMD *T*-score of ≥ −4.0 Excluded if conditions that influence bone metabolism, history of thrombosis, hormonal or bisphosphonate treatment within 6 months	• Placebo, *n* = 1885 • RLX, 60 mg per day, *n* = 1849	Daily calcium (≤ 1200 mg) and vitamin D (400–800 IU)	36 months	Percentage of new vertebral fractures, as determined by X-ray, at 36 months

continued

TABLE 15 Trial characteristics (*continued*)

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
MORE[51,102]	Randomised controlled trial, multicentre, Canada, Europe, South America, USA	Postmenopausal (≥ 2 years) women, femoral neck or lumbar spine BMD *T*-score of < –2.5; or one or more moderate or severe, or two or more mild or moderate, vertebral fractures Excluded if conditions that influence bone metabolism, history of thrombosis, hormonal therapy 2 months, bisphosphonates with 6 months, pathologic fractures, unevaluable by thoracic/lumbar X-ray	• Placebo, *n* = 2576 • RLX, 60 mg per day, *n* = 2557	Daily calcium (500 mg) and vitamin D (400–600 IU)	36 months	Incident vertebral fractures and BMD
Lufkin 1998[52]	Randomised controlled trial, two centres, USA	Postmenopausal (≥ 5 years) women, aged 45–75 years, ambulatory, lumbar spine or femoral neck BMD ≤ 10th percentile of normal and one or more non-traumatic vertebral fracture Excluded if conditions that influence bone metabolism, history of thrombosis, prior bisphosphonates, hormonal therapy within 6 months	• Control, *n* = 48 • RLX, 60 mg per day, *n* = 48	Daily calcium (750 mg) and vitamin D (800 IU)	12 months	Biochemical markers of bone turnover
Mok 2011[53] (NCT00371956)	Randomised placebo-controlled trial, Phase IV, two sites, China	Postmenopausal (≥ 1 year) women receiving long-term glucocorticoid treatment (prednisone, ≤ 10 mg per day or equivalent) for ≥ 6 months Excluded if history of thrombosis or hypercoagulability, prior bisphosphonates or PTH	• Placebo, *n* = 57 • RLX, 60 mg per day, *n* = 57	Daily calcium (1000 mg) and calcitrol (0.25 µg)	12 months	Lumbar spine and hip BMD percentage change from baseline at 12 months

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
ROMO vs. placebo						
FRAME: Cosman 2016[54]	International, randomised controlled trial – 25 countries across Latin America, Central and Eastern Europe, Western Europe, Australia or New Zealand, Asia Pacific and the USA	Women aged 55–90 years with a *T*-score of −2.5 to −3.5 at the total hip or femoral neck Excluded if had a history of hip or severe vertebral fracture, conditions or treatment affecting BMD, ONJ and low 25-hydroxyvitamin D level	• Placebo, $n = 3591$ • ROMO, 210 mg s.c., $n = 3589$ • Both once monthly for 12 months then DEN 60 mg s.c. every 6 months for 12 months open label (both groups)	• Daily calcium (500–1000 mg) and vitamin D_3 or D_2 (600–800 IU) • For patients with a baseline serum 25-hydroxyvitamin D level of ≤ 40 ng/ml, a loading dose of 50,000–60,000 IU of vitamin D was given	12 months from randomisation then a further 12 months open label following treatment-switching	New vertebral fractures
Ishibashi 2017[55] (NCT01992159)	Randomised placebo-controlled trial, Phase II, multicentre, Japan	Postmenopausal women aged 55–85 years, ambulatory, lumbar spine, femoral neck or total hip BMD *T*-score of ≤ −2.5, lumbar spine BMD of > −4.0, femoral neck or total hip BMD of > −3.5 Excluded if condition or prior treatment influencing bone metabolism, including i.v. bisphosphonates within 5 years, oral bisphosphonates within 6 months or for ≥ 1 months within 1 year, or > 3 years, or prior DEN within 18 months, or PTH within 1 year, history of vertebral or hip fracture	• Placebo, $n = 63$ • ROMO 210 mg per month, $n = 63$ • For 12 months	Daily calcium (≥ 500 mg) and vitamin D (≥ 600 IU)	15 months	Lumbar spine BMD percentagte change from baseline at 12 months
BRIDGE: (NCT02186171)[56]	Randomised placebo-controlled trial, Phase III, multicentre, Europe, Latin America, Japan, North America	Men aged 55–90 years, lumbar spine, total hip or femoral neck BMD *T*-score of ≤ −2.5, or ≤ −1.5 with fragility fracture, evaluable for lumbar spine and hip DXA Excluded if condition or current treatment influencing bone metabolism, hip or femoral neck *T*-score of ≤ −3.5, hip fracture	• Placebo, $n = 82$ • ROMO, 210 mg per month, $n = 163$ • For 12 months	Daily calcium (500–1000 mg) and vitamin D (600–800 IU)	15 months	Lumbar spine BMD percentage change from baseline at 12 months

continued

TABLE 15 Trial characteristics (*continued*)

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
TPTD vs. placebo						
Orwoll 2003[57]	International, randomised, placebo-controlled trial – 37 centres in 11 countries (countries NR)	Men aged 30–85 years with lumbar spine or proximal femur (neck or total hip) BMD at least 2 SD below the average for young, healthy men Secondary causes of metabolic bone disease, were excluded	• Placebo, $n = 147$ • TPTD, 20 µg s.c., $n = 151$ • Both daily	All subjects also received supplemental calcium and vitamin D	The study was stopped after a median duration of 11 months	Lumbar spine BMD percentage change from baseline
Miyauchi 2010[58] (NCT00433160)	Randomised placebo-controlled Phase III trial, multicentre, Japan	Postmenopausal (≥ 5 years) women and men, ambulatory, aged ≥ 55 years, lumbar spine BMD of < 80% YAM for Japanese subjects (approximate *T*-score −2.6) and one or more vertebral fragility fracture; or aged ≥ 65 years approximate lumbar spine BMD *T*-score of −1.7; or aged ≥ 55 years with lumbar spine BMD of < 65% YAM	• Placebo for 12 months then option of open-label TPTD for 12 months, $n = 70$ • TPTD for 12 months then open-label TPTD for 12 months, $n = 137$	Daily calcium (610 mg) and vitamin D (400 IU)	24 months	Lumbar spine BMD percentage change from baseline at 12 months
Miyauchi 2008[59]	Randomised placebo-controlled Phase II trial, multicentre, Japan	Postmenopausal (≥ 5 years) women, ambulatory, aged ≥ 55 years, lumbar spine BMD of < 80% YAM for Japanese subjects (approximate *T*-score of −2.6) and one or more moderate, or two or more mild, vertebral fragility fracture; or aged ≥ 65 years and < 70% YAM; or lumbar spine BMD of < 60% YAM Excluded if conditions that influence bone metabolism, treatment influencing bone metabolism within 24 months of randomisation	• Placebo for 6 months, $n = 38$ • TPTD, 20 µg daily for 6 months, $n = 39$	Daily calcium (610 mg) and vitamin D (400 IU)	6 months	Lumbar spine BMD percentage change from baseline at 24 weeks

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
ACTIVE[95] (NCT01343004)	Randomised placebo-controlled Phase III trial, multicentre, Argentina, Brazil, Czech Republic, Denmark, Estonia, Hong Kong, Lithuania, Poland, Romania, the USA	Postmenopausal women, age 49–86 years, femoral neck or lumbar spine BMD *T*-score of ≤ −2.5 or > −5.0 and two or more mild or one or more moderate vertebral fractures, or other low-trauma fracture within 5 years; or age ≥ 65 years and *T*-score of ≤ −2.0 or > −5.0; or age ≥ 65 years without fracture and *T*-score of ≤ −3.0 or > −5.0 Excluded if severe, or four or more mild/moderate, vertebral fractures, < 2 evaluable lumbar vertebrae, hip BMD unevaluable, conditions that influence bone metabolism, treatment influencing bone metabolism, bisphosphonates (≥ 3 months) within 5 years, DEN within 1 year	• Placebo for 18 months (blinded against abaloparatide), *n* = 821 • TPTD, 20 µg daily for 18 months, open label, *n* = 818	Adequate calcium and vitamin D (25-hydroxyvitamin D concentrations in serum > 37.5 nmol/l)	18 months	Percentage with one or more new vertebral fracture (as determined by X-ray)
Leder 2015[61]	Randomised, parallel-group, multicentre, dose-finding, double-blind, placebo-controlled trial – 30 centres in the USA, Argentina, India and the UK	Postmenopausal women aged 55–85 years with a *T*-score of ≤ −2.5 at the lumbar spine or femoral neck or total hip, or *T*-score of ≤ −2.0 plus low-trauma fracture, or *T*-score of ≤ −2.0 plus risk factor for osteoporosis Treatments and conditions affecting BMD were excluded	• Open label • Placebo, *n* = 45 • TPTD, 20 µg, *n* = 45 • Both daily	All subjects received supplemental calcium (500–1000 mg) and vitamin D (400–800 IU)	6 months plus a further 6-month extension to 12 months	BMD percentage change from baseline and bone turnover markers

continued

TABLE 15 Trial characteristics (*continued*)

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
FPT[62] (NCT00670501)	Randomised placebo-controlled Phase III trial, multicentre, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, Hungary, Israel, Italy, the Netherlands, New Zealand, Norway, Poland, Sweden, the USA	Postmenopausal (≥ 5 years) women, ambulatory, one or more moderate or two or more mild atraumatic vertebral fractures; or fewer than two moderate fractures, *T*-score BMD hip or lumbar spine of ≤ −1 Excluded if conditions that influence bone metabolism, bisphosphonates within 3 months before randomisation or for ≥ 60 days in the 24 months before randomisation, other prior treatment that influenced bone metabolism within 6 months	• Placebo • *n* = 544 • TPTD • 20 µg daily • *N* = 541 • Study halted at median 21 months	Daily calcium 1000 mg and vitamin D 400–1200IU	Trial stopped early. Maximum follow-up 24 months. Median follow-up of 21 months for radiographic outcomes and 19 for other outcomes	Percentage with 1 + new vertebral fracture (X-ray)
Sethi 2008[63] (NCT00500409)	Randomised placebo-controlled, open-label, Phase III trial, multicentre, India	Postmenopausal (≥ 3 years) women, aged 45–75 years, lumbar spine or femoral neck BMD *T*-score of ≤ −2.5 Excluded if conditions that influence bone metabolism, lumbar spine BMD unevaluable, prior treatment that influenced bone metabolism within 6 months, current steroids, anticoagulants or anticonvulsants	• Control, *n* = 41 • TPTD, 20 µg daily, *n* = 41	Daily calcium (1000 mg) and vitamin D	180 days	Lumbar spine BMD percentage change from baseline at 6 months

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Head-to-head non-bisphosphonates						
DATA[64] (NCT00926380); DATA-Switch[65]	Randomised controlled Phase II trial, open-label single centre, the USA	Postmenopausal women, aged ≥ 45 years, lumbar spine, femoral neck or hip *T*-score of ≤ −2.5; or *T*-score of ≤ −2.5 plus risk factor for fracture; or *T*-score of ≤ −1.0 plus fragility fracture Excluded if conditions that influence bone metabolism, history of i.v. bisphosphonates or strontium ranelate; glucocorticoids or oral bisphosphonates within 6 months; hormonal or calcium therapy with 3 months of randomisation	• TPTD, 20 µg daily for 24 months, *n* = 36 • DATA-Switch: TPTD followed by 24 months of DEN • DEN, 60 mg every 6 months for 24 months, *n* = 27 • DATA-Switch: DEN followed by 24 months of TPTD, *n* = 27	Daily calcium (1200 mg) and vitamin D (25-hydroxyvitamin D concentrations in serum > 50 nmol/l)	24 months	Lumbar spine BMD percentage change from baseline at 12 months
EUROFORS[66]	Randomised controlled open-label trial, multicentre, Austria, Belgium, Denmark, France, Germany, Greece, Iceland, Portugal, Spain, the UK	Postmenopausal (≥ 2 years) women, aged ≥ 55 years, lumbar spine or femoral neck or total hip BMD *T*-score of ≤ −2.5, one or more vertebral or non-vertebral fragility fracture within 3 years, ≥ 2 BMD evaluable lumbar vertebrae Excluded if conditions or treatments that influence bone metabolism	• Control 12 months, *n* = 102 • RLX, 60 mg daily, *n* = 100 • TPTD, 20 µg daily, *n* = 305 • All following 12 months of TPTD	Daily calcium (≥ 500 mg) and vitamin D (400–800 IU)	12 months post randomisation (24 months total)	Lumbar spine BMD percentage change from baseline at 24 months

continued

TABLE 15 Trial characteristics (*continued*)

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
STRUCTURE[67] (NCT01796301)	Randomised controlled trial, open-label, Phase III, multicentre, North America, Latin America, Europe	Postmenopausal osteoporosis (≥ 3 years); aged 55–90 years; vertebral fracture or non-vertebral after age 50; lumbar spine, femoral neck or total hip BMD *T*-score of ≤ –2.5; ≥ 3 years of bisphosphonate therapy; evaluable for hip and lumbar spine BMD Excluded if condition, or non-bisphosphonate treatment, influencing bone metabolism	• TPTD, 20 µg per day, *n* = 218 • ROMO, 210 mg per month, *n* = 218 • For 12 months • Following 12 months of ALN	Daily calcium (500–1000 mg) and vitamin D (600–800 IU)	12 months	Hip BMD percentage change from baseline at 12 months
McClung 2014[68]	Phase III, multicentre, international, randomised, placebo-controlled, parallel-group, eight-group study – 28 centres in Argentina, Austria, Belgium, Canada, Denmark, Spain, and the USA	Postmenopausal women aged 55–85 years with a *T*-score of ≤ –2.0 at the lumbar spine, total hip or femoral neck and ≥ –3.5 at each of these sites Treatments and conditions affecting BMD were excluded	• Open-label • ALN, 70 mg weekly, *n* = 51 • TPTD, 20 µg daily, *n* = 55 • Blind • Pooled placebo (mix of administrations), *n* = 52 • ROMO, 210 mg s.c. monthly, *n* = 55	All the participants were required to take at least 1000 mg of elemental calcium and 800 IU of vitamin D daily	12 months	Lumbar spine BMD percentage change from baseline

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
DEN vs. bisphosphonates						
DECIDE[69]	Randomised controlled trial, Phase III, non-inferiority, multicentre, Australia, Europe, North America, South America	Postmenopausal women, ambulatory, lumbar spine or total hip BMD *T*-score of ≤ −2.0, evaluable for hip and lumbar spine BMD Excluded if condition influencing bone metabolism, prior i.v. bisphosphonates, other treatments influencing bone metabolism within 3 months	• DEN, 60 mg every 6 months plus placebo, *n* = 594 • ALN, 70 mg per week plus placebo, *n* = 595	Daily calcium (≥ 500 mg) and vitamin D (400–800 IU)	12 months	Lumbar spine BMD percentage change from baseline at 12 months
STAND: Kendler 2010[70]	Phase III international, multicentre, randomised, double-blind, double-dummy, parallel-group. Countries NR	Women aged ≥ 55 years with a lumbar spine or total hip *T*-score of between −4.0 and −2.0, receiving ALN equivalent to 70 mg per week for at least 6 months Treatments and conditions affecting BMD were excluded	Open-label ALN, 70 mg weekly for 1 month then one of the following: • ALN, 70 mg weekly, *n* = 251 • DEN, 60 mg s.c., every 6 months, *n* = 253 • Both with placebo	Daily calcium (1000 mg) and at least 400 IU of vitamin D	12 months	Total hip BMD percentage change from baseline
DAPS: Kendler 2011[71] and 2012[109]	Multicentre, randomised, open-label, 2-year, crossover – 20 centres in the USA and five centres in Canada	Postmenopausal women with low BMD who had not received prior bisphosphonate or DEN therapy, with *T*-scores of between −4.0 and −2.0 at the lumbar spine, total hip or femoral neck Treatments and conditions affecting BMD were excluded	• ALN, 70 mg weekly, *n* = 124 • DEN, 60 mg s.c., every 6 months, *n* = 126 • Open label	Daily calcium (1000 mg) and vitamin D (≥ 400 IU) supplementation	12 months prior to crossover	Treatment adherence in the first 12 months

continued

TABLE 15 Trial characteristics (*continued*)

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
AMG 162 Bone Loss study: McClung 2006[72]	Randomised, placebo-controlled, dose-ranging study – 29 study centres in the USA	Osteopenic and osteoporotic postmenopausal women ages ≤ 80 years with a *T*-score of −1.8 to −4.0 at the lumbar spine or −1.8 to −3.5 at either the femoral neck or total hip Treatments and conditions affecting BMD were excluded	• Placebo s.c. every 3 months, *n* = 46 • ALN, 70 mg weekly, *n* = 47 (open label) • DEN 60 mg s.c., every 6 months, *n* = 47	Daily calcium (1 g) and vitamin D (400 IU)	12 months	Lumbar spine BMD percentage change from baseline
Recknor 2013[73]	Randomised, open-label, parallel-group study – 74 centres in the USA and Europe	Postmenopausal women aged ≥ 55 years with *T*-score of ≤ −2 or ≥ −4 at the total hip who had either discontinued or had insufficient adherence to bisphosphonates for ≥ 1 month before screening Treatments and conditions affecting BMD were excluded	• IBN, 150 mg every month, *n* = 416 • DEN, 60 mg s.c., every 6 months, *n* = 417	Daily calcium (≥ 500 mg) and vitamin D (≥800 IU)	12 months	Total hip BMD percentage change from baseline
Saag 2018[74]	Phase II, international, randomised, double-blind, double-dummy, active-controlled, non-inferiority study – 79 centres in 16 countries in Europe, Latin America, Asia and the USA	Women and men aged ≥ 18 years who were either continuing or initiating glucocorticoids (≥ 7.5 mg prednisone, or its equivalent, daily). Patients aged < 50 years had to have a history of osteoporosis-related fracture. Continuing patients had to have total hip, femoral neck or lumbar spine *T*-score of ≤ 2.0 or ≤ 1.0 with a history of fracture	• RIS, 5 mg daily, *n* = 397 • DEN, 60 mg s.c., every 6 months, *n* = 398 • Both groups received a placebo	At least 1000 mg of calcium and at least 800 IU of vitamin D daily	12 months	Lumbar spine BMD percentage change from baseline

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Miller 2016[75]	International, multicentre, randomised, double-blind, double-dummy, active-controlled, parallel-group study – 37 study centres in Belgium, Denmark, Poland, Spain, Canada, the USA and Australia	Postmenopausal women aged ≥ 55 years who received oral bisphosphonate therapy for ≥ 2 years with a *T*-score of ≤ 2.5 at the lumbar spine, total hip or femoral neck Treatments and conditions affecting BMD were excluded	• ZOL, 5 mg i.v. annually, $n = 322$ • DEN, 60 mg s.c., every 6 months, $n = 321$ • Both groups received a placebo	≥ 1000 mg of elemental calcium and ≥ 800 IU of vitamin D daily	12 months	Lumbar spine BMD percentage change from baseline
RLX vs. bisphosphonates						
EFFECT (International): Sambrook 2004[76]	Randomised, double-masked, double-dummy, multinational study – 50 centres in 16 countries throughout Europe, South America and Asia-Pacific	Postmenopausal women with low BMD at least 2.0 SD below the young normal mean at either the total hip or lumbar spine Treatments and conditions affecting BMD were excluded	• ALN, 10 mg, $n = 246$ • RLX, 60 mg, $n = 241$ • Both daily	Calcium and vitamin D	12 months	Lumbar spine BMD percentage change from baseline
EFFECT (USA): Luckey 2004[77]	Double-blind, randomised, active-controlled, multicentre study – 52 centres in the USA	Postmenopausal women aged > 40 years with low BMD at least 2.0 SD below the young normal mean at either the total hip or lumbar spine Treatments and conditions affecting BMD were excluded	• ALN, 70 mg weekly, $n = 223$ • RLX, 60 mg daily, $n = 233$ • Both groups received a placebo	500–1000 mg of calcium and 200 IU of vitamin D daily	12 months	Lumbar spine BMD percentage change from baseline
Johnell 2002[78]	Phase III, randomised, double-blind study – 30 centres in Australia, Belgium, Canada, Italy, Mexico, South Africa, Spain and Sweden	Postmenopausal women aged ≥ 75 years, femoral neck BMD ≥ 2.0 SD below peak bone mass for healthy premenopausal women Treatments and conditions affecting BMD were excluded	• Placebo (ALN and RLX), $n = 82$ • ALN, 10 mg and RLX placebo, $n = 83$ • RLX 60 mg and ALN placebo, $n = 82$ • All daily	Daily elemental calcium (500 mg) and vitamin D (400–600 IU)	12 months	Lumbar spine BMD and femoral neck BMD percentage change from baseline

continued

TABLE 15 Trial characteristics (*continued*)

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Muscoso 2004[79]	Randomised trial – centres and countries NR	Women with osteoporosis. No further details of inclusion or exclusion criteria reported	• ALN, 10 mg, $n = 1000$ • RIS, 5 mg, $n = 100$ • RLX, 60 mg, $n = 100$ • All daily	1000 mg of calcium and 800 IU of vitamin D daily	24 months	• NR • Lumbar spine BMD and incidence fractures reported
EVA: Recker 2007[80]	Randomised double-blind study – 13 centres in Canada and the USA (NCT00035971)	Postmenopausal women aged 50–80 years with femoral neck *T*-score of −2.5 to −4.0 and no prevalent vertebral fractures Treatments and conditions affecting BMD were excluded	• ALN, 10 mg, $n = 716$ • RLX, 60 mg, $n = 717$ • Both daily	Calcium (500 mg per day) and vitamin D (400 IU per day)	• 24 months • Assessments also planned at 3 and 5 years, but trial was stopped early	Number of women with one or more new osteoporotic vertebral or non-vertebral fractures
Sanad 2011[81]	Randomised clinical study – single centre, Egypt	Postmenopausal women aged 50–70 years with BMD at lumbar spine or femoral neck of −2.5 SDs below a reference population of young postmenopausal women Treatments and conditions affecting BMD were excluded	• ALN, 10 mg, $n = 44$ • RLX, 60 mg, $n = 46$ • Both daily	1500 mg of calcium carbonate and 400 IU of vitamin D_3	12 months	• NR • Lumbar spine, femoral neck and total hip BMD; bone turnover, and lipid metabolism reported
Michalska 2006[82]	Placebo-controlled, randomised trial – single centre, Austria	Postmenopausal women aged 50–80 years with previous treatment with ALN (10 mg per day) for > 3 years and lumbar spine or femoral neck *T*-score of < −2.5	• Open-label • ALN, 10 mg, $n = 33$ • Blind • Placebo, $n = 33$ • RLX, 60 mg, $n = 33$ • All daily	Calcium (500 mg per day) and vitamin D (800 IU per day)	12 months followed by 12 months open-label extension	Lumbar spine BMD percentage change from baseline

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
ROMO vs. bisphosphonates						
ARCH: Saag 2017[83]	Phase III, multicentre, international, randomised, double-blind trial – 137 centres (NCT01631214)	Postmenopausal women aged 55–90 years with either *T*-score of ≤ −2.5 at the total hip or femoral neck plus one or more moderate/severe or two or more mild vertebral fractures; or *T*-score of ≤ −2.0 with two or more moderate/severe vertebral or proximal femur fractures	• ALN, 70 mg weekly, *n* = 2047 • ROMO, 210 mg s.c. monthly, *n* = 2046 • Both for 12 months then ALN 70 mg weekly open label (both groups) for 12 months	Daily calcium and vitamin D	12 months from randomisation then a further 12 months open label following treatment-switching	Vertebral fractures and clinical fracture (non-vertebral and symptomatic vertebral fracture) at 24 months
TPTD vs. bisphosphonates						
FACT: McClung 2005[84]	Randomised, double-blind, active comparator study – 19 clinical sites globally	Postmenopausal women aged 45–84 years, with lumbar spine or femoral neck *T*-score of between −2.5 and −4.0 Treatments and conditions affecting BMD were excluded	• ALN, 10 mg, *n* = 101 • TPTD, 20 µg s.c., *n* = 102 • Both daily • Both groups received a placebo	Daily supplementation of calcium (1000 mg) and vitamin D (400–800 IU)	18 months	Lumbar spine and hip BMD percentage change from baseline
Saag 2009[85]	Randomised, double-blind, double-dummy, active comparator–controlled –13 countries at 76 centres	Women aged ≥ 21 years who had taken prednisone or its equivalent at a dosage of ≥ 5 mg per day for ≥ 3 months with lumbar spine, femoral neck, or total hip BMD *T*-score of ≤ −2 or of ≤ −1 plus a prevalent fracture	• ALN, 10 mg, *n* = 214 • TPTD, 20 µg s.c., *n* = 214 • Both daily • Both groups received a placebo	Calcium (1000 mg per day) and vitamin D (800 IU per day) were provided	36 months	Lumbar spine BMD percentage change from baseline
Panico 2011[86]	Randomised controlled trial, single centre, Italy	Postmenopausal women, lumbar spine or femoral neck BMD *T*-score of ≤ −2.5, two or more fractures, back pain, prior treatment for osteoporosis Excluded if condition influencing bone metabolism, increased risk of osteosarcoma	• TPTD, 20 µg daily, *n* = 42 • ALN, 70 mg per week, *n* = 39	Daily calcium (1000 mg) and vitamin D (800 IU)	18 months	Percentage change from baseline in biochemical markers of bone turnover

continued

TABLE 15 Trial characteristics (*continued*)

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
EuroGIOPs: Glüer 2013[87]	Phase III, randomised, open-label, active comparator-controlled study – 16 centres in Germany, Greece, Italy and Spain	Men aged ≥ 25 years with a lumbar spine, femoral neck or total hip *T*-score ≤ 1.5 SDs below normal young adult male taking glucocorticoids (≥ 5.0 mg of prednisone, or its equivalent, daily) for ≥ 3 months Treatments and conditions affecting BMD were excluded	• Open label • RIS, 35 mg weekly, *n* = 47 • TPTD, 20 µg s.c. daily, *n* = 45	1000 mg of calcium and 800–1200 IU of vitamin D per day	18 months	Lumbar spine BMD percentage change from baseline, measured by QCT
Anastasilakis 2008[88]	Randomised, open-label trial – Greece	Postmenopausal women with osteoporosis and *T*-score of < −2.5 (site NR) Treatments and conditions affecting BMD were excluded	• Open label • RIS, 35 mg weekly, *n* = 22 • TPTD, 20 µg s.c. daily, *n* = 22	500 mg of elemental calcium and 400 IU of vitamin D daily	12 months	Bone turnover markers
Walker 2013[89]	Randomised, double-blind, placebo-controlled trial – USA	Men aged 30–85 years with low BMD secondary to idiopathic osteoporosis, and lumbar spine, femoral neck or total hip *T*-score of < −2.0 Treatments and conditions affecting BMD were excluded	• RIS, 35 mg weekly, *n* = 10 • TPTD, 20 µg s.c. daily, *n* = 9 • Both groups received a placebo	500 mg of calcium and 400 IU of vitamin D daily	18 months	Lumbar spine BMD percentage change from baseline
VERO: Kendler 2018[99]	Randomised, double-blind, active-controlled, parallel-group trial – 123 centres 14 countries in Europe, South America and the USA	Postmenopausal women aged > 45 years with a lumbar spine, femoral neck or total hip *T*-score of ≥ −1.50 with prevalent vertebral fragility fracture Treatments and conditions affecting BMD were excluded	• RIS, 35 mg weekly, *n* = 683 • TPTD, 20 µg s.c. daily, *n* = 683 • Both groups received a placebo • 680 participants in each group started treatment	Daily supplements of 500–1000 mg of calcium and 400–800 IU of vitamin D_3 or D_2, or 2000 IU per day, if baseline serum 25-hydroxyvitamin D levels were ≤ 40 ng/ml	24 months	New radiographic vertebral fractures

Trial name: first author and year	Trial design	Population eligibility	Intervention and comparators, number randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Hadji 2012[91]	Randomised, parallel, double-blind, double-dummy, active-controlled trial – 72 international study locations (NCT00343252)	Postmenopausal women aged ≥ 45 years with a history of back pain likely to be caused by osteoporotic vertebral fracture, with lumbar spine, femoral neck or total hip *T*-score of ≤ −2; and a minimum of one moderate vertebral fracture Treatments and conditions affecting BMD were excluded	• RIS, 35 mg weekly, *n* = 350 • TPTD, 20 µg s.c. daily, *n* = 360 • Both groups received a placebo	1000 mg per day of calcium and 800 IU per day of vitamin D	18 months	Proportion of patients experiencing ≥ 30% reduction in worst back pain at 6 months
MOVE: Abtahi 2016[101] and Malouf-Sierra 2017[92]	Multinational, multicentre, prospective, randomised, active-controlled study – 17 countries including the USA and Mexico, and countries in Europe	Men and postmenopausal women with low bone mass (*T*-score of < −2.0 s at the total hip, femoral neck or lumbar spine who had sustained a recent unilateral pertrochanteric fracture	• RIS, 35 mg weekly, *n* = 113 • TPTD, 20 µg s.c. daily, *n* = 111 • Both groups received a placebo • Blind until 6 months then open label	Calcium (500–1000 mg per day) and vitamin D (800 IU per day). For patients with a baseline serum 25-hydroxyvitamin D level of ≤ 40 ng/ml, loading dose of 100,000 IU of vitamin D_2 or D_3	• 6 months[101] • 18 months[92]	Lumbar spine BMD percentage change from baseline
Cosman 2011[93]	Partial double-blinded, randomised, multicentre, multinational – centres and countries NR	Women aged 45–89 years with BMD *T*-scores of ≤ −2.5 at the femoral neck, total hip or lumbar spine or a BMD *T*-score of ≤ −2.0 at any site plus one or more documented vertebral or non-vertebral fractures Treatments and conditions affecting BMD were excluded	• ZOL, 5 mg i.v. annually, *n* = 137 • TPTD, 20 µg s.c. daily, *n* = 138 • Only those on TPTD received a placebo	Daily calcium (1000–1200 mg) and vitamin D (400–800 IU)	12 months	Lumbar spine BMD percentage change from baseline

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; NA, not applicable; NR, not reported; OLE, open-label extension; PTH, parathyroid hormone; QCT, quantitative computerised tomography; YAM, Young Adult Mean.

TABLE 16 Population baseline characteristics

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
DEN vs. placebo							
FREEDOM[41,104]	Placebo, *n* = 3906	72.3 (5.2)	100	−2.17 (0.71)	NR	915 (23.4)	0
	DEN, 60 mg s.c. every 6 months, *n* = 3902	72.3 (5.2)	100	−2.15 (0.72)	NR	929 (23.8)	0
ADAMO[42]	Placebo for 1 year, then open-label DEN for 1 year, *n* = 121	65.0 (SD 9.1)	0	−1.9 (0.6)	NR	48 (39.7)	NR
	DEN: 60 mg of DEN every 6 months for 2 years (1 year blinded, then 1 year open label), *n* = 121	64.9 (SD 10.5)	0	−1.9 (0.6)	NR	47 (38.8)	NR
DIRECT: Nakamura 2014[43]	Placebo, *n* = 480	69.0 (7.67)	95.0	−2.29 (0.71)	NR	471 (98.1)	NR
	DEN, 60 mg every 6 months, *n* = 472	69.9 (7.36)	95.1	−2.38 (0.70)	NR	466 (98.7)	NR
Nakamura 2012[44]	Placebo, *n* = 55	64.6 (7.0)	100	Lumbar spine: −3.02 (0.34)	Lumbar spine: 0.652 (0.040)	7 (12.7)	NR
	DEN, 60 mg every 6 months, *n* = 54	65.1 (6.3)	100	Lumbar spine: −3.10 (0.44)	Lumbar spine: 0.642 (0.051)	7 (13.0)	NR
Koh 2016[45] (NCT01457950)	Placebo for 6 months then open-label DEN for 6 months, *n* = 66	66.0 (4.77)	100	−2.4 (0.61)	NR	15 (23)	NR
	DEN, 60 mg for 6 months then open-label DEN for 6 months, *n* = 69	67.0 (4.86)	100	−2.5 (0.56)	NR	21 (30)	NR

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
RLX vs. placebo							
Adami 2008[46]	Placebo, *n* = 172	67.1 (6.5)	100	NR	0.62 (0.10)	NR	0
	RLX, 60 mg daily, *n* = 157	66.7 (6.4)	100	NR	0.64 (0.10)	NR	0
Morii 2003[47]	Placebo, *n* = 97	64.3 (6.5)	100	NR	0.64 (0.05)	26 (26.8)	NR
	RLX, 60 mg per day, *n* = 90	65.2 (6.2)	100	NR	0.66 (0.5)	22 (24.4)	NR
Liu 2004[48]	Placebo, *n* = 102	65.1 (5.4)	100	NR	NR	• Thoracic: 10 (9.8) • Lumbar: 6 (5.9)	0
	RLX, *n* = 102	165.5 (6.5)	100	NR	NR	• Thoracic: 11 (10.8) • Lumbar: 9 (8.8)	0
Gorai 2012[49]	Alfacalcidol, *n* = 46	165.2 (6.5)	100	NR	Lumbar spine: 0.663 (0.082)	NR	NR
	RLX, *n* = 42	164.4 (6.6)	100	NR	Lumbar spine: 0.678 (0.083)	NR	NR
	Alfacalcidol plus RLX, *n* = 45	65.1 (7.6)	100	NR	Lumbar spine: 0.670 (0.067)	NR	NR
Silverman 2008[50] (NCT00205777)	Placebo, *n* = 1885	66.5 (6.8)	100	−1.8 (0.9)	NR	981 (56.4)	NR
	RLX, *n* = 1849	66.4 (6.7)	100	1–1.7 (0.9)	NR	954 (56.3)	NR
MORE[51,102]	Placebo, *n* = 2576	66.6 (7.1)	100	NR	• Reported by subgroup • Mean ranged from 0.565 to 0.719	(36.4)	NR
	RLX, *n* = 2557	66.5 (7.0)	100	NR	• Reported by subgroup • Mean ranged from 0.569 to 0.720	(38.1)	NR

continued

TABLE 16 Population baseline characteristics (*continued*)

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
Lufkin 1998[52]	Control, *n* = 48	68.2 (0.7)	100	NR	LS 0.54 (0.01)	NR	NR
	RLX, *n* = 48	69.9 (0.5)	100	NR	LS 0.52 (0.01)	NR	NR
Mok 2011[53] (NCT00371956)	Placebo, *n* = 57	55.2 (7.6)	100	NR	0.683 (0.126)	2 (4)	5
	RLX, *n* = 57	55.4 (7.8)	100	NR	0.647 (0.117)	4 (7)	11
ROMO vs. placebo							
FRAME: Cosman 2016[54]	• Placebo, *n* = 3591 • Then DEN, 60 mg s.c. every 6 months for 12 months, open label	70.8 (6.9)	100	−2.74 (0.29)	NR	496 (13.8)	0
	• ROMO, 210 mg per month, *n* = 3589 • Then DEN, 60 mg s.c. every 6 months for 12 months, open label	70.9 (7.0)	100	−2.76 (0.28)	NR	506 (14.1)	0
Ishibashi 2017[55] (NCT01992159)	Placebo, *n* = 63	67.8 (7.2)	100	−2.31 (0.47)	NR	0	NR
	RLX, *n* = 63	68.3 (5.9)	100	−2.32 (0.59)	NR	0	NR
BRIDGE[56] (NCT02186171)	Placebo, *n* = 82	71.5 (6.9)	0	−2.3 (0.52)	NR	46 (56.1)	• Bisphosphonates 5 (6.1) • PTH 0 • DEN 3 (3.7)
	ROMO, *n* = 163	72.4 (7.4)	0	−2.34 (0.52)	NR	86 (52.8)	• Bisphosphonates 1 (0.6) • PTH 1 (0.6) • DEN 3 (1.8)

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
TPTD vs. placebo							
Orwoll 2003[57]	Placebo, *n* = 147	59 (13)	0	−2.7 (0.8)	Lumber spine BMD: 0.85 (0.14)	NR	8.16
	TPTD, 20 µg s.c. daily, *n* = 151	59 (13)	0	−2.6 (0.8)	0.89 (0.15)	NR	7.95
Miyauchi 2010[58]	Placebo for 12 months and then option of open-label TPTD for 12 months, *n* = 67	70.4 (5.4)	92.5	NR	Lumbar spine: 0.638 (0.079)	29 (43.3)	34.3
	TPTD for 12 months and then open-label TPTD for 12 months, *n* = 136	69.2 (6.3)	93.4	NR	Lumbar spine: 0.639 (0.069)	54 (39.7)	36.8
Miyauchi 2008[59]	Placebo, *n* = 38	69.9 (3.6)	100	NR	0.5068 (0.0802)	17 (44.7)	21.1
	TPTD, 20 µg daily, *n* = 39	71.5 (5.1)	100	NR	0.5168 (0.0927) (*n* = 38)	16 (41.0)	25.6
ACTIVE[95] (NCT01343004)	Placebo, *n* = 821	68.7 (6.5)	100	−2.2 (0.7)	0.732 (0.099)	514 (62.6)	NR
	TPTD, 20 µg daily, *n* = 818	68.8 (6.6)	100	−2.1 (0.7)	0.737 (0.096)	510 (62.3)	NR
Leder 2015[61]	Placebo, *n* = 45	65.0 (7.1)	100	−2.26 (0.72)	0.65 (0.11)	NR	0
	TPTD, 20 µg daily, *n* = 45	64.5 (7.5)	100	−2.09 (0.75)	0.66 (0.11)	NR	0
FPT[62] (NCT00670501)	Placebo, *n* = 448	69 (7)	100	NR	Lumbar spine: 0.82 (0.17)	448 (100)	15
	TPTD, 20 µg daily, *n* = 444	69 (7)	100	NR	Lumbar spine: 0.82 (0.17)	444 (100)	16
Sethi 2008[63] (NCT00500409)	Control, *n* = 41	63.0 (6.3)	100	−2.34 (0.73)	0.62 (0.09)	NR	NR
	TPTD, 20 µg daily, *n* = 41	61.0 (6.3)	100	−2.49 (0.55)	0.62 (0.08)	NR	NR

continued

TABLE 16 Population baseline characteristics (*continued*)

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
Head-to-head non-bisphosphonates							
DATA[64]	TPTD, 20 µg daily, *n* = 36	65.5 (7.9)	100	−1.9 (0.5)	0.643 (0.061)	16 (52)	Bisphosphonates: 42
	DEN, 60 mg every 6 months, *n* = 34	66.3 (8.3)	100	−1.9 (0.8)	0.641 (0.086)	12 (36)	Bisphosphonates: 36
EUROFORS[66]	• Control for 12 months, *n* = 102 • Following 12 months of TPTD	69.1 (8.6)	100	Lumbar spine: −3.1 (0.89)	Lumbar spine: 0.75 (0.11)	102 (100)	Antiresorptive: 62.7
	• RLX 12 months, *n* = 97 • Following 12 months of TPTD	69.4 (7.0)	100	Lumbar spine: −3.2 (0.85)	Lumbar spine: 0.75 (0.12)	97 (100)	Antiresorptive: 64.9
	• TPTD for 12 months, *n* = 304 • Following 12 months of TPTD	69.2 (7.2)	100	Lumbar spine: −3.2 (0.87)	Lumbar spine: 0.74 (0.11)	304 (100)	Antiresorptive: 72.4
STRUCTURE[67]	TPTD, *n* = 218	71.2 (7.7)	100	−2.43 (0.66)	NR	(99.5)	Bisphosphonates: 100
	ROMO, *n* = 218	71.8 (7.4)	100	−2.49 (0.67)	NR	(100)	Bisphosphonates: 100
McClung 2014[68]	Pooled placebo (mix of administrations), *n* = 52	67.0 (6.5)	100	−1.76 (0.56)	NR	NR	0
	Open-label ALN, 70 mg weekly, *n* = 51	67.1 (5.8)	100	−1.91 (0.61)	NR	NR	0
	TPTD, 20 µg daily, *n* = 54	66.8 (5.7)	100	−1.79 (0.67)	NR	NR	0
	ROMO 210 mg s.c. monthly, 55	66.3 (6.5)	100	−1.87 (0.58)	NR	NR	0

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
DEN vs. bisphosphonates							
DECIDE[69]	DEN plus placebo, $n = 594$	64.1 (8.6)	100	Lumbar spine: −2.57 (0.75)	NR	(40)	• Any: 23 • Bisphosphonates: 13
	ALN plus placebo, $n = 595$	64.6 (8.3)	100	Lumbar spine: −2.57 (0.75)	NR	(41)	• Any: 24 • Bisphosphonates: 11
STAND: Kendler 2010[70]	ALN, 70 mg per week plus placebo, $n = 251$	68.2 (7.7)	100	Lumbar spine *T*-score: −2.62 (0.79)	NR	NR	0
	DEN, 60 mg s.c., every 6 months plus placebo, $n = 253$	66.9 (7.8)	100	−2.64 (0.75)	NR	NR	0
DAPS: Kendler 2011[71] and 2012[109]	ALN, 70 mg per week, $n = 124$	65.3 (7.7)	100	−2.03 (0.62)	NR	NR	0
	DEN, 60 mg s.c., every 6 months, $n = 126$	65.1 (7.6)	100	−2.01 (0.55)	NR	NR	0
AMG 162 Bone Loss study[72]	Placebo, s.c. every 3 months, $n = 46$	63.7 (9.1)	100	−1.9 (0.6)	NR	0	0
	ALN, 70 mg per week, $n = 47$ (open label)	62.8 (8.2)	100	−1.9 (0.7)	NR	0	0
	DEN, 60 mg s.c., every 6 months, $n = 47$	63.1 (8.1)	100	−1.9 (0.7)	NR	0	0
Recknor 2013[73]	IBN, 150 mg every month, $n = 416$	66.2 (7.8)	100	−2.1 (0.7)	NR	NR	Prior bisphosphonate: 374 (89.9)
	DEN, 60 mg s.c., every 6 months, $n = 417$	67.2 (8.1)	100	−2.1 (0.7)	NR	NR	Prior bisphosphonate: 377 (90.4)

continued

TABLE 16 Population baseline characteristics (*continued*)

