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A systematic review and economic evaluation of non-bisphosphonates for the prevention of osteoporotic fragility fractures (ID901)

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Contributions of authors

Sarah Davis acted as the overall project lead. Emma Simpson and Marrissa Martyn-St James conducted the systematic review of clinical effectiveness studies. Edward Goka quality assured some of the fracture data extraction. Jean Hamilton conducted the network meta-analyses. Sarah Davis and Andrew Rawdin conducted the review of published cost-effectivenes studies. Andrew Rawdin conducted the review of health related quality of life following fracture. Sarah Davis conducted the economic evaluation. Ruth Wong conducted the searches. Peter Selby and Neil Gittoes provided clinical advice. All authors were involved in drafting and commenting on the final report.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of healthcare interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Care Excellence (NICE). ScHARR-TAG is part of a wider collaboration of a number of units from other regions including Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, The University of Warwick; the BMJ Group and Kleijnen Systematic Reviews.

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1 LIST OF ABBREVIATIONS

Abbreviations

ACTIVE	Trial name Abaloparatide Comparator Trial In Vertebral Endpoints
ADAMO	Trial name Denosumab Versus Placebo in Males With Osteoporosis
ALN	Alendronate
ARCH	Trial name Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk
BMD	bone mineral density
BNF	British National Formulary
BRIDGE	Trial name Phase 3 randomized placeBo-contRolled double-blind study evaluatIng the efficacy and safety of Romosozumab in treatinG mEn with osteoporosis
CrI	Credible interval
CODA	convergence diagnosis and output analysis
DAPS	Trial name Denosumab Adherence Preference Satisfaction
DATA	Trial name Denosumab and Teriparatide Administration
DECIDE	Trial name Determining Efficacy: Comparison of Initiating Denosumab versus Alendronate
DEN	Denosumab
DES	Discrete event simulation
DIRECT	Trial name Denosumab fracture Intervention RandomizEd placebo Controlled Trial
DVT	Deep vein thrombosis
EFFECT	Trial name EFficacy of FOSAMAX versus EVISTA Comparison Trial
eMIT	Electronic market information tool
EQ-5D	Euro Quality of Life-5 Dimensions
EQ-VAS	Euro Quality of Life – Visual Analogue Scale
EU	European Union
EUROFORS	Trial name European Study of Forsteo
EuroGIOPS	Trial name acronym meaning not reported; EUROFORS European Study of Forsteo
EVA	Trial name Evista Alendronate Comparison trial
FACT	Trial name Forteo Alendronate Comparator Trial
FN	femoral neck
FPT	Trial name fracture prevention trial
FRAME	Trial name Fracture Study in Postmenopausal Women with Osteoporosis

FREEDOM	Trial name Fracture Reduction Evaluation of Denosumab in Osteoporosis
GAM	generalised additive model
GP	General Practitioner
HES	Hospital Episode Statistics
HCHS	Hospital and community health services
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
i.v.	intravenous
IBN	ibandronate
ICDF	Inconsistency degrees of freedom
ICER	Incremental cost-effectiveness ratio
INMB	Incremental net monetary benefit
ITT LOCF	intention-to-treat last observation carried forward
ITT MI	intention-to-treat multiple imputation
LOCF	Last observation carried forward
LS	lumbar spine
LY	Life-years
MHRA/CHM	Medicines and Healthcare products Regulatory Agency/Commission on Human Medicines
mITT	modified intent to treat
MORE	Trial name European Study of Forsteo
MOVE	Trial name Trial name, acronym meaning not reported
NHS	Nationl Health Service
NMA	Network meta-analysis
NOGG	National Osteoporosis Guideline Group
NR	not reported
NT	No treatment
OLE	open label extension
ONJ	Osteonecrosis of the jaw
PB	probability of being the best ranking treatment
PBO	placebo
PE	Pulmonary embolism
PrI	Prediction interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis

PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
RCT	randomised controlled trial
RD	risk difference
RIS	Risedronate
RLX	Raloxifene
ROMO	Romosozumab
RR	risk ratio
s.c.	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
STAND	Trial name Study of Transitioning from Alendronate to Denosumab
STRUCTURE	Trial name Study to Evaluate the Effect of Treatment With Romosozumab or Teriparatide in Postmenopausal Women
TPTD	Teriparatide
TTO	Time-trade-off
VERO	VERtebral fracture treatment comparisons in Osteoporotic women
VTE	Venous thromboembolic events
WHO	World Health Organisation
ZOL	Zoledronate / Zoledronic acid

2 EXECUTIVE SUMMARY

2.1 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 World Health Organization [WHO] as a broken bone resulting from a fall from standing height or less). In the UK, the number of women and men age >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.

2.2 Objectives

To determine the clinical effectiveness and cost-effectiveness of Denosumab (DEN), Raloxifene (RLX), Romosozumab (ROMO) and Teriparatide (TPTD), within their licensed indications, for the prevention of osteoporotic fragility fractures as compared against each other, bisphosphonates or a non-active treatment.

2.3 Methods

A systematic review and network meta-analysis (NMA) of clinical effectiveness and safety evidence for interventions of interest was conducted. Nine electronic databases were searched up to July 2018. Studies were eligible for inclusion if they were randomised controlled trials (RCTs) comparing the non-bisphosphonates DEN, RLX, ROMO, or TPTD with each other, placebo (PBO) or bisphosphonates within their licensed indication for an osteoporosis population, and reported either fracture or BMD data. 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 within the company submissions. The identified cost-effectiveness analyses were compared to the model developed to inform the National Institute of Health and Care Excellence (NICE) Multiple Technology Appraisal (MTA) of bisphosphonates (TA464) to identify areas of difference. The model used in TA464 was then adapted to evaluate the cost-effectiveness of non-bisphosphonates when compared to either no treatment or treatment with bisphosphonate across the whole population eligible for fracture risk assessment (as defined by NICE Clinical Guideline (CG) 146). Incremental analyses were conducted for 10 risk categories based on deciles of risk when using either the QFracture or FRAX risk scoring algorithms to determine risk. In the economic analyses, treatment with ROMO was modelled as a treatment sequence of ROMO followed by the bisphosphonate

alendronate (ROMO/ALN). All of the other treatment strategies modelled consisted of a single intervention followed by no treatment.

2.4 Results

The systematic review of clinical effectiveness identified 7,898 citations. Fifty-two RCTs of non-bisphosphonates were included in the review, and 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 serious adverse event rates were: DEN 2% to 25.8%; RLX 2% to 18.6%; ROMO 3.2% to 12.9%; TPTD 0% to 33.0%.

NMAs were conducted for vertebral fractures (46 RCTs, 11 interventions), non-vertebral fractures (42 RCTs, 11 interventions), hip fractures (23 RCTs, 9 interventions), wrist fractures (15 RCTs, 8 interventions), proximal humerus fractures (13 RCTs, 8 interventions) and percentage change in 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. For vertebral, non-vertebral, hip and wrist fractures, TPTD provided the largest treatment effect, though in general the ranking of treatments varied for the different outcomes. For wrist and proximal humerus fractures there was less RCT 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 NMA were robust to these potential issues.

In the AG's economic evaluation, the incremental cost-effectiveness ratios (ICERs) versus no treatment were found to be above £30,000 per quality-adjusted life year (QALY) for all of the non-bisphosphonate treatments (RLX, DEN, TPTD, ROMO/ALN) 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 treatment effect to fall to zero after treatment stops (the offset period). The results of the regression of INMB against fracture risk suggest that DEN may have an ICER

under £30,000 compared to no treatment at very high levels of risk (FRAX score >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 DEN may be more favourable in high risk patients with specific characteristics.

2.5 Discussion

Fracture and BMD data were available for all four non-bisphosphonate interventions. All of these interventions were associated with beneficial effects compared to PBO.

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 within the population eligible for risk assessment under CG146. 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.