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
Saag 2018[74]	RIS, 5 mg daily plus placebo, *n* = 39	• Continuing GCC: RIS, 61.3 (11.1) • Initiating GCC: 64.4 (10.0)	• Continuing GCC, 73% • Initiating GCC, 64%	Lumbar spine *T*-score: • Continuing GCC, −2.0 (1.4) • Initiating GCC, −1.1 (1.6)	NR	• Continuing GCC, 80/252 (32) • Initiating GCC, 26/145 (18)	0
	DEN, 60 mg s.c., every 6 months plus placebo, *n* = 398	• Continuing GCC, 61.5 (11.6) • Initiating GCC, 67.5 (10.1)	• Continuing GCC, 73% • Initiating GCC, 64%	Lumbar spine *T*-score: • Continuing GCC, DEN −1.9 (1.4) • Initiating GCC, −0.9 (1.9)	NR	• Continuing GCC, 67/253 (26) • Initiating GCC, 21/145 (14)	0
Miller 2016[75]	ZOL, 5 mg i.v. annually plus placebo, *n* = 322	69.5 (7.7)	100	Lumbar spine *T*-score: −2.64 (0.86)	NR	159 (49.4)	Prior oral bisphosphonates (years), mean (SD): 6.4 (3.7)
	DEN, 60 mg s.c., every 6 months plus placebo, *n* = 321	68.5 (7.1)	100	−2.74 (0.83)	NR	169 (52.6)	Prior oral bisphosphonates, (years), mean (SD): 6.2 (3.8)
RLX vs. bisphosphonates							
EFFECT: Sambrook 2004[76]	ALN, 10 mg plus placebo, *n* = 246	61.5 (8.2)	100	Lumbar spine *T*-score: −2.89 (0.78)	NR	NR	0
	RLX, 60 mg daily plus placebo, *n* = 241	61.8 (7.7)	100	Lumbar spine *T*-score: −2.86 (0.76)	NR	NR	0
EFFECT: Luckey 2004[77]	ALN, 70 mg weekly plus placebo, *n* = 223	63.8 (9.9)	100	Lumbar spine *T*-score: −2.43 (0.78)	NR	NR	0
	RLX, 60 mg daily plus placebo, *n* = 233	64.7 (9.8)	100	Lumbar spine *T*-score: −2.5 (0.69)	NR	NR	0

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
Johnell 2002[78]	Placebo (ALN and RLX), *n* = 82	63.8 (5.3)	100	NR	0.62 (0.09)	NR	0
	ALN, 10 mg daily, and RLX placebo, *n* = 83	63.7 (6.0)	100	NR	0.62 (0.08)	NR	0
	RLX, 60 mg daily, and ALN placebo, *n* = 82	63.4 (6.3)	100	NR	0.62 (0.07)	NR	0
Muscoso 2004[79]	ALN, 10 mg daily, *n* = 1000	71 (8)	100	NR	NR	NR	NR
	RIS, 5 mg daily, *n* = 100	66 (9)	100	NR	NR	NR	NR
	RLX, 60 mg daily, *n* = 100	64 (3)	100	NR	NR	NR	NR
EVA: Recker 2007[80]	ALN, 10 mg daily, *n* = 716	65.7 (7.8)	100	−2.39 (0.56)	0.61 (0.09)	0	0
	RLX, 60 mg daily, *n* = 717	65.5 (7.7)	100	−2.39 (0.54)	0.61 (0.09)	0	0
Sanad 2011[81]	ALN, 10 mg daily, *n* = 31	61.7 (4.3	100	NR	0.63 (0.03)	NR	0
	RLX, 60 mg daily, *n* = 35	62.5 (3.9)	100	NR	0.63 (0.05);	NR	0
Michalska 2006[82]	Blind placebo, *n* = 33	64.5 (6.3)	100	NR	0.616 (0.075)	Non-vertebral, 18/33 (54.5)	100 (≥ 3 years ALN)
	Open-label ALN, 10 mg daily, *n* = 33	65.4 (6.8)	100	NR	0.609 (0.063)	9/33 (27.3)	100 (≥ 3 years ALN)
	RLX, 60 mg daily, *n* = 33	65.6 (7.1)	100	NR	0.633 (0.087)	16/33 (48.5)	100 (≥ 3 years ALN)
ROMO vs. bisphosphonates							
ARCH: Saag 2017[83]	ALN, 70 mg weekly (*n* = 2047) for 12 months then ALN 70 mg weekly open label, for 12 months	74.2 (7.5)	100	−2.90 (0.50)	NR	1964/2047 (95.9)	0
	ROMO, 210 mg s.c. monthly (*n* = 2046) for 12 months then ALN, 70 mg weekly open label, for 12 months	74.4 (7.5)	100	1–2.89 (0.49)	NR	1969/2046 (96.2)	0

continued

TABLE 16 Population baseline characteristics (*continued*)

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
TPTD vs. bisphosphonates							
FACT: McClung 2005[84]	ALN, 10 mg daily plus placebo, *n* = 101	66.6 (8.5)	100	−2.3 (0.8)	NR	NR	0
	TPTD, 20 µg s.c. daily plus placebo, *n* = 102	65.3 (8.4)	100	−2.3 (0.6)	NR	NR	0
Saag 2009[85] and 2007[103]	ALN, 10 mg daily plus placebo, *n* = 214	57.3 (14.0)	100	−2.1 (0.10)	0.721 (0.013)	X-ray confirmed, 53/214 (25)	0
	TPTD, 20 µg s.c. daily plus placebo, *n* = 214	56.1 (13.4)	100	−2.2 (0.10)	0.705 (0.013)	X-ray confirmed, 63/214 (30)	0
Panico 2011[86]	TPTD, *n* = 42	65 (9.0)	100	−3.07 (0.60)	NR	42 (100)	100
	ALN, *n* = 39	60 (14.4)	100	−3.02 (0.61)	NR	38 (97)	97
EuroGIOPs: Glüer 2013[87]	Open-label RIS, 35 mg weekly, *n* = 47	55.1 (15.5)	0	−1.82 (0.91)	NR	17/47 (36.2)	0
	TPTD, 20 µg s.c. daily, *n* = 45	57.5 (12.8)	0	−1.95 (0.78)	NR	19/45 (42.2)	0
Anastasilakis 2008[88]	Open-label RIS, 35 mg weekly, *n* = 22	64.7 (7.0)	100	NR	Lumbar spine BMD: 0.757 (0.08)	NR	0
	TPTD, 20 µg s.c. daily, *n* = 22	65.4 (7.5)	100	NR	Lumbar spine BMD: 0.764 (0.11)	NR	0
Walker 2013[89]	RIS, 35 mg weekly plus placebo, *n* = 10	54.0 (6.3)	100	−2.1 (0.63)	0.669 (0.09)	0	Bisphosphonates: 20
	TPTD, 20 µg s.c. daily plus placebo, *n* = 9	51.6 (11.7)	100	−2.0 (0.9)	0.659 (0.12)	33	Bisphosphonates: 33
VERO: Kendler 2018[99]	RIS, 35 mg weekly plus placebo, *n* = 680	71.6 (8.58)	100	−2.24 (0.74)	0.67 (0.11)	(100)	71
	TPTD, 20 µg s.c. daily plus placebo, *n* = 680	72.6 (8.77)	100	−2.27 (0.76)	0.66 (0.11)	(100)	73

Trial name: first author and year	Treatment arms (*n*)	Age (years), mean (SD)	Sex (% female)	*T*-score femoral neck (or lumbar spine if femoral neck not reported), mean (SD)	BMD at femoral neck (or lumbar spine if femoral neck not reported) (g/cm2), mean (SD)	Fractures (at baseline), *n* (%)	Prior treatment for osteoporosis (%)
Hadji 2012[91]	RIS, 35 mg weekly plus placebo, *n* = 350	71.6 (8.1)	100	−2.44 (0.67)	NR	90% confirmed by X-ray (all back pain likely to be due to vertebral fracture)	73.7
	TPTD, 20 µg s.c. daily plus placebo, *n* = 360	70.5 (8.8)	100	−2.32 (0.75)	NR	89.7% confirmed by X-ray (all back pain likely to be due to vertebral fracture)	74.2
MOVE: Abtahi 2016[101] and Malouf-Sierra 2017[92]	RIS, 35 mg weekly plus placebo, *n* = 85	76.4 (7.5)	77.6	−2.63 (0.657)	0.602 (0.116)	(100)	12.9
	TPTD, 20 µg s.c. daily plus placebo, *n* = 86	77.2 (8.0)	76.7	−2.63 (0.519)	0.603 (0.098)	(100)	14.0
Cosman 2011[93]	ZOL, 5 mg i.v. annually, *n* = 137	66.1 (9.0)	100	Lumbar spine *T*-score: −2.88 (0.883)	NR	21 (15.3)	0
	TPTD, 20 µg s.c. daily plus placebo, *n* = 138	63.8 (9.1)	100	Lumbar spine *T*-score: −2.87 (0.807)	NR	22 (15.9)	0

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; GCC, glucocorticoid; NR, not reported; PTH, parathyroid hormone.

Appendix 5 Clinical effectiveness results

TABLE 17 Vertebral fracture data reported by the included studies

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
DEN vs. placebo						
FREEDOM: Cummings 2009;[41] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: increase of at least Genant *et al.*[35] grade 1, ≥ 20% reduction in anterior, middle and/or posterior height and a reduction in area of 10–20%	• Placebo, 3906 • DEN, 3902	• Placebo, 3691 • DEN, 3702	36	• Placebo, 264/3691 (7.15) • DEN, 86/3702 (2.32) • (RD to 4.8, 95% CI 3.9 to 5.8; RR 0.32, 95% CI 0.26 to 0.41; $p < 0.001$)
FREEDOM: Cummings 2009;[41] postmenopausal women with osteoporosis	Efficacy	Clinical	• Placebo, 3906 • DEN, 3902	• Placebo, 3906 • DEN, 3902	36	• Placebo, 92/3906 (2.36) • DEN, 29/3902 (0.74) • (RD to 1.7, 95% CI 1.1 to 2.3; RR 0.31, 95% CI 0.20 to 0.47; $p < 0.001$)
FREEDOM: Cummings 2009;[41] postmenopausal women with osteoporosis	Efficacy	Morphometric, multiple (> 2)	• Placebo, 3906 • DEN, 3902	• Placebo, 3691 • DEN, 3702	36	• Placebo, 59/3691 (1.60) • DEN, 23/3702 (0.62) • (RD to 1.0, 95% CI 0.5 to 1.5; RR 0.39, 95% CI 0.24 to 0.63; $p < 0.001$)
FREEDOM: Bone 2017[104] postmenopausal women with osteoporosis	Efficacy	Morphometric, new	• Placebo, 3906 • DEN, 3902	• Placebo, 3691 • DEN, 3702	0–12	• Placebo, 82/3691 (2.22) • DEN, 32/3702 (0.86) • Estimated (from graph) RR 0.39, 95% CI 0.26 to 0.58; $p < 0.00001$
FREEDOM: Bone 2017[104] postmenopausal women with osteoporosis	Efficacy	Morphometric, new	As above	• Placebo, 3691 • DEN, 3702	12–24	• Placebo, 116/3691 (3.14) • DEN, 26/3702 (0.70) • Estimated (from graph), RR 0.22, 95% CI 0.15 to 0.34; $p < 0.00001$
FREEDOM: Bone 2017[104] postmenopausal women with osteoporosis	Efficacy	Morphometric, new	As above	• Placebo, 3691 • DEN, 3702	24–36	• Placebo, 114/3691 (3.09) • DEN, 40/3702 (1.08) • Estimated (from graph), RR 0.35, 95% CI 0.24 to 0.50; $p < 0.00001$

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
FREEDOM Bone 2017[105] OLE; postmenopausal women with osteoporosis	Efficacy	Morphometric, new	• Entered OLE • Placebo to DEN, 2207 • DEN to DEN, 2343	• Placebo/DEN, 1991 • DEN/DEN, 2116	84 from OLE	• Placebo/DEN, 145/1991 (7.30) • DEN/DEN, 149/2116 (7.04) • Estimated RR 0.97, 95% CI 0.78 to 1.21; $p = 0.76$
ADAMO: Orwoll 2012;[42] men with osteoporosis	Safety	Clinical	• Placebo, 121 • DEN, 121	• Safety Ns • Placebo, 120 • DEN, 120	12	• Placebo, 1/120 (0.83) • DEN, 0/120 (0) • Estimated RR 0.33, 95% CI 0.01 to 8.10; $p = 0.50$
DIRECT: Nakamura 2014;[43] women and men with osteoporosis	Efficacy	• Morphometric, new • Definition: increase of at least Genant *et al.*[35] grade 1, $\geq$ 20% reduction in anterior, posterior, or central vertebra height	• Placebo, 511 • DEN, 500	• Placebo, 480 • DEN, 472	24	• Placebo, 41/480 (8.60) • DEN, 10/472 (2.20) • (HR 0.260, 95% CI 0.129 to 0.521; $p < 0.0001$)
DIRECT: Nakamura 2014;[43] women and men with osteoporosis	Efficacy	Morphometric, new or worsening	As above	• Placebo, 480 • DEN, 472	24	• Placebo, 49/480 (10.30) • DEN, 17/472 (3.60) • (HR 0.343, 95% CI 0.194 to 0.606; $p = 0.0001$)
DIRECT: Sugimoto 2015;[106] women and men with osteoporosis	Efficacy	Morphometric, new	• Placebo to DEN, 406 • DEN to DEN, 404 • 12 months open label	• Placebo/DEN, 406 • DEN/DEN, 404	36 including 12 OLE	• Placebo/DEN, 42/406 (10.30) • DEN/DEN, 10/404 (2.50) • Estimated RR 0.24, 95% CI 0.12 to 0.47; $p < 0.0001$
DIRECT: Sugimoto 2015;[106] women and men with osteoporosis	Efficacy	Morphometric, new or worsening	As above	• Placebo/DEN, 406 • DEN/DEN, 404	36 including 12 OLE	• Placebo/DEN, 48/406 (11.80) • DEN/DEN, 15/404 (3.71) • Estimated RR 0.31, 95% CI 0.18 to 0.55; $p < 0.0001$
DIRECT: Sugimoto 2015;[106] women and men with osteoporosis	Efficacy	Morphometric, new	As above	• Placebo/DEN, 406 • DEN/DEN, 404	12 OLE	• Placebo/DEN, 8/406 (2.00) • DEN/DEN, 1/404 (0.25) • Estimated RR 0.13, 95% CI 0.02 to 1.00; $p = 0.05$

continued

TABLE 17 Vertebral fracture data reported by the included studies (*continued*)

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
DIRECT: Sugimoto 2015;[106] women and men with osteoporosis	Efficacy	Morphometric, new or worsening	As above	• Placebo/DEN, 406 • DEN/DEN, 404	12 OLE	• Placebo/DEN, 2/406 (0.50) • DEN/DEN, 1/404 (0.25) • Estimated RR 0.50, 95% CI 0.05 to 5.52; $p = 0.57$
Nakamura 2012;[44] postmenopausal women with osteoporosis	Efficacy	Morphometric, new or worsening	• Placebo, 55 • DEN, 54	• Placebo, 55 • DEN, 54	12	• Placebo, 0/55 (0) • DEN, 0/54 (0) • NE
RLX vs. placebo						
Morii 2003;[47] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• Placebo, 97 • RLX, 90	• Placebo, 87 • RLX, 79	12	• Placebo, 2/87 (2.30) • RLX, 0/79 (0) • Estimated RR 0.22, 95% CI 0.01 to 4.51; $p = 0.33$
Liu 2004;[48] postmenopausal women with osteoporosis	Efficacy	Clinical	• Placebo, 102 • RLX, 102	• Placebo, 102 • RLX, 102	12	• Placebo, 5/102 (4.90) • RLX, 0/102 (0) • (RR 0.09, 95% CI 0.005 to 1.580; $p > 0.05$)
Silverman 2008;[50] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• Placebo, 1855 • RLX, 1849	• Placebo, 1741 • RLX, 1696	36	• Placebo, 71/1741 (4.10) • RLX, 40/1696 (2.36) • (HR 0.58, 95% CI 0.38 to 0.89; $p < 0.05$)
Silverman 2008[50] and NCT00205777;[117] postmenopausal women with osteoporosis	Efficacy	Clinical	As above	• Placebo, 1741 • RLX, 1696	36	• Placebo, 16/1741 (0.92) • RLX, 15/1696 (0.88) • ($p = 0.89$)
MORE: Ettinger 1999;[51] women with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• Placebo, NR • RLX, NR	• Placebo, 1522 • RLX, 1490	36	• Placebo, 68/1522 (4.50) • RLX, 35/1490 (2.30) • (RR 0.5, 95% CI 0.4 to 0.9; estimated $p = 0.002$)
MORE: Ettinger 1999;[51] women with low BMD + fracture	Efficacy	Morphometric, new	• Placebo, NR • RLX, NR	• Placebo, 770 • RLX, 769	36	• Placebo, 163/770 (21.20) • RLX, 113/769 (14.70) • (RR 0.7, 95% CI 0.6 to 0.9; estimated $p = 0.001$)

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
MORE: Maricic 2002;[102] postmenopausal women with osteoporosis	Efficacy	Clinical	• Placebo, 2576 • RLX, 2557	• Placebo, 2292 • RLX, 2259	0–12	• Placebo, 19/2292 (0.80) • RLX, 6/2259 (0.20) • (RR 0.32, 95% CI 0.13 to 0.79; $p < 0.001$)
MORE: Maricic 2002;[102] postmenopausal women with osteoporosis	Efficacy	Clinical	As above	• Placebo, 2292 • RLX, 2259	12–24	• Placebo, 33/2292 (1.40) • RLX, 22/2259 (1.00) • Estimated RR 0.68, 95% CI 0.40 to 1.16; $p = 0.15$
MORE: Maricic 2002;[102] postmenopausal women with osteoporosis	Efficacy	Clinical	As above	• Placebo, 2292 • RLX, 2259	24–36	• Placebo, 29/2292 (1.30) • RLX, 19/2259 (0.80) • Estimated RR 0.66, 95% CI 0.37 to 1.18; $p = 0.16$
MORE: Maricic 2002;[102] postmenopausal women with osteoporosis	Efficacy	Clinical	As above	• Placebo, 2292 • RLX, 2259	36	• Placebo, 81/2292 (3.50) • RLX, 47/2259 (2.10) • Estimated RR 0.59, 95% CI 0.41 to 0.84; $p = 0.003$
MORE: Maricic 2002;[102] postmenopausal women with osteoporosis	Efficacy	Clinical	As above	• Placebo, 2292 • RLX, 2259	24	• Placebo, 35/2292 (1.54) • RLX, 22/2259 (0.97) • Estimated RR (from graph) 0.64, 95% CI 0.38 to 1.08; $p = 0.10$
Lufkin 1998;[52] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: 15% decrease in the same vertebra	• Placebo, 48 • RLX, 48	• Placebo, 45 • RLX, 43	12	• Placebo, 18/45 (40.00) • RLX, 21/43 (48.84) • Estimated RR 1.22, 95% CI 0.76 to 1.96; $p = 0.41$
Mok 2011;[53] postmenopausal women on long-term GCCs	Efficacy	• Morphometric, new • Definition: loss of at least 25% of vertebral height in previously normal vertebrae	• Placebo, 57 • RLX, 57	• Placebo, 56 • RLX, 51	12	• Placebo, 3/56 (5.36) • RLX, 0/51 (0) • ($p = 0.24$)

continued

TABLE 17 Vertebral fracture data reported by the included studies (*continued*)

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
ROMO vs. placebo						
FRAME: Cosman 2016;[54] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• Placebo, 3591 • ROMO, 3589	• Placebo, 3322 • ROMO, 3321	12	• Placebo, 59/3322 (1.78) • ROMO, 16/3321 (0.48) • (RR 0.27, 95% CI 0.16 to 0.47; nominal $p < 0.001$; adjusted $p < 0.001$)
FRAME: Cosman 2016;[54] postmenopausal women with osteoporosis	Efficacy	Morphometric, multiple or worsening	As above	• Placebo, 3322 • ROMO, 3321	12	• Placebo, 9/3322 (0.27) • ROMO, 1/3321 (0.03) • (RR 0.11, 95% CI 0.01 to 0.87; nominal $p = 0.011$)
FRAME: Cosman 2016;[54] postmenopausal women with osteoporosis	Efficacy	Morphometric, new	• Placebo to DEN, 3591 • ROMO to DEN, 3589 • 12 months open label	• Placebo, 3327 • ROMO, 3325	24	• Placebo/DEN, 84/3327 (2.52) • ROMO/DEN, 21/3325 (0.63) • (RR 0.25, 95% CI 0.16 to 0.40; nominal $p < 0.001$; adjusted $p < 0.001$)
FRAME: Cosman 2016;[54] postmenopausal women with osteoporosis	Efficacy	Morphometric, multiple or worsening	As above	• Placebo, 3327 • ROMO, 3325	24	• Placebo/DEN, 17/3327 (0.51) • ROMO/DEN, 1/3325 (0.03) • (RR 0.06, 95% CI 0.01 to 0.44; nominal $p < 0.001$)
FRAME: Cosman 2016;[20] postmenopausal women with osteoporosis	Efficacy	Morphometric, new	• Placebo to DEN, 3591 • ROMO to DEN, 3589 • 12 months open label	• Placebo, 3327 • ROMO, 3325	36	• Placebo/DEN, 94/3327 (2.8) • ROMO/DEN, 32/3327 (1.0) • (RR reduction 66%, 95% CI 49% to 77%; RR 0.34; nominal $p < 0.001$)
FRAME: Cosman 2016;[20] postmenopausal women with osteoporosis	Efficacy	Morphometric, multiple or worsening	As above	• Placebo, 3327 • ROMO, 3325	36	• Placebo/DEN, 94/3327 (2.8) • ROMO/DEN, 33/3327 (1.0) • (RR reduction 65%, 95% CI 48% to 76%, RR 0.35; nominal $p < 0.001$)

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
TPTD vs. placebo						
ACTIVE: Miller 2016;[95] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• Placebo, 821 • TPTD, 818	• Placebo, 821 • TPTD, 818	18	• Placebo, 30/711 (4.20) • TPTD, 6/717 (0.80) • (RD −3.38, 95% CI −5.18 to −1.80; RR 0.20, 95% CI 0.08 to 0.47; $p < 0.001$)
ACTIVE: Miller 2016;[95] postmenopausal women with osteoporosis	Efficacy	Clinical	As above	• Placebo, 821 • TPTD, 818	18	• Placebo, 9/821 (1.10) • TPTD, 3/818 (0.40) • Estimated RR 0.59, 95% CI 0.29 to 1.17; $p = 0.10$
Miyauchi 2010;[58] women and men with osteoporosis	Efficacy	Morphometric, any	• Placebo, 70 • TPTD, 137	• Placebo, 67 • TPTD, 136	12	• Placebo, 4/67 (5.97) • TPTD, 6/136 (4.41) • Estimated RR 0.33, 95% CI 0.09 to 1.23; $p = 0.63$
Miyauchi 2010;[58] women and men with osteoporosis	Efficacy	• Morphometric, new • Definition: deterioration of at least one grade by Genant *et al.*[35] method	As above	• Placebo, 67 • TPTD, 136	12	• Placebo, 4/67 (5.97) • TPTD, 5/136 (3.68) • Estimated RR 0.74, 95% CI 0.22 to 2.53; $p = 0.46$
Miyauchi 2010;[58] women and men with osteoporosis	Efficacy	• Morphometric, worsening • Definition: deterioration of at least one grade by Genant *et al.*[35] method	As above	• Placebo, 67 • TPTD, 136	12	• Placebo, 0/67 (0) • TPTD, 2/136 (1.47) • Estimated RR 0.62, 95% CI 0.17 to 2.22; $p = 0.56$
FPT: Neer 2001;[62] postmenopausal women with osteoporosis	Efficacy	• Morphometric, one or more fractures • Definition: Genant *et al.*[35] method	• Placebo, 544 • TPTD, 541	• Placebo, 448 • TPTD, 444	24 (trial stopped early; mean time to last radiograph was 21 months)	• Placebo, 64/448 (14.00) • TPTD,22/444 (5.00) • (RR 0.35, 95% CI 0.22 to 0.55; reduction in absolute risk to 9%; $p \leq 0.001$)

continued

TABLE 17 Vertebral fracture data reported by the included studies (*continued*)

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
FPT: Neer 2001;[62] postmenopausal women with osteoporosis	Efficacy	Morphometric, one or more fractures	As above	As above	24 (trial stopped early; mean time to last radiograph was 21 months)	• Placebo, 22/448 (5.00) • TPTD, 5/444 (1.00) • (RR 0.23, 95% CI 0.09 to 0.60; reduction in absolute risk to 4%; $p \leq 0.001$)
FPT: Neer 2001;[62] postmenopausal women with osteoporosis	Efficacy	Morphometric, one or more moderate or severe fractures	As above	As above	24 (trial stopped early; mean time to last radiograph was 21 months)	• Placebo, 42/448 (9.00) to TPTD, 4/444 (0.90) • (RR 0.10, 95% CI 0.04 to 0.27; reduction in absolute risk to 9%; $p \leq 0.001$)
Head-to-head non-bisphosphonates						
EUROFORS: Eastell 2009;[66] postmenopausal women with osteoporosis pre treated with TPTD	Efficacy	Clinical	• TPTD, 304 • RLX, 97 • Control,[a] 102	• TPTD, 304 • RLX, 97 • Control, 102	12	• TPTD, 4/304 (1.32) • RLX, 0/97 (0) • Control, 0/102 (0) • (Not significant, *p*-value NR)
DEN vs. bisphosphonates						
Saag 2018;[74] women and men on GCCs with osteoporosis or low BMD + fracture	Efficacy	Clinical	• RIS, 397 • DEN, 398 • Both with placebo	• RIS, 397 • DEN, 398	12	• RIS, 15/342 (4.0) • DEN, 10/333 (3.00) • Estimated RR 0.67, 95% CI 0.30 to 1.52; $p = 0.34$
Miller 2016[75]	Safety	NR	• ZOL, 322 • DEN, 321 • Both with placebo	• ZOL, 320 • DEN, 320	12	• ZOL, 4 fractures • DEN, 0 fractures • Number of participants NR

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
RLX vs. bisphosphonates						
EFFECT: Sambrook 2004[76] (international not including USA); postmenopausal women with osteoporosis	Safety	NR	• ALN, 246 • RLX, 241 • Both with placebo	• ALN, 246 • RLX, 241	12	• ALN, 0/246 (0) • RLX, 0/241 (0) • NE
Muscoso 2004;[79] postmenopausal women with osteoporosis	Efficacy	NR	• ALN, 1000 • RLX, 100 • RIS, 100 • All daily open label	• ALN, 1000 • RLX, 100 • RIS, 100	0–12	• ALN, 2/1000 (0.2) • RLX, 0/100 (0) • RIS, 0/100 (0) • ALN vs. RLX: estimated RR 1.99, 95% CI 0.09 to 41.68; $p = 0.66$ • RIS vs. RLX: NE
Muscoso 2004;[79] postmenopausal women with osteoporosis	Efficacy	NR	As above	• ALN, 1000 • RLX, 100 • RIS, 100	12–24	• ALN, 4/1000 (0.4) • RLX, 0/100 (0) • RIS, 0/100 (0) • ALN vs. RLX: estimated RR 1.10, 95% CI 0.06 to 20.61; $p = 0.95$ • RIS vs. RLX: NE
EVA: Recker 2007;[80] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• ALN, 716 • RLX, 707 • Both with placebo	• ALN, 255 • RLX, 259	Mean 312 (SD 252) days	• ALN, 8/255 (3.14) • RLX, 5/259 (1.93) • Estimated RR 0.62, 95% CI 0.20 to 1.86; $p = 0.39$
EVA: Recker 2007;[80] postmenopausal women with osteoporosis	Efficacy	• Morphometric, moderate/severe • Definition: Genant *et al.*[35] method > 25% loss of height	• ALN, 716 • RLX, 707 • Both with placebo	• ALN, 255 • RLX, 259	Mean 312 (SD 252) days	• ALN, 4/255 (1.57) • RLX, 0/259 (0) • Estimated RR 0.11, 95% CI 0.01 to 2.02; $p = 0.14$
EVA: Recker 2007;[80] postmenopausal women with osteoporosis	Efficacy	Clinical	As above	• ALN, 713 • RLX, 699	Mean 312 (SD 252) days	• ALN, 3/713 (0.40) • RLX, 0/699 (0) • Estimated RR 0.15, 95% CI 0.01 to 2.82; $p = 0.20$

continued

TABLE 17 Vertebral fracture data reported by the included studies (*continued*)

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
ROMO vs. bisphosphonates						
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new ITT MI • Definition: Genant[35] method	• ALN, 2047 • ROMO, 2046 • Both with placebo	• ALN, 2047 • ROMO, 2046	12	• ALN, 128/2047 (6.3) • ROMO, 82/2046 (4.00) • (RR 0.63, 95% CI 0.47 to 0.85; $p = 0.003$)
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	Efficacy	Morphometric, new, ITT LOCF	As above	• ALN, 1703 • ROMO, 1696	12	• ALN, 85/1703 (5.00) • ROMO, 55/1696 (3.20) • (RR 0.64, 95% CI 0.46 to 0.89; $p = 0.008$)
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	Efficacy	Morphometric new or worsening	As above	• ALN, 1703 • ROMO, 1696	12	• ALN, 101/1703 (5.90) • ROMO, 67/1696 (4.00) • (RR 0.66, 95% CI 0.49 to 0.89; $p = 0.006$)
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	Efficacy	Clinical	As above	• ALN, 2047 • ROMO, 2046	12	• ALN, 18/2047 (0.90) • ROMO, 10/2046 (0.50) • (HR 0.56, 95% CI 0.26 to 1.22; $p = 0.14$)
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	Efficacy	Morphometric, new, ITT MI	• ALN to ALN, 2047 • ROMO to ALN, 2046 • Open label	• ALN/ALN, 2047 • ROMO/ALN, 2046	24	• ALN/ALN, 243/2047 (11.90) • ROMO/ALN, 127/2046 (6.20) • (RR 0.52, 95% CI 0.40 to 0.66; $p < 0.001$)
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	Efficacy	Morphometric, new, ITT LOCF	As above	• ALN/ALN, 1843 • ROMO/ALN, 1825	24	• ALN/ALN, 147/1834 (8.00) • ROMO/ALN, 74/1825 (4.55) • (RR 0.50, 95% CI 0.38 to 0.66; $p < 0.001$)
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	Efficacy	Morphometric, new or worsening	As above	• ALN/ALN, 1843 • ROMO/ALN, 1825	24	• ALN/ALN, 168/1834 (9.20) • ROMO/ALN, 87/1825 (4.77) • (RR 0.52, 95% CI 0.40 to 0.66; $p < 0.001$)

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
TPTD vs. bisphosphonates						
Saag 2009;[103] women and men on GCCs with osteoporosis or low BMD + fracture	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• Women and men • ALN, 214 • TPTD, 214 • Both with placebo	• ALN, 165 • TPTD, 171	18	• ALN, 10/165 (6.10) • TPTD, 1/171 (0.6) • ($p = 0.004$)
Saag 2009;[103] women and men on GCCs with osteoporosis or low BMD + fracture	Efficacy	Clinical	As above	• ALN, 165 • TPTD, 171	18	• ALN, 3/165 (1.80) • TPTD, 0/171 (0) • ($p = 0.07$)
Saag 2009;[103] women and men on GCCs with osteoporosis or low BMD + fracture	Efficacy	Morphometric, new	As above	• ALN, 169 • TPTD, 173	36	• ALN, 13/169 (7.70) • TPTD, 3/173 (1.70) • ($p = 0.007$)
Saag 2009[85]	Efficacy	Clinical	As above	• ALN, 169 • TPTD, 173	36	• ALN, 4/169 (2.40) • TPTD, 0/173 (0) • ($p = 0.037$)
Langdahl 2009;[107] women and men on GCCs with osteoporosis or low BMD + fracture	Efficacy	Morphometric, new	• Women • ALN, 173 • TPTD, 171 • Both with placebo	• ALN, 134 • TPTD, 139	18	• ALN, 6/134 (4.48) • TPTD, 1/139 (0.72) • Estimated RR 0.16, 95% CI 0.02 to 1.32; $p = 0.09$
Langdahl 2009;[107] women and men on GCCs with osteoporosis or low BMD + fracture	Efficacy	Morphometric, new	• Men • ALN, 41 • TPTD, 42 • Both with placebo	• ALN, 31 • TPTD, 31	18	• ALN, 4/31 (12.90) • TPTD, 0/31 (0) • Estimated RR 0.11, 95% CI 0.01 to 1.98; $p = 0.13$
Panico 2011;[86] postmenopausal women with severe osteoporosis + fracture and on treatment for osteoporosis	Efficacy	Morphometric, new	• ALN weekly, 39 • TPTD, 42 • Without placebo	• ALN, 39 • TPTD, 42	18	• ALN 6/39 (15.7) • TPTD 1/42 (2.4) • Estimated RR 0.15, 95% CI 0.02 to 1.23; $p = 0.08$

continued

TABLE 17 Vertebral fracture data reported by the included studies (*continued*)

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
Walker 2013;[89] men with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• RIS weekly, 10 • TPTD, 9 • Both with placebo	• RIS, 10 • TPTD, 9	18	• RIS, 1/10 (10.00) • TPTD, 0/9 (0) • Estimated RR 0.37, 95% CI 0.02 to 8.01; $p = 0.52$
Hadji 2012;[91] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• RIS weekly, 350 • TPTD, 360 • Both with placebo	• RIS, 350 • TPTD, 360	6	• RIS, 18/350 (5.10) • TPTD, 15/360 (4.20) • ($p = 0.6$)
Hadji 2012;[91] postmenopausal women with osteoporosis	Efficacy	Morphometric, new or worsening	As above	• RIS, 350 • TPTD, 360	6	• RIS, 22/350 (6.30) • TPTD, 23/360 (6.40) • ($p = 1.00$)
Hadji 2012;[91] postmenopausal women with osteoporosis	Efficacy	Morphometric, new	As above	• RIS, 350 • TPTD, 360	18	• RIS, 3/350 (9.40) • TPTD, 16/360 (4.40) • ($p = 0.01$)
Hadji 2012;[91] postmenopausal women with osteoporosis	Efficacy	Morphometric, new or worsening	As above	• RIS, 350 • TPTD, 360	18	• RIS, 39/350 (11.10) • TPTD, 24/360 (6.70) • ($p < 0.05$)
VERO: Kendler 2018;[99] postmenopausal women with osteoporosis	Efficacy	• Morphometric, new • Definition: Genant *et al.*[35] method	• RIS weekly, 680 • TPTD, 680 • Both with placebo	• RIS, 533 • TPTD, 516	24	• RIS, 64/533 (12.00) • TPTD, 28/516 (5.00) • (RR 0.44, 95% CI 0.29 to 0.68; $p < 0.0001$)
VERO: Kendler 2018;[99] postmenopausal women with osteoporosis	Efficacy	Morphometric, new and worsening	As above	• RIS, 533 • TPTD, 516	24	• RIS, 69/533 (13.00) • TPTD, 31/516 (6.00) • (RR 0.46, 95% CI 0.31 to 0.68; $p < 0.0001$)
VERO: Kendler 2018;[99] postmenopausal women with osteoporosis	Efficacy	Morphometric, multiple	As above	• RIS, 533 • TPTD, 516	24	• RIS, 12/533 (2.00) • TPTD, 2/516 (0.39) • (RR 0.16, 95% CI 0.04 to 0.74; $p = 0.007$)
VERO: Kendler 2018;[99] postmenopausal women with osteoporosis	Efficacy	Morphometric, multiple	As above	• RIS, 533 • TPTD, 516	12	• RIS, 11/533 (2.10) • TPTD, 4/516 (0.78) • Estimated RR (from graph) 0.38, 95% CI 0.12 to 1.17; $p = 0.09$

Trial name: first author and year; population	Efficacy or safety outcome	Method of vertebral fracture assessment (clinical/morphometric)	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Vertebral fracture outcomes *n/N* (%) (reported between-group difference)
MOVE: Aspenberg 2016;[108] women and men with low BMD + recent hip fracture surgery	Safety	Clinical	• RIS daily, 113 • TPTD, 111 • Both with placebo	• RIS, 113 • TPTD, 111	6	• RIS, 0/110 (0) • TPTD, 0/116 (0) • NE
MOVE: Malouf-Sierra 2017;[92] women and men with low BMD + recent hip fracture surgery	Safety	Clinical	As above	• RIS, 113 • TPTD, 111	18	• RIS, 1/110 (1.00) • TPTD, 0/116 (0) • ($p = 1.00$)
Cosman 2011;[93] postmenopausal women with osteoporosis	Safety	AE	• ZOL,[b] 137 • TPTD + ZOL Placebo, 138	• ZOL, 137 • TPTD + placebo, 138	12	• ZOL, 5/137 (3.70) • TPTD + placebo, 1/137 (0.70) • Estimated RR 0.20, 95% CI 0.02 to 1.69; $p = 0.14$

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; CI, confidence interval; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; GCC, glucocorticoid; ITT, intention to treat; MI, multiple imputation; MORE, Multiple Outcomes of Raloxifene Evaluation; NE, not estimable; NR, not reported; OLE, open-label extension; RD, risk difference.

a No active treatment.

b Not placebo controlled for TPTD.

Notes

Definition of morphometric not provided in all studies.

ALN, 10 mg daily or 70 mg weekly; DEN, 60 mg s.c. every 6 months; IBN, 150 mg oral every month; RLX, 60 mg daily; ROMO, 210 mg s.c. monthly; TPTD, 20 µg s.c. daily; ZOL, 5 mg i.v. annually.

TABLE 18 Non-vertebral fracture outcomes

Trial name or first author and year	Efficacy or safety outcome	Treatments, *n* randomised	Follow-up (months)	Non-vertebral fractures, *n/N* (%) (reported between-group difference)
DEN vs. placebo				
FREEDOM[41]	Efficacy	• Placebo, 3906 • DEN, 3902	36	• Placebo, 293/3906 (7.50) • DEN, 238/3902 (6.10) • (RD 1.5, 95% CI 0.3 to 2.7; RR 0.80, 95% CI 0.67 to 0.95; $p = 0.01$)
FREEDOM[104]	Efficacy	• Placebo, 3906 • DEN, 3902	0–12	• Placebo, 120/3906 (3.06) • DEN, 101/3902 (2.59) • Values estimated from graph
FREEDOM[104]	Efficacy	• Placebo, 3906 • DEN, 3902	12–24	• Placebo, 113/3906 (2.89) • DEN, 82/3902 (2.09) • Values estimated from graph
FREEDOM[104]	Efficacy	• Placebo, 3906 • DEN, 3902	24–36	• Placebo, 98/3906 (2.50) • DEN, 84/3902 (2.15) • Values estimated from graph
FREEDOM OLE[105]	Efficacy	• Entered OLE • Placebo/DEN, 2207 • DEN/DEN, 2343	84 from OLE	• Placebo/DEN, 219/2207 (9.92) • DEN/DEN, 172/2343 (7.34)
ADAMO[42]	Safety	• Placebo, 121 • DEN, 121	12	• Placebo, 2/120 (1.67) • DEN, 1/120 (0.83)
DIRECT[43]	Efficacy	• Placebo, 511 • DEN, 500	24	All: • Placebo, 20/480 (4.10) • DEN, 19/472 (4.10) • (HR 1.002, 95% CI 0.521 to 1.926; $p = 0.9951$) Major (proximal humerus, forearm, ribs/clavicle, pelvis, hip, distal femur, and proximal tibia): • Placebo, 18/480 (3.70) • DEN, 8/472 (1.60) • (HR 0.434, 95% CI 0.178 to 1.055; $p = 0.0577$) Non-major: • Placebo, 2/480 (0.40) • DEN, 12/472 (2.50) • (HR 5.552, 95% CI 1.231 to 25.042; $p = 0.0120$)
DIRECT[106]	Efficacy	• Placebo to DEN, 406 • DEN to DEN, 404	36 including 12 OLE	All: • Placebo/DEN, 27/406 (6.65) • DEN/DEN, 21/404 (5.20) Major (proximal humerus forearm ribs/clavicle pelvis hip distal femur and proximal tibia): • Placebo/DEN, 22/406 (5.42) • DEN/DEN, 8/404 (1.98)

TABLE 18 Non-vertebral fracture outcomes (*continued*)

Trial name or first author and year	Efficacy or safety outcome	Treatments, *n* randomised	Follow-up (months)	Non-vertebral fractures, *n/N* (%) (reported between-group difference)
Koh 2016[45]	Safety	• Placebo, 66 • DEN, 69	6	• Placebo, 1/66 (1.52) • DEN, 1/69 (1.45)
Koh 2016 OLE[45]	Safety	• Placebo to DEN, 66 • DEN to DEN, 69	6–12 OLE	• Placebo, 1/63 (1.60) • DEN, 0/60 (0)
RLX vs. placebo				
Morii 2003[47]	Efficacy	• Placebo, 97 • RLX, 90	12	• Placebo, 4/97 (4.12) • RLX, 0/88 (0)
Silverman 2008[50] (NCT00205777)	Efficacy	• Placebo, 1855 • RLX, 1849	36	• Placebo, 118/1885 (5.70) • RLX, 109/1849 (6.30) • Non-significant *p*-value NR
Lufkin 1998[52]	Efficacy	• Placebo, 48 • RLX, 48	12	• Placebo, 3/45 (6.67) • RLX, 0/43 (0)
ROMO vs. placebo				
FRAME[54]	Efficacy	• Placebo, 3591 • ROMO, 3589	12	• Placebo, 75/3591 (2.1) • ROMO, 56/3589 (1.6) • (HR 0.75, 95% CI 0.53 to 1.05; $p = 0.096$)
FRAME[54]	Efficacy	• Placebo to DEN, 3591 • ROMO to DEN, 3589	24	• Placebo, 129/3591 (3.6) • ROMO, 96/3589 (2.7) • (HR 0.75, 95% CI 0.57 to 0.97; $p = 0.029$)
Ishibashi 2017[55]	Safety	• Placebo, 63 • ROMO, 63	12	• Placebo, 1/63 (1.59) • ROMO, 2/63 (3.17)
TPTD vs. placebo				
Miyauchi 2010[58]	Efficacy	• Placebo, 70 • TPTD, 137	12	• Placebo, 4/67 (6.00) • TPTD, 3/136 (2.20) Fragility: • Placebo, 1/67 (1.50) • TPTD, 1/136 (0.70)
Miyauchi 2010[58]	Efficacy	• Entered extension • Placebo to TPTD, 59 • TPTD to TPTD, 119	12–18 OLE	• Placebo/TPTD, 4/59 (6.78) • TPTD/TPTD, 3/119 (2.52) • Estimated from graph
Miyauchi 2010[58]	Efficacy	• Entered extension • Placebo to TPTD, 59 • TPTD to TPTD, 119	18–24 OLE	• Placebo/TPTD, 4/50 (8.0) • TPTD/TPTD, 3/102 (2.94) • Estimated from graph
ACTIVE[95]	Efficacy	• Placebo, 821 • TPTD, 818	18	• Placebo, 33/821 (4.70) • TPTD, 24/818 (3.30) • (RD −1.46, 95% CI −3.50 to 0.58; HR 0.72, 95% CI 0.42 to 1.22; $p = 0.22$)
FPT[62]	Efficacy	• Placebo, 544 • TPTD, 541	24 (trial stopped early; mean time to last visit was 19 months)	• Placebo, 53/544 (9.74) • TPTD, 34/541 (6.28) • ($p = 0.04$) Fragility: • Placebo, 30/544 (5.51) • TPTD, 14/541 (2.59) • ($p = 0.02$)

continued

TABLE 18 Non-vertebral fracture outcomes (*continued*)

Trial name or first author and year	Efficacy or safety outcome	Treatments, *n* randomised	Follow-up (months)	Non-vertebral fractures, *n/N* (%) (reported between-group difference)
Head-to-head non-bisphosphonates				
EUROFORS[66]	Efficacy	• TPTD, 304 • RLX, 97 • Control, 102	12	• TPTD, 9/304 (2.96) • RLX, 2/97 (2.06) • No treatment, 1/102 (0.98) • Non-significant *p*-value NR
STRUCTURE[67]	Safety	• ROMO, 218 • TPTD, 218	12	• ROMO, 7/218 (3.21) • TPTD, 8/214 (3.67)
Non-bisphosphonates vs. bisphosphonates				
STAND[70]	Safety	• ALN, 251 • DEN, 253	12	• ALN, 4/249 (1.61) • DEN, 8/253 (3.16)
DAPS[109]	Safety	• ALN, 124 • DEN, 126	12	• ALN, 1/118 (0.85) • DEN, 1/125 (0.80)
DAPS[109]	Safety	• ALN to DEN, 106 • DEN to ALN, 115	12–24	• ALN/DEN, 3/106 (2.83) • DEN/ALN, 1/110 (0.90)
Saag 2018[74]	Efficacy	• RIS plus placebo, 397 • DEN plus placebo, 398	12	• RIS, 10/397 (3.0) • DEN, 17/398 (4.0)
EFFECT (USA)[77]	Safety	• ALN, 223 • RLX, 233	12	• ALN, 5/199 (2.51) • RLX, 8/206 (3.88)
Muscoso 2004[79]	Efficacy	• ALN, 1000 • RLX, 100 • RIS, 100	0–12	• ALN, 2/1000 (0.2) • RLX, 0/100 (0) • RIS, 0/100 (0)
Muscoso 2004[79]	Efficacy	• ALN, 1000 • RLX, 100 • RIS, 100	12–24	• ALN, 2/1000 (0.2) • RLX, 0/100 (0) • RIS, 0/100 (0)
EVA[80]	Efficacy	• ALN, 716 • RLX, 707	Mean 312 (SD 252) days	• ALN, 14/713 (2.00) • RLX, 15/699 (2.20) • (RR 0.92, 95% CI 0.45 to 1.86)
Michalska 2006[82]	Safety	• Placebo, 33 • RLX, 33 • Open-label ALN, 33	24	• Placebo, 2/33 (6.06) • RLX, 1/33 (3.03) • ALN, 1/33 (3.03)
ARCH[83]	Efficacy	• ALN, 2047 • ROMO, 2046	12	• ALN, 95/2047 (4.60) • ROMO, 70/2046 (3.40) • (HR 0.74, 95% CI 0.54 to 1.01; $p = 0.057$)
ARCH[83]	Efficacy	• ALN, 2047 • ROMO, 2046	12	Major (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm and hip): • ALN, 88/2047 (4.30) • ROMO, 59/2046 (2.90) • (HR 0.67, 95% CI 0.48 to 0.94; $p = 0.019$)
ARCH[83]	Efficacy	• ALN to ALN, 2047 • ROMO to ALN, 2046	24	• ALN/ALN, 217/2047 (10.60) • ROMO/ALN, 178/2046 (8.70) • (HR 0.81, 95% CI 0.66 to 0.99; $p = 0.037$)

TABLE 18 Non-vertebral fracture outcomes (*continued*)

Trial name or first author and year	Efficacy or safety outcome	Treatments, *n* randomised	Follow-up (months)	Non-vertebral fractures, *n/N* (%) (reported between-group difference)
ARCH[83]	Efficacy	• ALN to ALN, 2047 • ROMO to ALN, 2046	24	Major (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm and hip): • ALN/ALN, 196/2047 (9.60) • ROMO/ALN, 146/2046 (7.10) • (HR 0.73, 95% CI 0.59 to 0.90; $p = 0.004$)
Saag 2009[103]	Efficacy	Men and women • ALN, 214 • TPTD, 214	18	• ALN, 8/214 (3.70) • TPTD, 12/214 (5.60) • ($p = 0.36$)
Saag 2009[103]	Efficacy	Men and women • ALN, 214 • TPTD, 214	36	• ALN, 15/214 (7.00) • TPTD, 16/214 (7.50) • ($p = 0.843$)
Saag 2009[107]	Efficacy	Men • ALN, 41 • TPTD, 42	18	• ALN, 2/71 (2.82) • TPTD, 1/42 (2.38) • ($p = 0.58$)
Saag 2009[107]	Efficacy	Women • ALN, 173 • TPTD, 171	18	• ALN, 6/173 (3.47) • TPTD, 11/171 (6.43) • (Postmenopausal $p = 0.36$; premenopausal $p = 0.32$)
EuroGIOPs[87]	Safety	• RIS, 47 • TPTD, 45	18	• RIS, 5/47 (10.60) • TPTD, 0/45 (0) • ($p = 0.056$)
VERO[99]	Efficacy	• RIS plus placebo, 680 • TPTD plus placebo, 680	24	• RIS, 38/680 (6.00) • TPTD, 25/680 (4.00) • (HR 0.66, 95% CI 0.39 to 1.10; $p = 0.10$)
VERO[99]	Efficacy	• RIS plus placebo, 680 • TPTD plus placebo, 680	12	• RIS, 23/680 (3.32) • TPTD, 15/680 (2.21) • Estimated from graph
Hadji 2012[91]	Efficacy	• RIS, 350 • TPTD, 360	6	• RIS, 29/350 (8.30) • TPTD, 28/360 (7.80) • ($p = 0.89$)
MOVE[92]	Safety	• RIS, 350 • TPTD, 360	18	• RIS, 10/110 (9.10) • TPTD, 5/116 (4.70) • ($p = 0.286$)
Cosman 2011[93]	Safety	• ZOL (no placebo), 137 • TPTD plus placebo, 138	12	• ZOL, 8/137 (5.84) • TPTD + placebo, 7/137 (5.11)

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; CI, confidence interval; DAPS, Denosumab Adherence Preference Satisfaction; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; NR, not reported; OLE, open label extension; RD, risk difference; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy.

Note

All reported treatment arms at licensed dose.

TABLE 19 Fractures of the hip, wrist or proximal humerus

Trial name or first author and year	Treatment arms	Follow-up (months)	Fracture, *n/N* (%) (reported between-group difference)		
			Hip	Wrist	Proximal humerus
DEN vs. placebo					
FREEDOM[41]	Placebo	0–36	43/3906 (1.2)	NR	NR
	DEN		• 26/3902 (0.7) • Difference 0.3 (95% CI −0.1 to 0.7) • HR 0.60 (95% CI 0.37 to 0.97) • $p = 0.04$	NR	NR
FREEDOM[104]	Placebo	1–12	21/3906 (0.55)	NR	NR
	DEN		• 11/3902 (0.29) • Non-significant (*p*-value NR)	NR	NR
	Placebo	12–24	14/3906 (0.36)	NR	NR
	DEN		• 3/3902 (0.08) • Non-significant (*p*-value NR)	NR	NR
	Placebo	24–36	11/3906 (0.27)	NR	NR
	DEN		• 12/3902 (0.32) • Non-significant (*p*-value NR)	NR	NR
ADAMO[42]	Placebo	12	NR	NR	1/120 (0.8)
	DEN		NR	NR	0/120 (0)
DIRECT[43]	Placebo	24	2/480 (0.4)	NR	NR
	DEN		0/472 (0)	NR	NR
RLX vs. placebo					
Silverman 2008;[50] NCT00205777[117]	Placebo	36	6/1885 (0.3)	31/1885 (1.6)	NR
	RLX		5/1849 (0.3)	46/1849 (2.5)[117]	NR
Lufkin 1998[52]	Placebo	12	0/45 (0)	0/45 (0)	NR
	RLX		0/43 (0)	0/43 (0)	NR
ROMO vs. placebo					
FRAME[54]	Placebo	12	13/3591 (0.4)	NR	NR
	ROMO		• 7/3589 (0.2) • HR 0.54 (95% CI 0.22 to 1.35); $p = 0.18$	NR	NR
FRAME[54]	Placebo followed by DEN	24	22/3591 (0.6)	NR	NR
	ROMO followed by DEN		• 11/3589 (0.3) • HR 0.50 (95% CI 0.24 to 1.04); $p = 0.059$	NR	NR
Ishibashi 2017[55]	Placebo	12	NR	0/63 (0)	NR
	ROMO		NR	1/63 (1.6)	NR

TABLE 19 Fractures of the hip, wrist or proximal humerus (*continued*)

Trial name or first author and year	Treatment arms	Follow-up (months)	Fracture, *n/N* (%) (reported between-group difference)		
			Hip	Wrist	Proximal humerus
TPTD vs. placebo					
ACTIVE[95]	Placebo	18	2/821 (0.2)	15/821 (1.8)	3/821 (0.4)
	TPTD		• 0/818 (0) • NR	• 17/818 (2.1) • NR	• 2/818 (0.2) • NR
FPT[62]	Placebo	24 (trial stopped early; mean time to last visit was 19 months)	All: • 4/544 (0.7) Fragility: • 4/544 (0.7)	All: • 13/544 (2.4) Fragility: • 7/544 (1.3)	All: • 5/544 (0.9) Fragility: • 2/544 (0.4)
	TPTD		All: • 2/541 (0.4) Fragility: • 1/541 (0.2)	All: • 7/541 (1.3) Fragility: • 2/541 (0.4)	All: • 4/541 (0.7) Fragility: • 2/541 (0.4)
Head-to-head non-bisphosphonates					
EUROFORS[66]	No active treatment (for 12 months) (following pre-randomisation TPTD for 12 months)	24	0/102 (0)	0/102 (0)	0/102 (0)
	RLX (following TPTD)		0/97 (0)	0/97 (0)	1/97 (1.0)
	TPTD (for 12 months) (following 12 months of pre-randomisation TPTD)		1/304 (0.3)	3/304 (1.0)	0/304 (0)
STRUCTURE[67]	TPTD	12	0/218 (0)	4/218 (1.8)	1/218 (0.5)
	ROMO		1/218 (0.5)	1/218 (0.5)	0/218 (0)
Non-bisphosphonates vs. bisphosphonates					
STAND[70]	ALN	12	NR	2/249 (0.8)	0/249 (0)
	DEN		NR	3/253 (1.2)	1/253 (0.4)
Saag 2018[74]	RIS	12	1/397 (0.3)	NR	3/397 (0.8)
	DEN		1/398 (0.3)	NR	3/398 (0.8)
EFFECT (International)[76]	RLX plus placebo	12	1/241 (0.4)	NR	NR
	ALN plus placebo		0/246 (0)	NR	NR
EFFECT (USA)[77]	RLX plus placebo	12	NR	1/206 (0.5)	1/206 (0.5)
	ALN plus placebo		NR	0/199 (0)	0/199 (0)

continued

TABLE 19 Fractures of the hip, wrist or proximal humerus (*continued*)

Trial name or first author and year	Treatment arms	Follow-up (months)	Fracture, *n/N* (%) (reported between-group difference)		
			Hip	Wrist	Proximal humerus
Muscoso 2004[79]	ALN	12	1/1000 (0.1)	1/1000 (0.1)	NR
	RLX		10/100 (0)	0/100 (0)	NR
	RIS		0/100 (0)	0/100 (0)	NR
	ALN	12–24	2/1000 (0.2)	0/1000 (0)	NR
	RLX		0/100 (0)	0/100 (0)	NR
	RIS		0/100 (0)	0/100 (0)	NR
EVA[80]	RLX	24	2/699 (0.3)	8/699 (1.1)	NR
	ALN		• 1/713 (0.1) • RR 0.49 (95% CI 0.04 to 3.77)	• 6/713 (0.8) • RR 0.74 (95% CI 0.27 to 2.02)	NR
ARCH[83]	ROMO	12	14/2046 (0.7)	NR	NR
	ALN		• 22/2047 (1.1) • $p = 0.19$	NR	NR
	ROMO followed by ALN	Median 2.7 years	41/2046 (2.0)	NR	NR
	ALN followed by ALN		• 66/2047 (3.2) • $p = 0.015$	NR	NR
EUROGIOPs[87]	RIS	18	1/47 (2.1)	NR	1/47 (2.1)
	TPTD		0/45 (0)	NR	0/45(0)
VERO[99]	RIS	24	5/680 (0.7)	15/680 (2.2)	2/680 (0.3)
	TPTD		2/680 (0.3)	6/680 (0.9)	14/680 (0.6)
Hadji 2012[91]	RIS	18	2/350 (0.6)	2/350 (0.6)	5/350 (1.4)
	TPTD		5/360 (1.4)	4/360 (1.1)	4/360 (1.1)
MOVE[101]	RIS	6	5/110 (4.5)	NR	1/110 (0.9)
	TPTD		2/106 (1.9)	NR	1/106 (0.9)
MOVE[92]	RIS	18	7/110 (6.4)	NR	1/110 (0.9)
	TPTD		2/106 (1.9)	NR	1/106 (0.9)

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; NR, not reported; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy.

Note

All reported arms at licensed dose.

TABLE 20 Femoral neck BMD data reported by the included studies

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
DEN vs. placebo						
FREEDOM: Bone 2017;[104] postmenopausal women with osteoporosis	• Placebo, 3906 • DEN, 3902	• Placebo, 3906 • DEN, 3902	36	• Placebo, + 7.1 (NR) • DEN, + 9.0 (NR)	Nothing	• NR • (NE)
FREEDOM: Bone 2017 OLE;[105] postmenopausal women with osteoporosis	• Entered OLE • Placebo to DEN, 2207 • DEN to DEN, 2343	• Placebo/DEN, 2809 • DEN/DEN, 2210	84 from OLE	• Placebo/DEN, + 7.40 (5.83) • DEN/DEN, + 3.40 (6.00)	Nothing	• NR • (MD −4.00, 95% CI −4.35 to −3.65; $p < 0.00001$)
ADAMO: Orwoll 2012;[42] men with osteoporosis	• Placebo, 121 • DEN, 121	• Placebo, 117 • DEN, 111	12	• Placebo, 0.00 (3.31[a]) • DEN, + 2.10 (3.35[a])	95% CIs	$p < 0.0001$
DIRECT: Nakamura 2014;[43] women and men with osteoporosis	• Placebo, 511 • DEN, 500	• Placebo, 480 • DEN, 472	24	• Placebo, −1.10 (4.30[a]) • DEN, + 4.00 (4.82[a])	95% CIs	$p < 0.0001$
DIRECT: Sugimoto 2015;[106] women and men with osteoporosis	• Placebo to DEN, 406 • DEN to DEN, 404	• Placebo/DEN, 406 • DEN/DEN, 404	36 including 12 OLE	• Placebo/DEN, + 1.1 (4.32[a]) • DEN/DEN, + 4.8 (4.61[a])	95% CIs	• NR • (MD + 3.70, 95% CI 3.08 to 4.32; $p < 0.00001$)
DIRECT: Sugimoto 2015;[106] women and men with osteoporosis	• Placebo to DEN, 406 • DEN to DEN, 404	• Placebo/DEN, 406 • DEN/DEN, 404	24–36 OLE	• Placebo/DEN, + 0.8 (NR) • DEN/DEN, + 2.30 (NR)	Nothing	• NR • (NE)
Koh 2016;[45] postmenopausal women with osteoporosis	• Placebo, 66 • DEN, 69	• Placebo, 66 • DEN, 68	6	• Placebo, + 0.73 (2.88[a]) • DEN, + 4.37 (4.50[a])	Means and 95% CIs	MD between groups in percentage change: 1.4% (95% CI 0.4% to 2.3%; $p = 0.0042$
Koh 2016;[45] postmenopausal women with osteoporosis	• Entered OLE • Placebo to DEN, 63 • DEN to DEN, 60	• OLE • Placebo/DEN, 59 • DEN/DEN, 59	6–12 OLE	• Placebo/DEN, + 3.48 (3.29[a]) • DEN/DEN, + 5.59 (4.04[a])	Means and 95% CIs	• NR • (MD + 2.11, 95% CI 0.78 to 3.44; $p = 0.002$)

continued

TABLE 20 Femoral neck BMD data reported by the included studies (*continued*)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
RLX vs. placebo						
Adami 2008;[46] postmenopausal women with osteoporosis pre treated with TPTD	• Placebo, 172 • RLX, 157	• Placebo, 154 • RLX, 145	12	• Placebo, + 0.20 (3.72[b]) • RLX, + 2.30 (4.82[b])	Nothing	$p < 0.001$
Adami 2008;[46] postmenopausal women with osteoporosis pre treated with TPTD	• OLE • Placebo to RLX, 172 • RLX to RLX, 157	• Placebo/RLX, 146 • RLX/RLX, 139	36 including 24 OLE	• Placebo, 1.70 (4.83[b]) • RLX, 2.20 (5.89[b])	Nothing	• NR • (MD + 0.50, 95% CI −0.75 to 1.75; $p = 0.43$)
Liu 2004;[48] postmenopausal women with osteoporosis	• Placebo, 102 • RLX, 102	• Placebo, 102 • RLX, 102	12	• Placebo, −0.40 (5.80) • RLX, 0.9 (5.40)	Nothing	• NR • (MD + 1.30, 95% CI −0.24 to 2.84; $p = 0.10$)
Silverman 2008;[50] postmenopausal women with osteoporosis	• Placebo, 1855 • RLX, 1849	• Placebo, 1711 • RLX, 1662	36	• Placebo, −1.30 (6.20[b]) • RLX, 0.80 (6.11[b])	Nothing	• NR • (MD + 2.10, 95% CI 1.68 to 2.52; $p < 0.00001$)
MORE: Ettinger 1999;[51] women with osteoporosis	• Placebo, NR • RLX, NR	• Placebo, 1522 • RLX, 1490	36	NR	Nothing	RLX group increased by 2.1% compared with placebo, $p < 0.001$
Mok 2011;[53] postmenopausal women on long-term GCCs	• Placebo, 57 • RLX, 57	• Placebo, 56 • RLX, 51	12	• Placebo, −0.45 (4.71[b]) • RLX, −0.59 (3.86[b])	Mean and SEMs	• NR • (MD −0.14, 95% CI −1.77 to 1.49; $p = 0.87$)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
ROMO vs. placebo						
FRAME: Cosman 2016;[54] postmenopausal women with osteoporosis	• Placebo, 3591 • ROMO, 3589	Substudy • Placebo, 62 • ROMO, 66	12	• Placebo, −0.70 (8.60[a]) • ROMO, + 5.20 (8.10[a])	95% CIs	ROMO group compared with placebo: 5.9% (95% CI 4.3 to 7.4); $p < 0.001$
FRAME: Cosman 2016;[54] postmenopausal women with osteoporosis	• Placebo to DEN, 3591 • ROMO to DEN, 3589 • 12 months' open label	• Placebo/DEN, 62 • ROMO/DEN, 66	24	• Placebo/DEN, + 0.60 (8.30[a]) • ROMO/DEN, + 6.60 (8.70[a])	95% CIs	ROMO group compared with placebo: 6.0% (95% CI 4.4 to 7.7); $p < 0.001$
Ishibashi 2017;[55] postmenopausal women with osteoporosis	• Placebo, 63 • ROMO, 63	• Placebo, 59 • ROMO, 59	12	• Placebo, + 0.30 (3.53[a]) • ROMO, + 3.80 (4.31[a])	Nothing	ROMO group compared with placebo: 3.5% (one-sided 95% CI 2.3%, NA); ($p < 0.00001$)
BRIDGE;[56] men with osteoporosis	• Placebo, 82 • ROMO, 63	• Placebo, 79 • ROMO, 158	12	• Placebo, −0.20 (4.00[a]) • ROMO, + 2.20 (4.60[a])	95% CIs	$p < 0.001$
TPTD vs. placebo						
ACTIVE: Miller 2016;[95] postmenopausal women with osteoporosis	• Placebo, 821 • TPTD, 818	• Placebo, 821 • TPTD, 818	18	• Placebo, −0.44 (3.57) • TPTD, + 2.26 (3.57)	Nothing	$p < 0.0001$
Orwoll 2003;[57] men with osteoporosis	• Placebo, 147 • TPTD, 151	• Placebo, 147 • TPTD, 151	12	• Placebo, + 0.31 (4.1) • TPTD, + 1.53 (3.95)	Nothing	$p = 0.029$
Miyauchi 2010;[58] women and men with osteoporosis	• Placebo, 70 • TPTD, 137	• Placebo, 67 • TPTD, 136	12	• Placebo, + 0.46 (3.89) • TPTD, + 2.24 (6.01)	Nothing	$p = 0.015$
Miyauchi 2010;[58] women and men with osteoporosis	• Placebo to TPTD, 59 • TPTD to TPTD, 119	• Placebo/TPTD, 58 • TPTD/TPTD, 117	12–18 OLE	• Placebo, + 1.22 (4.72) • TPTD, + 2.92 (4.83)	Nothing	• NR • (MD + 1.70, 95% CI 0.20 to 3.20; $p = 0.03$)

continued

TABLE 20 Femoral neck BMD data reported by the included studies (*continued*)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
Miyauchi 2010;[58] women and men with osteoporosis	• Placebo to TPTD, 50 • TPTD to TPTD, 102	• Placebo/TPTD, 48 • TPTD/TPTD, 95	18–24 OLE	• Placebo, + 2.43 (4.99) • TPTD, + 3.25 (4.49)	Nothing	• NR • (MD + 0.82, 95% CI −0.86 to 2.50; $p = 0.34$)
Miyauchi 2008;[59] postmenopausal women with osteoporosis	• Placebo, 39 • TPTD, 39	• Placebo, 34 • TPTD, 36	6	• Placebo, −0.71 (4.68) • TPTD, + 0.96 (4.86)	Nothing	• NR • MD + 1.67, 95% CI −0.56 to 3.90; $p = 0.14$)
Leder 2015;[61] postmenopausal women with osteoporosis	• Placebo, 45 • TPTD, 45	• Placebo, 41 • TPTD, 38	6	• Placebo, + 0.8 (4.8) • TPTD, + 1.1 (4.6)	Nothing	$p < 0.01$
Leder 2015;[61] postmenopausal women with osteoporosis	• Entered extension • Placebo, 11 • TPTD, 14	• Placebo, 11 • TPTD, 14	12	• Placebo, + 1.0 (NR) • TPTD, + 2.2 (NR)	Nothing	• NR • (NE)
Neer 2001;[62] postmenopausal women with osteoporosis	• Placebo, 544 • TPTD, 541	• Placebo, 479 • TPTD, 479	24 (trial stopped early; mean time to last visit was 19)	• Placebo, −0.7 (5.4) • TPTD, + 2.8 (5.7)	Nothing	$p < 0.001$
Sethi 2008;[63] postmenopausal women with osteoporosis	• Calcium + vitamin D, 41	• Calcium + vitamin D, 35 • TPTD + calcium + vitamin D, 38	6	• Calcium + vitamin D, + 2.12 (5.92) • TPTD + calcium + vitamin D, + 1.97 (4.25)	Nothing	• NR • (MD −0.15, 95% CI −2.53 to 2.23; $p = 0.90$)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
Head-to-head non-bisphosphonates						
DATA: Tsai 2013;[64] postmenopausal women with osteoporosis	• TPTD, 36 • DEN, 34 • Without placebo open-label	• TPTD, 31 • DEN, 33	12	• TPTD, + 0.80 (4.10) • DEN, + 2.10 (3.80)	Nothing	$p = 0.1939$
DATA: Leder 2014;[110] postmenopausal women with osteoporosis	As above	• TPTD, 31 • DEN, 33	24	• TPTD, + 2.80 (3.90) • DEN, + 4.10 (3.80)	Nothing	$p = 0.23$
DATA-Switch[65]	• OLE • TPTD to DEN, 27 • DEN to TPTD, 27	• TPTD/DEN, 27 • DEN/TPTD, 27	0–24	• TPTD/DEN, + 8.30 (5.83[a]) • DEN/TPTD, + 4.90 (7.02[a])	Nothing	$p < 0.0005$
DATA-Switch[65]	• OLE • TPTD to DEN, 27 • DEN to TPTD, 27	• TPTD/DEN, 27 • DEN/TPTD, 27	24–48	• TPTD/DEN, + 5.60 (4.77[a]) • DEN/TPTD, + 1.20 (5.83[a])	Nothing	$p < 0.0005$
EUROFORS: Eastell 2009;[66] postmenopausal women with osteoporosis pre treated with TPTD	• TPTD, 304 • RLX, 97 • Control,[c] 102	• TPTD, 304 • RLX, 97 • Control, 102	24	• TPTD, + 1.30 (NR) • RLX, + 3.10 (NR) • Control, + 3.50 (NR)	Nothing	• $p < 0.05$ TPTD vs. no active treatment; other comparisons NR • (NE)
STRUCTURE;[67] postmenopausal women with osteoporosis pre treated with ALN	• TPTD, 218 • ROMO, 218 • Without placebo, open label	• TPTD, 209 • ROMO, 206	12	• TPTD, −0.20 (4.43[a]) • ROMO, + 3.20 (3.30[a])	Nothing	$p < 0.0001$

continued

TABLE 20 Femoral neck BMD data reported by the included studies (*continued*)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
McClung 2014;[68] postmenopausal women with osteoporosis	• Placebo, 52 • TPTD, 55 • ROMO, 52 • ALN, 51	• Placebo, 47 • TPTD, 46 • ROMO, 50 • ALN, 47	12	• Placebo, + 1.10 (3.15[a]) • TPTD, + 1.10 (3.11[a]) • ROMO, + 1.40 (3.25[a]) • ALN, + 1.2 (3.15[a])	Nothing	• NR • (TPTD vs. ROMO – MD −0.30, 95% CI −1.59 to 0.99; $p = 0.65$) • (ROMO vs. placebo, $p = 0.0002$) • (TPTD vs. placebo, $p = 0.0007$) • (ROMO vs. ALN, $p = 0.73$) • (TPTD vs. ALN, $p = 0.88$)
DEN vs. bisphosphonates						
DECIDE;[69] postmenopausal women with osteoporosis	• ALN, 595 • DEN, 594 • Both with placebo	• ALN, 586 • DEN, 593	12	• ALN, + 1.80 (3.77[a]) • DEN, + 2.40 (3.17[a])	95% CIs	Absolute treatment difference 0.6% (95% CI 0.3 to 1.0); $p = 0.0001$
STAND;[70] postmenopausal women with osteoporosis already on ALN	• ALN, 251 • DEN, 253 • Without placebo	• ALN, 233 • DEN, 241	12	• ALN, + 0.41 (3.81[a]) • DEN, + 1.40 (3.34[a])	Means and 95% CIs	$p < 0.0121$
DAPS;[71] postmenopausal women with osteoporosis	• ALN, 124 • DEN, 126 • Without placebo	• ALN, 106 • DEN, 113	12	• ALN, + 2.00 (3.60) • DEN, + 2.90 (3.50)	Nothing	• NR • (MD + 0.90, 95% CI −0.04 to 1.84; $p = 0.06$)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
DAPS:[109] postmenopausal women with osteoporosis	• Cross-over • ALN to DEN, 92 • DEN to ALN, 102	• ALN/DEN, 92 • DEN/ALN, 102	12–24 (post cross-over)	• ALN/DEN, −0.10 (NR) • DEN/ALN, + 1.70 (NR)	Nothing	• NR • (NE)
McClung 2006;[72] postmenopausal women with osteoporosis or osteopenia	• Placebo for DEN, 46 • ALN, 47 • DEN, 47	• Placebo, 40 • ALN, 45 • DEN, 42	12	• Placebo, −0.30 (3.16[b]) • ALN, + 2.10 (3.35[b]) • DEN, + 2.10 (3.24[b])	Nothing	ALN and DEN vs. placebo, both $p < 0.001$ (ALN vs. DEN MD 0.00, 95% CI −1.38 to 1.38; $p = 1.00$)
Recknor 2013;[73] postmenopausal women with osteoporosis	• IBN, 416 • DEN, 414 • Without placebo	• IBN, 368 • DEN, 399	12	• IBN, + 0.70 (4.79[a]) • DEN, + 1.70 (3.96[a])	95% CIs	$p < 0.001$
Saag 2018;[74] women and men continuing GCCs with osteoporosis or low BMD + fracture	• RIS, 252 • DEN, 145 • Both with placebo	• RIS, 215 • DEN, 217	12	• RIS, + 0.60 (3.37[a]) • DEN, + 1.60 (3.76[a])	95% CIs	$p = 0.004$
Saag 2018;[74] women and men initiating GCCs with osteoporosis or low BMD + fracture	• RIS, 253 • DEN, 145 • Both with placebo	• RIS, 128 • DEN, 119	12	• RIS, −0.20 (4.33[a]) • DEN, + 0.90 (4.17[a])	95% CIs	$p = 0.020$
Miller 2016;[75] postmenopausal women with osteoporosis previously treated with bisphosphonates	• ZOL, 322 • DEN, 321 • Both with placebo	• ZOL, 309 • DEN, 311	12	• ZOL, −0.10 (3.34[a]) • DEN, + 1.20 (3.96[a])	Nothing	$p < 0.0001$

continued

TABLE 20 Femoral neck BMD data reported by the included studies (*continued*)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
RLX vs. bisphosphonates						
EFFECT: Sambrook 2004[76] (international not including USA); postmenopausal women with osteoporosis	• ALN, 246 • RLX, 241 • Both with placebo	• ALN, 246 • RLX, 241	12	• ALN, + 2.20 (5.02[b]) • RLX, + 1.00 (4.66[b])	SEMs	1.3%, 95% CI 0.5 to 2.1; $p = 0.0001$
EFFECT (USA);[77] postmenopausal women with osteoporosis	• ALN, 223 • RLX, 233 • Both with placebo	• ALN, 199 • RLX, 206	12	• ALN, + 1.72 (4.23[b]) • RLX, + 1.35 (4.59[b])	Means and SEMs	$p = 0.396$
Johnell 2002;[78] postmenopausal women with osteoporosis	• Placebo, 82 • ALN, 83 • RLX, 82	• Placebo, 77 • ALN, 77 • RLX, 77	12	• Placebo, + 0.20 (3.51[b]) • RLX, + 1.70 (3.51[b]) • ALN, + 2.70 (4.39[b])	Nothing	• ALN and RLX both significantly different to placebo ($p < 0.05$) • ALN significantly different to RLX ($p < 0.05$)
EVA: Recker 2007;[80] postmenopausal women with osteoporosis	• ALN, 716 • RLX, 707 • Both with placebo	• ALN, 64 • RLX, 58	24	• ALN, + 3.88 (4.96[b]) • RLX, + 2.31 (3.96[b])	SEMs	$p = 0.002$
Sanad 2011;[81] postmenopausal women with osteoporosis	• ALN weekly, 46 • RLX, 44 • Without placebo	• ALN, 31 • RLX, 35	12	• ALN, + 3.11 (NR) • RLX, + 3.48 (NR)	Means	• NR • (NE)
Michalska 2006;[82] postmenopausal women with osteoporosis previously treated with bisphosphonates	• Placebo, 33 • RLX, 33 • ALN, 33	• Placebo, 33 • RLX, 33 • ALN, 33	12	• Placebo, + 1.11 (NR) • RLX, + 2.07 (NR) • ALN, + 2.32 (NR)	Means (SEMs in graph overlap – unable to extract)	• $p \geq 0.05$ • (NE)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
Michalska 2006;[82] postmenopausal women with osteoporosis previously treated with bisphosphonates	• OLE • No treatment, 33 • RLX, 33 • ALN, 33	• No treatment, 33 • RLX, 33 • ALN, 33	24 including 12 OLE	• No treatment, + 0.89 (3.27[b]) • RLX, + 1.14 (2.81[b]) • ALN, + 2.86 (3.73[b])	Means and SEMs	• NR • (RLX vs. ALN MD −1.72, 95% CI −3.31 to −0.13; $p = 0.03$) • (RLX vs. no treatment MD + 0.25, 95% CI −1.22 to 1.72; $p = 0.74$)
ROMO vs. bisphosphonates						
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	• ALN, 2047 • ROMO, 2046 • Both with placebo	• ALN, 1826 • ROMO, 1829	12	• ALN, + 1.70 (5.67[a]) • ROMO, + 4.90 (6.33[a]) • ITT LOCF	Nothing	$p < 0.001$
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	• ALN to ALN, 2047 • ROMO to ALN, 2046 • Open label	• ALN/ALN, 1826 • ROMO/ALN, 1829	24	• ALN/ALN, + 2.30 (6.65[a]) • ROMO/ALN, + 6.00 (7.42[a]) • ITT LOCF	Nothing	$p < 0.001$
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	As above	• ALN/ALN, 1826 • ROMO/ALN, 1829	36	• ALN/ALN, + 2.40 (7.19[a]) • ROMO/ALN, + 6.00 (7.90[a]) • ITT LOCF	Nothing	$p < 0.001$
TPTD vs. bisphosphonates						
FACT;[84] postmenopausal women with osteoporosis	• ALN, 101 • TPTD, 102 • Both with placebo	• ALN, 101 • TPTD, 102	18	• ALN, + 3.50 (3.18[a]) • TPTD, + 3.90 (4.51[a])	95% CIs	$p = 0.05$
Saag 2009;[103] women and men on GCCs with osteoporosis or low BMD + fracture	• ALN, 214 • TPTD, 214 • Both with placebo	• ALN, 113 • TPTD, 120	36	• ALN, + 3.40 (4.93[a]) • TPTD, + 6.29 (5.03[a])	95% CIs	$p < 0.001$
EUROGIOPs;[87] men on GCCs with osteoporosis	• RIS, 47 • TPTD, 45 • Without placebo; open label	• RIS, 37 • TPTD, 38	18	• RIS, −1.10 (7.00[b]) • TPTD, + 1.52 (6.66[b])	SEMs	$p = 0.026$

continued

TABLE 20 Femoral neck BMD data reported by the included studies (*continued*)

Trial name: first author and year; population	Treatments, *n* randomised	Treatments, *n* analysed	Follow-up (months)	Femoral neck BMD, percentage change from baseline, mean (SD)	Which data were estimated from graph?	Femoral neck BMD, reported (estimated) between-group difference
Walker 2013;[89] men with osteoporosis	• RIS weekly, 10 • TPTD, 9 • Both with placebo	• RIS, 10 • TPTD, 9	18	• RIS, + 0.5 (5.38[b]) • TPTD, + 3.89 (5.10[b])	Nothing	$p \geq 0.05$
Hadji 2012;[91] postmenopausal women with osteoporosis	• RIS weekly, 350 • TPTD, 360 • Both with placebo	• RIS, 338 • TPTD, 351	18	• RIS, + 0.77 (7.35[b]) • TPTD, + 2.11 (7.58[b])	Nothing	$p = 0.02$
MOVE: Malouf-Sierra 2017;[92] women and men with low BMD + recent hip fracture surgery	• RIS daily, 113 • TPTD, 111 • Both with placebo	• RIS, 81 • TPTD, 80	18	• RIS, −1.19 (NR) • TPTD, + 1.96 (NR)	Nothing	$p = 0.003$
Cosman 2011;[93] postmenopausal women with osteoporosis	• ZOL,[d] 137 • TPTD + ZOL placebo, 138	• ZOL, 129 • TPTD + placebo, 129	12	• ZOL, + 1.90 (5.22[b]) • TPTD + placebo, + 0.09 (4.20[b])	Nothing	$p < 0.05$

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; CI, confidence interval; DAPS, Denosumab Adherence Preference Satisfaction; DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus alendronate; FACT, Forteo Alendronate Comparator Trial; GCC, glucocorticoid; ITT, intention to treat; MORE, Multiple Outcomes of Raloxifene Evaluation; NE, not estimable; NR, not reported; OLE, open-label extension; SEM, standard error of the mean; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy.

a Estimated from 95% CI.

b Estimated from standard error.

c No active treatment.

d Not placebo controlled for TPTD.

Note

ALN, 10 mg daily or 70 mg weekly.

DEN, 60 mg s.c. every 6 months.

IBN, 150 mg oral every month.

RLX, 60 mg daily.

ROMO, Romosozumab 210 mg s.c. monthly.

TPTD, 20 µg s.c. daily.