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

2.6 Conclusions

The non-bisphosphonate interventions (RLX, DEN, TPTD and ROMO) are all clinically effective at reducing vertebral fracture risk when compared to 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 ICERS compared with no treatment are above the NICE threshold of £20,000 per QALY for all non-bisphosphonate interventions across the range of QFracture and FRAX scores expected in the population eligible for fracture risk assessment. The ICER for DEN may be below £30,000 per QALY in very high risk patients (FRAX >45%), but the estimates of cost-effectiveness in high risk patients are very uncertain.

3 BACKGROUND

3.1 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 resulting from a fall at standing height or less). The definition provided by the World Health Organization (1994) defines the condition as bone mineral density (BMD) 2.5 standard deviations (SDs) below peak bone mass (20-29 year-old healthy female average) as measured by DXA (dual energy X-ray absorptiometry).[1] 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 less.[1] Whilst 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 European Union 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) being sustained.[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 women (T score≤-2.5 SD), 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%.

3.2 Current service provision

3.2.1 Clinical Guidelines

Currently, related NICE guidance includes a clinical guideline for identifying women and men at risk of fracture (CG146[8]) and three technology appraisals of treatments for osteoporosis (TA464,[9] TA204,[10] TA161[11]).

3.2.2 Current NICE Technology Appraisal Guidance

NICE technology appraisal guidance 464 (TA464[9]), recommends oral bisphosphonates (ALN, IBN and 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 guideline 146 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 technology appraisal guidance 464[9] should be applied clinically in conjunction with the NICE quality standard 149 on osteoporosis[12] that defines the clinical intervention thresholds. These thresholds are based on the NICE-accredited National Osteoporosis Guideline Group (NOGG) guideline.[13]

NICE technology appraisal guidance 204[10] recommends DEN 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 no longer marketed in the UK), or have an intolerance of, or a contraindication to, those treatments. Technology appraisal guidance 204[10] also recommends DEN 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 ALN and either RIS or etidronate, or have an intolerance of or a contraindication to ALN and either RIS or etidronate.

NICE technology appraisal guidance 161, recommends RLX and strontium ranelate (currently discontinued), and TPTD 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]

3.2.3 Current service cost

Hernlund *et al.* (2013)[25] reviewed the literature on fracture incidence and costs of fractures in the 27 European Union (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 €37 billion. 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; and "other fractures" represented 39 %. The estimated number of life-years lost in the EU due to incident fractures was approximately 26,300 in 2010. The total health burden, measured in terms of lost 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.*[14] at €103 million (£91.8 million in 2017 prices) for pharmacological fracture prevention, €3,977 million (£3546 million in 2017 prices) for cost of fractures, and €1328 million (£1185 million in 2017 prices) for cost of long-term disability. The 2010 cost of UK osteoporosis fracture in relation to population and healthcare spending was €5408 million (£4822 million in 2017 prices). The 2010 prices reported by Hernlund *et al.* in Euros have been converted back to £ sterling (2006 prices). The conversion ratio from 2006 prices to 2010 used by Hernlund *et al.* was estimated by ScHARR at 1.4065 by comparing the unit cost for nursing home stay against the cited UK specific source data from 2006.[15] Costs have then been uplifted to 2017 prices using the hospital and community health services (HCHS) inflation indices from the Personal Social Services Research Unit (PSSRU)[16] (302.3 for 2016/17 versus 240.9 for 2005/6).

3.2.4 Current treatment pathway

The NICE 2018 osteoporosis overview pathway[17] and Fragility fracture risk assessment pathway[18] cover NICE guidance on osteoporosis in adults (18 years and older), 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 are summarised later in section 3.4.3).

3.3 Description of technology under assessment

3.3.1 Interventions considered in the scope of this report

Four interventions will be considered within this assessment: DEN, RLX, ROMO and TPTD.