ZOL, 5 mg i.v. annually

TABLE 21 Adverse events: mortality

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	Overall mortality, *n/N* (%)	Reported between-group difference
DEN vs. placebo				
FREEDOM: Cummings 2009[41] and Bone 2017[104]	• Placebo, 3876 • DEN, 3882	36	• Placebo, 90/3876 (2.3) • DEN, 70/3886 (1.8)[41]	$p = 0.08$
ADAMO: Orwoll 2012[42]	• Placebo, 120 • DEN, 120 • Both for 12 months then DEN open label (both groups) for 12 months	12	• 1/120 (0.8) • 1/120 (0.8)	NR
ADAMO: Langdahl 2015[111]	• Placebo, 116 • DEN, 111 • Both for 12 months then DEN open label (both groups) for 12 months	12–24	• 0/116 (0) • 1/111 (1)	NR
DIRECT: Nakamura 2014[43]	• Placebo, 481 • DEN, 475	24	• 5/481 (1.0) • 5/475 (1.1)	NR
DIRECT: Sugimoto 2015[106]	• Placebo, 406 • DEN, 404 • Both for 24 months then DEN open label (both groups) for 12 months	24–36	• 2/406 (0.5) • 4/404 (1.0)	NR
Nakamura 2012[44]	• Placebo, 55 • DEN, 54	12	• NR	NR
Koh 2016[45] (NCT01457950)	• Placebo, 66 • DEN, 69	6	• 0/66 (0) • 1/69 (< 1)	NR
Koh 2016[45] (NCT01457950)	• Placebo, 63 • DEN, 60 • Both for 6 months then DEN open label (both groups) for 12 months	6–12	• 0/63 (0) • 0/60 (0)	NR
RLX vs. placebo				
Adami 2008[46]	All TPTD for 12 months then: • Placebo, 172 • RLX, 157	12	NR	NR
Morii 2003[47]	• Placebo, 97 • RLX, 90	12	NR	NR
Liu 2004[48]	• Placebo, 102 • RLX, 102	12	• 0/102 (0) • 0/102 (0)	NR
Gorai 2012[94]	• Alfacalcidol, 44 • RLX, 45 • Alfacalcidol plus RLX, 48	12	NR	NR
Silverman 2008[50] (NCT00205777)	• Placebo, 1885 • RLX, 1849	36	• 11/1885 (0.6) • 19/1849 (1.0)	NR

continued

TABLE 21 Adverse events: mortality (*continued*)

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	Overall mortality, *n/N* (%)	Reported between-group difference
MORE: Ettinger 1999[51] and Maricic 2002[102]	• Placebo, 2576 • RLX, 2557	36	NR	NR
Lufkin 1998[52]	• Control (no active treatment), 48 • RLX, 48	12	NR	NR
Mok 2011[53] (NCT00371956)	• Placebo, 57 • RLX, 57	12	NR	NR
ROMO vs. placebo				
BRIDGE: Lewiecki 2018;[56] (NCT02186171)	• Placebo, 82 • ROMO, 163	12	• Placebo, 1/81 (1.2) • ROMO, 2/163 (1.2)	NR
FRAME: Cosman 2016[54]	• Placebo, 3591 • ROMO, 3589 • For 12 months then DEN for 12 months open label (both groups)	12 and 24	12 months: • Placebo, 23/3576 (0.6) • ROMO, 29/3581 (0.8) 24 months: • Placebo-DEN, 47/3576 (1.3) • ROMO-DEN, 52/3581 (1.5)	NR
Ishibashi 2017[55] (NCT01992159)	• Placebo, 63 • ROMO, 63	12	• Placebo, 0/63 (0) • ROMO, 0/63 (0)	NR
TPTD vs. placebo				
Orwoll 2003[57]	• Placebo, 147 • TPTD, 151	Median 11	• Placebo, 0/147 (0) • TPTD, 2/151 (1.3)	NR
Miyauchi 2010[58]	• Placebo, 67 • TPTD, 136 • Both for 12 months then TPTD open label (both groups) for 12 months	24	• 0/67 (0) • 0/136 (0)	NR
Miyauchi 2008[59]	• Placebo, 38 • TPTD, 39	6	• 0/38 (0) • 0/39 (0)	NR
ACTIVE[95] (NCT01343004)	• Placebo, 820 • TPTD, 818	18	• 5/820 (0.6) • 3/818 (0.4)	NR
Leder 2015[61]	• Placebo, 45 • TPTD, 45 • Open label	6, plus a further 6-month extension to 12 months	6 months: • Placebo, 0/45 (0) • TPTD, 0/45 (0) 12 months NR	NR
Neer 2001[62] (NCT00670501)	• Placebo, 544 • TPTD months, 541	24 (stopped early; mean time to last visit was 19 months)	NR	Reports no significant difference. Data NR
Sethi 2008[63] (NCT00500409)	• Control (calcium + vitamin D), 41 • TPTD and calcium + vitamin D, 41	6	• 0/41 (0) • 0/41 (0)	Reports no significant difference

TABLE 21 Adverse events: mortality (*continued*)

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	Overall mortality, *n/N* (%)	Reported between-group difference
Head-to-head non-bisphosphonates				
DATA[64]	• DEN, 34 • TPTD, 36	12	NR	NR
DATA[64] (NCT00926380)	• DEN, 34 • TPTD, 36	24	NR	NR
DATA-Switch[65]	• DEN, 27 • TPTD, 27 • Both for 24 months then DEN switched to TPTD and TPTD switched to DEN open label for 12 months	24–48	NR	NR
EUROFORS: Eastell 2009[66]	• All TPTD for 12 months then: • Control (no active treatment), 102 • TPTD, 304 • RLX, 97	24	NR	NR
STRUCTURE[67]	• ROMO, 218 • TPTD, 214	12	• 1/218 (0.5) • 1/214 (0.5)	NR
McClung 2014[68]	• ROMO, 51 (blind) • TPTD, 55 (open-label) • Pooled placebo (mix of ALN, TPTD and ROMO administrations), 50 (blind) • ALN, 51 (open label)	12	• ROMO, 0/51 (0) • TPTD, 0/54 (0) • Placebo, 1/50 (2) • ALN, 0/51 (0)	NR
DEN vs. bisphosphonates				
DECIDE[69]	• ALN, 586 • DEN, 593 • Both plus placebo	12	• 1/593 (0.2) • 1/586 (0.2)	• NR • (Not significant)
STAND: Kendler 2010[70]	• ALN, 251 • DEN, 253	12	• ALN, 0/249 (0) • DEN, 1/253 (0.4)	$p = 1.0000$
DAPS: Kendler 2011[71] and Freemantle 2012[109]	• ALN, 124 • DEN, 126 • Open label	12	NR	NR
McClung 2006[72]	• Placebo for abaloparatide s.c. every 3 months, 46 • ALN open-label, 47 • DEN, 47	12	• Placebo, 0/46 (0) • ALN, 0/46 (0) • DEN, 0/47 (0)	NR
Recknor 2013[73]	• IBN, 416 • DEN, 417	12	• IBN, 1/410 (0.2) • DEN, 0/411 (0)	$p = 0.299$
Saag 2018[74] (NCT01575873)	• RIS, 384 • DEN, 394 • Both with placebo	12	• RIS, 9/384 (2.34) • DEN, 13/394 (3.30)	NR
Miller 2016[75]	• ZOL, 322 • DEN, 321 • Both with placebo	12	Fatal AEs: • ZOL, 1/320 (0.3) • DEN, 0/320 (0.0)	NR

continued

TABLE 21 Adverse events: mortality (*continued*)

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	Overall mortality, *n/N* (%)	Reported between-group difference
RLX vs. bisphosphonates				
EFFECT (international, excluding USA): Sambrook 2004[76]	• ALN, 246 • RLX, 241	12	• ALN, 0/246 (0) • RLX, 1/241 (< 1)	• NR • (Not significant)
EFFECT (USA): Luckey 2004[77]	• ALN, 223 • RLX, 233 • Both groups received placebo	12	NR	NR
Johnell 2002[78]	• Placebo (ALN and RLX), 82 • ALN, 83 • RLX, 82 • ALN and RLX received placebo	12	NR	NR
Muscoso 2004[79]	• ALN, 1000 • RIS, 100 • RLX, 100 • All daily	24	NR	NR
EVA: Recker 2007[80]	• ALN, 716 • RLX, 707	24	• ALN, 1/716 (< 1) • RLX, 1/707 (< 1)	• NR • (Not significant)
Sanad 2011[81]	• ALN, 44 • RLX, 46	12	NR	NR
Michalska 2006[82]	Open label: • ALN, 33 Blind: • Placebo, 33 • RLX, 33	12, followed by 12 months' open-label extension	NR	NR
ROMO vs. bisphosphonates				
ARCH: Saag 2017[83]	• ALN, 2014 • ROMO, 2040 • Both for 12 months then ALN open label (both groups) for 12 months	12 from randomisation, then a further 12 open label, following treatment-switching	0–12 months: • ALN, 21/2014 (1.0) • ROMO, 30/2040 (1.5) 0–24 months • ALN/ALN, 90/2014 (4.5) • ROMO/ALN, 90/2040 (4.4)	NR

TABLE 21 Adverse events: mortality (*continued*)

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	Overall mortality, *n/N* (%)	Reported between-group difference
TPTD vs. bisphosphonates				
FACT: McClung 2005[84]	• ALN, 101 • TPTD, 102 • Both with placebo	18	NR	NR
Saag 2009[85] (NCT01575873)	• ALN, 214 • TPTD, 214 • Both with placebo	36	• ALN, 4/214 (1.87) • TPTD 2/214 (0.93)	• NR • (Not significant)
Panico 2011[86]	• ALN, 39 • TPTD, 42 • Open label	18	NR	NR
EuroGIOPs: Glüer 2013[87]	• RIS, 47 • TPTD, 45 • Open label	18	• RIS, 1/47 (2.1) • TPTD, 2/45 (4.4)	$p = 0.613$
Anastasilakis 2008[88]	• RIS, 22 • TPTD, 22 • Open label	12	NR	NR
Walker 2013[89]	• RIS, 10 • TPTD, 9 • Both with placebo	18	NR	NR
Hadji 2012[91]	• RIS, 350 • TPTD, 360 • Both with placebo	18	• RIS, 5/350 (1.4) • TPTD, 4/360 (1.1)	$p = 0.75$
VERO: Kendler 2018[99]	• RIS, 680 • TPTD, 680 • Both with placebo	24	• RIS, 7/680 (1.0) • TPTD, 15/690 (2.2)	$p = 0.13$
MOVE: Abtahi 2016[101]	• RIS, 110 • TPTD, 106 • Both with placebo	6	• RIS, 5/110 (4.5) • TPTD, 2/106 (1.9)	$p = 0.446$
MOVE: Malouf-Sierra 2017[92]	• Blind until 6 months then open label	24	• RIS, 7/110 (6.4) • TPTD, 2/106 (1.9)	$p = 0.171$
Cosman 2011[93]	• ZOL, 137 • TPTD, 137 • Only TPTD group received placebo	12	• ZOL, 1/137 (< 1) • TPTD, 0/137 (0)	NR

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; DAPS, Denosumab Adherence Preference Satisfaction; DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus alendronate; FACT, Forteo Alendronate Comparator Trial; MORE, Multiple Outcomes of Raloxifene Evaluation; NR, not reported; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy.

Notes

ALN, 10 mg daily or 70 mg weekly.
DEN, 60 mg s.c. every 6 months.
IBN, 150 mg oral every month.
RLX, 60 mg daily.
ROMO, 210 mg s.c. monthly.
RIS, 5 mg daily or 35 mg weekly.
TPTD, 20 µg s.c. daily.
ZOL, 5 mg i.v. annually.

TABLE 22 Adverse events and SAEs

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
DEN vs. placebo						
FREEDOM: Cummings 2009[41] and Bone 2017[104]	• Placebo, 3876 • DEN, 3886 • Both every 6 months	36	• Placebo, 972/3876 (25.1) • DEN, 1004/3886 (25.8)[41]	$p = 0.61$	• Placebo, 3607/3876 (93.1) • DEN, 3605/3886 (92.8)[41]	$p = 0.91$
ADAMO: Orwoll 2012[42]	• Placebo, 120 • DEN, 120 • Both for 12 months then DEN open-label (both groups) for 12 months	12	• Placebo, 10/120 (8.3) • DEN, 11/120 (9.2)	NR	• Placebo, 84/120 (70.0) • DEN, 86/120 (71.7)	NR
ADAMO: Langdahl 2015[111]	• Placebo, 116 • DEN, 111 • Both for 12 months then DEN open-label (both groups) for 12 months	12–24	• Placebo, 5/116 (4) • DEN, 9/111 (8)	NR	• Placebo, 60/116 (52) • DEN 70/111 (63)	NR
DIRECT: Nakamura 2014[43]	• Placebo, 481 • DEN, 475	24	• Placebo, 68/481 (14.1) • DEN, 66/475 (13.9)	NR	• Placebo, 446/481 (92.7) • DEN, 448/475 (94.3)	NR
DIRECT[106]	• Placebo, 406 • DEN, 404 • Both for 24 months then DEN open label (both groups) for 12 months	24–36	• Placebo, 27/406 (6.7) • DEN, 30/404 (7.4)	NR	• Placebo, 339/406 (83.5) • DEN, 343/404 (84.9)	NR

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
Nakamura 2012[44]	• Placebo, 55 • DEN, 54	12	• Placebo, 4/54 (7.4) • DEN, 6/53 (11.3)	NR	• Placebo, 49/54 (90.7) • DEN, 47/54 (87.0)	NR
Koh 2016[45] (NCT01457950)	• Placebo, 66 • DEN, 69	6	• Placebo, 1/66 (2) • DEN, 2/69 (3)	NR	• Placebo, 32/66 (48) • DEN, 38/69 (55)	NR
Koh 2016[45] (NCT01457950)	• Placebo, 63 • DEN, 60 • Both for 6 months then DEN open label (both groups) for 12 months	6–12	• Placebo /DEN, 3/63 (5) • DEN, 1/60 (2)	NR	• Placebo/DEN, 29/63 (46) • DEN, 22/60 (37)	NR
RLX vs. placebo						
Adami 2008[46]	All TPTD for 12 months then: • Placebo, 172 • RLX, 157	12	NR	NR	NR	NR
Morii 2003[47]	• Placebo, 97 • RLX, 90	12	• Placebo, 7 (7.2) • RLX, 5 (5.4)	$p = 0.452$	• Placebo, TEAE • 33 (34.0) • RLX, TEAE • 32 (34.8)	• $p = 0.444$ • [All AEs (number NR) $p = 0.851$]
Liu 2004[48]	• Placebo, 102 • RLX, 102	12	• Placebo, 5/102 (4.9) • RLX, 2/102 (2.0)	Not significant at $p < 0.05$	NR	
Gorai 2012[94]	• Alfacalcidol, 44 • RLX, 45 • Alfacalcidol plus RLX, 48	12	NR	NR	• Alfacalcidol 11/44 (25.0) • RLX, 17/45 (37.8) • Alfacalcidol plus RLX 13/48 (27.1)	NR
Silverman 2008[50] (NCT00205777)	• Placebo, 1885 • RLX, 1849	36	• Placebo, 353/1885 (18.7) • RLX, 344/1849 (18.6)	NR	• Placebo, 1813/1885 (96.2) • RLX, 1775/1885 (96.0)	NR

continued

TABLE 22 Adverse events and SAEs (*continued*)

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
MORE: Ettinger 1999[51] and Maricic 2002[102]	• Placebo, 2576 • RLX, 2557	36	NR	NR	NR	NR
Lufkin 1998[52]	• Control (no active treatment), 48 • RLX, 48	12	NR	NR	NR	NR
Mok 2011[53] (NCT00371956)	• Placebo, 57 • RLX, 57	12	NR	NR	NR	NR
ROMO vs. placebo						
BRIDGE[56] (NCT02186171)	• Placebo, 82 • ROMO, 163	12	• TEAE placebo, 10/81 (12.3) • ROMO TEAE, 21/163 (12.9)	NR	• TEAE placebo, 65/81 (80.2) • TEAE ROMO, 123/163 (75.5)	NR
FRAME: Cosman 2016[54]	• Placebo, 3591 • ROMO, 3589 • For 12 months then DEN for 12 months open label (both groups)	12 from randomisation, then a further 12 following treatment-switching	12 months: • Placebo, 312/3576 (8.7) • ROMO, 344/3581 (9.6) 24 months: • Placebo-DEN, 550/3576 (15.1) • ROMO-DEN, 565/3581 (15.8)	NR	12 months: • Placebo, 2850/3576 (79.7) • ROMO, 2806/3581 (78.4) 24 months: • Placebo DEN, 3069/3576 (85.8) • ROMO-DEN, 3053/3581 (85.3)	NR
Ishibashi 2017[55] (NCT01992159)	• Placebo, 63 • ROMO, 63	12	• Placebo, 4/63 (6.3) • ROMO, 2/63 (3.2)	NR	• Placebo, 43/63 (68.3) • ROMO, 47/63 (74.6)	NR

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
TPTD vs. placebo						
Orwoll 2003[57]	• Placebo, 147 • TPTD, 151 • Both daily	Median 11	NR	NR	Reports that the overall incidence of AEs was similar across groups. No data	NR
Miyauchi 2010[58]	• Placebo, 67 • TPTD, 136 • Both for 12 months then TPTD open label (both groups) for 12 months	24	• Placebo,13/67 (19.4) • TPTD, 12/136 (8.8)	Reported as not significant. *p*-value NR	• Placebo, 64/67 (95.5) • TPTD, 125/136 (91.9)	Reported as not significant. *p*-value NR
Miyauchi 2008[59]	• Placebo, 38 • TPTD, 39	6	NR as number of participants with SAE		• Placebo, TEAE 29 (76.3) • TPTD, TEAE 33 (84.6)	NR
ACTIVE[95] (NCT01343004)	• Placebo, 820 • TPTD, 818	18	• Placebo, 90/820 (11.0) • TPTD, 82/818 (10.0)	NR	• Placebo, 718/820 (87.6) • TPTD, 727/818 (88.9)	NR
Leder 2015[61]	• Placebo, 45 • TPTD, 45 • Open label	6, plus a further 6-month extension to 12 months	6 months: • Placebo, 1/45 (2.2) • TPTD, 0/45 (0) 12 months: • Placebo, 1/45 (2.2) • TPTD, 0/45 (0)	NR	6 months: • Placebo, 32/45 (71.1) • TPTD, 35/45 (77.8) 12 months: • Placebo, 16/45 (36) • TPTD, 14/45 (30)	NR

continued

TABLE 22 Adverse events and SAEs (*continued*)

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
Neer 2001[62] (NCT00670501)	• Placebo, 544 • TPTD, 541	24 (stopped early; mean time to last visit was 19 months)	• Placebo, NR • [Withdrew because of AE 32 (6%)] • TPTD, NR	NR	NR	NR
Sethi 2008[63] (NCT00500409)	• Control (calcium + vitamin D), 41 • TPTD and calcium + vitamin D, 41	6	• Control, 0/41 (0) • TPTD, 0/41 (0)	Reported as not significant. *p*-value NR	• Control, 9/41 (21.9) • TPTD, 9/41 (21.9)	Reported as not significant. *p*-value NR
Head-to-head non-bisphosphonates						
DATA[64]	• DEN, 34 • TPTD, 36	12	• DEN, 1/34 (2.9) • TPTD, NR – three events	NR	NR	NR
DATA[64] (NCT00926380)	• DEN, 34 • TPTD, 36	24	• DEN, 1/33 (3.0) • TPTD, 2/31 (6.5)	NR	• TPTD, 5/31 (16.1) • DEN, 4/33 (12.1)	NR
DATA-Switch[65]	• DEN, 27 • TPTD, 27 • Both for 24 months then DEN switched to TPTD and TPTD switched to DEN open label for 12 months	24–48	• DEN/TPTD, 4/27 (14.8) • TPTD/DEN, 6/27 (22.2)	NR	NR	NR
STRUCTURE[67]	• ROMO, 218 • TPTD, 214	12	• TPTD, 23/214 (11) • ROMO, 17/218 (8)	NR	• TPTD, 148/214 (69) • ROMO, 164/218 (75)	NR
EUROFORS[66]	All TPDT for 12 months then: • Control (no active treatment), 102 • TPTD, 304 • RLX, 97	24	NR	NR	• Control, TEAE, 56/102 (54.9) • TPTD, TEAE, 174/304 (57.0) • RLX, TEAE, 53/97 (54.6)	Not significant at $p < 0.05$

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
McClung 2014[68]	• ROMO, 51 (blind) • TPTD, 55 (open-label) • Pooled placebo (mix of ALN, TPTD and ROMO administrations), 50 (blind) • ALN, 51 (open label)	12	• ROMO, 5/51 (10) • TPTD, 5/54 (9) • Placebo, 7/50 (14) • ALN, 4/51 (8)	NR	• ROMO, 42/51 (82) • TPTD, 37/54 (69) • Placebo, 45/50 (90) • ALN, 44/51 (86)	NR
DEN vs. bisphosphonates						
DECIDE[69]	• ALN, 586 • DEN,593 • Both plus placebo	12	• ALN, 37/586 (6.3) • DEN, 34/593 (5.7)	0.71	• ALN, 482/586 (82.3) • DEN, 480/593 (80.9)	Non-significant $p = 0.60$
STAND: Kendler 2010[70]	• ALN, 251 • DEN, 253	12	• ALN, 16/249 (6.4) • DEN, 15/253 (5.9)	$p = 0.8546$	• ALN, 196/249 (78.7) • DEN, 197/253 (77.9)	$p = 0.8294$
DAPS: Kendler 2011[71] and 2012[109]	• ALN, 124 • DEN, 126 • Open label	12	• ALN, 5/117 (4.3) • DEN, 3/125 (2.4)	NR	• ALN, 75/117 (64.1) • DEN, 90/125 (72.0)	$p = 0.403$
McClung 2006[72]	• Placebo for abaloparatide s.c. every 3 months, 46 • ALN open-label, 47 • DEN, 47	12	• Placebo, 2/46 (4.3) • ALN, 1/46 (2.2) • DEN, NR • 18/314 (5.7) across all DEN dosing arms	NR	• Placebo, 41/46 (89.1) • ALN, 42/46 (91.3) • DEN, NR • 274/314 (87.3) across all DEN dosing arms	NR
Recknor 2013[73]	• IBN, 416 • DEN, 417	12	• IBN, 22/410 (5.4) • DEN, 39/411 (9.5)	$p = 0.046$	• IBN, 230/410 (56.1) • DEN, 245/411 (59.6)	$p = 0.635$
Saag 2018[74]	• RIS, 384 • DEN, 394 • Both with placebo	12	• RIS, 65/384 (17) • DEN, 63/394 (16)	NR	• RIS, 265/384 (69) • DEN, 285/394 (72)	NR
Miller 2016[75]	• ZOL, 322 • DEN, 321 • Both with placebo	12	• ZOL 29/320 (9.1) • DEN, 25/320 (7.8)	NR	• ZOL, 199/320 (62.2) • DEN, 199/320 (62.2)	NR

continued

TABLE 22 Adverse events and SAEs (*continued*)

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
RLX vs. bisphosphonates						
EFFECT (international excluding USA); Sambrook 2004[76]	• ALN, 246 • RLX, 241	12	• ALN, 11/246 (4.5) • RLX, 14/241 (5.8)	$p = 0.543$	• ALN, 154/246 (62.6) • RLX, 157/241 (65.1)	$p = 0.573$
EFFECT (USA); Luckey 2004[77]	• ALN, 223 • RLX, 233 • Both groups received placebo	12	• ALN, 11/221 (5.0) • RLX, 16/230 (7.0)	$p = 0.43$	• ALN, 164/221 (74.2) • RLX, 173/230 (75.2)	$p = 0.83$
Johnell 2002[78]	• Placebo (ALN and RLX), 82 • ALN, 83 • RLX, 82 • ALN and RLX received placebo	12	NR	NR	NR	NR
Muscoso 2004[79]	• ALN, 1000 • RIS, 100 • RLX, 100 • All daily	24	NR	NR	NR	NR
EVA: Recker 2007[80]	• ALN, 716 • RLX, 707	24	NR	NR	• ALN, 397/716 (55.5) • RLX, 390/707 (55.2)	$p = 0.92$
Sanad 2011[81]	• ALN, 44 • RLX, 46	12	NR	NR	NR	NR
Michalska 2006[82]	Open label: • ALN, 33 Blind: • Placebo, 33 • RLX, 33	12, followed by 12 months' open-label extension	NR	NR	• Placebo, 2/33 (6) • ALN, 4/33 (12) • RLX, 8/33 (24)	$p = 0.126$

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
ROMO vs. bisphosphonates						
ARCH: Saag 2017[83]	• ALN, 2014 • ROMO, 2040 • Both for 12 months then ALN open label (both groups) for 12 months	12 from randomisation, then a further 12 open label, following treatment-switching	0–12 months: • ALN, 278/2014 (13.8) • ROMO, 262/2040 (12.8) 0–24 months: • ALN/ALN, 605/2014 (30.0) • ROMO/ALN, 586/2040 (28.7)	NR	0–12 months: • ALN, 1584/2014 (78.6) • ROMO, 1544/2040 (75.7) 0–24 months: • ALN/ALN, 1784/2014 (88.6) • ROMO/ALN, 1766/2040 (86.6)	NR
TPTD vs. bisphosphonates						
FACT: McClung 2005[84]	• ALN, 101 • TPTD, 102 • Both with placebo	18	NR	NR	NR	NR
Saag 2009[85]	• ALN, 214 • TPTD, 214 • Both with placebo	36	• ALN, 64/214 (30) • TPTD, 70/214 (33)	$p = 0.518$	• ALN, 184/214 (86) • TPTD, 194/214 (91)	$p = 0.116$
Panico 2011[86]	• ALN, 39 • TPTD, 42 • Open label	18	NR	NR	NR	NR
EuroGIOPs: Glüer 2013[87]	• RIS, 47 • TPTD, 45 • Open label	12	• RIS, 22/47 (46.8) • TPTD, 13/45 (28.9)	$p = 0.089$	• RIS, 35/45 (74.5) • TPTD, 25/47 (55.6)	$p = 0.080$
Anastasilakis 2008[88]	• RIS, 22 • TPTD, 22 • Open label	12	NR	NR	• RIS, 7/22 (33.3) • TPTD, 11/22 (39.1)	Not significant at $p < 0.05$
Walker 2013[89]	• RIS, 10 • TPTD, 9 • Both with placebo	18	NR	NR	NR	NR

continued

TABLE 22 Adverse events and SAEs (*continued*)

Trial name: first author and year	Treatment arm (*n* participants)	Follow-up (months)	One or more SAE(s), *n/N* (%)	Reported between-group difference	One or more AE(s), *n/N* (%)	Reported between-group difference
Hadji 2012[91]	• RIS, 350 • TPTD, 360 • Both with placebo	18	• RIS, 65/350 (18.6) • TPTD, 55/360 (15.3)	$p = 0.27$	• RIS, 285/350 (81.4) • TPTD, 285/360 (79.2)	$p = 0.45$
VERO: Kendler 2018[99]	• RIS, 680 • TPTD, 680 • Both with placebo	24	• RIS, 115/680 (16.9) • TPTD, 137/680 (20.1)	$p = 0.13$	• RIS, 500/680 (73.5) • TPTD, 495/680 (72.8)	$p = 0.76$
MOVE: Abtahi 2016[101]	• RIS, 110 • TPTD, 106 • Both with placebo	6	• RIS, 21/110 (19.1) • TPTD, 14/106 (13.2)	$p = 0.271$	• RIS, 50/110 (45.5) • TPTD, 52/106 (49.1)	$p = 0.683$
MOVE: Malouf-Sierra 2017[92]	• Blind until 6 months then open label	24	• RIS, 27/110 (24.5) • TPTD, 21/106 (19.8)	$p = 0.418$	• RIS, 58/110 (52.7) • TPTD, 59/106 (55.7)	$p = 0.684$
Cosman 2011[93] (NCT00439244)	• ZOL, 137 • TPTD, 137 • Only TPTD received placebo	12	• ZOL, 20/137 (14.60) • TPTD, 15/137 (10.95)	NR	• ZOL, 115/137 (83.94) • TPTD, 96/137 (70.07)	NR

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; BRIDGE, phase III randomized placeBo-contRolled double-blind study evaluatIng the efficacy and safety of Romosozumab in treatinG mEn with osteoporosis; DAPS, Denosumab Adherence Preference Satisfaction; DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus alendronate; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; FACT, Forteo Alendronate Comparator Trial; MORE, Multiple Outcomes of Raloxifene Evaluation; NR, not reported; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy; TEAE, treatment-emergent adverse event.

TABLE 23 Lumbar spine BMD for studies not reporting femoral neck BMD

Trial	Intervention and comparators (*n*)	Follow-up duration (months)	Lumbar spine BMD percentage change from baseline, mean (SD) (reported between-group difference)
Nakamura 2012[44]	Placebo, $n = 55$	12	• 3.2 (NR) • Estimated from graph, $p < 0.0001$
	DEN, $n = 54$		16.73 (NR)
Morii 2003[47]	Placebo, $n = 97$	12	• 0.0 (SE 0.3) • Estimated from graph, $p < 0.001$
	RLX, $n = 90$		• 3.5 (SE 0.3) • Estimated from graph
Gorai 2012[49]	Alfacalcidol, $n = 34$	24	−0.8 (4.6)
	RLX, $n = 33$		• 2.8 (3.9) • Significant increase compared with alfacalcidol (*p*-value NR)
	Alfacalcidol plus RLX, $n = 31$		• 4.7 (4.4) • Significant increase compared with alfacalcidol (*p*-value NR)
Lufkin 1998[52]	Control, $n = 48$	12	• 1.44 (0.74), non-significant • *p*-value NR
	RLX, $n = 48$		1.34 (1.02)
Muscoso 2004[79]	ALN, $n = 1000$	24	7.2 (1.9)
	RIS, $n = 100$		6.2 (2.0)
	RLX, $n = 100$		2.4 (1.1)
Anastasilakis 2008[88]	RIS, $n = 22$	12	• 3.3 (NR) • Calculated • Non-significant • *p*-value NR
	TPTD, $n = 22$		• 5.9 (NR) • Calculated

NR, not reported; SE, standard error.

Appendix 6 Health-related quality of life

TABLE 24 Published results of validated HRQoL measures

Trial	Measure	Follow-up	Treatment group	Results (change from baseline)
FREEDOM[116,118]	OPAQ-SV[329]	36 months	Placebo, *n* = NR	Mean: • Physical function, −1.2 • Emotional status, −1.6 • Back pain, 4.3
			DEN, *n* = NR (*n* across both groups: • Physical function, 6152 • Emotional status, 6154 • Back pain, 6164)[116]	• Mean: ○ Physical function, −1.3 ○ Emotional status, −1.4 ○ Back pain, 4.1 • Non-significant between groups • *p*-value NR
Silverman 2008[50] (NCT00205777)	Women's Health Questionnaire[330]	36 months	Placebo, *n* = 1179 RLX, *n* = 1168	Least squares, mean (SE): 0.005 (0.005) • Least squares, mean (SE): 0.005 (0.005) • Non-significant between groups • 0.98
	QUALEFFO-41[331]	36 months	Placebo, *n* = 1176 RLX, *n* = 1168	Least squares, mean (SE): −0.35 (0.3) • Least squares, mean (SE): 0.26 (0.3) • Non-significant between groups • *p* = 0.11
	EQ-VAS[332]	36 months	Placebo, *n* = 1120 RLX, *n* = 1092	Least squares, mean (SE): 4.66 (1.70) • Least squares, mean (SE): 1.60 (1.71) • Non-significant between groups • *p* = 0.16
	EQ-5D Health State Profile Utility Score[332]	36 months	Placebo, *n* = 1128 RLX, *n* = 1111	Least squares, mean (SE): −0.00 (0.01) • Least squares, mean (SE): −0.01 (0.01) • Non-significant between groups • *p* = 0.92
Panico 2011[86]	QUALEFFO-41[331]	18 months	ALN, *n* = 39	• Pain, −9.7% • Everyday activities, 11% • Domestic job, 2.9% • Locomotor function, 11.5% • Social activities, 105% • Health perception, 12.8% • Mood, 1.8%
			TPTD, *n* = 42	• Pain, −22.0% • Everyday activities, 27.3% • Domestic job, 29% • Locomotor function, 37.8% • Social activities, 28.4% • Health perception, 33.9% • Mood, 29.7%

continued

TABLE 24 Published results of validated HRQoL measures (*continued*)

Trial	Measure	Follow-up	Treatment group	Results (change from baseline)
VERO[90]	EQ-VAS UK[332]	24 months	RIS plus placebo	• Least squares, mean 0.04 • Baseline: 0.62 (SD 0.228) • 24 months: 0.68 (SD 0.205)
			TPTD plus placebo	• Least squares, mean 0.06 • Baseline: 0.59 (SD 0.243) • 24 months: 0.65 (SD 0.249) • Between groups −0.0, 95% CI −0.03 to 0.02; $p = 0.757$
MOVE[101]	SF-36 Physical Function Component (post surgery)[333]	26 weeks	RIS plus placebo	Mean (SD): • Baseline, 31.8 (1.53) • 26 weeks, 45.8 (1.55)
			TPTD plus placebo	Mean (SD): • Baseline, 30.1 (1.51) • 26 weeks, 46.4 (1.59) Between groups $p = 0.267$

NR, not reported; OPAQ-SV, Osteoporosis Assessment Questionnaire-Short Version; SE, standard error; SF-36, Short Form questionnaire-36 items.

The UCB S.A. company submission[20] reported that, in both the FRAME[54] (ROMO vs. PBO) and the ARCH[83] (ROMO vs. ALN) studies, there was (confidential information has been removed) between treatment groups in HRQoL, (confidential information has been removed).

The Amgen Inc. company submission[100] reported that the Determining Efficacy: Comparison of Initiating Denosumab versus alendronate (DECIDE)[69] study found (confidential information has been removed) difference between DEN and ALN, as measured by the EQ-5D.

Appendix 7 Specific adverse events

Bisphosphonate studies: specific adverse events

Three additional bisphosphonate RCTs[130,137,138] were identified by the search (*Table 25*). Of these, two RCTs assessed atypical femoral fractures and found no incidences of atypical femoral fractures in participants treated with ZOL compared with those treated with ALN,[138] or those treated with ZOL compared with those treated with placebo.[130] One study assessed ONJ and found no incidences in participants treated with ZOL or placebo.[130]

Non-bisphosphonate studies: specific adverse events

Venous thromboembolism

Across the studies comparing a non-bisphosphonate with placebo, five reported thrombotic events of venous origin,[43,46,47,50,51] and one study reported on arterial limb thrombosis.[42] Across these studies, event rates were $\leq 1\%$. The estimated between-group differences were not statistically significant at $p < 0.05$ (p-values not presented), with the exception of one study comparing RLX with placebo at 36 months in postmenopausal women with osteoporosis, which was statistically significantly in favour of placebo (estimated $p = 0.005$).[51]

None of the studies that compared bisphosphonates with non-bisphosphonates head-to-head reported on VTE.

Across the studies comparing a non-bisphosphonate with a bisphosphonate, two studies reported on thrombosis but did not specify whether this was venous or arterial in origin,[72,74] eight reported on thrombotic events of venous origin,[74,77,80,81,91,98,99,103] and one reported on peripheral artery thrombosis.[75] Across these studies, event rates were $\leq 3\%$. The estimated between-group differences were not statistically significant at $p < 0.05$ (p-values not presented).

Stroke

Across the studies comparing a non-bisphosphonate with placebo, four reported on stroke.[41,50,56,111] Across these studies, event rates were $\leq 2\%$ and no statistically significant between-group differences were evident (reported or estimated).

TABLE 25 Specific AEs: additional bisphosphonate trials

			AE			
Trial name: first author and year	**Treatment arms (*n*)**	**Follow-up (months)**	**VTE(s), *n/N* (%)**	**Stroke, *n/N* (%)**	**ONJ, *n/N* (%)**	**Atypical femoral fractures, *n/N* (%)**
TRIO: Paggiosi 2014[137]	• ALN, 57 • IBN, 57 • RIS, 58	24	NR	NR	NR	NR
Tan 2016[138]	• ALN, 53 • ZOL, 52	36	NR	NR	NR	• ALN, 0/53 (0) • ZOL, 0/52 (0)
ZONE[130]	• Placebo, 331 • ZOL, 330	24	NR	NR	• Placebo, 0/331 • ZOL, 0/330	• Placebo, 0/331 (0) • ZOL, 0/330 (0)

NR, not reported; ZONE, ZOledroNate treatment in Efficacy to osteoporosis.

None of the studies that compared bisphosphonates with non-bisphosphonates head-to-head reported on stroke.

Across the studies comparing a non-bisphosphonate with placebo, eight reported on stroke.[72,74,83,91,93,98,99,103] Across these studies, event rates were ≤ 2%. The estimated between-group differences were not statistically significant at $p < 0.05$ (p-values not presented). However, the estimated between-group difference in stoke for one of these studies comparing ROMO with ALN in postmenopausal women with osteoporosis was statistically significant at 24 months following treatment-switching to ALN, in favour of the continued ALN group ($p = 0.004$).[83]

Osteonecrosis of the jaw

Osteonecrosis of the jaw was reported by nine studies comparing a non-bisphosphonate with placebo,[41,42,44,45,54–56,111] one study comparing non-bisphosphonates head to head[67] and three studies comparing a non-bisphosphonate with a bisphosphonate.[71,74,83] Across these studies, event rates were ≤ 1% and no statistically significant between-group differences were evident (reported or estimated).

Atypical femoral fracture

Atypical femoral fracture was reported by nine studies comparing a non-bisphosphonate with placebo,[41,42,45,54–56,106,111,334] one study comparing non-bisphosphonates head to head[67] and three studies comparing a non-bisphosphonate with a bisphosphonate.[74,75,83,109] Across these studies, event rates were ≤ 1% and no statistically significant between-group differences were evident (reported or estimated).

TABLE 26 Specific AEs: non-bisphosphonate studies

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
DEN vs. placebo						
FREEDOM: Cummings 2009;[41] postmenopausal women with osteoporosis	• Placebo, 3607 • DEN, 3886	36	NR	• Placebo, 54/3607 (1.4) • DEN, 56/3886 (1.4) • $p = 0.89$[41]	• Placebo, 0/3607 (0) • DEN, 0/3886 (0)[41]	• Placebo, 0/3607 (0) • DEN, 0/3886 (0)[335]
ADAMO: Orwoll 2012;[42] men with osteoporosis	• Placebo, 120 • DEN, 120	12	Arterial limb thrombosis • Placebo, 0/120 (0) • DEN, 1/120 (1.7)	NR	• Placebo, 0/120 (0) • DEN, 0/120 (0)	• Placebo, 0/120 (0) • DEN, 0/120 (0)
ADAMO: Langdahl 2015;[111] men with osteoporosis	• Placebo to DEN, 120 • DEN to DEN, 120	24, including 12 OLE	NR	Transient ischaemic attack • Placebo/DEN, 1/120 (< 1) • DEN/DEN, 0/120 (0)	• Placebo/DEN, 0/120 (0) • DEN/DEN, 0/120 (0)	• Placebo/DEN, 0/120 (0) • DEN/DEN, 0/120 (0)
DIRECT: Nakamura 2014;[334] women and men with osteoporosis (NCT00680953)	• Placebo, 481 • DEN, 475	24	• 1/481 (0.21) • 0/475 (0)	NR	• Placebo, 0/481 (0) • DEN, 0/475 (0)	• Placebo, 0/481 (0) • DEN, 0/475 (0)
DIRECT: Sugimoto 2015;[106] women and men with osteoporosis	• Placebo to DEN, 406 • DEN to DEN, 404 • 12 months, open label	24–36	NR	NR	• Placebo/DEN, 1/406 (0.2) (0) • DEN/DEN, 0/404 (0)	• Placebo/DEN, 0/406 (0) • DEN/DEN, 0/404 (0)

continued

TABLE 26 Specific AEs: non-bisphosphonate studies (*continued*)

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
Nakamura 2012;[44] postmenopausal women with osteoporosis	• Placebo, 54 • DEN, 54	12	NR	NR	• Placebo, 0/54 (0) • DEN, 0/54 (0)	NR
Koh 2016;[45] postmenopausal women with osteoporosis	• Placebo, 66 • DEN, 69	6	NR	NR	• Placebo, 0/69 (0) • DEN, 0/69 (0)	• Placebo, 0/69 (0) • DEN, 0/69 (0)
Koh 2016;[45] postmenopausal women with osteoporosis	• Entered OLE • Placebo to DEN, 63 • DEN to DEN, 60	6–12 OLE	NR	NR	• Placebo/DEN, 0/63 (0) • DEN/DEN, 0/60 (0)	• Placebo/DEN, 0/63 (0) • DEN/DEN, 0/60 (0)
RLX vs. placebo						
Adami 2008;[46] postmenopausal women with osteoporosis pre treated with TPTD	• Placebo, 172 • RLX, 157	12 months	• Placebo, 0/172 (0%) • RLX, 1/157 (< 1%) retinal vein thrombosis	NR	NR	NR
Morii 2003;[47] postmenopausal women with osteoporosis	• Placebo, 97 • RLX, 90	12	• Placebo, 0/97 (0%) • RLX, 0/90 (0%)	NR	NR	NR

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
Liu 2004;[48] postmenopausal women with osteoporosis	• Placebo, 102 • RLX, 102	12	• Placebo, 0/102 (0%) • RLX, 0/102 (0%)	NR	NR	NR
Gorai 2012;[94] postmenopausal women with low osteopenia	• Alfacalcidol, 44 • RLX, 45 • Alfacalcidol + RLX, 48	12	NR	NR	NR	NR
Silverman 2008;[50,117] postmenopausal women with osteoporosis	• Placebo, 1855 • RLX, 1849	36	• DVT • Placebo, 1/1855 (0.1%) • RLX, 8/1849 (0.4%) • PE • Placebo, 4/1855 (0.2%) • RLX, 4/1849 (0.2%) • Retinal • Placebo, 3/1855 (0.2%) • RLX, 0/1849 (0%)	• Placebo, 20/1855 (1.1%) • RLX, 15/1849 (0.8%)	NR	NR
MORE: Ettinger 1999;[51] women with osteoporosis	• Placebo, 2576 • RLX, 2557	36	• 8/2576 (0.3%) • 25/2557 (1.0%) • Estimated $p = 0.005$	NR	NR	NR
Lufkin 1998;[52] postmenopausal women with osteoporosis	• Placebo, 48 • RLX, 48	12	• Placebo, 0/48 (0%) • RLX, 0/48 (0%)	NR	NR	NR
Mok 2011;[53] postmenopausal women on long-term GCCs	• Placebo, 57 • RLX, 57	12	• Placebo, 0/57 (0%) • RLX, 0/57 (0%)	NR	NR	NR

continued

TABLE 26 Specific AEs: non-bisphosphonate studies (*continued*)

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
ROMO vs. placebo						
FRAME: Cosman 2016;[54] postmenopausal women with osteoporosis	• Placebo, 3591 • ROMO, 3589	12	NR	NR	• Placebo, 0/3576 (0) • ROMO, 1/3581 (< 0.1)	• Placebo, 0/3576 (0) • ROMO, 1/3581 (< 0.1)
FRAME: Cosman 2016;[54] postmenopausal women with osteoporosis	• Placebo to DEN, 3591 • ROMO to DEN, 3589 • 12 months, open label	24	NR	NR	• Placebo-DEN, 0/3576 (0) • ROMO-DEN, 2/3581 (< 0.1)	• Placebo-DEN, 0/3576 (0) • ROMO-DEN, 1/3581 (< 0.1)
Ishibashi 2017;[55] postmenopausal women with osteoporosis	• Placebo, 63 • ROMO, 63	12	NR	NR	• Placebo, 0/63 (0) • ROMO, 0/63 (0)	• Placebo, 0/63 (0) • ROMO, 0/63 (0)
BRIDGE;[56] men with osteoporosis	• Placebo, 82 • ROMO, 163	12	NR	• Placebo, 1/82 (1.2) • ROMO, 3/163 (1.8)	• Placebo, 0/82 (0) • ROMO, 0/163 (0)	• Placebo, 0/82 (0) • ROMO, 0/163 (0)
TPTD vs. placebo						
ACTIVE: Miller 2016;[95] postmenopausal women with osteoporosis	• Placebo, 820 • TPTD, 818	18	NR	NR	NR	NR
Orwoll 2003;[57] men with osteoporosis	• Placebo, 147 • TPTD, 151	The study was stopped after a median duration of 11 months	NR	NR	NR	NR
Miyauchi 2010;[58] women and men with osteoporosis	• Placebo, 67 • TPTD, 136	12	NR	NR	NR	NR

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
Miyauchi 2010;[58] women and men with osteoporosis	• Placebo to TPTD, 59 • TPTD to TPTD, 119	24, including 12 OLE	NR	NR	NR	NR
Miyauchi 2008;[59] postmenopausal women with osteoporosis	• Placebo, 38 • TPTD, 39	6	NR	NR	NR	NR
Leder 2015;[61,336] postmenopausal women with osteoporosis	• Placebo, 45 • TPTD, 45	6	NR	NR	NR	NR
Neer 2001;[62] postmenopausal women with osteoporosis	• Placebo, 544 • TPTD, 541	24 (stopped early; mean time to last visit was 19 months)	NR	NR	NR	NR
Sethi 2008;[63] postmenopausal women with osteoporosis	• Calcium + vitamin D, 41 • TPTD + calcium + vitamin D, 41	6	NR	NR	NR	NR
Head-to-head non-bisphosphonates						
DATA: Tsai 2013;[64] postmenopausal women with osteoporosis	• TPTD, 36 • DEN, 34 • Without placebo, open label	12	NR	NR	NR	NR
DATA: Leder 2014;[110] postmenopausal women with osteoporosis	• TPTD, 36 • DEN, 34 • Without placebo, open label	24	NR	NR	NR	NR

continued

TABLE 26 Specific AEs: non-bisphosphonate studies (*continued*)

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
EUROFORS: Eastell 2009;[66] postmenopausal women with osteoporosis pre treated with TPTD	• TPTD, 304 • RLX, 97 • Control,[a] 102	24	NR	NR	NR	NR
STRUCTURE;[67] postmenopausal women with osteoporosis pre treated with ALN	• TPTD, 218 • ROMO, 218 • Without placebo, open label	12	NR	NR	• TPTD, 0/218 (0) • ROMO, 0/218 (0)	• TPTD, 0/218 (0) • ROMO, 0/218 (0)
McClung 2014;[68] postmenopausal women with osteoporosis	• Placebo, 52 • TPTD, 55 • ROMO, 52 • ALN, 51	12	NR	NR	NR	NR
DEN vs. bisphosphonates						
DECIDE;[69] postmenopausal women with osteoporosis	• ALN, 586 • DEN, 593 • Both with placebo	12	NR	NR	NR	NR
STAND;[70] postmenopausal women with osteoporosis already on ALN	• ALN, 251 • DEN, 253 • Both with placebo	12	NR	NR	NR	NR
DAPS;[71] postmenopausal women with osteoporosis	• ALN, 124 • DEN, 126 • Without placebo	12	NR	NR	• ALN, 0/117 (0) • DEN, 0/125 (0)	NR
DAPS;[109] postmenopausal women with osteoporosis	• Cross-over • ALN to DEN, 92 • DEN to ALN, 102	24	NR	NR	• ALN, 0/228 (0) • DEN, 0/230 (0)	• ALN, 0/228 (0) • DEN, 0/230 (0)

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
McClung 2006;[72,337] postmenopausal women with osteoporosis or osteopenia	• Placebo for DEN, 46 • ALN, 47 • DEN, 47	12	Thrombosis • Placebo, 0/46 (0.00) • ALN, 0/46 (0.00) • DEN, 0/47 (0.00)	• Placebo, 0/46 (0.00) • ALN, 0/46 (0.00) • DEN, 0/47 (0.00)	NR	NR
Recknor 2013;[73] postmenopausal women with osteoporosis	• IBN, 416 • DEN, 417 • Without placebo	12	NR	NR	NR	NR
Saag 2018;[74,338] women and men on GCCs with osteoporosis or low BMD + fracture (NCT01575873)	• RIS, 384 • DEN, 394 • Both with placebo	12	DVT • RIS, 2/385 (0.52) • DEN, 0/394 (0.00) Thrombosis • RIS, 1/385 (0.26) • DEN, 0/394 (0.00)	• RIS, 1/384 (0.26) • DEN, 3/394 (0.76)	• RIS, 0/384 (0) • DEN, 0/394 (0)	• RIS, 0/384 (0) • DEN, 1/394 (< 1)
Miller 2016;[75,339] postmenopausal women with osteoporosis previously treated with bisphosphonates (NCT01732770)	• ZOL, 322 • DEN, 321 • Both with placebo	12	Peripheral artery thrombosis • ZOL, 1/320 (0.31) • DEN, 0/320 (0.00)	NR	NR	• ZOL, 1/320 (0.3) • DEN, 2/320 (0.6)
RLX vs. bisphosphonates						
EFFECT: Sambrook 2004[76] (international not including USA); postmenopausal women with osteoporosis	• ALN, 246 • RLX, 241 • Both with placebo	12	NR	NR	NR	NR

continued

TABLE 26 Specific AEs: non-bisphosphonate studies (*continued*)

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
EFFECT (USA);[77] postmenopausal women with osteoporosis	• ALN, 223 • RLX, 233 • Both with placebo	12	• ALN, 0/221 (0) • RLX, 1/230 (< 1)	NR	NR	NR
Johnell 2002;[78] postmenopausal women with osteoporosis	• Placebo, 82 • ALN, 83 • RLX, 82	12	NR	NR	NR	NR
Muscoso 2004;[79] postmenopausal women with osteoporosis	• ALN, 1000 • RLX, 100 • RIS, 100 • All daily open label	24	NR	NR	NR	NR
EVA: Recker 2007;[80] postmenopausal women with osteoporosis	• ALN, 716 • RLX, 707 • Both with placebo	24	DVT: • ALN, 1/716 (< 1) PE: • RLX, 1/707 (< 1)	NR	NR	NR
Sanad 2011;[81] postmenopausal women with osteoporosis	• ALN weekly, 31 • RLX, 35 • Without placebo	12	• DVT, 0/31 (0) • ALN, 1/35 (2.9)	NR	NR	NR
Michalska 2006;[82] postmenopausal women with osteoporosis previously treated with bisphosphonates	• Placebo, 33 • RLX, 33 • ALN, 33	12	NR	NR	NR	NR

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
ROMO vs. bisphosphonates						
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	• ALN, 2047 • ROMO, 2046 • Both with placebo	12	NR	• ALN, 7/2014 (0.3) • ROMO, 16/2040 (0.8)	• ALN, 0/2014 (0) • ROMO, 0/2040 (0)	• ALN, 0/2014 (0) • ROMO, 0/2040 (0)
ARCH: Saag 2017;[83] postmenopausal women with osteoporosis	• ALN to ALN, 2047 • ROMO to ALN, 2046 • Open label	24, including 12 months' OLE	NR	• ALN/ALN, 27/2014 (1.3) • ROMO/ALN, 45/2040 (2.2) • Estimated $p = 0.004$	• ALN/ALN, 1/2014 (< 0.1) • ROMO/ALN, 1/2040 (< 0.1)	• ALN/ALN, 4/2014 (< 0.2) • ROMO/ALN, 2/2040 (< 0.1)
TPTD vs. bisphosphonates						
FACT;[84] postmenopausal women with osteoporosis	• ALN, 101 • TPTD, 102 • Both with placebo	18	NR	NR	NR	NR
Saag 2009,[103] Langdahl 2009[107] and Lips 1999;[340] women and men on GCCs with osteoporosis or low BMD + fracture (NCT01732770)	• ALN, 214 • TPTD, 214 • Both with placebo	36	DVT: • ALN, 1/214 (0.47) • TPTD, 2/214 (0.93) VTE: • ALN, 0/214 (0) • TPTD, 1/214 (0.47)	• ALN, 1/214 (0.47) • TPTD, 0/214 (0)	NR	NR
Panico 2011;[86] postmenopausal women with severe osteoporosis +fracture and on treatment for osteoporosis	• ALN weekly, 39 • TPTD, 42 • Without placebo	18	NR	NR	NR	NR

continued

TABLE 26 Specific AEs: non-bisphosphonate studies (*continued*)

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
Anastasilakis 2008[88]	• RIS, 22 • TPTD, 22 • Without placebo, open label	12	NR	NR	NR	NR
EUROGIOPs;[87] men with osteoporosis on GCCs	• RIS, 47 • TPTD, 45 • Without placebo, open label	18	NR	NR	NR	NR
Walker 2013;[89] men with osteoporosis	• RIS weekly, 10 • TPTD, 9 • Both with placebo	18	NR	NR	NR	NR
Hadji 2012;[91] postmenopausal women with osteoporosis (NCT00343252)	• RIS weekly, 350 • TPTD, 360 • Both with placebo	18	DVT • 1/350 (0.29) • 0/360 (0.00) Pulmonary thrombosis • 1/350 (0.29) • 0/360 (0.00)	• RIS, 6/350 (1.71) • TPTD, 1/360 (0.28)	NR	NR
VERO: Kendler 2018;[99] postmenopausal women with osteoporosis (NCT01709110)	• RIS weekly, 680 • TPTD, 680 • Both with placebo	24	DVT • RIS, 3/683 (0.44) • TPTD, 2/683 (0.29) Vena cava thrombosis • RIS, 1/683 (0.15) • TPTD, 0/683 (0.00)	• RIS, 1/683 (0.15) • TPTD, 2/683 (0.29)	NR	NR

Trial name: first author and year; population	Treatment arms (*n*)	Follow-up (months)	AE			
			VTE(s), *n/N* (%)	Stroke, *n/N* (%)	ONJ, *n/N* (%)	Atypical femoral fractures, *n/N* (%)
MOVE: Aspenberg 2016[98] and Malouf-Sierra 2017[92,128] (NCT00887354)	• RIS, 110 • TPTD, 106 • Both with placebo to 6 months then OLE to 12 months	NR	Venous thrombosis • RIS, 1/110 (0.91) • TPTD, 0/106 (0.00)	• RIS, 2/110 (1.82) • TPTD, 0/106 (0.00)	NR	NR
Cosman 2011;[93] postmenopausal women with osteoporosis (NCT00439244)	• ZOL,[b] 137 • TPTD + ZOL placebo, 138	12	NR	• ZOL, 0/137 (0.00) • TPTD, 0/137 (0.00)	NR	NR

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; BRIDGE, phase III randomized placeBo-contRolled double-blind study evaluatIng the efficacy and safety of Romosozumab in treatinG mEn with osteoporosis; DAPS, Denosumab Adherence Preference Satisfaction; DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus alendronate; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; FACT, Forteo Alendronate Comparator Trial; GCC, glucocorticoid; MORE, Multiple Outcomes of Raloxifene Evaluation; NR, not reported; OLE, open-label extension; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy.

a No active treatment.

b Not placebo controlled for TPTD.

Notes

ALN, ALN 10 mg daily or 70 mg weekly.
DEN, DEN 60 mg s.c. every 6 months.
IBN, 150 mg oral every month.
RLX, RLX 60 mg daily.
ROMO, 210 mg s.c. Monthly.
TPTD, 20 µg s.c. daily.
ZOL, ZOL 5 mg i.v. annually.

Appendix 8 Statistical methods for the network meta-analysis

Statistical model for the network meta-analysis of fracture outcomes

The RCTs presented data in terms of the number of individuals experiencing at least one fracture. For each fracture type, r_{ik} is defined as the number of events out of the total number of participants, n_{ik}, where the participants are receiving treatment t_{ik} in arm k of trial i. The data generation process is assumed to follow a binomial likelihood such that:

$$r_{ik} \sim bin(p_{ik}, n_{ik}), \tag{1}$$

where p_{ik} represents the probability of an event in arm k of trial i ($i = 1, \ldots ns$, $k = 1 \ldots na$) after follow-up time f_i. For all RCTs, the number of arms included in the analysis is two (i.e. $na = 2$) and the number of RCTs, ns, varies according to fracture type.

To account for different trial durations, an underlying Poisson process is assumed for each trial arm, so that t_{ik} (the time until a fracture occurs in arm k of study i) follows an exponential distribution, $t_{ik} \sim \exp(\lambda_{ik})$, where λ_{ik} is the event rate in arm k of study i, assumed constant over time. The probability that there are no events at time f_i is given by the survivor function $P(T_{ik} > f_i) = \exp(-\lambda_{ik} f_i)$. For each study, i, the probability of an event in arm k after follow-up time f_i can be written as:

$$p_{ik} = 1 - P(T_{ik} > f_i) = 1 - \exp(-\lambda_{ik} f_i), \tag{2}$$

which is dependent on follow-up time. The probabilities of fracture are non-linear functions of event rates, and so were modelled using the complementary log–log link function:

$$cloglog(p_{ik}) = \log(f_i) + \mu_i + \delta_{i,\,1k} I_{k \neq 1}. \tag{3}$$

Here, the μ_i are trial-specific baselines, representing the log-hazards of fracture in the baseline treatment, which is assumed to be arm $k = 1$ for all trials. Note that, for some trials, the baseline may be an active treatment rather than placebo. The trial-specific treatment effects, $\delta_{i,1k}$, are log-hazard ratios of fracture for the treatment in arm k, relative to the baseline treatment.

As described later, two different modelling strategies were considered for the treatment effects: (1) standard independent random (treatment) effects model and (2) exchangeable treatment effects (i.e. a class effect) for bisphosphonate treatments with unrelated treatment effects for all other interventions. The main results are based on model 2, and the results for the standard independent random-effects model are provided here for comparison.

Standard independent random-effects model

The trial-specific treatment effects, $\delta_{i,1k}$, were assumed to arise from a common population distribution with mean treatment effect relative to the reference treatment, which was defined as placebo for this analysis, such that:

$$\delta_{i,\,1k} \sim N(d_{t_{i1}t_{ik}}, \tau^2), \tag{4}$$

where $d_{t_{i1}t_{ik}}$ represents the mean effect of the treatment in arm k of study i (t_{ik}) compared with the treatment in arm 1 of study i (t_{i1}) and τ^2 represents the between-study variance in treatment effects (heterogeneity), which is assumed to be the same for all treatments.

The model was completed by specifying prior distributions for the parameters. When there were sufficient sample data, conventional reference prior distributions were used:

- trial-specific baseline, $\mu_i \sim N(0,100^2)$
- treatment effects relative to reference treatment, $d_{1k} \sim N(0,100^2)$
- between-study SD of treatment effects, $\tau \sim U(0,2)$.

For hip, wrist and proximal humerus fracture outcomes, there were relatively few RCTs to allow Bayesian updating (i.e. estimation of parameters from the sample data alone) of the reference prior distribution for the between-study SD. When prior distributions do not represent reasonable prior beliefs, then, in the absence of sufficient sample data, posterior distributions will not represent reasonable posterior beliefs. Therefore, rather than using a reference prior distribution, a weakly informative prior distribution was used for the between-study SD, such that $\tau \sim HN(0,0.32^2)$.

Primary analysis model

In the previous NICE assessment for bisphosphonates, a class-effects model was used. Not all RCTs contributing wrist fracture data provide evidence about all bisphosphonates; in particular, there was no evidence about ZOL. To allow an assessment of the uncertainty associated with ZOL for inclusion in the economic model, a class-effects model was fitted, from which the predictive distribution of a new intervention in the same class can be generated. This modelling approach also has the benefit of addressing data sparsity in the hip network.

For the primary analysis model, a class effects was assumed for bisphosphonate treatments only. Under a class-effects model, the trial-specific treatment effects are again assumed to be normally distributed as in equation (3), but the mean effects of each treatment are assumed to be exchangeable and assumed to arise from a normal distribution with mean, D, with variance τ_D^2:

$$d_{t_i t_k} \sim N(D\tau_D^2). \tag{5}$$

The model was completed by specifying prior distributions for the parameters:

- mean bisphosphonate effect, $D \sim N(0,100^2)$
- between-treatment SD, $\tau_D \sim U(0,2)$.

For hip, wrist and proximal humerus outcomes, a weakly informative prior was used for the between-treatment SD, such that: $\sigma_D^2 \sim HN(0,0.32^2)$.

Predicting effects in new randomised controlled trials

To account for heterogeneity in the effect of treatments between RCTs, results are also presented for the predictive distributions of the effect of treatment in a new (randomly chosen) study.

From equation (4), it follows that the study-specific population log-hazard ratio, $\delta_{i,j}$, for study i, evaluating any given treatment j in reference to the control treatment can be written as:

$$\delta_{i,\,j} = d_{1j} + \varepsilon_{ij}, \tag{6}$$

where $\varepsilon_{ij} \sim N(0,\tau^2)$. The predictive distribution for the effect of a particular treatment $\delta_{i,j}$ in a new study is as follows:

$$\delta_{new,\,j} \sim N(d_{1j}, \tau^2), \tag{7}$$

The class-effects model also allows generation of the predictive distribution of a new, randomly chosen bisphosphonate treatment from the same class. From *Equation 5*, it follows that the population log-hazard ratio for each treatment can be written as:

$$d_{1j} = D + \xi_j, \tag{8}$$

where $\xi \sim N(0, \tau_D^2)$. Therefore, combining *Equations 6* and *8*, the study-specific population log-hazard ratio, $\delta_{i,j}$, for study *i* evaluating bisphosphonate *j* is:

$$\delta_{i,\,j} = D + \zeta_j + \varepsilon_{ij}, \tag{9}$$

For a new, randomly chosen bisphosphonate, the expectation is $E[\delta_{ij}] = E[D + \zeta_j + \varepsilon_{ij}] = D$, with variance:

$$V[\delta_{ij}] = V[D + \zeta_j + \varepsilon_{ij}] = \tau^2 + \tau_D^2. \tag{10}$$

Therefore, the predictive distribution for the effect of a new, randomly chosen, study from the same class is:

$$\delta_{new} \sim N(D, \tau_D^2 + \tau^2), \tag{11}$$

which accounts for both between-study, τ^2, and between-treatment within class, τ_D^2, heterogeneity for any (including a new) treatment.

It is the predictive distribution of a new treatment within the class and the predictive distribution of a new study for a new treatment within the class that we use to characterise the uncertainty about the effect of ZOL for hip fractures.

Statistical model for the network meta-analysis of femoral neck bone mineral density

Data for femoral neck BMD outcomes were presented in two different formats: either as the percentage change in femoral neck BMD for each treatment group or as the mean difference in the percentage change between treatment groups. Two different data generation (i.e. likelihood) models are therefore required.

Percentage change in femoral neck bone mineral density

The majority of RCTs presented data as the percentage change in femoral neck BMD, y_{ik}, and associated standard errors, se_{ik}, for arm *k* of trial *i* with study duration f_i years. The data generation process is assumed to follow a normal likelihood, such that:

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2), \tag{12}$$

where the population variance of the mean, se_{ik}^2, is assumed to be known and equal to the sample estimate. The parameters of interest, θ_{ik}, are modelled using the identity link function and, to account for differing trial durations, study duration was included as a trial-level covariate. The link function is given by:

$$\theta_{ik} = \mu_i + \left(\delta_{i,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})f_i\right)I_{k\neq 1}, \quad (13)$$

Where $\beta_{11} = 0$, and $\beta_{1k}(k = 2, \ldots na)$ are the treatment-specific interactions, describing the relationship between the effect of treatment on percentage change in femoral neck BMD and duration of study. The trial baselines, μ_i, represent the percentage change in femoral neck BMD from baseline in the reference arm. The treatment effects, $\delta_{i,1k}$, represent the difference between the percentage change in the treatment group and the reference group. Assumptions about the relationship between the interaction terms are described further in the meta-regression section.

Difference between treatments in mean change in femoral neck bone mineral density

Some RCTs provided data in terms of the mean difference in percentage change in femoral neck BMD between two treatments, defined as:

$$MD_{i,1k} = y_{ik} - y_{i1}, \quad (14)$$

together with the associated standard errors of the mean difference, $\nu_{i,1k}$, rather than the percentage change in femoral neck BMD for individual treatments. The difference between treatments in the mean change are also assumed to be normally distributed, such that:

$$MD_{i,1k} \sim N(\theta'_{ik}, v_{i1k}^2), \quad (15)$$

where the population standard error of the difference, v_{i1k}^2, is assumed to be known and equal to the sample estimate. From the mean differences, no trial-specific effects of the baseline treatment can be estimated. The linear predictor is then given by:

$$\theta'_{ik} = (\delta_{i,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})f_i)I_{k\neq 1}. \quad (16)$$

The study-specific treatment effects, $\delta_{i,1k}$, have the same interpretation as those from *Equation 13*; thus, they can be combined to estimate the mean effects for each treatment, regardless of the way the data were reported.

A class-effects model was assumed such that the treatment effects of the individual bisphosphonates were assumed to be exchangeable and to arise from a normal distribution with mean, D, with variance τ_D^2:

$$d_{t_{i1}t_{ik}} \sim N(D, \tau_D^2). \quad (17)$$

The model was completed by specifying prior distributions for the parameters, using conventional reference prior distributions:

- trial-specific baseline, $\mu_i \sim N(0,100^2)$
- treatment effects relative to reference treatment, $d_{1k} \sim N(1,100^2)$
- between-study SD of treatment effects, $\tau \sim U(0,100)$.
- mean of related treatment effects, $D \sim N(0,100^2)$
- between-treatment SD, $\tau_D \sim U(0,100)$.

Meta-regression

When appropriate, heterogeneity in treatment effects was explored by considering potential treatment effect modifiers. Meta-regression was used to test for interactions between the treatment effects and trial-level covariates, as described in Dias *et al.*:[121]

An interaction term, β, is introduced on the treatment effect by replacing:

$$\tilde{\delta}_{i,\,1k} = \delta_{i,\,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})(x_i - \bar{x}), \tag{18}$$

Where x_i is the trial-level covariate for trial i and may represent a subgroup, continuous covariate or baseline risk (as described in more detail later), and $\beta_{11} = 0$. The regression is centred at the mean value of the covariate across the RCTs so that the interpretation of the treatment effect is as the effect at the average value of the covariate.

Different assumptions can be made about the relationship between the interaction terms for each treatment. For the main analysis, we assume a common interaction for each treatment relative to treatment 1, such that:

$$\beta_{1,\,t_{ik}} = b, \tag{19}$$

for $k = 2, \ldots, na$. We also considered a model in which the interaction terms for each treatment were considered to be related but not identical (i.e. exchangeable), such that:

$$\beta_{1,\,t_{ik}} \sim N(b, \tau_B^2). \tag{20}$$

Meta-regression on baseline risk/response

Baseline risk/response can be used as a proxy for differences in patient characteristics across trials that may be modifiers of treatment effect, and so introduce a potential source of heterogeneity in the NMA. Adjustment for baseline risk/response was assessed using the method of Achana *et al.*[122]

Dependence on baseline risk is introduced through an interaction term, so that:

$$\tilde{\delta}_{i,\,1k} = d_{t_{i1}t_{ik}} + \beta_{t_{i1}t_{ik}}(\mu_{iP} - \bar{\mu}_P) + \varepsilon_{i,\,t_{i1}t_{ik}}, \tag{21}$$

where $\varepsilon_{i,\,t_{i1}t_{ik}} \sim N(0, \tau^2)$ The updated study-specific treatment effects, $\tilde{\delta}_{i,1k}$, are now adjusted using the 'true' but unobserved baseline risk/response in the placebo arm of trial i, μ_{iP}. The coefficient, $\beta_{t_{i1}t_{ik}}$, represents the change in the treatment effect (e.g. log HR or difference between treatments in mean change) per unit change in the baseline risk/response. The baseline risk/response is centred on $\bar{\mu}_P$, the observed mean (e.g. log HR or difference between treatments in mean change) in the placebo group, and $\beta_{11} = 0$.

For RCTs with an active treatment control, ($t_{11} \neq P$), there is no direct estimate of the placebo baseline risk/response. Under the consistency of evidence arising from the exchangeability assumption, the substitution $d_{t_{i1}t_{ik}} = d_{Pt_{ik}} - d_{Pt_{i1}}$ can be made, allowing *Equation 21* to be expressed as:

$$\tilde{\delta}_{i,\,1k} = (d_{Pt_{ik}} - d_{Pt_{i1}}) + (\beta_{Pt_{ik}} - \beta_{Pt_{ik}})(\mu_{iP} - \bar{\mu}_P). \tag{22}$$

Although a placebo treatment may not be included in all RCTs, the assumption of exchangeability means that the treatment arms can be assumed missing at random without loss to efficacy, and the baseline risk/response in RCTs without a placebo arm can be estimated, borrowing strength from other RCTs.

As previously described, some RCTs report data on the mean differences in percentage change between two treatments. Under the model described in *Equations 15* and *16*, study-specific effects of the baseline treatment cannot be estimated. These RCTs still contribute to the model through estimation of the treatment effects, but do not directly contribute to estimation of the slope in the meta-regression.

Appendix 9 Data contributing to the network meta-analysis

TABLE 27 Data contributing to the NMA of vertebral fractures

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm			Main analysis	SA1	SA2	SA3	SA4
	1	2	3		1	2	3	1	2	3					
Liberman 1995[134]	Placebo	ALN	–	36	355	175	–	22	5	–	1	0	0	0	1
Orwoll 2000[286]	Placebo	ALN	–	24	94	146	–	7	1	–	1	0	0	0	1
FIT I: Black 1996[280]	Placebo	ALN	–	36	965	981	–	192	83	–	1	0	0	1	1
FIT I: Black 1996[280]	Placebo	ALN	–	36	1000	1000	–	50	23	–	0	0	1	0	0
FIT II: Cummings 1998[281]	Placebo	ALN	–	48	2077	2057	–	78	43	–	1	0	0	1	1
Dursun 2001[131]	Placebo	ALN	–	12	35	38	–	14	12	–	1	1	0	0	1
Carfora 1998[134]	Placebo	ALN	–	30	34	34	–	4	1	–	1	0	0	0	0
Cohen 1999[296]	Placebo	RIS	–	12	35	34	–	5	2	–	1	1	0	1	1
Fogelman 2000[297]	Placebo	RIS	–	24	125	112	–	17	8	–	1	0	0	1	1
VERT-USA: Harris 1999[298]	Placebo	RIS	–	36	678	696	–	93	61	–	1	0	0	1	1
VERT-USA: Harris 1999[298]	Placebo	RIS	–	12	660	669	–	42	16	–	0	1	0	0	0
VERT-EU: Reginster 2000[300]	Placebo	RIS	–	36	346	344	–	89	53	–	1	0	0	1	1
VERT-EU: Reginster 2000[300]	Placebo	RIS	–	12	334	333	–	45	19	–	0	1	0	0	0
Hooper 2005[132]	Placebo	RIS	–	24	125	129	–	10	10	–	1	0	0	0	1
Reid 2000[303]	Placebo	RIS	–	12	60	60	–	9	3	–	1	1	0	1	1
Boonen 2009[295]	Placebo	RIS	–	24	80	179	–	0	2	–	1	0	0	1	0
Ringe 2006[304]	Placebo	RIS	–	12	158	158	–	20	8	–	1	1	1	1	1
Boonen 2012[309]	Placebo	ZOL	–	24	574	533	–	28	9	–	1	0	0	1	1
Boonen 2012[309]	Placebo	ZOL	–	12	574	553	–	16	5	–	0	1	0	0	0
HORIZON-PFT: Black 2007[133]	Placebo	ZOL	–	36	3861	3875	–	84	19	–	0	0	1	0	0
HORIZON-PFT: Black 2007[133]	Placebo	ZOL	–	12	3861	3875	–	143	58	–	0	1	0	0	0
HORIZON-PFT: Black 2007[133]	Placebo	ZOL	–	36	3861	3875	–	310	92	–	1	0	0	0	0

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm			Main analysis	SA1	SA2	SA3	SA4
	1	2	3		1	2	3	1	2	3					
HORIZON-RFT: Lyles 2007[307]	Placebo	ZOL	–	36	1062	1065	–	39	21	–	1	0	1	1	0
HORIZON-RFT: Lyles 2007[307]	Placebo	ZOL	–	12	1057	1054	–	21	13	–	0	1	0	0	0
BONE: Chesnut 2004[136]	Placebo	IBN daily	–	36	975	977	–	73	37	–	1	0	0	0	1
BONE: Chesnut 2004[136]	Placebo	IBN daily	–	12	889	929	–	24	13	–	0	1	0	0	0
BONE: Chesnut 2004[136]	Placebo	IBN daily	–	36	975	977	–	41	22	–	0	0	1	0	0
HORIZON-SIO Reid 2009[317]	RIS	ZOL	–	12	381	378	–	3	5	–	1	1	0	1	1
MOTION: Miller 2008[308]	ALN	IBN monthly	–	12	859	874	–	5	5	–	1	1	1	1	1
ZONE: Nakamura 2017[130]	Placebo	ZOL	–	24	327	330	–	29	10	–	1	0	0	1	1
ZONE: Nakamura 2017[130]	Placebo	ZOL	–	24	331	330	–	17	5	–	0	0	1	0	0
ZONE: Nakamura 2017[130]	Placebo	ZOL	–	12	331	330	–	6	4	–	0	1	0	0	0
FREEDOM: Bone 2017[104]	Placebo	DEN	–	36	3691	3702	–	264	86	–	1	0	0	1	1
FREEDOM: Bone 2017[104]	Placebo	DEN	–	36	3906	3902	–	92	29	–	0	0	1	0	0
FREEDOM: Bone 2017[104]	Placebo	DEN	–	12	3691	3702	–	82	32	–	0	1	0	0	0
FRAME: Cosman 2016[54]	Placebo	ROMO	–	12	3322	3321	–	59	16	–	1	1	0	1	1
FRAME: Cosman 2016[54]	Placebo	ROMO	–	12	3591	3589	–	17	3	–	0	0	0	0	0
ADAMO: Orwoll 2012[42]	Placebo	DEN	–	12	120	120	–	1	0	–	1	1	1	1	1
DIRECT: Nakamura 2014[43]	Placebo	DEN	–	24	480	472	–	41	10	–	1	0	0	0	1
DIRECT: Nakamura 2014[43]	Placebo	DEN	–	12	480	472	–	9	6	–	0	1	0	0	0
Miyauchi 2010[58]	Placebo	TPTD	–	12	67	136	–	4	5	–	1	1	0	1	0
ACTIVE: Miller 2016[75]	Placebo	TPTD	–	18	711	717	–	30	6	–	1	0	0	0	1
ACTIVE: Miller 2016[75]	Placebo	TPTD	–	18	821	818	–	9	3	–	0	0	1	0	0
Neer 2001[62]	Placebo	TPTD	–	24	448	444	–	64	22	–	1	0	0	0	0
Morii 2003[47]	Placebo	RLX	–	12	87	79	–	2	0	–	1	1	0	1	1

continued

TABLE 27 Data contributing to the NMA of vertebral fractures (*continued*)

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm			Main analysis	SA1	SA2	SA3	SA4
	1	2	3		1	2	3	1	2	3					
Liu 2004[48]	Placebo	RLX	–	12	102	102	–	5	0	–	1	1	1	1	1
Silverman 2008[50]	Placebo	RLX	–	36	1741	1696	–	71	40	–	1	0	0	0	1
Silverman 2008[50]	Placebo	RLX	–	36	1741	1696	–	16	15	–	0	0	1	0	0
MORE: Maricic 2002[102]	Placebo	RLX	–	12	2292	2259	–	19	6	–	0	1	0	0	0
MORE: Maricic 2002[102]	Placebo	RLX	–	36	2292	2259	–	81	47	–	0	0	1	0	0
MORE: Maricic 2002[102]	Placebo	RLX	–	36	2292	2259	–	231	148	–	1	0	0	1	1
Lufkin 1998[52]	Placebo	RLX	–	12	45	43	–	18	21	–	1	1	0	1	1
Saag 2007[103]	ALN	TPTD	–	36	169	173	–	13	3	–	1	0	0	1	1
Saag 2007[103]	ALN	TPTD	–	36	169	173	–	4	0	–	0	0	1	0	0
Walker 2013[89]	RIS	TPTD	–	18	10	9	–	1	0	–	1	0	0	1	1
VERO: Kendler 2017[99]	RIS	TPTD	–	24	533	516	–	64	28	–	1	0	0	1	0
VERO: Kendler 2017[99]	RIS	TPTD	–	12	533	516	–	11	4	–	0	1	1	0	0
Hadji 2012[91]	RIS	TPTD	–	18	309	317	–	33	16	–	1	0	0	1	0
MOVE: Malouf-Sierra 2017[92]	RIS	TPTD	–	18	106	116	–	1	0	–	1	0	1	0	1
Cosman 2011[93]	ZOL	TPTD	–	12	137	137	–	5	1	–	1	1	0	0	1
EVA: Recker 2007[80]	ALN	RLX	–	10.26	255	259	–	8	5	–	1	0	0	0	1
EVA: Recker 2007[80]	ALN	RLX	–	10.26	713	699	–	3	0	–	0	0	1	0	0
Muscoso 2004[79]	ALN	RLX	RIS	12	1000	100	100	2	0	0	0	1	0	0	0
Muscoso 2004[79]	ALN	RLX	RIS	24	1000	100	100	6	0	0	1	0	0	1	0
ARCH: Saag 2017[83]	ALN	ROMO	–	12	1703	1696	–	85	55	–	0	1	0	0	0
ARCH: Saag 2017[83]	ALN	ROMO/ALN	–	24	1834	1825	–	147	74	–	1	0	0	1	1
ARCH: Saag 2017[83]	ALN	ROMO/ALN	–	24	2047	2046	–	18	10	–	0	0	1	0	0

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm			Main analysis	SA1	SA2	SA3	SA4
	1	2	3		1	2	3	1	2	3					
Panico 2011[86]	ALN	TPTD	–	18	39	42	–	6	1	–	1	0	0	0	1
Saag 2018[74]	RIS	DEN	–	12	342	333	–	15	10	–	1	1	0	1	1
Mok 2011[53]	Placebo	RLX	–	12	56	51	–	3	0	–	1	1	0	1	0
Miller 2004[129]	Placebo	ALN	–	12	41	80	–	3	6	–	1	1	0	0	1
Miller 2004[129]	Placebo	ALN	–	12	58	109	–	3	5	–	0	0	1	0	0

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; BONE, iBandronate Osteoporosis vertebral fracture trial in North America and Europe; FIT, Fracture Intervention Trial; MORE, Multiple Outcomes of Raloxifene Evaluation; MOTION, Monthly Oral Therapy with Ibandronate for Osteoporosis iNtervention; PFT, Pivotal Fracture Trial; RFT, Recurrent Fracture Trial; SIO, steroid induced osteoporosis; VERT, Vertebral Efficacy with Risedronate Therapy; ZONE, ZOledroNate treatment in Efficacy to osteoporosis.

TABLE 28 Data contributing to the NMA of non-vertebral fractures

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm		
	1	2	3		1	2	3	1	2	3
FREEDOM: Cummings 2009[41]	Placebo	DEN	–	36	3906	3902	–	293	238	–
FRAME: Cosman 2016[54]	Placebo	ROMO	–	12	3591	3589	–	75	56	–
Orwoll 2003[57]	Placebo	TPTD	–	12	147	151	–	3	2	–
ADAMO: Orwoll 2012[42]	Placebo	DEN	–	12	120	120	–	2	1	–
DIRECT: Nakamura 2014[43]	Placebo	DEN	–	24	480	472	–	20	19	–
Koh 2016[45]	Placebo	DEN	–	6	66	69	–	1	1	–
Miyauchi 2010[58]	Placebo	TPTD	–	12	67	136	–	1	1	–
ACTIVE: Miller 2016[95]	Placebo	TPTD	–	18	821	818	–	33	24	–
Neer 2001[62]	Placebo	TPTD	–	24	544	541	–	30	14	–
Silverman 2008[50]	Placebo	RLX	–	36	1885	1849	–	118	109	–
Ishibashi 2017[55]	Placebo	RLX	–	12	63	63	–	1	2	–
STRUCTURE: Langdahl 2017[67]	ROMO	TPTD	–	12	218	214	–	7	8	–
STAND: Kendler 2010[70]	ALN	DEN	–	12	249	253	–	4	8	–
DAPS: Freemantle 2012[109]	ALN	DEN	–	12	118	125	–	1	1	–
Saag 2009[85]	ALN	TPTD	–	36	214	214	–	15	16	–
EuroGIOPs: Glüer 2013[87]	RIS	TPTD	–	18	47	45	–	5	0	–
VERO: Kendler 2017[99]	RIS	TPTD	–	24	680	680	–	38	25	–
Hadji 2012[91]	RIS	TPTD	–	18	350	360	–	29	28	–
Malouf-Sierra 2017[92]	RIS	TPTD	–	18	110	106	–	10	5	–
Cosman 2011[93]	ZOL	TPTD	–	12	137	137	–	8	7	–
Muscoso 2004[79]	ALN	RLX	RIS	24	1000	100	100	4	0	0
ARCH: Saag 2017[83]	ALN	ROMO/ALN	–	32.4	2047	2046	–	217	178	–
EFFECT (USA): Luckey 2004[77]	ALN	RLX	–	12	199	206	–	5	8	–
ZONE: Nakamura 2017[130]	Placebo	ZOL	–	24	331	330	–	37	20	–
Lufkin 1998[52]	Placebo	RLX	–	12	45	43	–	3	0	–
Saag 2018[74]	RIS	DEN	–	12	397	398	–	10	17	–
Michalská 2006[82]	Placebo	ALN	RLX	24	33	33	33	2	1	1
Fogelman 2000[297]	Placebo	RIS	–	36	125	112	–	13	7	–
VERT-USA: Harris 1999[298]	Placebo	RIS	–	36	815	812	–	52	33	–
VERT-EU: Reginster 2000[300]	Placebo	RIS	–	24	406	406	–	51	36	–
Hooper 2005[132]	Placebo	RIS	–	12	125	129	–	6	5	–
Ringe 2006[304]	Placebo	RIS	–	48	158	158	–	17	10	–
FIT I: Black 1996[280]	Placebo	ALN	–	36	1005	1022	–	148	122	–
FIT II: Cummings 1998[281]	Placebo	ALN	–	48	2218	2214	–	294	261	–
Orwoll 2000[286]	Placebo	ALN	–	24	94	146	–	5	6	–
FOSIT: Pols 1999[287]	Placebo	ALN	–	12	958	950	–	37	19	–

TABLE 28 Data contributing to the NMA of non-vertebral fractures (*continued*)

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm		
	1	2	3		1	2	3	1	2	3
Bone 2000[282]	Placebo	ALN	–	24	50	92	–	4	5	–
HORIZON-PFT: Black 2007[133]	Placebo	ZOL	–	11	3861	3875	–	388	292	–
HORIZON-RFT: Lyles 2007[307]	Placebo	ZOL	–	36	1062	1065	–	107	79	–
BONE: Chesnut 2004[136]	Placebo	IBN daily	–	36	975	977	–	80	89	–
MOTION: Miller 2008[311]	ALN	IBN monthly	–	12	859	874	–	12	14	–
Morii 2003[47]	Placebo	RLX	–	12	97	88	–	4	1	–

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; BONE, iBandronate Osteoporosis vertebral fracture trial in North America and Europe; DAPS, Denosumab Adherence Preference Satisfaction; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; FIT, Fracture Intervention Trial; FOSIT, FOSamax International Trial; MOTION, Monthly Oral Therapy with Ibandronate for Osteoporosis iNtervention; PFT, Pivotal Fracture Trial; RFT, Recurrent Fracture Trial; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy; VERT, Vertebral Efficacy with Risedronate Therapy; ZONE, ZOledroNate treatment in Efficacy to osteoporosis.