3.3.2 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 states that ROMO leads to "an increase in bone formation and reduction in bone resorption" suggesting that it is both bone forming and anti-resportive properties.[20]

3.3.3 Marketing license and administration method

DEN (Prolia, Amgen) is a monoclonal antibody that reduces osteoclast activity, and so reduces bone breakdown. It is administered as a single 60 mg subcutaneous 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]

RLX (Evista, Daiichi Sankyo) is a selective oestrogen receptor modulator. It is administered orally at a dose of 60mg daily. RLX has a marketing authorisation in the UK for the treatment and prevention of osteoporosis in postmenopausal women. Non-proprietary RLX (Sandoz, Consilient Health, Actavis UK, Mylan UK) is also available for the same indication.[19]

ROMO (Evenity, UCB and Amgen) is a monoclonal antibody that inhibits the protein sclerostin, increasing bone formation and decreasing bone breakdown. It is administered as a subcutaneous injection. It does not currently have a marketing authorisation in the UK for treating osteoporosis. 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] It is administered as a subcutaneous injection once monthly. A treatment dose is not yet licenced.

TPTD (Forsteo, Eli Lilly) 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 for fracture. Biosimilar versions of TPTD (Movymia, Internis Pharmaceuticals[21]; Terrosa, Gedeon Richter[22]) have been licensed for the same indications.[19].

3.3.4 Contraindications, special warnings and precautions

The summary of product characteristics (SmPC) for each intervention describes the contraindications and special warnings for bisphosphonates.[23-25]

DEN 60 mg subcutaneous injection 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.[23] Special warnings and precautions include hypocalcaemia, renal impairment, skin infections, osteonecrosis of the jaw (ONJ), and atypical femoral fracture.[23]

RLX orally at a dose of 60mg daily is contraindicated in women with child bearing potential, in patients with: active or past history of venous thromboembolic events (VTE), including deep vein thrombosis (DVT), pulmonary embolism (PE) and retinal vein thrombosis; hepatic impairment including cholestasis, severe renal impairment, unexplained uterine bleeding, with signs or symptoms of endometrial cancer, or with hypersensitivity to the active substance or to any of the excipients.[24]

The draft Summary of Product Characteristics for ROMO, notes special precautions in patients [redacted]. Special warnings and precautions include [redacted].[25]

TPTD administered subcutaneously at a dose of 20 μg daily is contraindicated in women who are pregnant or breast-feeding, patients with: pre-existing hypercalcaemia, severe renal impairment, metabolic bone diseases (including hyperparathyroidism and Paget's disease of the 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.[24] Precautions include elevations of serum calcium concentrations, active or recent urolithiasis, orthostatic hypotension, and renal impairment.[24]

3.3.5 Place in treatment pathway

DEN is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures 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.[26]

RLX 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 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.[26]

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

TPTD 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 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 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures.[27]

3.3.6 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 effect the impact of fracture on lifetime costs and outcomes.[19]

3.3.7 Current usage in the National Health Service (NHS)

Data from the 2017 Prescription Cost Analysis were analysed to determine the level of non-bisphosphonate usage within primary care across England in 2017.[28] It can be seen from the data summarised in Table 1 that branded DEN was the most commonly prescribed preparation in primary care. The prescribing costs in hospitals and the community in England 2016/17 for treatment of osteoporosis was £11,930,475 for DEN, £355,530 for RLX, and £4,409,696 for TPTD.[29]

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

Drug	Generic or branded	Dosing schedule	Prescriptions in thousands*	Description of preparations
DEN	Branded	Once every six months	7911.635	Prolia Injection 60mg/1ml Pfs
RLX	Branded	Daily	44.345	Evista_Tablet 60mg
	Generic	Daily	241.475	RLX HCl_Tablet 60mg
TPTD	Branded	Daily	402.111	Forsteo_Injection 250mcg/ml 2.4ml Pf Pen

* Prescription items dispensed in the community in 2017[28]

3.3.8 Anticipated costs associated with interventions

Table **2** summarises the 2018 net costs associated with the interventions based on their list prices.[30]