TABLE 29 Data contributing to the NMA of hip fractures

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm		
	1	2	3		1	2	3	1	2	3
FREEDOM: Cummings 2009[41]	Placebo	DEN	–	36	3906	3902	–	43	26	–
FRAME: Cosman 2016[54]	Placebo	ROMO	–	12	3591	3589	–	13	7	–
DIRECT: Nakamura 2014[43]	Placebo	DEN	–	24	480	472	–	2	0	–
ACTIVE: Miller 2016[75]	Placebo	TPTD	–	18	821	818	–	2	0	–
Neer 2001[62]	Placebo	TPTD	–	24	544	541	–	4	1	–
STRUCTURE: Langdahl 2017[67]	ROMO	TPTD	–	12	218	218	–	1	0	–
Miller 2016[75]	ZOL	DEN	–	12	320	320	–	2	1	–
EuroGIOPs: Glüer 2013[87]	RIS	TPTD	–	18	47	45	–	1	0	–
VERO: Kendler 2017[99]	RIS	TPTD	–	24	680	680	–	5	2	–
Hadji 2012[91]	RIS	TPTD	–	18	350	360	–	2	5	–
EFFECT: Sambrook 2004[76]	ALN	RLX	–	12	246	241	–	0	1	–
MOVE: Malouf-Sierra 2017[92]	RIS	TPTD	–	18	110	106	–	7	2	–
Muscoso 2004[79]	ALN	RLX	RIS	24	1000	100	100	3	0	0
ARCH: Saag 2017[83]	ALN	ROMO/ALN	–	32.4	2047	2046	–	66	41	–
Saag 2018[74]	RIS	DEN	–	12	397	398	–	1	1	–
Silverman 2008[50]	Placebo	RLX	–	36	1885	1849	–	6	5	–
VERT-USA: Harris 1999[298]	Placebo	RIS	–	36	815	812	–	15	12	–

continued

TABLE 29 Data contributing to the NMA of hip fractures (*continued*)

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm		
	1	2	3		1	2	3	1	2	3
VERT-EU: Reginster 2000[300]	Placebo	RIS	–	36	406	406	–	11	9	–
FIT I: Black 1996[280]	Placebo	ALN	–	36	1005	1022	–	22	11	–
FIT II: Cummings 1998[281]	Placebo	ALN	–	48	2218	2214	–	24	19	–
Greenspan 2002[283]	Placebo	ALN	–	24	164	163	–	4	2	–
HORIZON-PFT: Black 2007[133]	Placebo	ZOL	–	36	3861	3875	–	88	52	–
HORIZON-RFT: Lyles 2007[307]	Placebo	ZOL	–	36	1062	1065	–	33	23	–

EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; FIT, Fracture Intervention Trial; PFT, Pivotal Fracture Trial; RFT, Recurrent Fracture Trial; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy; VERT, Vertebral Efficacy with Risedronate Therapy.

TABLE 30 Data contributing to the NMA of wrist fractures

Study	Treatment			Assessment time point	Number of participants in study arm			Number of events in study arm		
	1	2	3		1	2	3	1	2	3
ACTIVE: Miller 2016[95]	Placebo	TPTD	–	18	821	818	–	15	17	–
Neer 2001[62]	Placebo	TPTD	–	24	544	541	–	7	2	–
Ishibashi 2017[55]	Placebo	RLX	–	12	63	63	–	0	1	–
STRUCTURE: Langdahl 2017[67]	ROMO	TPTD	–	12	218	218	–	1	4	–
STAND: Kendler 2010[70]	ALN	DEN	–	12	249	253	–	2	3	–
VERO: Kendler 2017[99]	RIS	TPTD	–	24	680	680	–	15	6	–
Hadji 2012[91]	RIS	TPTD	–	18	350	360	–	2	4	–
Muscoso 2004[79]	ALN	RLX	RIS	24	1000	100	100	1	0	0
EFFECT (USA): Luckey 2004[77]	ALN	RLX	–	12	199	206	–	0	1	–
Silverman 2008[50]	Placebo	RLX	–	36	1885	1849	–	31	46	–
VERT-USA: Harris 1999[298]	Placebo	RIS	–	36	815	812	–	22	14	–
VERT-EU: Reginster 2000[300]	Placebo	RIS	–	36	406	406	–	21	15	–
FIT I: Black 1996[280]	Placebo	ALN	–	36	1005	1022	–	41	22	–
FIT II: Cummings 1998[281]	Placebo	ALN	–	48	2218	2214	–	70	83	–
McClung 2009[291]	Placebo	IBN monthly	–	12	83	77	–	0	1	–

EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; FIT, Fracture Intervention Trial; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy; VERT, Vertebral Efficacy with Risedronate Therapy.

TABLE 31 Data contributing to the NMA of proximal humerus fractures

Study	Treatment		Assessment time point	Number of participants in study arm		Number of events in study arm	
	1	2		1	2	1	2
ADAMO: Orwoll 2012[42]	Placebo	DEN	12	120	120	1	0
ACTIVE: Miller 2016[95]	Placebo	TPTD	18	821	818	3	2
Neer 2001[62]	Placebo	TPTD	24	544	541	2	2
STRUCTURE: Langdahl 2017[67]	ROMO	TPTD	12	218	218	0	1
STAND: Kendler 2010[70]	ALN	DEN	12	249	253	0	1
EuroGIOPs: Glüer 2013[87]	RIS	TPTD	18	47	45	1	0
VERO: Kendler 2017[99]	RIS	TPTD	24	680	680	2	4
Hadji 2012[91]	RIS	TPTD	18	350	360	5	4
MOVE: Malouf-Sierra 2017[92]	RIS	TPTD	18	110	106	1	1
EFFECT (USA): Luckey 2004[77]	ALN	RLX	12	199	206	0	1
Saag 2018[74]	RIS	DEN	12	391	398	3	3
VERT-MN Harris 1999[298]	Placebo	RIS	36	815	812	10	4
VERT-MN Reginster 2000[300]	Placebo	RIS	36	406	406	14	7

ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety DenosumAb versus placebo in Males with Osteoporosis; EFFECT, EFficacy of Fosamax versus Evista Comparison Trial; STAND, Study of Transitioning from Alendronate to Denosumab; STRUCTURE, STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy; VERT-MN, Vertebral Efficacy with Risedronate Therapy-Multinational.

Appendix 10 Network meta-analysis results from random-effects model

Treatment effects versus placebo from the random-effects model is shown in *Figure 13*, and a summary of model fit and heterogeneity is shown in *Table 32*. For all outcomes the DIC was larger for the random-effects model, implying that the primary model (class effect for bisphosphonate treatments, and unrelated treatment effects for all other interventions) provides a better fit to the data. Treatment effects from the random-effects model are generally consistent with primary model.

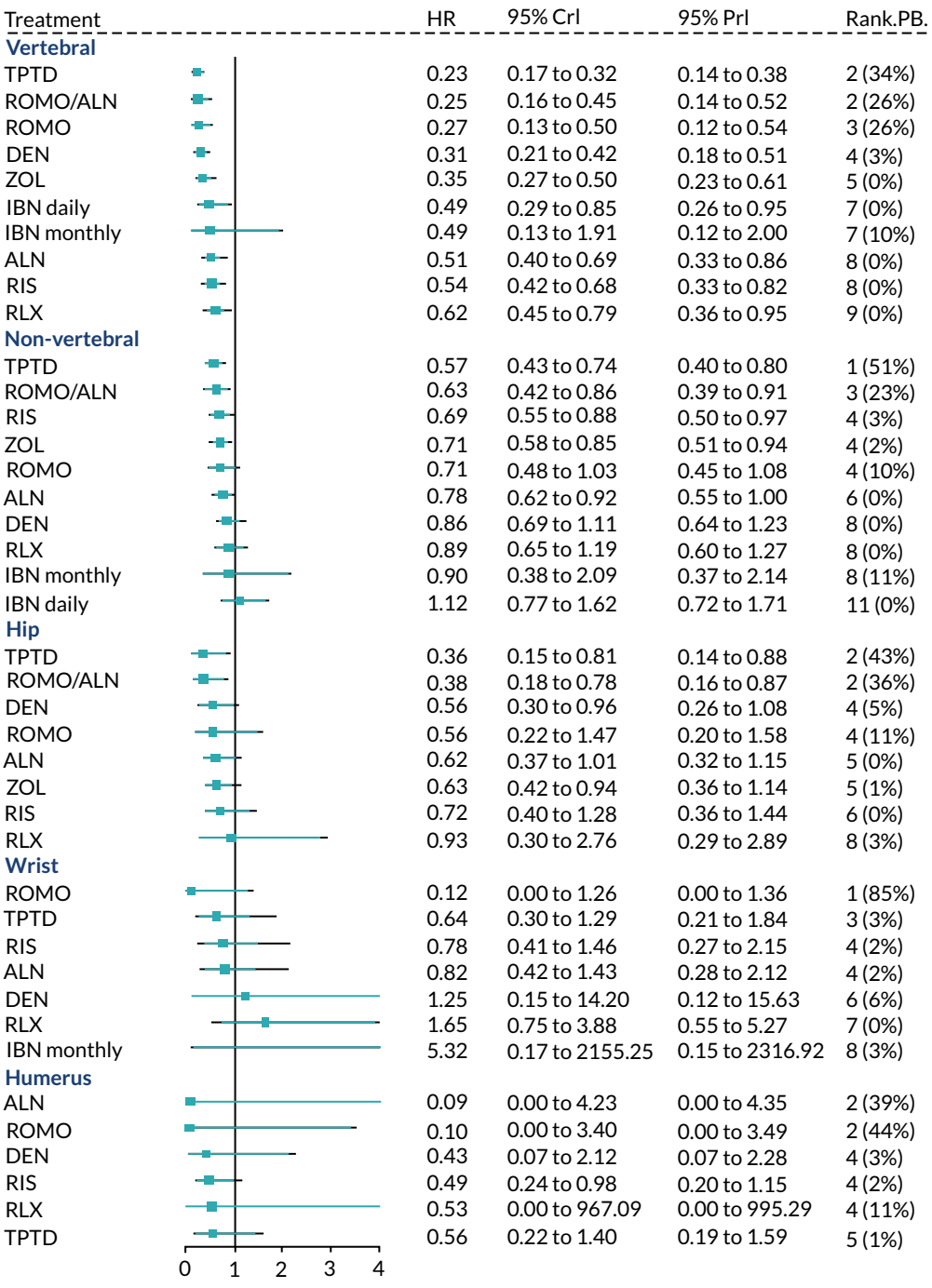

FIGURE 13 Forest plot of HRs for all fracture outcomes using a random-effects model.

TABLE 32 Model fit and heterogeneity for random-effects sensitivity analysis: all outcomes

Outcome	Absolute model fit		DIC	SD[b] (95% CI)
	D_{res}[a]	Data points		
Vertebral fractures	93.42	93	156.43	0.15 (0.01 to 0.37)
Non-vertebral fractures	73.93	86	129.50	0.08 (0.01 to 0.24)
Hip[c]	39.58	47	72.37	0.13 (0.01 to 0.45)
Wrist[c]	30.76	31	56.63	0.34 (0.05 to 0.71)
Proximal humerus[c]	22.87	26	44.02	0.17 (0.01 to 0.58)
Femoral neck BMD				

a Total residual deviance.
b Between-study SD.
c For hip, wrist and humerus fractures, weakly informative priors were used for the between-study and between-treatment SDs.

Treatment effects from the two models appear most different for proximal humerus fractures. Using a random-effects model, ALN has a highly beneficial HR (0.09, 95% CrI 0 to 4.23) and PB of 0.39. Under the class-effects model, the HR for ALN is less extreme (0.46, 95% CrI 0.15 to 1.27) as it is also influenced by the estimate for RIS (the only other bisphosphonate included in the network). The estimate for ALN is only contributed by one study[77] with zero events in the ALN arm and one event in the RLX arm, and so is highly uncertain.

Appendix 11 Vertebral fracture sensitivity analyses

Four sensitivity analyses were conducted for the vertebral fracture network:

- SA1: 12-month data only
- SA2: clinically assessed fractures only
- SA3: exclusion of studies with quality issues
- SA4: exclusion of studies in which prior bisphosphonate treatment had been received.

Treatment effects versus placebo is summarised in *Figure 14*, and a summary of model fit and heterogeneity is shown in *Table 33*.

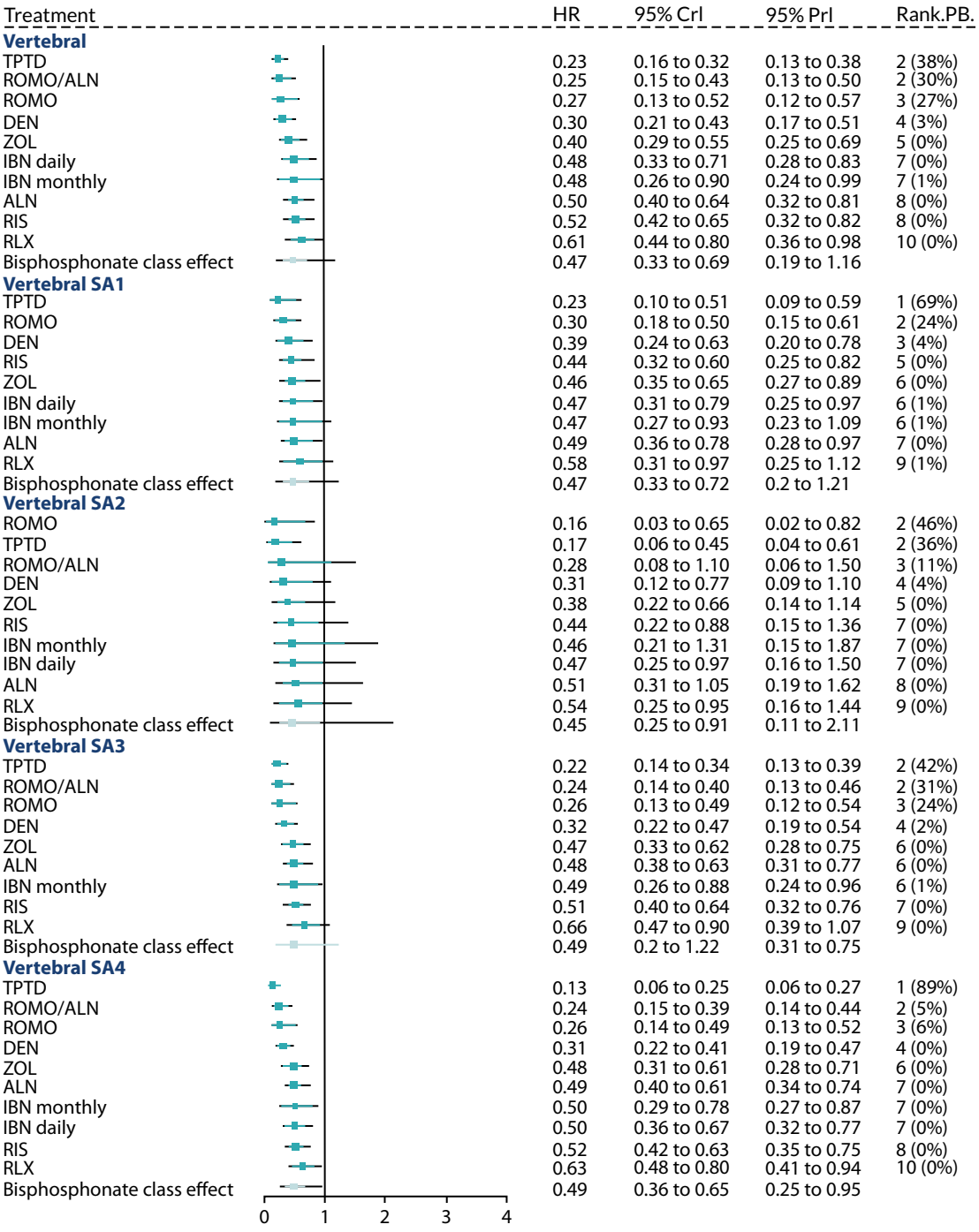

FIGURE 14 Forest plot of vertebral fracture network sensitivity analyses.

TABLE 33 Summary of model fit and heterogeneity between studies and between treatments for vertebral fracture network sensitivity analyses

	Absolute model fit			Heterogeneity, SD (95% CrI)	
Outcome	D_{res} [a]	Data points	DIC	Between study	Between treatment
Vertebral fractures	91.21	93	153.31	0.17 (0.02 to 0.37)	0.21 (0.01 to 0.90)
SA1: 12-month data	56.17	59	95.94	0.17 (0.01 to 0.51)	0.15 (0.01 to 0.86)
SA2: clinical fractures	40.14	40	72.49	0.32 (0.02 to 0.89)	0.29 (0.02 to 1.33)
SA3: excluding studies with quality issues	58.27	61	99.4	0.13 (0.01 to 0.38)	0.149 (0.01 to 1.04)
SA4: excluding studies with prior treatment	69.83	72	117.47	0.11 (0.01 to 0.34)	0.117 (0.01 to 0.69)

a Total residual deviance.

Appendix 12 Pairwise summary tables

Pairwise summary tables for all outcomes are shown in this appendix. Median HR and 95% CrIs are presented below the diagonal, median HR and 95% PrI are shown above the diagonal.

TABLE 34 Pairwise comparisons, vertebral fractures main analysis

	Placebo	ALN	RIS	ZOL	IBN daily	IBN monthly	DEN	ROMO	TPTD	RLX	ROMO/ALN
Placebo		0.50 (0.32 to 0.81)	0.52 (0.32 to 0.82)	0.39 (0.25 to 0.69)	0.48 (0.28 to 0.83)	0.48 (0.24 to 0.99)	0.31 (0.17 to 0.51)	0.27 (0.12 to 0.57)	0.23 (0.13 to 0.38)	0.62 (0.36 to 0.98)	0.25 (0.13 to 0.50)
ALN	**0.50 (0.40 to 0.64)**		1.06 (0.53 to 1.90)	0.78 (0.42 to 1.61)	0.98 (0.47 to 1.87)	0.96 (0.42 to 2.16)	0.61 (0.29 to 1.20)	0.53 (0.21 to 1.28)	0.47 (0.23 to 0.88)	1.24 (0.60 to 2.29)	0.49 (0.23 to 1.06)
RIS	**0.52 (0.42 to 0.65)**	1.03 (0.77 to 1.39)		0.74 (0.42 to 1.63)	0.93 (0.47 to 1.86)	0.92 (0.41 to 2.17)	0.58 (0.29 to 1.19)	0.51 (0.20 to 1.25)	0.44 (0.23 to 0.85)	1.17 (0.59 to 2.28)	0.47 (0.22 to 1.09)
ZOL	**0.40 (0.29 to 0.55)**	0.81 (0.54 to 1.08)	0.77 (0.52 to 1.08)		1.23 (0.57 to 2.43)	1.19 (0.53 to 2.91)	0.79 (0.34 to 1.50)	0.68 (0.24 to 1.60)	0.60 (0.26 to 1.11)	1.58 (0.68 to 2.90)	0.63 (0.26 to 1.37)
IBN daily	**0.48 (0.33 to 0.71)**	0.98 (0.63 to 1.43)	0.95 (0.61 to 1.37)	1.18 (0.82 to 1.99)		0.99 (0.42 to 2.40)	0.63 (0.29 to 1.32)	0.55 (0.21 to 1.40)	0.48 (0.23 to 0.99)	1.27 (0.59 to 2.56)	0.51 (0.22 to 1.21)
IBN monthly	**0.48 (0.26 to 0.90)**	0.98 (0.51 to 1.75)	0.95 (0.47 to 1.71)	1.14 (0.68 to 2.50)	1.00 (0.49 to 1.98)		0.64 (0.25 to 1.52)	0.55 (0.19 to 1.56)	0.48 (0.19 to 1.13)	1.28 (0.52 to 2.91)	0.51 (0.20 to 1.34)
DEN	**0.30 (0.21 to 0.43)**	**0.61 (0.39 to 0.91)**	**0.58 (0.40 to 0.88)**	0.77 (0.46 to 1.19)	0.63 (0.38 to 1.03)	0.64 (0.31 to 1.26)		0.87 (0.33 to 2.23)	0.76 (0.36 to 1.57)	2.01 (0.95 to 4.14)	0.81 (0.35 to 1.97)
ROMO	**0.27 (0.13 to 0.52)**	0.53 (0.25 to 1.06)	0.51 (0.25 to 1.03)	0.67 (0.30 to 1.35)	0.55 (0.25 to 1.16)	0.55 (0.22 to 1.36)	0.87 (0.40 to 1.86)		0.87 (0.34 to 2.22)	2.31 (0.89 to 5.79)	0.93 (0.33 to 2.71)
TPTD	**0.23 (0.16 to 0.32)**	**0.46 (0.31 to 0.66)**	**0.44 (0.32 to 0.61)**	**0.58 (0.36 to 0.90)**	**0.47 (0.29 to 0.77)**	**0.48 (0.25 to 0.95)**	0.76 (0.46 to 1.20)	0.87 (0.41 to 1.87)		2.65 (1.28 to 5.45)	1.06 (0.48 to 2.61)
RLX	**0.61 (0.44 to 0.80)**	1.23 (0.82 to 1.71)	1.17 (0.82 to 1.68)	1.54 (0.94 to 2.32)	1.26 (0.78 to 1.97)	1.27 (0.65 to 2.47)	2.01 (1.25 to 3.13)	2.30 (1.09 to 4.83)	2.66 (1.72 to 4.11)		0.40 (0.18 to 0.98)
ROMO/ ALN	**0.25 (0.15 to 0.43)**	**0.50 (0.30 to 0.80)**	**0.47 (0.28 to 0.86)**	0.62 (0.33 to 1.11)	**0.51 (0.28 to 0.98)**	0.51 (0.24 to 1.12)	0.81 (0.44 to 1.59)	0.93 (0.40 to 2.29)	1.06 (0.60 to 2.06)	**0.40 (0.23 to 0.78)**	

Pairwise HR and 95% CrIs (lower triangle, not shaded), predictive effects in a new study and 95% PrI (upper triangle, shaded).
Bold font shows comparisons that indicate a statistically significant difference between interventions.

TABLE 35 Pairwise comparisons, non-vertebral fractures main analysis

	Placebo	ALN	RIS	ZOL	IBN daily	IBN monthly	DEN	ROMO	TPTD	RLX	ROMO/ALN
Placebo		0.78 (0.56 to 0.99)	0.73 (0.53 to 0.98)	0.73 (0.54 to 0.95)	0.89 (0.60 to 1.38)	0.79 (0.50 to 1.31)	0.86 (0.64 to 1.23)	0.71 (0.45 to 1.09)	0.58 (0.41 to 0.81)	0.90 (0.60 to 1.29)	0.63 (0.40 to 0.92)
ALN	**0.77 (0.64 to 0.90)**		0.95 (0.65 to 1.43)	0.94 (0.65 to 1.42)	1.15 (0.75 to 1.91)	1.02 (0.63 to 1.78)	1.10 (0.76 to 1.84)	0.92 (0.56 to 1.56)	0.75 (0.51 to 1.18)	1.16 (0.74 to 1.87)	0.81 (0.52 to 1.27)
RIS	**0.73 (0.59 to 0.88)**	0.96 (0.73 to 1.19)		1.00 (0.66 to 1.48)	1.22 (0.76 to 2.11)	1.07 (0.65 to 1.96)	1.18 (0.79 to 1.91)	0.97 (0.57 to 1.65)	0.80 (0.52 to 1.20)	1.23 (0.76 to 1.97)	0.86 (0.51 to 1.38)
ZOL	**0.73 (0.61 to 0.85)**	0.96 (0.76 to 1.17)	1.00 (0.79 to 1.28)		1.23 (0.77 to 2.08)	1.07 (0.65 to 1.93)	1.18 (0.79 to 1.90)	0.97 (0.58 to 1.63)	0.80 (0.52 to 1.24)	1.24 (0.76 to 1.94)	0.86 (0.52 to 1.37)
IBN daily	0.88 (0.67 to 1.32)	1.13 (0.91 to 1.76)	1.20 (0.93 to 1.98)	1.20 (0.93 to 1.91)		0.91 (0.47 to 1.49)	0.95 (0.57 to 1.69)	0.79 (0.43 to 1.43)	0.65 (0.38 to 1.09)	1.00 (0.57 to 1.71)	0.70 (0.39 to 1.19)
IBN monthly	0.78 (0.54 to 1.27)	1.01 (0.70 to 1.66)	1.05 (0.74 to 1.84)	1.05 (0.74 to 1.83)	0.93 (0.50 to 1.32)		1.08 (0.61 to 1.98)	0.90 (0.47 to 1.68)	0.74 (0.40 to 1.28)	1.14 (0.61 to 2.00)	0.79 (0.43 to 1.38)
DEN	0.86 (0.69 to 1.12)	1.12 (0.87 to 1.57)	1.18 (0.90 to 1.63)	1.18 (0.91 to 1.63)	0.97 (0.62 to 1.46)	1.09 (0.65 to 1.73)		0.83 (0.46 to 1.38)	0.68 (0.41 to 1.05)	1.05 (0.60 to 1.65)	0.74 (0.40 to 1.16)
ROMO	0.71 (0.48 to 1.03)	0.92 (0.62 to 1.39)	0.97 (0.64 to 1.49)	0.97 (0.64 to 1.47)	0.79 (0.47 to 1.28)	0.90 (0.50 to 1.53)	0.82 (0.51 to 1.26)		0.82 (0.48 to 1.41)	1.27 (0.71 to 2.25)	0.88 (0.48 to 1.57)
TPTD	**0.58 (0.45 to 0.76)**	0.76 (0.57 to 1.02)	0.80 (0.61 to 1.04)	0.80 (0.60 to 1.08)	**0.66 (0.40 to 0.96)**	0.74 (0.42 to 1.14)	**0.68 (0.47 to 0.94)**	0.82 (0.53 to 1.28)		1.55 (0.93 to 2.53)	1.08 (0.62 to 1.79)
RLX	0.90 (0.65 to 1.21)	1.17 (0.84 to 1.63)	1.23 (0.85 to 1.77)	1.23 (0.87 to 1.74)	1.01 (0.62 to 1.53)	1.14 (0.66 to 1.83)	1.05 (0.68 to 1.49)	1.27 (0.78 to 2.05)	**1.55 (1.03 to 2.28)**		0.70 (0.40 to 1.19)
ROMO/ ALN	**0.63 (0.44 to 0.86)**	0.81 (0.61 to 1.09)	0.86 (0.58 to 1.25)	0.86 (0.59 to 1.23)	0.70 (0.42 to 1.06)	0.79 (0.46 to 1.26)	0.73 (0.46 to 1.06)	0.88 (0.53 to 1.44)	1.08 (0.70 to 1.62)	0.70 (0.44 to 1.08)	

Pairwise HR and 95% CrIs (lower triangle, not shaded), predictive effects in a new study and 95% PrI (upper triangle, shaded).
Bold font shows comparisons that indicate a statistically significant difference between interventions.

TABLE 36 Pairwise comparisons, hip fractures main analysis

	Placebo	ALN	RIS	ZOL	DEN	ROMO	TPTD	RLX	ROMO/ALN
Placebo		0.64 (0.39 to 1.04)	0.66 (0.40 to 1.12)	0.63 (0.39 to 1.01)	0.56 (0.28 to 1.04)	0.56 (0.20 to 1.50)	0.34 (0.14 to 0.78)	0.93 (0.29 to 2.82)	0.39 (0.19 to 0.80)
ALN	**0.64 (0.45 to 0.88)**		1.03 (0.56 to 2.01)	1.00 (0.54 to 1.85)	0.88 (0.38 to 1.94)	0.88 (0.29 to 2.64)	0.54 (0.20 to 1.37)	1.48 (0.44 to 4.81)	0.62 (0.29 to 1.28)
RIS	**0.66 (0.46 to 0.99)**	1.02 (0.71 to 1.63)		0.97 (0.51 to 1.79)	0.85 (0.36 to 1.84)	0.85 (0.27 to 2.63)	0.52 (0.21 to 1.23)	1.41 (0.42 to 4.71)	0.59 (0.26 to 1.32)
ZOL	**0.64 (0.47 to 0.86)**	1.00 (0.70 to 1.44)	0.99 (0.62 to 1.38)		0.88 (0.39 to 1.91)	0.88 (0.29 to 2.65)	0.54 (0.20 to 1.34)	1.48 (0.44 to 4.82)	0.62 (0.27 to 1.37)
DEN	**0.56 (0.31 to 0.94)**	0.88 (0.45 to 1.63)	0.85 (0.43 to 1.57)	0.88 (0.46 to 1.59)		1.00 (0.31 to 3.31)	0.61 (0.21 to 1.77)	1.68 (0.47 to 5.95)	0.70 (0.28 to 1.89)
ROMO	0.56 (0.22 to 1.43)	0.88 (0.33 to 2.41)	0.85 (0.31 to 2.33)	0.88 (0.33 to 2.36)	1.01 (0.33 to 3.04)		0.61 (0.17 to 2.19)	1.65 (0.37 to 7.39)	0.70 (0.21 to 2.41)
TPTD	**0.35 (0.15 to 0.73)**	0.54 (0.23 to 1.19)	0.52 (0.23 to 1.06)	0.54 (0.23 to 1.18)	0.62 (0.24 to 1.58)	0.61 (0.19 to 1.97)		2.74 (0.68 to 11.24)	1.14 (0.40 to 3.51)
RLX	0.94 (0.31 to 2.67)	1.48 (0.49 to 4.20)	1.42 (0.45 to 4.21)	1.47 (0.48 to 4.27)	1.69 (0.50 to 5.45)	1.64 (0.41 to 6.67)	2.73 (0.73 to 10.19)		0.42 (0.12 to 1.52)
ROMO/ALN	**0.39 (0.21 to 0.72)**	0.62 (0.36 to 1.03)	0.59 (0.31 to 1.12)	0.61 (0.32 to 1.13)	0.70 (0.32 to 1.62)	0.70 (0.22 to 2.14)	1.14 (0.44 to 3.09)	0.42 (0.13 to 1.39)	

Pairwise HR and 95% CrIs (lower triangle, not shaded), predictive effects in a new study and 95% PrI (upper triangle, shaded).
Bold font shows comparisons that indicate a statistically significant difference between interventions.

TABLE 37 Pairwise comparisons, wrist fractures main analysis

	Placebo	ALN	RIS	IBN monthly	DEN	ROMO	TPTD	RLX
Placebo		**0.82 (0.28 to 2.12)**	**0.78 (0.27 to 2.15)**	**5.34 (0.15 to 2316.92)**	**1.24 (0.12 to 15.63)**	**0.12 (0.00 to 1.36)**	**0.64 (0.21 to 1.84)**	**1.64 (0.55 to 5.27)**
ALN	**0.82 (0.42 to 1.43)**		**0.96 (0.24 to 4.30)**	**6.77 (0.16 to 3022.57)**	**1.55 (0.15 to 20.29)**	**0.14 (0.00 to 2.15)**	**0.79 (0.18 to 3.59)**	**2.01 (0.50 to 9.64)**
RIS	**0.78 (0.41 to 1.46)**	**0.96 (0.42 to 2.43)**		**6.89 (0.16 to 3288.50)**	**1.59 (0.13 to 23.95)**	**0.15 (0.00 to 2.04)**	**0.83 (0.21 to 3.19)**	**2.10 (0.47 to 10.22)**
IBN monthly	**5.32 (0.17 to 2155.25)**	**6.60 (0.20 to 2849.07)**	**6.89 (0.19 to 2995.07)**		**0.22 (0.00 to 18.93)**	**0.02 (0.00 to 1.60)**	**0.12 (0.00 to 5.15)**	**0.31 (0.00 to 13.60)**
DEN	**1.25 (0.15 to 14.20)**	**1.54 (0.20 to 16.36)**	**1.60 (0.17 to 18.83)**	**0.23 (0.00 to 15.84)**		**0.08 (0.00 to 2.91)**	**0.52 (0.03 to 6.41)**	**1.31 (0.09 to 17.37)**
ROMO	**0.12 (0.00 to 1.26)**	**0.14 (0.00 to 1.72)**	**0.15 (0.00 to 1.62)**	**0.02 (0.00 to 1.42)**	**0.09 (0.00 to 2.37)**		**5.57 (0.46 to 188.50)**	**14.49 (0.99 to 574.10)**
TPTD	**0.64 (0.30 to 1.29)**	**0.79 (0.32 to 2.08)**	**0.82 (0.39 to 1.70)**	**0.12 (0.00 to 4.25)**	**0.51 (0.04 to 4.92)**	**5.44 (0.57 to 159.42)**		**2.55 (0.57 to 12.79)**
RLX	**1.65 (0.75 to 3.88)**	**2.02 (0.82 to 5.87)**	**2.12 (0.79 to 6.12)**	**0.31 (0.00 to 11.44)**	**1.32 (0.11 to 13.41)**	**14.42 (1.17 to 500.04)**	**2.57 (0.92 to 7.92)**	

Pairwise HR and 95% CrIs (lower triangle, not shaded), predictive effects in a new study and 95% PrI (upper triangle, shaded).
Bold font shows comparisons that indicate a statistically significant difference between interventions.

TABLE 38 Pairwise comparisons, humerus fractures main analysis

	Placebo	ALN	RIS	DEN	ROMO	TPTD	RLX
Placebo		0.46 (0.13 to 1.43)	0.48 (0.20 to 1.13)	0.55 (0.11 to 2.60)	0.10 (0.00 to 3.80)	0.55 (0.19 to 1.59)	2.48 (0.06 to 1215.07)
ALN	0.46 (0.15 to 1.27)		1.03 (0.36 to 3.52)	1.21 (0.24 to 6.59)	0.23 (0.00 to 10.16)	1.22 (0.32 to 4.89)	5.48 (0.16 to 2806.02)
RIS	**0.49 (0.23 to 0.96)**	1.01 (0.47 to 2.78)		1.13 (0.24 to 5.46)	0.22 (0.00 to 8.19)	1.15 (0.38 to 3.48)	5.27 (0.14 to 2596.20)
DEN	0.55 (0.12 to 2.41)	1.21 (0.26 to 5.68)	1.14 (0.28 to 4.57)		0.19 (0.00 to 9.50)	1.00 (0.18 to 5.72)	4.63 (0.09 to 2621.17)
ROMO	0.10 (0.00 to 3.66)	0.23 (0.00 to 9.49)	0.22 (0.00 to 7.54)	0.19 (0.00 to 8.82)		5.11 (0.16 to 2773.07)	34.06 (0.14 to 132817.46)
TPTD	0.55 (0.21 to 1.41)	1.22 (0.39 to 4.05)	1.15 (0.50 to 2.63)	1.00 (0.20 to 5.02)	5.10 (0.17 to 2692.22)		4.63 (0.11 to 2511.00)
RLX	2.46 (0.06 to 1204.07)	5.43 (0.17 to 2598.02)	5.19 (0.15 to 2496.67)	4.64 (0.10 to 2526.10)	33.91 (0.15 to 126105.00)	4.58 (0.12 to 2345.00)	

Pairwise HR and 95% CrIs (lower triangle, not shaded), predictive effects in a new study and 95% PrI (upper triangle, shaded).
Bold font shows comparisons that indicate a statistically significant difference between interventions.

TABLE 39 Pairwise comparisons, femoral neck BMD main analysis

	Placebo	ALN	RIS	ZOL	IBN daily	IBN monthly	IBN i.v.	DEN	ROMO	TPTD	RLX	ROMO/ALN
Placebo		2.48 (0.71 to 4.25)	1.80 (0.01 to 3.58)	3.16 (1.27 to 5.04)	1.84 (−0.30 to 3.85)	2.30 (0.41 to 4.24)	2.38 (0.06 to 4.56)	3.35 (1.51 to 5.16)	4.20 (2.24 to 6.17)	2.58 (0.77 to 4.40)	1.52 (−0.33 to 3.42)	6.09 (3.55 to 8.61)
ALN	**2.49 (2.05 to 2.91)**		−0.70 (−3.20 to 1.78)	0.68 (−1.91 to 3.19)	−0.65 (−3.37 to 1.98)	−0.19 (−2.74 to 2.37)	−0.12 (−2.97 to 2.66)	0.87 (−1.69 to 3.36)	1.71 (−0.94 to 4.34)	0.10 (−2.41 to 2.57)	−0.97 (−3.49 to 1.60)	3.60 (0.57 to 6.64)
RIS	**1.80 (1.22 to 2.37)**	−0.69 (−1.29 to −0.09)		1.36 (−1.22 to 3.95)	0.03 (−2.66 to 2.70)	0.51 (−2.03 to 3.10)	0.58 (−2.30 to 3.37)	1.56 (−0.95 to 4.08)	2.40 (−0.25 to 5.10)	0.79 (−1.70 to 3.30)	−0.26 (−2.84 to 2.35)	4.27 (1.25 to 7.38)
ZOL	**3.17 (2.38 to 3.95)**	0.68 (−0.09 to 1.49)	**1.37 (0.41 to 2.28)**		−1.32 (−4.14 to 1.41)	−0.86 (−3.48 to 1.85)	−0.77 (−3.72 to 2.08)	0.18 (−2.39 to 2.77)	1.04 (−1.67 to 3.76)	−0.58 (−3.21 to 2.06)	−1.63 (−4.24 to 1.02)	2.92 (−0.15 to 5.99)
IBN daily	**1.85 (0.53 to 2.93)**	−0.63 (−1.97 to 0.41)	0.05 (−1.24 to 1.15)	−1.31 (−2.86 to −0.06)		0.48 (−2.17 to 3.17)	0.54 (−2.18 to 3.28)	1.52 (−1.20 to 4.27)	2.39 (−0.52 to 5.22)	0.75 (−1.94 to 3.51)	−0.29 (−3.05 to 2.52)	4.25 (1.07 to 7.52)
IBN monthly	**2.32 (1.50 to 3.13)**	−0.16 (−0.99 to 0.63)	0.51 (−0.33 to 1.41)	−0.83 (−1.95 to 0.15)	0.47 (−0.56 to 1.73)		0.07 (−2.80 to 2.88)	1.04 (−1.55 to 3.64)	1.91 (−0.87 to 4.59)	0.29 (−2.38 to 2.87)	−0.78 (−3.47 to 1.87)	3.78 (0.64 to 6.90)
IBN i.v.	**2.39 (0.83 to 3.78)**	−0.10 (−1.66 to 1.32)	0.56 (−0.92 to 2.09)	−0.73 (−2.53 to 0.64)	0.52 (−0.69 to 1.92)	0.06 (−1.47 to 1.54)		0.97 (−1.90 to 3.87)	1.82 (−1.16 to 4.85)	0.21 (−2.62 to 3.15)	−0.86 (−3.69 to 2.15)	3.72 (0.33 to 7.10)
DEN	**3.36 (2.74 to 3.97)**	**0.87 (0.24 to 1.49)**	**1.56 (0.83 to 2.30)**	0.19 (−0.70 to 1.09)	**1.52 (0.33 to 2.91)**	**1.04 (0.16 to 1.95)**	0.97 (−0.50 to 2.60)		0.85 (−1.79 to 3.53)	−0.78 (−3.31 to 1.80)	−1.82 (−4.36 to 0.80)	2.73 (−0.36 to 5.83)
ROMO	**4.20 (3.23 to 5.16)**	**1.71 (0.67 to 2.75)**	**2.40 (1.28 to 3.51)**	1.03 (−0.22 to 2.28)	**2.36 (0.88 to 3.95)**	**1.88 (0.65 to 3.12)**	**1.82 (0.10 to 3.65)**	0.84 (−0.30 to 1.96)		−1.63 (−4.27 to 1.00)	−2.66 (−5.40 to 0.03)	1.88 (−1.33 to 5.12)
TPTD	**2.58 (2.00 to 3.17)**	0.09 (−0.56 to 0.75)	**0.78 (0.02 to 1.54)**	−0.59 (−1.52 to 0.35)	0.73 (−0.47 to 2.14)	0.25 (−0.68 to 1.22)	**0.19 (−1.30 to 1.85)**	−0.78 (−1.57 to 0.01)	−1.62 (−2.63 to −0.60)		−1.04 (−3.65 to 1.56)	3.51 (0.41 to 6.59)
RLX	**1.53 (0.78 to 2.31)**	−0.95 (−1.74 to −0.14)	−0.26 (−1.19 to 0.66)	−1.63 (−2.70 to −0.56)	−0.30 (−1.64 to 1.17)	−0.79 (−1.86 to 0.31)	−0.85 (−2.42 to 0.87)	−1.82 (−2.77 to −0.86)	−2.66 (−3.89 to −1.42)	−1.04 (−1.98 to −0.09)		4.55 (1.42 to 7.67)
ROMO/ALN	**6.08 (4.25 to 7.91)**	**3.59 (1.81 to 5.37)**	**4.29 (2.40 to 6.14)**	**2.92 (0.93 to 4.86)**	**4.26 (2.14 to 6.42)**	**3.76 (1.79 to 5.73)**	**3.70 (1.41 to 6.03)**	**2.72 (0.83 to 4.61)**	1.89 (−0.22 to 3.98)	**3.50 (1.57 to 5.41)**	**4.55 (2.57 to 6.50)**	

Pairwise HR and 95% CrIs (lower triangle, not shaded), predictive effects in a new study and 95% PrI (upper triangle, shaded).
Bold font shows comparisons that indicate a statistically significant difference between interventions.

Appendix 13 Assessment of inconsistency

Vertebral fractures

Twelve treatment contrasts have both direct and indirect evidence; however, only 10 of these were assessed for consistency. RIS–ALN was not assessed because the direct comparison is contributed by one small study[79] with a zero count in the control arm. ZOL–TPTD was not assessed because the direct comparison is contributed by one small study,[93] with only one event in the TPTD arm. Multiple testing should be taken into account when considering *p*-values.

Comparing the DIC for the different node-splits with that of the full consistency NMA model, only the placebo–ZOL comparison provides a lower DIC when the node is split. However, the difference is small (–0.7); therefore, there is not a clear advantage of one model over the other. The HRs from both the direct and indirect evidence favour ZOL and the combined estimate is more heavily influenced by the direct studies. It was concluded that there is no strong evidence for inconsistency in the network.

Non-vertebral fractures

Fourteen treatment contrasts have both direct and indirect evidence; however, only 13 of these were assessed for consistency. RIS–ALN was not assessed because the direct comparison is contributed by one small study[79] with a zero count in the RIS arm. Multiple testing should be taken into account when considering *p*-values.

Comparing the DIC for the different node-splits with that of the full consistency NMA model, only the placebo–ALN comparison provides a lower DIC when the node is split. However, the difference is small; therefore, there is not a clear advantage of one model over the other, and the *p*-values are large for all comparisons. It was concluded that there is no strong evidence for inconsistency in the network.

Hip fractures

Fourteen treatment contrasts have both direct and indirect evidence; however, only nine of these were assessed for consistency. For five of these (RIS–ALN, RIS–DEN, RIS–RLX, ZOL–DEN, ROMO–TPTD), the direct comparison is contributed by small studies.[67,79,341] Multiple testing should be taken into account when considering *p*-values.

Comparing the DIC for the different node-splits with that of the full consistency NMA model, for all comparisons there is a higher DIC (indicating a less favourable model) when the node is split and the *p*-values are large. It was concluded that there is no strong evidence for inconsistency in the network.

Wrist

Eight treatment contrasts have both direct and indirect evidence; however, only five of these were assessed for consistency. For three of these (RIS–ALN, ALN–RLX, RIS–RLX), the direct comparison is contributed by small studies.[77,79] Multiple testing should be taken into account when considering *p*-values.

Comparing the DIC for the different node-splits with that of the full consistency NMA model, for all comparisons there is a higher DIC (indicating a less favourable model) when the node is split and the *p*-values are large. It was concluded that there is no strong evidence for inconsistency in the network.

TABLE 40 Assessment of inconsistency between direct and indirect evidence for vertebral fractures, assessed through node-splitting in the NMA

		Heterogeneity		Model fit		HRs (95% CrI)			
Treatment 1	Treatment 2	SD[a] (95% CrI)	SDt[b] (95% CrI)	D_{res}[c]	DIC	All evidence	Direct	Indirect	*p*-value[d]
Placebo	ALN	0.14 (0.01 to 0.34)	0.42 (0.05 to 1.48)	90.4	152.7	0.50 (0.40 to 0.64)	0.46 (0.36 to 0.62)	0.76 (0.43 to 1.68)	0.18
Placebo	RIS	0.16 (0.01 to 0.37)	0.19 (0.01 to 0.86)	92.31	155	0.52 (0.41 to 0.65)	0.57 (0.42 to 0.74)	0.45 (0.32 to 0.65)	0.31
Placebo	ZOL	0.12 (0.01 to 0.31)	0.13 (0.00 to 0.92)	91.29	151.6	0.40 (0.29 to 0.55)	0.33 (0.25 to 0.45)	0.56 (0.38 to 1.25)	0.03
Placebo	TPTD	0.17 (0.02 to 0.37)	0.19 (0.01 to 0.89)	90.18	153.33	0.23 (0.16 to 0.32)	0.30 (0.19 to 0.49)	0.18 (0.11 to 0.28)	0.12
RIS	ZOL	0.16 (0.01 to 0.35)	0.23 (0.02 to 0.97)	92.07	155.02	0.78 (0.52 to 1.08)	1.78 (0.40 to 9.98)	0.73 (0.49 to 1.05)	0.26
RIS	DEN	0.18 (0.01 to 0.38)	0.21 (0.01 to 0.91)	91.95	155.44	0.59 (0.39 to 0.88)	0.67 (0.26 to 1.65)	0.56 (0.35 to 0.90)	0.72
RIS	TPTD	0.18 (0.02 to 0.39)	0.20 (0.01 to 0.90)	91.82	155.24	0.44 (0.32 to 0.61)	0.44 (0.27 to 0.68)	0.45 (0.27 to 0.72)	0.94
Placebo	RLX	0.16 (0.01 to 0.36)	0.20 (0.01 to 0.90)	91.58	154.34	0.61 (0.44 to 0.80)	0.64 (0.47 to 0.85)	0.30 (0.09 to 0.90)	0.19
Placebo	DEN	0.18 (0.02 to 0.38)	0.21 (0.01 to 0.90)	91.97	155.54	0.30 (0.21 to 0.43)	0.29 (0.19 to 0.43)	0.35 (0.14 to 0.90)	0.72
ALN	TPTD	0.15 (0.01 to 0.35)	0.22 (0.02 to 0.92)	90.5	153.26	0.46 (0.31 to 0.66)	0.18 (0.04 to 0.51)	0.53 (0.35 to 0.77)	0.06
Consistency model									
		0.17 (0.02 to 0.37)	0.20 (0.01 to 0.91)	91.24	152.34				

a Between-study SD.
b Between-bisphosphonate treatment SD.
c Total residual deviance.
d Bayesian *p*-value.

TABLE 41 Assessment of inconsistency between direct and indirect evidence for non-vertebral fractures, assessed through node-splitting in the NMA

		Heterogeneity		Model fit		HRs (95% CrI)			
Treatment 1	Treatment 2	SD[a] (95% CrI)	SDt[b] (95% CrI)	D_{res}[c]	DIC	All evidence	Direct	Indirect	*p*-value[d]
Placebo	RLX	0.88 (0.62 to 1.19)	1.14 (0.39 to 3.23)	74.61	129.85	0.90 (0.65 to 1.21)	0.88 (0.62 to 1.19)	1.14 (0.39 to 3.23)	0.65
Placebo	ALN	0.81 (0.65 to 0.95)	0.66 (0.39 to 0.91)	73.06	127.94	0.77 (0.64 to 0.90)	0.81 (0.65 to 0.95)	0.66 (0.39 to 0.91)	0.31
Placebo	RIS	0.65 (0.48 to 0.86)	0.80 (0.59 to 1.12)	73.8	128.78	0.73 (0.59 to 0.88)	0.65 (0.48 to 0.86)	0.80 (0.59 to 1.12)	0.28
Placebo	ZOL	0.71 (0.57 to 0.86)	0.78 (0.42 to 1.33)	74.3	129.46	0.73 (0.61 to 0.85)	0.71 (0.57 to 0.86)	0.78 (0.42 to 1.33)	0.65
Placebo	DEN	0.82 (0.65 to 1.05)	1.34 (0.69 to 2.61)	73.41	128.2	0.86 (0.69 to 1.12)	0.82 (0.65 to 1.05)	1.34 (0.69 to 2.61)	0.19
Placebo	ROMO	0.75 (0.49 to 1.14)	0.50 (0.16 to 1.46)	74.45	129.95	0.71 (0.48 to 1.03)	0.75 (0.49 to 1.14)	0.50 (0.16 to 1.46)	0.49
Placebo	TPTD	0.60 (0.39 to 0.89)	0.57 (0.40 to 0.80)	74.6	129.91	0.58 (0.45 to 0.76)	0.60 (0.39 to 0.89)	0.57 (0.40 to 0.80)	0.88
ALN	TPTD	1.06 (0.52 to 2.23)	0.71 (0.52 to 0.96)	73.84	128.86	0.76 (0.57 to 1.02)	1.06 (0.52 to 2.23)	0.71 (0.52 to 0.96)	0.3
RIS	DEN	1.75 (0.78 to 4.16)	1.12 (0.85 to 1.57)	74.15	129.18	1.18 (0.90 to 1.63)	1.75 (0.78 to 4.16)	1.12 (0.85 to 1.57)	0.33
RIS	TPTD	0.69 (0.47 to 0.99)	0.97 (0.66 to 1.46)	72.89	128.22	0.80 (0.61 to 1.04)	0.69 (0.47 to 0.99)	0.97 (0.66 to 1.46)	0.22
ZOL	TPTD	0.85 (0.29 to 2.51)	0.79 (0.58 to 1.07)	74.84	130.26	0.80 (0.60 to 1.08)	0.85 (0.29 to 2.51)	0.79 (0.58 to 1.07)	0.89
ROMO	TPTD	1.15 (0.37 to 3.53)	0.77 (0.46 to 1.24)	74.43	129.92	0.82 (0.53 to 1.28)	1.15 (0.37 to 3.53)	0.77 (0.46 to 1.24)	0.49
ALN	DEN	0.07 (0.00 to 0.23)	0.16 (0.01 to 0.74)	74.49	129.77	1.12 (0.87 to 1.57)	1.83 (0.58 to 6.33)	1.09 (0.84 to 1.52)	0.39
Consistency model									
		0.08 (0 to 0.24)	0.15 (0.01 to 0.73)	74.047	128.4				

a Between-study SD.
b Between-bisphosphonate treatment SD.
c Total residual deviance.
d Bayesian *p*-value.

TABLE 42 Assessment of inconsistency between direct and indirect evidence for hip fractures, assessed through node-splitting in the NMA

		Heterogeneity		Model Fit		HRs (95% CrI)			
Treatment 1	Treatment 2	SD[a] (95% CrI)	SDt[b] (95% CrI)	D_{res}[c]	DIC	All evidence	Direct	Indirect	*p*-value[d]
Placebo	ALN	0.16 (0.01 to 0.63)	0.38 (0.02 to 1.77)	39.72	73.1	0.64 (0.41 to 0.94)	0.62 (0.35 to 1.07)	0.62 (0.16 to 1.92)	0.98
Placebo	RIS	0.15 (0.00 to 0.61)	0.32 (0.01 to 1.70)	39.32	72.68	0.67 (0.43 to 1.10)	0.80 (0.40 to 1.58)	0.57 (0.19 to 1.22)	0.45
Placebo	ZOL	0.16 (0.01 to 0.63)	0.43 (0.02 to 1.81)	39.58	72.92	0.64 (0.44 to 0.92)	0.62 (0.39 to 1.02)	0.72 (0.20 to 4.39)	0.76
Placebo	DEN	0.15 (0.01 to 0.59)	0.24 (0.01 to 1.59)	39.76	73.08	0.56 (0.29 to 0.99)	0.57 (0.28 to 1.05)	0.41 (0.04 to 2.75)	0.73
Placebo	ROMO	0.14 (0.01 to 0.58)	0.23 (0.01 to 1.60)	40.01	73.68	0.56 (0.20 to 1.48)	0.52 (0.17 to 1.48)	1.97 (0.05 to 642.60)	0.49
Placebo	TPTD	0.15 (0.01 to 0.59)	0.25 (0.01 to 1.60)	39.75	73.33	0.34 (0.15 to 0.77)	0.19 (0.02 to 1.03)	0.39 (0.14 to 0.98)	0.49
Placebo	RLX	0.14 (0.01 to 0.58)	0.23 (0.01 to 1.57)	39.91	73.18	0.94 (0.31 to 2.85)	0.83 (0.22 to 3.08)	1.10 (0.10 to 7.81)	0.84
ALN	RLX	0.15 (0.01 to 0.58)	0.23 (0.01 to 1.57)	40.03	73.46	1.49 (0.47 to 4.66)	1.73 (0.16 to 11.56)	1.31 (0.31 to 5.34)	0.83
RIS	TPTD	0.15 (0.01 to 0.58)	0.25 (0.01 to 1.58)	39.42	72.97	0.51 (0.23 to 1.07)	0.59 (0.24 to 1.41)	0.27 (0.04 to 1.33)	0.42
Consistency model									
		0.14 (0.01 to 0.56)	0.23 (0.01 to 1.54)	39.0876	71.572				

a Between-study SD.
b Between-bisphosphonate treatment SD.
c Total residual deviance.
d Bayesian *p*-value.

TABLE 43 Assessment of inconsistency between direct and indirect evidence for wrist fractures, assessed through node-splitting in the NMA

		Heterogeneity		Model Fit		HR's (95% CrI)			
Treatment 1	Treatment 2	SD[a] (95% CrI)	SDt[b] (95% CrI)	D_{res}[c]	DIC	All evidence	Direct	Indirect	*p*-value[d]
Placebo	ALN	0.34 (0.06 to 0.71)	0.20 (0.01 to 0.69)	30.48	55.35	0.83 (0.51 to 1.30)	0.85 (0.43 to 1.52)	0.77 (0.29 to 1.86)	0.85
Placebo	RIS	0.31 (0.04 to 0.68)	0.20 (0.01 to 0.68)	30.44	55.17	0.82 (0.50 to 1.30)	0.79 (0.32 to 1.79)	0.99 (0.49 to 2.24)	0.40
Placebo	TPTD	0.31 (0.04 to 0.68)	0.17 (0.01 to 0.62)	30.80	55.57	0.66 (0.33 to 1.26)	0.79 (0.32 to 1.79)	0.47 (0.15 to 1.43)	0.45
Placebo	RLX	0.32 (0.05 to 0.68)	0.17 (0.01 to 0.61)	31.21	56.44	1.65 (0.78 to 3.65)	1.59 (0.70 to 3.75)	2.29 (0.18 to 24.15)	0.79
RIS	TPTD	0.31 (0.04 to 0.67)	0.17 (0.01 to 0.62)	30.83	55.65	0.81 (0.40 to 1.58)	0.62 (0.24 to 1.65)	1.05 (0.37 to 2.68)	0.45
Consistency model									
		0.32 (0.04 to 0.67)	0.17 (0.01 to 0.62)	30.38	54.64				

a Between-study SD.
b Between-bisphosphonate treatment SD.
c Total residual deviance.
d Bayesian *p*-value.

Humerus

Five treatment contrasts have both direct and indirect evidence; however, only four of these were assessed for consistency. For the placebo–DEN comparison, the direct comparison is contributed by one small study[42] with zero events in the DEN arm. Multiple testing should be taken into account when considering *p*-values.

Comparing the DIC for the different node-splits with that of the full consistency NMA model, for all comparisons there is a higher DIC (indicating a less favourable model) when the node is split and the *p*-values are large. It was concluded that there is no strong evidence for inconsistency in the network.

TABLE 44 Assessment of inconsistency between direct and indirect evidence for proximal humerus fractures, assessed through node-splitting in the NMA

		Heterogeneity		Model fit		HRs (95% CrI)			
Treatment 1	Treatment 2	SD[a] (95% CrI)	SDt[b] (95% CrI)	D_{res}[c]	DIC	All evidence	Direct	Indirect	*p*-value[d]
Placebo	RIS	0.18 (0.01 to 0.59)	0.21 (0.01 to 0.71)	22.98	43.98	0.48 (0.24 to 0.96)	0.45 (0.19 to 0.98)	0.63 (0.12 to 3.00)	0.71
Placebo	TPTD	0.17 (0.01 to 0.60)	0.21 (0.01 to 0.72)	22.86	43.99	0.55 (0.21 to 1.41)	0.77 (0.17 to 3.30)	0.42 (0.11 to 1.47)	0.53
RIS	DEN	0.17 (0.01 to 0.58)	0.22 (0.01 to 0.72)	23.05	43.93	1.14 (0.28 to 4.57)	0.97 (0.15 to 5.91)	1.40 (0.13 to 14.31)	0.8
RIS	TPTD	0.17 (0.01 to 0.59)	0.21 (0.01 to 0.72)	22.61	43.46	1.15 (0.50 to 2.63)	1.00 (0.38 to 2.65)	1.80 (0.33 to 9.58)	0.54
Consistency model									
		0.17 (0.01 to 0.57)	0.21 (0.01 to 0.7)	21.9908	41.832				

a Between-study SD.
b Between-bisphosphonate treatment SD.
c Total residual deviance.
d Bayesian *p*-value.

Appendix 14 Network meta-analysis results of meta-regressions

A summary of meta-regression models (covariate estimate, model fit, heterogeneity) is provided in *Table 45* for all outcomes.

Note that, for age and sex, a common meta-regression coefficient is assumed for all treatments (see Dias *et al.*[121] for further details). Alternative models were also considered, but did not improve model fit.

For meta-regressions on baseline response, the results for all outcomes assume a common meta-regression coefficient for all treatments (as for age and sex), and the baselines of each study were assumed to follow a normal distribution with common mean and between-treatment variance (see Achana *et al.*[122] for further details). Alternative models were also considered, but did not improve model fit. Results are provided in *Table 45*.

Meta-regression on baseline risk, model selection

For the vertebral fractures network, four different baseline risk models were considered, allowing different assumptions about the model for baseline risk and covariate treatment interaction:

- A1: unconstrained baseline and common slope
- A2: normal distribution for baseline risk and common slope
- B1: unconstrained baseline and common slope
- B2: normal distribution for baseline risk and common slope.

Alternative models were considered for vertebral fractures only (which provide the largest network of evidence). Models with an unconstrained baseline (A1, B1) had a high DIC. Model A2, with normal distribution for baseline risk and assumption of common slope parameter for treatment–covariate interaction, was chosen for the main meta-regression model because this provided the lowest DIC. The results of using this model are provided in *Table 45* for all outcomes.

TABLE 45 Results of meta-analysis on sex, age and baseline response for all outcomes

Outcome/model	Absolute model fit			Heterogeneity, SD (95% CI)			Baseline parameters	
	D_{res}[a]	Data points	DIC	SD[b]	SDt[c]	Covariate estimate (95% CI)	Covariate	SD
Vertebral								
Age	92.15	93	155.19	0.176 (0.018 to 0.378)	0.191 (0.011 to 0.882)	−0.028 (−0.227 to 0.192)	NA	NA
Sex	91.31	93	154.81	0.185 (0.03 to 0.379)	0.2 (0.01 to 0.939)	0.06 (−0.117 to 0.263)	NA	NA
Baseline response	88.57	93	147.16	0.18 (0.02 to 0.37)	0.17 (0.01 to 0.8)	0.13 (−0.04 to 0.3)	−3.1 (−3.41 to −2.8)	0.96 (0.76 to 1.23)
Non-vertebral								
Age	74.62	86	130.01	0.08 (0.003 to 0.244)	0.166 (0.009 to 0.768)	0.014 (−0.16 to 0.207)		
Sex	74.75	86	129.92	0.077 (0.004 to 0.236)	0.14 (0.006 to 0.694)	0.062 (−0.132 to 0.256)		
Baseline response M2	73.44	86	119.99	0.1 (0.01 to 0.28)	0.15 (0.01 to 0.76)	0.05 (−0.16 to 0.32)	−3.41 (−3.61 to −3.22)	0.53 (0.39 to 0.73)
Hip								
Age	39.83	47	72.83	0.12 (0.007 to 0.434)	0.266 (0.011 to 1.594)	−0.103 (−0.782 to 0.538)	NA	NA
Sex	39.55	47	72.39	0.135 (0.006 to 0.47)	0.248 (0.01 to 1.6)	−0.118 (−1.048 to 0.845)	NA	NA
Baseline response M2	39.14	47	67.24	0.13 (0.01 to 0.47)	0.29 (0.01 to 1.66)	0.08 (−0.37 to 0.74)	−5.21 (−5.62 to −4.77)	0.77 (0.48 to 1.29)
Wrist								
Age	30.91	31	55.58	0.24 (0.01 to 0.63)	0.47 (0.02 to 1.85)	−0.67 (−1.58 to 0.16)	NA	NA
Baseline response M2	28.82	31	49.16	0.34 (0.03 to 0.70)	0.46 (0.02 to 1.82)	0.35 (−1.56 to 3.18)		

Outcome/model	Absolute model fit			Heterogeneity, SD (95% CI)		Covariate estimate (95% CI)	Baseline parameters	
	D_{res}[a]	Data points	DIC	SD[b]	SDt[c]		Covariate	SD
Humerus								
Age	23.92	26	46.12	0.179 (0.008 to 0.619)	0.998 (0.049 to 1.953)	0.273 (−2.788 to 3.6)	NA	NA
Sex	24.01	26	46.38	0.171 (0.008 to 0.582)	0.988 (0.052 to 1.951)	0.412 (−1.351 to 3.199)	NA	NA
Baseline response	22.17	26	38.53	0.18 (0.01 to 0.59)	1 (0.05 to 1.95)	−0.26 (−1.36 to 3.04)	−5.15 (−6.03 to −3.73)	0.72 (0.13 to 3.09)
Femoral neck BMD								
Age	144.5	137	259.24	0.86 (0.65 to 1.14)	0.76 (0.25 to 2.28)	−0.01 (−0.07 to 0.05)	NA	NA
Sex	145.7	137	258.73	0.80 (0.59 to 1.08)	0.77 (0.28 to 2.34)	0.01 (0 to 0.02)	NA	NA
Baseline response	NA	137	NA	0.81 (0.61 to 1.08)	0.67 (0.24 to 1.65)	0.16 (−0.32 to 0.81)	−0.31 (−0.57 to −0.04)	1.92 (0.91 to 4.18)

NA, not applicable.
a Total residual deviance.
b Between-study SD.
c Between-bisphosphonate treatment SD.

TABLE 46 Meta-regression on baseline risk, comparison of alternative models, vertebral fractures

Model	Absolute model fit			Heterogeneity, SD (95% CrI)		Covariate treatment interaction		Baseline parameters	
	D_{res}[a]	Data points	DIC	SD[b]	SDt[c]	Estimate (95% CrI)	SD (95% CrI)	Covariate (95% CrI)	SD covariate (95% CrI)
A1	89.91	93	171.57	1.06 (0.06 to 1.4)	0.31 (0.01 to 1.47)	−1 (−1.01 to 0.09)	NA	NA	NA
A2	**88.57**	**93**	**147.16**	**0.18 (0.02 to 0.37)**	**0.17 (0.01 to 0.8)**	**0.13 (−0.04 to 0.3)**	**NA**	**−3.1 (−3.41 to −2.8)**	**0.96 (0.76 to 1.23)**
B1	92.85	93	157.38	0.16 (0.02 to 0.39)	0.2 (0.01 to 1.11)	0.03 (−0.16 to 0.22)	0.13 (0.01 to 0.6)	NA	NA
B2	89.48	93	148.39	0.17 (0.02 to 0.37)	0.18 (0.01 to 0.94)	0.14 (−0.03 to 0.33)	0.09 (0.01 to 0.47)	−3.11 (−3.41 to −2.81)	0.96 (0.77 to 1.24)

NA, not applicable.
a Total residual deviance.
b Between-study SD.
c Between-bisphosphonate treatment SD.
Results in bold indicate the model with the lowest DIC.

Appendix 15 Studies excluded, at full-text sift, from the review of published economic evaluations

Citation	Reason for exclusion
Alexander W, Strom O, Macarios D. American Society for Bone and Mineral Research: DEN (Prolia): a cost-effectiveness model. *P T* 2009;**34**:633	Abstract only
Davies A, Compston J, Ferguson S, McClosky E, Shearer A, Taylor A. Cost-effectiveness of DEN in the treatment of postmenopausal osteoporosis in Scotland. *Value Health* 2011;**14**:A310	Abstract only
Hagen G. Comparative Effectiveness and Cost-Effectiveness of Generic ALN, RIS, DEN and zolendronic acid for secondary prevention of fragility fractures – perliminay results. *Value Health* 2015;**18**:A648	Abstract only
Liu H, Michaud K, Nayak S, Karpf DB, Owens DK, Garber AM. The cost-effectiveness of therapy with TPTD and ALN in women with severe osteoporosis. *Arch Intern Med* 2006;**166**:1209–17	Non-UK
Meadows ES, Klein R, Rousculp MD, Smolen L, Ohsfeldt RL, Johnston JA. Cost-effectiveness of preventative therapies for postmenopausal women with osteopenia. *BMC Womens Health* 2007;**7**:6	Non-UK
Mobley LR, Hoerger TJ, Wittenborn JS, Galuska DA, Rao JK. Cost-effectiveness of osteoporosis screening and treatment with hormone replacement therapy, RLX, or ALN. *Med Decis Making* 2006;**26**:194–206	Non-UK
Murphy DR, Klein RW, Smolen LJ, Klein TM, Roberts SD. Using common random numbers in health care cost-effectiveness simulation modelling. *Health Serv Res* 2013;**48**:1508–25	Non-UK
O'Hanlon CE, Parthan A, Kruse M, Cartier S, Stollenwerk B, Jiang Y, *et al.* A Model for assessing the clinical and economic benefits of bone-forming agents for reducing fractures in postmenopausal women at high, near-term risk of osteoporotic fracture. *Clin Ther* 2017;**39**:1276–90	Non-UK
Pfister AK, Welch CA, Lester MD, Emmett MK, Saville PD, Duerring SA. Cost-effectiveness strategies to treat osteoporosis in elderly women. *South Med J* 2006;**99**:123–31	Non-UK
Turner DA, Khioe RFS, Shepstone L, Lenaghan E, Cooper C, Gittoes N, *et al.* The cost-effectiveness of screening in the community to reduce osteoporotic fractures in older women in the UK: economic evaluation of the SCOOP study. *J Bone Miner Res* 2018;**33**:845–51	Not a relevant comparison – compares screening with usual care with treatment after screening directed by clinician
Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B. Cost-effectiveness of the treatment and prevention of osteoporosis – a review of the literature and a reference model. *Osteoporos Int* 2007;**18**:9–23	Non-UK

Appendix 16 Health-related quality of life: review of utility values following fracture

To inform the model, data were needed on the proportionate decrease in HRQoL that occurs in the year following fracture and in subsequent years. This was then used to calculate a utility multiplier, which was applied to the pre-fracture utility value to calculate the post-fracture utility. For example, a proportionate decrease of 10% would translate into a utility multiplier of 0.9. If a patient's prior fracture utility is 0.8, then the post-fracture utility would be 0.72. Data on the absolute HRQoL after fracture can be obtained from studies that measure HRQoL of patients who have experienced a recent fracture. However, the proportionate decrease can be obtained only if there is some estimate of pre-fracture utility. Ideally, HRQoL would be measured prospectively in a cohort of patients at risk of fracture and these patients would be followed up with HRQoL re-measured at regular intervals with the time of any incident fracture being recorded so that the correlation between HRQoL and incident fracture can be obtained after adjusting for other confounding factors. However, many studies simply recruit patients at the time of fracture and ask them to recall their pre-fracture health state, which is subject to recall bias. Other studies may compare the HRQoL of individuals who have fractured with that of matched controls or population norms, in which case the estimates may be confounded by differences in other factors between cases and controls.

Our intention was to conduct a rapid update of the systematic review of HRQoL data conducted for TA464.[34] Systematic searches were undertaken to identify studies reporting on health utilities associated with different states for osteoporosis published since 2014. Searches were undertaken in July 2018 in the following electronic databases:

- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: Ovid, 1946–2018.
- EMBASE: Ovid, 1974–2018.

In line with the NICE reference case,[139] and the approach taken previously for TA464, the searches focused specifically on studies that reported HRQoL estimates for health states that were measured and valued using the EQ-5D. The search strategy comprised sensitive Medical Subject Headings (MeSH) or Emtree Thesauri terms and free-text synonyms for 'osteoporosis' combined with free-text synonyms for 'EQ-5D'. The search strategies are presented in *Appendix 1*.

This search retrieved 111 unique references. The results of the economic searches described above were combined with the results of the searches conducted for the review of published cost-effectieness studies (see *Chapter 4*, *Systematic review of existing cost-effectiveness evidence*, *Methods*), to give a total of 3853 unique references, and a combined sift was conducted to pick up any cross-relevant papers. This initial sift of paper titles by a first reviewer reduced the number thought to be relevant to the HRQoL review to 131. A further sift of the abstracts by a second reviewer identified 53 citations that could be excluded (48 conference proceedings, three non-English papers and two commentaries), leaving 81 studies reporting health utility in patients with an incident osteoporotic fracture. However, values measured during RCTs were excluded because of the possibility that the study interventions may affect HRQoL independently of their impact on fracture. Studies reporting the quality-of-life impact of prevalent fractures were also excluded on the basis that there is no way of knowing how long ago the prevalent fracture was sustained. Furthermore, studies reporting the HRQoL associated with osteoporotic fractures using instruments other than the EQ-5D, such as the Health Utilities Index or Short Form questionnaire-6 Dimensions, were excluded. A further study[342] that fulfilled these inclusion criteria was excluded because resulting EQ-5D utilities at specific time points following fracture were presented only graphically, rather

than numerically, which means that accurate estimates of the utility values were impossible. This left four studies. A PRISMA flow diagram representing this process is presented in *Figure 15*.

These four remaining studies[209,210,212,213] are summarised in *Table 47*. All four studies reported outcomes from ICUROS. As this study had been previously identified in the review conducted for TA464,[34] no new quality appraisal of this study was required. However, the four new papers identified reported additional data. All four provided HRQoL data for hip fracture, three provided it for wrist (distal forearm) fracture,[209,210,213] three for vertebral fracture[209,210,213] and one for fracture of the proximal humerus (shoulder).[210] One study also reported HRQoL for fracture of the ankle and other fracture.[210]

All four studies were based on ICUROS: two of the papers presented values for individual countries in the ICUROS cohort (Australia[210] and Estonia[212]) and two presented values for groups of ICUROS counties.[209,213] One of these papers presented HRQoL utility values for patients in 10 ICUROS countries (Austria, Australia, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain and the UK) who sustained a hip, vertebral and wrist fracture.[213] Utility was measured pre fracture (recall), post fracture (within 2 weeks of the fracture being sustained), 4 months post fracture, 12 months post fracture and 18 months post fracture. However, only data from patients who completed all instruments (not just the EQ-5D) at all time points are included. The second paper presents HRQoL utility values for patients in 11 ICUROS countries (Austria, Australia, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain, the UK and the USA) who sustained a hip, vertebral and wrist fracture.[209] Utility was measured pre fracture

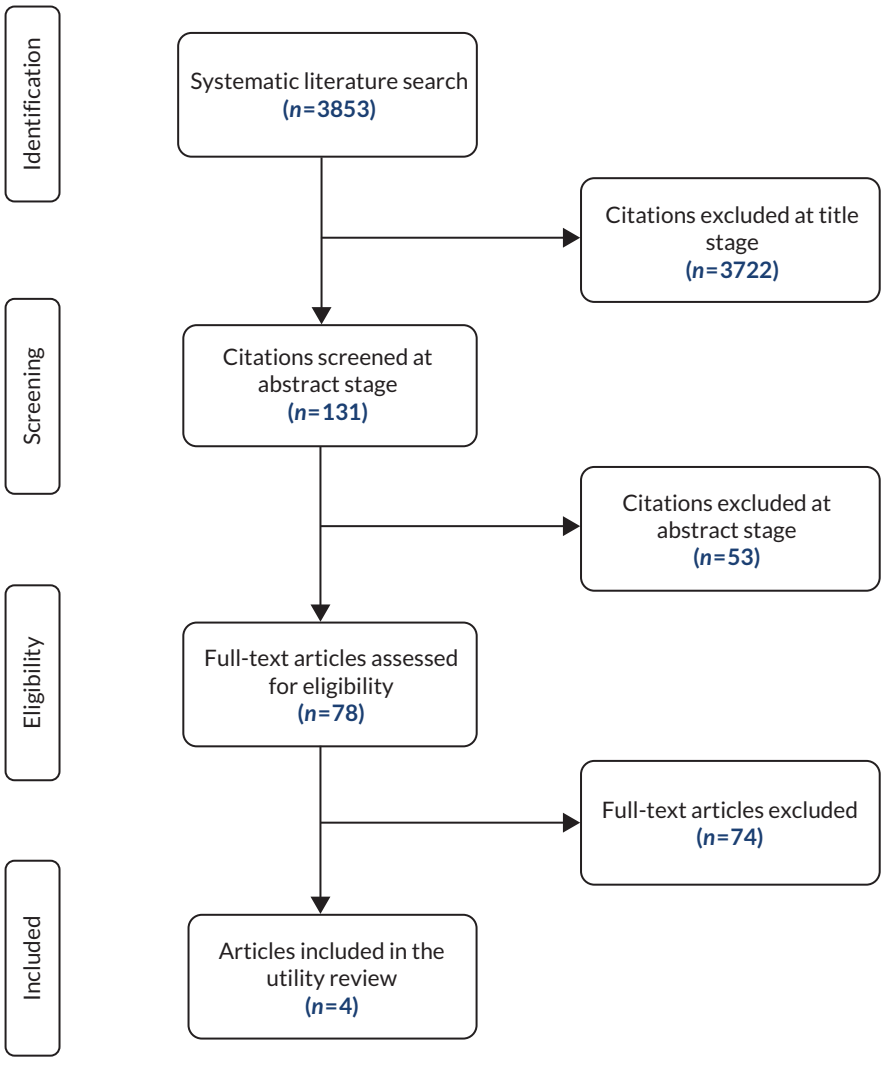

FIGURE 15 The PRISMA flow diagram for study selection for the review of HRQoL.

TABLE 47 Summary of included papers reporting EQ-5D quality-of-life measures associated with osteoporotic fracture

First author and year of publication	Country	Study design	Cohort description	Sample size at baseline and % of missing data	Valuation set used for EQ-5D
Svedbom 2018[213]	Multicentre (10 countries)	Prospective observational cohort study	• ICUROS included patients aged ≥ 50 years living in their own home prior to fracture who sustained a low-energy fracture • Initial post-fracture assessment of HRQoL taking place within 2 weeks of fracture	• Hip fracture, *n* = 505 • Vertebral fracture, *n* = 316 • Distal forearm fracture, *n* = 589 • (Patients lost to follow-up were excluded from analyses)	UK (TTO)
Svedbom 2018[209]	Multicentre (11 countries)	Prospective observational cohort study		• Hip fracture, *n* = 1415 • Vertebral fracture, *n* = 559 • Distal forearm fracture, *n* = 1047 • (Patients lost to follow-up were excluded from analyses)	UK (TTO)
Abimanyi-Ochom 2015[210]	Australia	Prospective observational cohort study		• All fractures, *n* = 915 (41%)[a] • Hip fracture, *n* = 224 (49%)[a] • Distal forearm fracture, *n* = 308 (24%)[a] • Vertebral fracture, *n* = 92 (45%)[a] • Humerus fracture, *n* = 65 (48%)[a] • Ankle fracture, *n* = 89 (48%)[a] • Other fracture, *n* = 137 (53%)[a]	UK (TTO)
Jurisson 2016[212]	Estonia	Prospective observational cohort study		Hip fracture, *n* = 205 (18%)	UK (TTO)

TTO, time trade-off.
a Percentage of baseline cohort lost by 18 months.

(recall), post fracture (within 2 weeks of the fracture being sustained), 4 months post fracture, 12 months post fracture and 18 months post fracture. However, in this analysis, data were included from patients who completed the EQ-5D instrument at all time points. Thus, the HRQoL utility values in the latter of these two studies[209] was based on significantly more data (1415 patients for hip fracture, 559 patients for vertebral fracture and 1047 patients for distal forearm (wrist) fracture, compared with 505 patients for hip fracture, 316 patients for vertebral fracture and 589 for distal forearm (wrist) fracture). As a result, the latter of these two studies[209] was chosen to provide HRQoL values for hip, vertebral and wrist fracture in the model.

Health-related quality-of-life values associated with proximal humerus fracture were still required by the model, and the only study to provide such values was the study concerned with the Australian ICUROS cohort[210] in which the UK value set was used to convert the dimension scores into a utility value. In this study, 65 patients provided HRQoL values at baseline (pre fracture and immediately post fracture), 57 patients provided them at 4 months, 54 patients at 12 months and 34 patients at 18 months. Only 52% of baseline patients survived to 18 months and only 63% of the patients who survived to 12 months survived to 18 months.

Values from four papers[209,210,212,213] all came from one study (ICUROS), which included patients aged at least 50 years living in their own home prior to fracture who sustained a low-energy fracture. Initial post-fracture assessment of HRQoL took place within 2 weeks of fracture. Patients who sustained another fracture in the follow-up period were excluded as were people who were lost to follow-up. However, although two of the papers[209,213] ensured that data relating to patients excluded at some later point in the study were removed from summary HRQoL utility data at all time points, the remaining two papers [210,212] did not and used all available data at each time point.

The two multicentre papers reported broadly similar values at all time points, except for those recorded at 2 weeks following fracture: those reported in the paper with the larger data set[209] were lower than those reported in the paper that excluded more patients for incomplete data[213] (hip fracture: –0.11, vertebral fracture: 0.17 and wrist fracture: 0.41, compared with hip fracture: –0.02, vertebral fracture: 0.27 and wrist fracture: 0.47). The study using Australian data but with a UK tariff[210] reported values that were, again, higher at 2 weeks following fracture (hip fracture: 0.11, vertebral fracture: 0.32 and wrist fracture: 0.53); these higher values were also reflected at 4 months and 12 months, although by a lessening degree, until the increase had become negligible by 18 months. The Estonian study, which again used the UK tariff,[212] also reported higher values at 2 weeks following fracture (0.07). This may raise concerns about the values used in the model, even though they are based on a significantly larger sample size. However, the excluded paper,[342] which presented utility values in a graphical rather than a numerical format, suggests similar values to the international ICUROS data set[209] for a UK population, with the HRQoL utility value at 2 weeks post fracture being approximately –0.15.

For hip, vertebral and wrist fractures, the utility multipliers for 0–12 months, 12–24 months and > 24 months are presented by Svedbom *et al.*,[209] together with 95% confidence intervals, enabling SD to be calculated. However, we assume that improvements in utility in the period between 12 and 24 months post fracture are subject to significant uncertainty; thus, we apply the utility values presented for the period > 24 months post fracture in the paper for any period beyond 12 months post fracture in the model. For proximal humerus fracture, we assume that the utility drops at the point of fracture to the value measured in the first 2 weeks post fracture and remains at this value for the first 2 weeks by a gradual linear improvement to 4 months, 12 months and, finally, 18 months. We assume that utility at 18 months is maintained indefinitely. The utility multiplier for the first year post fracture was calculated by dividing the total utility accrued by 12 months by the pre-fracture utility value. The utility value observed at 12 months is assumed to persist in the long term, so the multiplier for the second and subsequent years was calculated by dividing the total utility accrued between month 13 and month 24 again by the pre-fracture utility value. These data are presented in *Table 48* and graphically in *Figures 16–19*.

TABLE 48 Utility values after fracture used in the TA464 Health Technology Assessment report[34] and in the new review

	Hip fracture		Vertebral fracture		Humerus fracture		Distal forearm fracture	
Description	TA464[34]	ICUROS[209]	TA464[34]	ICUROS[209]	TA464[34]	ICUROS[210]	TA464[34]	ICUROS[209]
Baseline number of patients	282	1415	76	559	38	65	325	1047
Utility index								
Pre fracture	0.81	0.77	0.74	0.83	0.65	0.81	0.90	0.89
Post fracture	0.19	−0.11	0.18	0.17	0.36	0.21	0.56	0.41
4 months	0.64	0.49	0.49	0.60	0.58	0.70	0.83	0.77
12 months	0.69	0.59	0.49	0.70	0.65	0.77	0.88	0.85
18 months	0.72	0.66	0.49	0.70	–	0.83	0.90	0.88
Utility multiplier *Year 1*								
Mean	0.69	0.55	0.57	0.68	0.86	0.78	0.88	0.83
SD	0.02	0.01	0.03	0.01	0.08	0.03	0.02	0.01
Subsequently								
Mean	0.85	0.86[a]	0.66	0.85[a]	1.00	1.00[b]	0.98	0.99[a]
SD	NR	0.01	NR	0.01	NR	0.04	NR	0.01

NR, not reported.
a We apply the utility multipliers presented in the paper for year 3 onwards to our model from year 2 onwards.
b Capped at 1.0000.

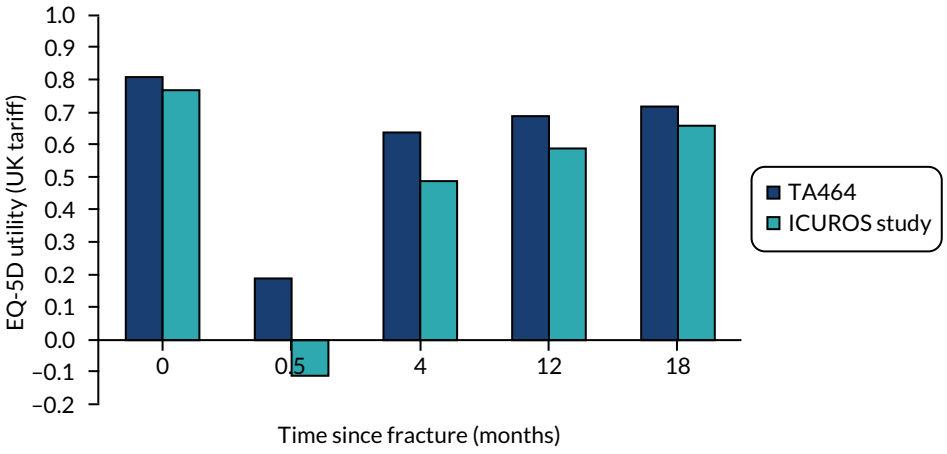

FIGURE 16 Utility associated with vertebral fracture used in the TA464 Health Technology Assessment report and that chosen from ICUROS.

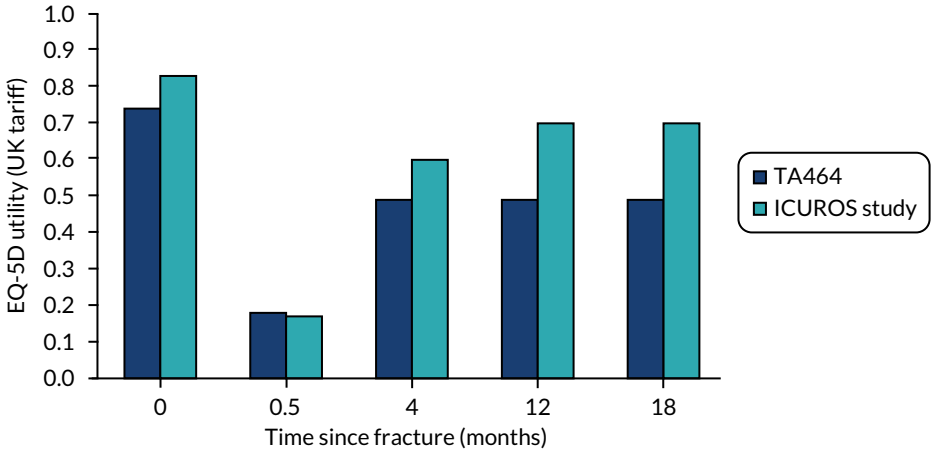

FIGURE 17 Utility associated with hip fracture used in the TA464 Health Technology Assessment report and that chosen from ICUROS.