Table 2: Acquisition costs associated with DEN, RLX, and TPTD

Drug	Generic or branded	Unit type and dose	Price per unit
DEN	Branded	Prolia Injection 60mg/1ml 1 pre-filled disposable injection	NHS indicative price = £183.00 Drug Tariff (Part VIIIA Category C) price = £183.00
RLX	Branded	Evista_Tablet 60mg 28 tablet	NHS indicative price = £17.06 Drug Tariff (Part VIIIA Category M) price = £3.27
	Generic	RLX HCl_Tablet 60mg 28 tablet	Activis UK: NHS indicative price = £4.60 Drug Tariff (Part VIIIA Category M) price = £3.27
TPTD	Branded	Forsteo_Injection 250mcg/ml 2.4ml Pf Pen 1 pre-filled disposable injection (i.e. 30 daily doses)	NHS indicative price = £271.88 Drug Tariff (Part VIIIA Category C) price = £271.88

3.4 Impact of health problem

3.4.1 Significance for patients

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

3.4.2 Significance for the NHS

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

3.4.3 Measurement of disease

Quantitative diagnosis in the UK relies on the assessment of BMD, usually by central dual energy X-ray absorptiometry (DXA). BMD at the femoral neck provides the reference site. It is defined as a value for BMD 2.5 SD or more below the young female adult mean (T-score less than or equal to –2.5 SD). Severe osteoporosis (established osteoporosis) describes osteoporosis in the presence of 1 or more fragility fractures.[31]

NICE Clinical Guideline 146 (CG146)[8] recommends the estimation of absolute risk of fragility fracture when assessing risk of fracture and recommends the use either FRAX,[32] (without a BMD value if a DXA scan has not previously been undertaken) or QFracture,[33] within their allowed age ranges, to estimate 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 recommends that assessment is indicated in all women aged 65 years and over and all men aged 75 years and over and in women aged under 65 years and men aged under 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 more than 14 units per week for women and more than 21 units per week for men).[8] The guideline recommends not routinely assessing fracture risk in people aged under 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).[8] The guideline also recommends interpretation of the estimated absolute risk of fracture in people aged over 80 years with caution, because predicted 10-year fracture risk may underestimate their short-term fracture risk.[8]

4 DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

This assessment will address the 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 against each other, bisphosphonates or a non-active treatment?"

4.2 Overall aims and objectives of assessment

1) To evaluate the clinical effectiveness of each intervention, in terms of osteoporotic fragility fractures, and femoral neck (FN) BMD.

Population: Adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146.

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 FN.

2) To evaluate the incremental cost-effectiveness of each intervention compared against (i) each other, (ii) the bisphosphonates ALN, IBN (oral or i.v.), RIS and ZOL, and (iii) no active treatment.

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

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

A systematic review of the literature, and network meta-analyses (NMAs), were conducted in order 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.[34]

5.1 Methods for reviewing effectiveness

5.1.1 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 in 11th July 2018:

- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and MEDLINE (Ovid) 1946 to 2018
- Embase (Ovid) 1974 to 2018
- Cochrane Database of Systematic Reviews (Wiley Interscience) 1996-2018
- Database of Abstract of Reviews of Effects (Wiley Interscience) 1995-2015
- Cochrane Central Register of Controlled Trials (Wiley Interscience) 1898-2018
- Health Technology Assessment Database (Wiley Interscience) 1995-2016
- Science Citation Index Expanded (Web of Science) 1900-2018
- Conference Proceedings Citation Index - Science (Web of Science) 1990-2018
- WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) [Accessed online 11th July 2018]

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

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, where appropriate. Industry submissions and relevant systematic reviews were also hand-searched in order to identify any further relevant clinical trials. The WHO International Clinical Trials Registry Platform was searched for on-going 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 Reference Manager bibliographic software, (version X8.2, Clarivate Analytics) 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 NICE technology appraisal 464 "Bisphosphonates for preventing osteoporotic fragility fractures".[35] As the searches for this technology appraisal were last updated in September 2014, more recent studies were sought from the database searches.

Where 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.