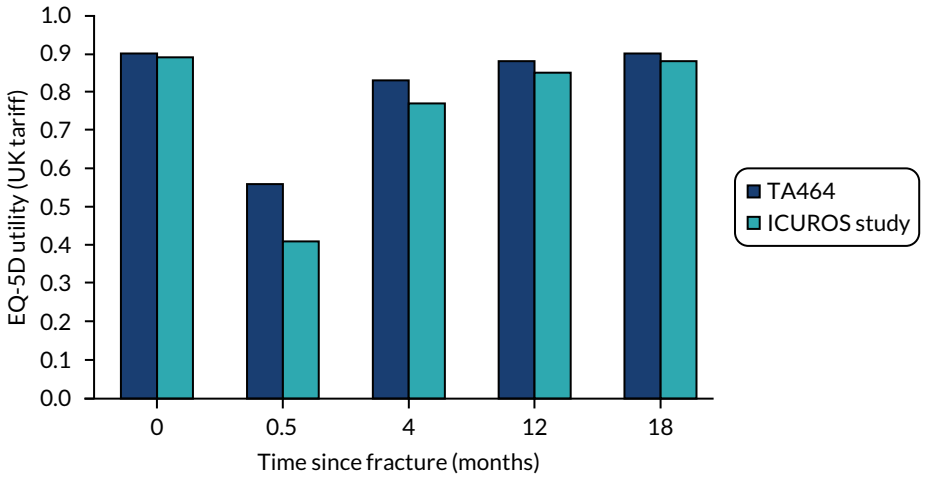

FIGURE 18 Utility associated with distal forearm (wrist) fracture used in the TA464 Health Technology Assessment report and that chosen from ICUROS.

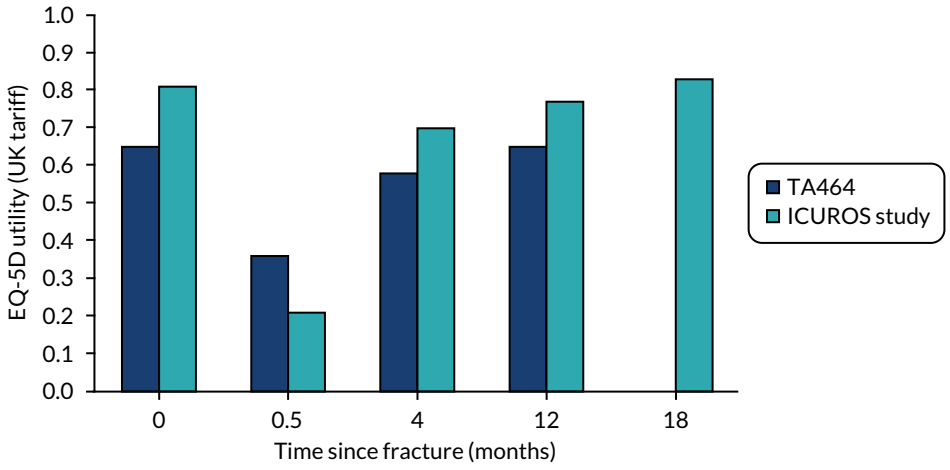

FIGURE 19 Utility associated with humerus (shoulder) fracture used in the TA464 Health Technology Assessment report and that chosen from ICUROS.

Appendix 17 Model validation methods

The model is designed to operate in several different modes, which facilitates debugging and validation. When running the model with fixed patient chacteristics, using determinisitic inputs and with random number control switched on, the model generates identical results each time it is run. This feature has been used to check that the model continues to operate in a consistent manner when any change is made to the VBA code that aims to restructure the code without altering the basic functioning of the model. The model can also be run in debug mode, whereby it outputs a detailed list of the events experienced and their individual times for each patient. This has been used extensively during model adaptations to check that the model is operating as intended. For example, it was used to check that the additional dummy events required for the new intervention lines were occurring at the correct times.

The code has been extensively commented, with any changes made since T464 identied by the date of change. When making alterations to the VBA code, the developer set up break points where any new code was implemented, allowing the model to be run quickly as far as the new code and then for the new code to be stepped through under observation to check that it behaves as intended. The locals window, within the VBA development environment, which allows the values of any object (variable, array, etc.) to be checked, was used to observe that the various arrays and variables had been filled with the intended data and to see changes to these variables when stepping through the code. The developer also used the immediate window to output specific variables at specific points in the code when trying to verify model behaviour. Error-handling was incorporated to ensure that inputs to functions were within their required ranges and to initiate message boxes describing errors identified and the values of inputs prior to the error.

To assess the face validity of the clinical outcomes predicted by model, the fractures prevented for each treatment (broken down into the four main fractures types) were graphed and compared with the absolute risk reduction for each fracture type multiplied by the 'effective treatment duration', which is dependent on both the time on treatment and the offset period (i.e. a drug with a 5-year treatment period and an additional 5-year offset period would have a 7.5-year effective treatment duration). This was done for the outcomes of both the PSA model and the version using mean parameter inputs.

Table 49 lists the main changes to the model made since TA464 and the methods used to validate each adapatation.

TABLE 49 Model validation steps for key changes

Description of adaptation needed	Description of key changes to model	Validation method
Increase the number of treatment strategies that can be modelled	The model was already set up to pull in drug-specific inputs as arrays. These arrays were extended to allow for up to 15 lines of treatment to be modelled, with 11 being used in the final analysis (no treatment, nine interventions, with two needed to capture the ROMO/ALN sequence)	The structural changes to the VBA code required to incorporate additional intervention lines were made without any changes to model inputs, allowing outputs to be compared with the TA464 version of the model. New outputs were incoporated only once the model was verified to be equivalent for the additional intervention lines Model inputs for interventions 6–10 and 11–15 were set equal to inputs for interventions 1–5. Model was run in debug mode and patient-level results were checked to ensure that identical outputs were being generated for intervention lines with identical inputs
Allow for drug-specific offset periods	In the TA464 version, the offset period was twice the treatment period for all drugs except ZOL and specific VBA code was used to adjust the offset period for ZOL. In the revised model, an array of offset inputs were pulled into the model, allowing a unique offset period for each drug	Results were run (with the model set up to produce reproducible outputs) before and after the code for handling the offset period was altered and the outputs were compared
Allow for sequences of treatments to be modelled	Two additional input arrays were added: one that says whether or not a treatment switch should occur and one that says which intervention should be swiched to. VBA code for processing the end of treatment event was adapated to reset the treatment period and offset period to the second drug in the sequence. VBA code was adapted to differentiate between the treatment sequence being modelled (drug_index_int) and the current drug, which changes after the swich (person_curr_drug). Costs, efficacy and AEs were made dependent on person_curr_drug	Intervention 6 was set up to have same outcomes as intervention 1, but to achieve this through a treatment switch to intervention 11. To do this, intervention 6 was set to have half the treatment duration of intervention 1, but to switch to intervention 11 on completion. Intervention 11 was set to have half the treatment duration of intervention 1 but the same offset period (as it is the second drug in the sequence that determines the offset period). Costs for intervention 6 and intervention 11 were set equal to the cost for intervention 1 The model was run in debug mode to check that outputs for intervention 6 were identical to outputs for intervention 1
Allow resource use for monitoring and administration to be specified for each drug	In TA464, no monitoring costs were included and administration costs were included only for i.v. IBN and i.v. ZOL. Total intervention costs per annum were handled as a single variable. In the revised model, separate arrays are specified for drug costs, resource use and unit costs	Adapatations were made to incorporate the new arrays. The model was run and code was stepped through, with break points placed on the revised code to check that it was performing as expected The model was run in debug mode and patient-level outputs were checked to see if the total undiscounted costs matched the total treatment costs (i.e. drug, administration and monitoring) expected for patients experiencing no fracture events
Additional inputs required for non-bisphosphonates and new inputs for bisphosphonates	The main changes were to drug costs, efficacy inputs, treatment persistence, teatment offset periods, resource use for administration and monitoring, costs and QALY adjustments for AEs (VTE, ONJ and cellulitis) and post-fracture costs and utilities	Cells that had inputs updated from TA464 were highlighted in orange and were double-checked against the values described in final report Cells that were not marked as changed were double-checked against the model used in TA464

Appendix 18 Summary clinical outcomes when using FRAX

TABLE 50 Clinical outcomes across the whole population eligible for fracture risk assessment when using FRAX to estimate fracture risk

	Number of adverse clinical outcomes avoided per 100,000 patients treated, when compared with no treatment							Total life-years gained per patient vs. no treatment
	Total fractures	Hip fracture	Vertebral fracture	Proximal humerus fracture	Wrist fracture	Nursing home/ residential care admission	Fatal fracture	
When using FRAX to estimate risk of fracture								
ALN	988	201	245	138	405	33	30	0.0026
RIS	1047	191	239	154	464	33	32	0.0026
Oral IBN	847	182	243	107	315	30	30	0.0027
i.v. IBN	419	115	162	38	103	20	18	0.0015
ZOL	1787	333	467	254	733	53	54	0.0048
RLX	336	−11	164	95	88	20	−35	−0.0029
DEN	1611	407	587	212	404	89	29	0.0023
TPTD	1857	390	414	269	784	64	59	0.0052
ROMO/ ALN	2589	553	549	400	1088	106	89	0.0062

Appendix 19 Base-case results from the probabilistic sensitivity analysis for QFracture

TABLE 51 Base-case results from 200,000 PSA samples for QFracture risk category 1 (average 10-year fracture risk of 0.5%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	683	16.6049	0	–	0	0	0	
ALN	777	16.6050	94	0.0001	675,004	−91	−90	£675,004
RIS	778	16.6050	94	0.0001	829,832	−92	−91	Dominated
RLX	778	16.6032	95	−0.0016	−58,385	−127	−143	Dominated
IBN (oral)	781	16.6050	97	0.0001	948,571	−95	−94	Dominated
ZOL	1403	16.6048	720	−0.0001	−9,181,178	−721	−722	Dominated
IBN (i.v.)	1541	16.6044	858	−0.0005	−1,784,152	−867	−872	Dominated
DEN	2454	16.6059	1770	0.0010	1,794,421	−1750	−1741	Extendedly dominated
ROMO/ALN	Confidential information has been removed	16.6071	Confidential information has been removed	0.0022	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	6502	16.6055	5819	0.0007	8,610,782	−5805	−5798	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 52 Base-case results from 200,000 PSA samples for QFracture risk category 2 (average 10-year fracture risk of 0.7%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	1152	15.3523	0	–	0	0	0	
RIS	1243	15.3525	91	0.0003	319,027	−85	−82	Extendedly dominated
ALN	1243	15.3526	91	0.0003	290,229	−85	−82	290,229
IBN (oral)	1246	15.3526	94	0.0003	301,165	−88	−85	Extendedly dominated
RLX	1297	15.3507	145	−0.0015	−96,336	−175	−190	Dominated
ZOL	1864	15.3525	713	0.0002	2,984,339	−708	−705	Dominated
IBN (i.v.)	2009	15.3518	857	−0.0004	−1,958,289	−866	−870	Dominated
DEN	2961	15.3539	1809	0.0017	1,092,301	−1776	−1760	1,279,494
ROMO/ALN	Confidential information has been removed	15.3539	Confidential information has been removed	0.0016	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	6961	15.3532	5809	0.0010	5,871,874	−5790	−5780	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 53 Base-case results from 200,000 PSA samples for QFracture risk category 3 (average 10-year fracture risk of 1.0%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	2260	14.0458	0	–	0	0	0	
RIS	2349	14.0465	89	0.0007	129,889	−75	−68	Extendedly dominated
ALN	2349	14.0465	89	0.0007	125,805	−75	−67	Extendedly dominated
IBN (oral)	2352	14.0466	92	0.0008	119,370	−77	−69	£119,370
RLX	2378	14.0436	118	−0.0023	−52,066	−163	−186	Dominated
ZOL	2968	14.0467	707	0.0009	808,583	−690	−681	Extendedly dominated
IBN (i.v.)	3113	14.0457	853	−0.0002	−5,378,179	−856	−858	Dominated
DEN	4041	14.0468	1781	0.0010	1,868,896	−1762	−1752	Extendedly dominated
ROMO/ALN	Confidential information has been removed	14.0475	Confidential information has been removed	0.0017	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	8059	14.0474	5799	0.0016	3,731,997	−5768	−5752	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 54 Base-case results from 200,000 PSA samples for QFracture risk category 4 (average 10-year fracture risk of 1.4%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	2722	12.6966	0	–	0	0	0	
ALN	2804	12.6973	82	0.0007	126,025	−69	−63	Extendedly dominated
RIS	2804	12.6974	83	0.0008	100,618	−66	−58	£100,618
IBN (oral)	2813	12.6973	91	0.0007	137,375	−78	−71	Dominated
RLX	2847	12.6952	126	−0.0014	−91,201	−153	−167	Dominated
ZOL	3421	12.6976	699	0.0010	723,860	−680	−670	Extendedly dominated
IBN (i.v.)	3572	12.6964	850	−0.0002	−4,066,084	−854	−856	Dominated
DEN	4487	12.6994	1766	0.0028	632,830	−1710	−1682	£855,463
ROMO/ALN	Confidential information has been removed	12.7002	Confidential information has been removed	0.0036	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	8497	12.6985	5776	0.0019	3,083,847	−5738	−5720	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 55 Base-case results from 200,000 PSA samples for QFracture risk category 5 (average 10-year fracture risk of 2.0%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	2936	11.6723	0	–	0	0	0	
ALN	3016	11.6734	80	0.0010	77,059	−59	−49	£77,059
RIS	3019	11.6733	82	0.0010	81,404	−62	−52	Dominated
IBN (oral)	3021	11.6732	84	0.000	93,736	−66	−57	Dominated
RLX	3067	11.6712	130	−0.0011	−118,232	−153	−164	Dominated
ZOL	3625	11.6739	688	0.0016	442,296	−657	−642	Extendedly dominated
IBN (i.v.)	3784	11.6722	848	−0.0001	−11,357,805	−849	−850	Dominated
DEN	4695	11.6757	1759	0.0034	523,142	−1692	−1658	£721,645
ROMO/ALN	Confidential information has been removed	11.6763	Confidential information has been removed	0.0040	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	8695	11.6748	5759	0.0024	2,356,350	−5710	−5686	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 56 Base-case results from 200,000 PSA samples for QFracture risk category 6 (average 10-year fracture risk of 2.7%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	3064	10.6107	0	–	0	0	0	
ALN	3142	10.6119	78	0.0012	65,281	−54	−42	Dominated
RIS	3143	10.6119	79	0.0012	64,979	−55	−42	£64,979
IBN (oral)	3147	10.6119	83	0.0012	68,805	−59	−47	Dominated
RLX	3164	10.6095	100	−0.0012	−83,809	−124	−136	Dominated
ZOL	3753	10.6126	689	0.0019	353,780	−650	−631	Extendedly dominated
IBN (i.v.)	3908	10.6109	843	0.0002	4,373,315	−840	−838	Dominated
DEN	4774	10.6141	1710	0.0034	502,655	−1642	−1608	£745,595
ROMO/ALN	Confidential information has been removed	10.6150	Confidential information has been removed	0.0043	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	8798	10.6136	5733	0.0029	1,964,475	−5675	−5646	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 57 Base-case results from 200,000 PSA samples for QFracture risk category 7 (average 10-year fracture risk of 3.9%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	3277	9.5502	0	–	0	0	0	
ALN	3339	9.5522	62	0.0020	30,452	−21	−1	£30,452
RIS	3340	9.5521	63	0.0020	32,482	−24	−5	Dominated
IBN (oral)	3345	9.5521	68	0.0020	34,713	−29	−9	Dominated
RLX	3448	9.5476	171	−0.0026	−65,412	−223	−249	Dominated
ZOL	3933	9.5533	656	0.0031	210,441	−594	−562	£552,756
IBN (i.v.)	4109	9.5509	832	0.0007	1,250,818	−819	−812	Dominated
DEN	5009	9.5539	1733	0.0037	462,072	−1658	−1620	Extendedly dominated
ROMO/ALN	Confidential information has been removed	9.5562	Confidential information has been removed	0.0060	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	8954	9.5544	5677	0.0042	1,366,400	−5594	−5553	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 58 Base-case results from 200,000 PSA samples for QFracture risk category 8 (average 10-year fracture risk of 5.5%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	3958	8.4539	0	–	0	0	0	
ALN	4001	8.4568	43	0.0029	14,820	15	44	£14,820
RIS	4007	8.4568	48	0.0028	17,119	8	36	Dominated
IBN (oral)	4021	8.4568	63	0.0029	21,840	−5	23	Extendedly dominated
RLX	4081	8.4531	123	−0.0008	−146,142	−139	−148	Dominated
ZOL	4591	8.4589	633	0.0050	127,491	−534	−484	£273,143
IBN (i.v.)	4784	8.4554	826	0.0015	564,407	−796	−782	Dominated
DEN	5613	8.4605	1655	0.0066	250,729	−1523	−1457	£625,518
ROMO/ALN	Confidential information has been removed	8.4637	Confidential information has been removed	0.0098	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPT	9593	8.4597	5635	0.0058	971,695	−5519	−5461	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 59 Base-case results from 200,000 PSA samples for QFracture risk category 9 (average 10-year fracture risk of 8.4%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	6197	6.6409	0	–	0	0	0	
ALN	6221	6.6451	24	0.0042	5622	60	102	£5622
RIS	6227	6.6450	30	0.0041	7235	53	94	Dominated
IBN (oral)	6234	6.6448	37	0.0039	9443	41	80	Dominated
RLX	6308	6.6391	110	−0.0017	−63,265	−145	−163	Dominated
ZOL	6794	6.6472	597	0.0064	93,903	−470	−406	£266,114
IBN (i.v.)	6998	6.6429	801	0.0020	398,475	−761	−741	Dominated
DEN	7730	6.6501	1533	0.0092	166,441	−1349	−1257	£327,719
ROMO/ALN	Confidential information has been removed	6.6513	Confidential information has been removed	0.0105	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	11,717	6.6491	5520	0.0082	671,001	−5355	−5273	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 60 Base-case results from 200,000 PSA samples for QFracture risk category 10 (average 10-year fracture risk of 16.0%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
ALN	13,370	4.0837	−51	0.0058	−8820	167	225	
RIS	13,384	4.0833	−37	0.0054	−6896	144	197	Dominated
IBN (oral)	13,393	4.0831	−28	0.0051	−5417	130	181	Dominated
No treatment	13,421	4.0779	0	–	0	0	0	Dominated
RLX	13,524	4.0760	103	−0.0019	−53,780	−141	−160	Dominated
ZOL	13,897	4.0858	477	0.0079	60,300	−318	−239	£250,205
IBN (i.v.)	14,165	4.0807	744	0.0028	266,492	−689	−661	Dominated
DEN	14,768	4.0886	1347	0.0107	126,392	−1134	−1028	£315,774
ROMO/ALN	Confidential information has been removed	4.0919	Confidential information has been removed	0.0140	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	18,604	4.0893	5183	0.0113	457,894	−4957	−4844	Dominated

a ICER vs. next least costly non-dominated strategy.

Appendix 20 Base-case results from the probabilistic sensitivity analysis for FRAX

TABLE 61 Base-case results from 200,000 PSA samples for FRAX risk category 1 (average 10-year fracture risk of 3.1%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	4241	13.6665	0	–	0	0	0	
RIS	4315	13.6687	73	0.0023	32,429	−28	−5	Extendedly dominated
ALN	4315	13.6690	73	0.0026	28,541	−22	4	£28,541
IBN (oral)	4319	13.6687	78	0.0023	34,519	−33	−10	Dominated
RLX	4350	13.6641	109	−0.0023	−47,105	−156	−179	Dominated
ZOL	4926	13.6705	685	0.0040	170,998	−605	−565	£427,431
IBN (i.v.)	5088	13.6671	846	0.0007	1,214,068	−832	−825	Dominated
DEN	5981	13.6708	1740	0.0044	398,751	−1653	−1609	Extendedly dominated
ROMO/ALN	Confidential information has been removed	13.6726	Confidential information has been removed	0.0061	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	10,011	13.6711	5770	0.0046	1,254,448	−5678	−5632	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 62 Base-case results from 200,000 PSA samples for FRAX risk category 2 (average 10-year fracture risk of 4.3%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	4487	13.6230	0	–	0	0	0	
RLX	4524	13.6228	37	−0.0002	−199,169	−41	−43	Dominated
RIS	4555	13.6255	68	0.0025	27,654	−19	6	Extendedly dominated
ALN	4556	13.6256	69	0.0025	27,325	−19	7	£27,325
IBN (oral)	4557	13.6256	70	0.0026	27,349	−19	7	£28,946
ZOL	5151	13.6276	664	0.0046	145,587	−572	−527	£297,575
IBN (i.v.)	5331	13.6240	844	0.0010	853,480	−825	−815	Dominated
DEN	6159	13.6297	1672	0.0067	250,782	−1539	−1472	£478,086
ROMO/ALN	Confidential information has been removed	13.6320	Confidential information has been removed	0.0090	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	10,236	13.6282	5749	0.0052	1,115,769	−5646	−5595	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 63 Base-case results from 200,000 PSA samples for FRAX risk category 3 (average 10-year fracture risk of 5.0%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost	QALY				
No treatment	4976	13.8999	0	–	0	0	0	
RIS	5033	13.9035	57	0.0037	15,575	16	53	£15,575
ALN	5037	13.9035	61	0.0037	16,808	12	48	Dominated
IBN (oral)	5039	13.9034	63	0.0035	17,728	8	43	Dominated
RLX	5045	13.8992	69	−0.0007	−105,444	−83	−89	Dominated
ZOL	5635	13.9058	659	0.0059	110,846	−540	−481	£263,566
IBN (i.v.)	5810	13.9017	834	0.0019	443,563	−797	−778	Dominated
DEN	6636	13.9084	1660	0.0085	195,106	−1489	−1404	£390,788
ROMO/ALN	Confidential information has been removed	13.9117	Confidential information has been removed	0.0118	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	10,708	13.9067	5732	0.0069	832,835	−5594	−5526	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 64 Base-case results from 200,000 PSA samples for FRAX risk category 4 (average 10-year fracture risk of 5.6%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	5465	14.2478	0	–	0	0	0	
ALN	5521	14.2515	56	0.0036	15,524	16	53	£15,524
IBN (oral)	5524	14.2514	59	0.0036	16,459	13	49	Dominated
RIS	5525	14.2513	60	0.0035	17,389	9	44	Dominated
RLX	5558	14.2458	94	−0.0020	−47,071	−133	−153	Dominated
ZOL	6116	14.2546	651	0.0068	96,012	−516	−448	£189,147
IBN (i.v.)	6295	14.2497	831	0.0019	430,771	−792	−773	Dominated
DEN	7152	14.2555	1687	0.0076	220,601	−1534	−1458	£1,197,064
ROMO/ALN	Confidential information has been removed	14.2569	Confidential information has been removed	0.0091	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	11,185	14.2555	5720	0.0077	745,024	−5567	−5490	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 65 Base-case results from 200,000 PSA samples for FRAX risk category 5 (average 10-year fracture risk of 6.2%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	5792	12.8154	0	–	0	0	0	
ALN	5845	12.8201	54	0.0047	11,362	41	88	Extendedly dominated
RIS	5846	12.8202	54	0.0048	11,265	42	90	£11,265
IBN (oral)	5849	12.8200	57	0.0047	12,209	36	83	Dominated
RLX	5873	12.8144	81	−0.0010	−82,569	−101	−110	Dominated
ZOL	6435	12.8232	644	0.0078	82,355	−487	−409	£194,815
IBN (i.v.)	6623	12.8178	831	0.0024	342,182	−783	−758	Dominated
DEN	7435	12.8243	1643	0.0089	184,386	−1465	−1375	Extendedly dominated
ROMO/ALN	Confidential information has been removed	12.8286	Confidential information has been removed	0.0132	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	11,479	12.8244	5687	0.0090	632,511	−5507	−5417	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 66 Base-case results from 200,000 PSA samples for FRAX risk category 6 (average 10-year fracture risk of 7.3%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	5868	11.0066	0	–	0	0	0	
RIS	5906	11.0111	39	0.0044	8736	50	95	£8736
ALN	5910	11.0114	43	0.0048	8951	53	101	£11,817
IBN (oral)	5922	11.0110	54	0.0044	12,389	33	77	Dominated
RLX	6012	11.0049	145	−0.0018	−82,686	−180	−197	Dominated
ZOL	6491	11.0142	623	0.0076	82,446	−472	−396	£209,233
IBN (i.v.)	6692	11.0089	825	0.0023	362,332	−779	−756	Dominated
DEN	7557	11.0154	1690	0.0087	193,385	−1515	−1428	Extendedly dominated
ROMO/ALN	Confidential information has been removed	11.0208	Confidential information has been removed	0.0142	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	11,507	11.0157	5640	0.0091	622,664	−5459	−5368	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 67 Base-case results from 200,000 PSA samples for FRAX risk category 7 (average 10-year fracture risk of 8.8%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
No treatment	5488	9.3617	0	–	0	0	0	
ALN	5508	9.3671	20	0.0054	3791	87	140	£3,791
RIS	5511	9.3667	23	0.0050	4572	77	128	Dominated
IBN (oral)	5518	9.3667	30	0.0050	6035	70	120	Dominated
RLX	5584	9.3615	96	−0.0002	−455,927	−100	−102	Dominated
ZOL	6070	9.3709	582	0.0092	63,432	−399	−307	£147,034
IBN (i.v.)	6301	9.3639	813	0.0022	367,423	−769	−747	Dominated
DEN	7082	9.3731	1594	0.0113	140,582	−1367	−1254	Extendedly dominated
ROMO/ALN	Confidential information has been removed	9.3788	Confidential information has been removed	0.0170	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	11,069	9.3720	5581	0.0103	542,248	−5375	−5272	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 68 Base-case results from 200,000 PSA samples for FRAX risk category 8 (average 10-year fracture risk of 10.7%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
ALN	5754	8.1143	−11	0.0066	−1716	142	208	
RIS	5764	8.1143	−2	0.0065	−297	132	198	Dominated
No treatment	5766	8.1077	0	–	0	0	0	Dominated
IBN (oral)	5770	8.1141	5	0.0064	734	123	187	Dominated
RLX	5820	8.1087	54	0.0009	57,050	−35	−26	Dominated
ZOL	6308	8.1184	542	0.0106	51,057	−330	−224	£136,054
IBN (i.v.)	6556	8.1114	790	0.0037	215,680	−717	−680	Dominated
DEN	7247	8.1233	1482	0.0156	95,158	−1170	−1014	£189,738
ROMO/ALN	Confidential information has been removed	8.1266	Confidential information has been removed	0.0189	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	11,275	8.1203	5510	0.0125	439,478	−5259	−5133	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 69 Base-case results from 200,000 PSA samples for FRAX risk category 9 (average 10-year fracture risk of 14.9%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
ALN	8078	7.0926	−43	0.0082	−5233	208	290	
RIS	8082	7.0923	−39	0.0080	−4904	200	280	Dominated
IBN (oral)	8085	7.0922	−36	0.0079	−4537	194	273	Dominated
No treatment	8121	7.0843	0	–	0	0	0	Dominated
RLX	8251	7.0837	130	−0.0006	−206,484	−142	−148	Dominated
ZOL	8615	7.0974	494	0.0131	37,737	−232	−101	£110,826
IBN (i.v.)	8881	7.0890	760	0.0047	163,225	−666	−620	Dominated
DEN	9560	7.1004	1439	0.0161	89,300	−1116	−955	£312,269
ROMO/ALN	Confidential information has been removed	7.1056	Confidential information has been removed	0.0213	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	13,523	7.1000	5402	0.0157	343,693	−5088	−4930	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 70 Base-case results from 200,000 PSA samples for FRAX risk category 10 (average 10-year fracture risk of 25.1%)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
ALN	13,031	4.7140	−129	0.0110	−11,748	348	458	
RIS	13,040	4.7134	−120	0.0104	−11,572	327	431	Dominated
IBN (oral)	13,048	4.7130	−112	0.0100	−11,122	312	413	Dominated
No treatment	13,160	4.7030	0	–	0	0	0	Dominated
RLX	13,276	4.7012	116	−0.0018	−63,139	−153	−172	Dominated
ZOL	13,487	4.7191	327	0.0161	20,257	−4	157	£88,002
IBN (i.v.)	13,853	4.7092	693	0.0062	111,944	−569	−507	Dominated
DEN	14,370	4.7236	1210	0.0206	58,730	−798	−592	£197,979
ROMO/ALN	Confidential information has been removed	4.7303	Confidential information has been removed	0.0273	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	18,252	4.7238	5092	0.0208	244,558	−4676	−4468	Dominated

a ICER vs. next least costly non-dominated strategy.

Appendix 21 Sensitivity analyses for economic evaluation

Note that these sensitivity analyses are based on the model using mid-point parameter inputs, rather than the average outcomes across the PSA with the exception of *Tables 74* and *75*, which used 500,000 PSA samples but fixed patient characteristics.

TABLE 71 The ICERs vs. no treatment by risk deciles for QFracture and FRAX when using the base-case scenario

	ICERs by risk decile (£)										
Drug	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**All**
Qfracture score (%)	***0.5***	***0.7***	***1.0***	***1.4***	***2.0***	***2.7***	***3.9***	***5.5***	***8.4***	***16.0***	***NA***
ALN	498,737	412,005	157,211	149,958	68,492	44,834	37,197	16,884	745	Dominates	29,766
RIS	565,069	441,369	160,348	158,750	69,748	47,388	38,372	16,920	2190	Dominates	31,628
IBN (oral)	463,164	427,947	156,817	144,798	70,576	46,196	37,906	17,487	837	Dominates	30,561
IBN (i.v.)	Dominated	Dominated	Dominated	Dominated	4,767,171	1,413,543	1,040,966	650,661	307,706	199,398	1,066,308
ZOL	241,951,112	21,001,049	1,200,415	870,723	469,207	308,198	227,473	133,550	79,528	58,085	233,405
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
DEN	1,998,145	1,741,276	1,143,632	887,398	609,344	492,380	386,626	243,281	163,466	115,933	382,864
TPTD	7,503,596	6,096,105	4,057,889	3,088,025	2,244,920	1,700,544	1,405,530	910,295	608,736	453,776	1,361,877
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
FRAX score (%)	***3.1***	***4.3***	***5.0***	***5.6***	***6.2***	***7.3***	***8.8***	***10.7***	***14.9***	***25.1***	***NA***
ALN	24,918	22,192	15,189	16,287	10,585	3769	1096	Dominates	Dominates	Dominates	1350
RIS	25,690	22,982	15,820	17,515	10,337	3911	1349	Dominates	Dominates	Dominates	1814
IBN (oral)	25,107	23,022	15,393	16,536	11,305	3733	1713	Dominates	Dominates	Dominates	1756
IBN (i.v.)	671,930	761,291	455,094	398,749	365,350	261,759	262,550	184,121	140,596	82,567	248,478
ZOL	152,696	146,559	111,458	96,479	78,835	66,241	57,551	48,346	33,954	18,654	63,969
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	18,508,020	158,275	115,977	56,599	Dominated
DEN	325,050	281,011	205,252	190,057	166,993	147,494	130,881	106,085	81,500	52,679	137,302
TPTD	1,123,470	983,834	869,760	767,917	670,930	601,318	482,831	444,825	330,544	232,180	532,666
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

TABLE 72 The ICERs vs. no treatment by risk deciles for QFracture and FRAX when assuming full persistence with treatment

	ICERs by risk decile (£)										
Drug	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**All**
Qfracture score (%)	***0.5***	***0.7***	***1.0***	***1.4***	***2.0***	***2.7***	***3.9***	***5.5***	***8.4***	***16.0***	***NA***
ALN	251,941	168,092	119,902	79,284	60,970	31,766	21,485	10,432	932	Dominates	24,274
RIS	268,409	173,111	121,180	81,223	62,848	33,001	22,356	11,356	1273	Dominates	25,717
IBN (oral)	249,462	167,996	116,962	80,518	62,242	32,880	21,962	10,972	1310	Dominates	25,052
IBN (i.v.)	6,829,412	3,436,012	2,239,222	1,466,327	1,139,102	652,143	477,492	326,477	231,761	173,580	568,098
ZOL	1,872,105	1,080,025	721,322	481,417	368,038	222,443	160,376	110,764	74,556	54,055	191,981
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
DEN	1,961,321	1,264,758	1,002,128	693,856	526,207	357,560	265,653	186,577	128,911	94,665	322,714
TPTD	7,552,870	5,127,678	4,294,267	2,966,878	2,601,782	1,717,937	1,230,354	814,753	600,894	406,640	1,288,454
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
FRAX score (%)	***3.1***	***4.3***	***5.0***	***5.6***	***6.2***	***7.3***	***8.8***	***10.7***	***14.9***	***25.1***	***NA***
ALN	20,826	13,265	10,205	8667	7096	4570	Dominates	Dominates	Dominates	Dominates	629
RIS	21,225	13,435	10,374	9194	7051	4739	Dominates	Dominates	Dominates	Dominates	1061
IBN (oral)	21,651	13,923	10,577	9059	7570	5066	26	Dominates	Dominates	Dominates	1060
IBN (i.v.)	424,242	313,920	269,844	243,798	238,418	216,521	174,715	133,701	114,229	84,510	187,936
ZOL	134,229	99,921	85,457	75,996	71,730	65,020	51,386	39,131	32,428	20,158	57,147
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	697,741	196,074	107,583	Dominated
DEN	243,364	184,578	159,477	141,243	137,427	120,484	97,963	77,542	63,636	42,333	109,566
TPTD	1,059,530	914,573	769,066	691,834	637,242	550,881	495,976	388,142	323,503	230,761	505,256
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

TABLE 73 The ICERs vs. no treatment by risk deciles for QFracture and FRAX when using the class effect estimates for bisphosphonates

	ICERs by risk decile (£)										
Drug	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**All**
Qfracture score (%)	***0.5***	***0.7***	***1.0***	***1.4***	***2.0***	***2.7***	***3.9***	***5.5***	***8.4***	***16.0***	***NA***
ALN	799,955	486,510	172,280	106,937	85,656	59,255	27,980	12,480	5185	Dominates	31,647
RIS	799,955	486,510	172,280	106,937	85,656	59,255	27,980	12,480	5185	Dominates	31,647
IBN (oral)	826,668	502,375	178,069	110,735	88,733	61,464	29,355	13,378	5907	Dominates	33,205
IBN (i.v.)	Dominated	Dominated	Dominated	Dominated	7,531,872	2,733,301	981,482	435,481	360,520	206,403	1,086,629
ZOL	Dominated	10,002,667	1,313,565	794,622	556,859	336,315	196,111	130,628	100,210	62,599	248,980
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
DEN	2,346,041	1,613,668	1,005,637	823,644	638,855	487,738	330,852	227,692	185,220	122,045	383,999
TPTD	8,161,900	5,841,080	4,235,494	3,154,275	2,175,649	1,968,959	1,205,259	885,276	714,965	481,048	1,415,644
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
FRAX score (%)	***3.1***	***4.3***	***5.0***	***5.6***	***6.2***	***7.3***	***8.8***	***10.7***	***14.9***	***25.1***	***NA***
ALN	27,834	19,286	16,881	14,023	10,907	4553	1530	Dominates	Dominates	Dominates	2591
RIS	27,834	19,286	16,881	14,023	10,907	4553	1530	Dominates	Dominates	Dominates	2591
IBN (oral)	28,967	20,169	17,695	14,715	11,600	5160	2044	Dominates	Dominates	Dominates	3131
IBN (i.v.)	616,244	408,882	418,532	337,957	325,277	287,300	226,977	183,012	142,975	97,801	240,853
ZOL	178,326	130,666	122,750	96,355	106,623	78,832	63,178	54,261	38,658	24,279	72,230
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	115,828	80,087	Dominated
DEN	321,955	245,827	211,101	175,962	177,597	153,423	127,213	109,102	83,514	56,914	138,658
TPTD	1,187,281	940,410	859,389	720,901	666,582	583,940	499,370	437,612	348,992	252,450	541,645
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

TABLE 74 Scenario results for high-risk patient with FRAX risk of 30% (based on 500,000 PSA samples with fixed patient characteristics)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
ALN	7476	6.6254	−235	0.0199	−11,804	634	834	
RIS	7479	6.6248	−232	0.0193	−12,014	618	811	Dominated
IBN (oral)	7509	6.6242	−202	0.0187	−10,776	576	764	Dominated
No treatment	7711	6.6055	0	–	0	0	0	Dominated
RLX	7832	6.6067	121	0.0012	105,283	−98	−87	Dominated
ZOL	8001	6.6308	290	0.0253	11,427	217	471	Extendedly dominated
IBN (i.v.)	8329	6.6193	618	0.0138	44,785	−342	−204	Dominated
DEN	8491	6.6631	780	0.0576	13,544	372	948	£26,977
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	12,820	6.6418	5109	0.0363	140,684	−4383	−4020	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 75 Scenario results for high-risk patient with QFracture risk of 13.3% (based on 500,000 PSA samples with fixed patient characteristics)

Treatment strategy	Mean outcomes (discounted)		Incremental outcomes vs. no treatment (discounted)		ICER vs. no treatment (£)	Net benefit at £20,000 per QALY (£)	Net benefit at £30,000 per QALY (£)	Incremental analysis[a]
	Cost (£)	QALY	Cost (£)	QALY				
ALN	2782	6.8336	−24	0.0071	−3393	167	238	
RIS	2782	6.8335	−24	0.0069	−3463	163	233	Dominated
IBN (oral)	2794	6.8331	−12	0.0065	−1819	143	208	Dominated
No treatment	2806	6.8265	0	–	0	0	0	Dominated
RLX	2947	6.8256	141	−0.0009	−152,373	−159	−169	Dominated
ZOL	3387	6.8352	581	0.0087	66,928	−407	−321	Extendedly dominated
IBN (i.v.)	3577	6.8307	771	0.0042	183,707	−687	−645	Dominated
DEN	4205	6.8478	1399	0.0212	65,851	−974	−761	£100,788
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
TPTD	8315	6.8398	5509	0.0133	414,209	−5243	−5110	Dominated

a ICER vs. next least costly non-dominated strategy.

TABLE 76 The ICERs vs. no treatment by risk deciles for QFracture and FRAX when making alternative assumptions for the offset period[a]

	ICERs by risk decile (£)										
Drug	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**All**
Qfracture score (%)	***0.5***	***0.7***	***1.0***	***1.4***	***2.0***	***2.7***	***3.9***	***5.5***	***8.4***	***16.0***	***NA***
ALN	667,007	344,843	154,562	158,993	79,839	96,437	32,481	16,709	9373	Dominating	37,101
RIS	833,648	378,035	155,152	176,091	87,929	98,283	33,908	19,143	9239	Dominating	39,904
IBN (oral)	613,050	300,939	153,457	165,724	80,313	98,014	33,897	17,620	10,028	Dominating	38,227
IBN (i.v.)	Dominated	Dominated	Dominated	Dominated	6,497,796	Dominated	984,778	539,348	428,815	189,330	1,167,465
ZOL	Dominated	Dominated	3,032,964	2,134,060	694,683	813,434	266,397	215,493	141,142	79,915	359,734
RLX	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
DEN	1,875,580	1,067,021	725,687	574,802	412,867	409,288	226,792	186,474	119,740	84,928	277,008
TPTD	7,103,236	5,463,987	4,344,868	4,130,127	2,585,616	2,577,445	1,336,591	1,136,165	771,301	499,965	1,581,013
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
FRAX score (%)	***3.1***	***4.3***	***5.0***	***5.6***	***6.2***	***7.3***	***8.8***	***10.7***	***14.9***	***25.1***	***NA***
ALN	43,692	29,116	20,888	16,881	14,815	10,289	6445	1671	Dominating	Dominating	5789
RIS	41,868	30,603	20,138	17,014	15,644	11,783	7082	2179	Dominating	Dominating	6585
IBN (oral)	43,872	29,515	21,422	17,188	15,311	10,602	7219	2062	Dominating	Dominating	6353
IBN (i.v.)	1,135,784	620,464	432,254	341,331	362,455	346,713	338,155	209,343	172,366	96,099	280,111
ZOL	292,309	212,340	171,060	135,810	139,460	124,920	113,027	81,472	62,310	33,641	106,395
RLX	Dominated	Dominated	Dominated	316,965	Dominated	Dominated	Dominated	450,493	132,412	50,539	11,272,491
DEN	228,836	180,468	152,041	132,978	126,706	114,716	105,110	74,266	59,072	38,160	101,453
TPTD	1,492,180	1,109,874	933,843	782,904	858,530	704,890	658,543	504,232	418,570	280,094	637,237
ROMO/ALN	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

a Assuming offset period equal to treatment time for ZOL, RLX and DEN, and assuming offset period equal to 1 year for ALN, RIS, IBN (oral), IBN (i.v.) and TPTD.

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