5.1.2 Study selection

All titles and abstracts identified by the searches were screened by one reviewer, and ten percent screened by a second reviewer. Full text articles were assessed by one reviewer with queries addressed by a second reviewer, and discrepancies 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 [36]

5.1.2.1 Inclusion criteria

Population

Adults at risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146 CG146[8] (section 3.4.3).

Interventions

Four interventions will be considered within this assessment: DEN RLX, ROMO and TPTD. The interventions were assessed in accordance with their licensed indications, at licensed dose. 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 summary of product characteristics as provided by the Company Submission).[37]

Comparators

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

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

Where studies planned treatment sequences or open-label extensions with participants in allocated randomised groups, these were included.

Outcomes

The main outcome sought was osteoporotic fragility fracture. Vertebral fractures, where data allowed, were considered separately for clinical/symptomatic fractures and morphometric/radiographic fractures. Radiographic fractures defined according to Genant were those resulting in a 20% or greater reduction in vertebral height, however if the study did not specify that the Genant[38] definition was used, morphometric/radiographic fracture data were still included. Non-vertebral fracture data were sought, and where reported, hip fracture, wrist fracture, and proximal humerus fractures were considered separately. Although planned, data on concordance were not extracted due to time constraints.

In addition, BMD at the FN, assessed by dual energy X-ray absorptiometry (DXA), data were sought. Only FN BMD data were included in the NMA, however where trials did not report this data, BMD measured at the lumbar spine was tabulated.

The following outcome measures were also included: mortality (overall or following fracture); adverse effects of treatment; health-related quality of life.

Study design

Randomised controlled trials (RCTs) were included. Studies published as abstracts or conference presentations were only included 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 clinical guidelines were used only as potential sources of additional RCTs of efficacy evidence.

5.1.2.2 Exclusion criteria

Studies in patients with normal or unspecified BMD.

Studies in patients with other indications for the same drugs. Cancer populations at risk of osteoporosis which are covered by NICE guideline [NG101] Early and locally advanced breast cancer: diagnosis and management, and NICE guideline [CG175] Prostate cancer: diagnosis and management.

Studies where interventions are administered not in accordance with licensed indications.

Studies where interventions are co-administered with any other therapy with the potential to augment bone, unless concomitant treatments are specified in the summary of product characteristics.

Studies which were considered methodologically unsound in terms of study design or the method used to assess outcomes.

Reports published as abstracts or conference presentations only, where insufficient details are reported to allow an assessment of study quality or results.

Studies which were only published in languages other than English.

Studies based on animal models, preclinical and biological studies.

Narrative reviews, editorials, opinions.

5.1.3 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. Study arms where 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.[35]

Methodological quality of RCTs identified for inclusion were assessed using the Cochrane Collaboration risk of bias assessment criteria.[39] Risk of bias plots were produced using Cochrane Review Manager (RevMan) software (version 5.3).[40]

The revised tool to assess the risk of bias in randomized trials (RoB 2.0) published in September 2018 (https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2 [Accessed 21 November 2018]), was not applied as this review commenced prior to the publication of the revised RoB version.

RCTs were classified as being at high risk of attrition bias where drop-out in any treatment arm was ≥10%.[41]

5.1.4 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. Where these were not reported by included studies, these were estimated using Cochrane Review Manager (RevMan) software (version 5.3),[40] as either relative risk (RR) or mean difference (MD).

Data were pooled across studies in network meta-analyses, the methods of which are described in Section 5.3.1.

5.2 Results

5.2.1 Quantity and quality of research available

5.2.1.1 Quantity of research available

Study selection is shown in Figure 1. As a result of the searches described in Section 3.1, a total of 7,898 citations were identified for the clinical review. At abstract sift, 7,792 were excluded. At full text sift 34 records were excluded. These are listed in Appendix 2 with reasons for exclusion. Fifty-two RCTs of the interventions of interest were included (published in 69 references).

In addition, three bisphosphonate RCTs were identified and added to the 48 RCTs of bisphosphonates identified from TA464[35] (see Appendix 3).

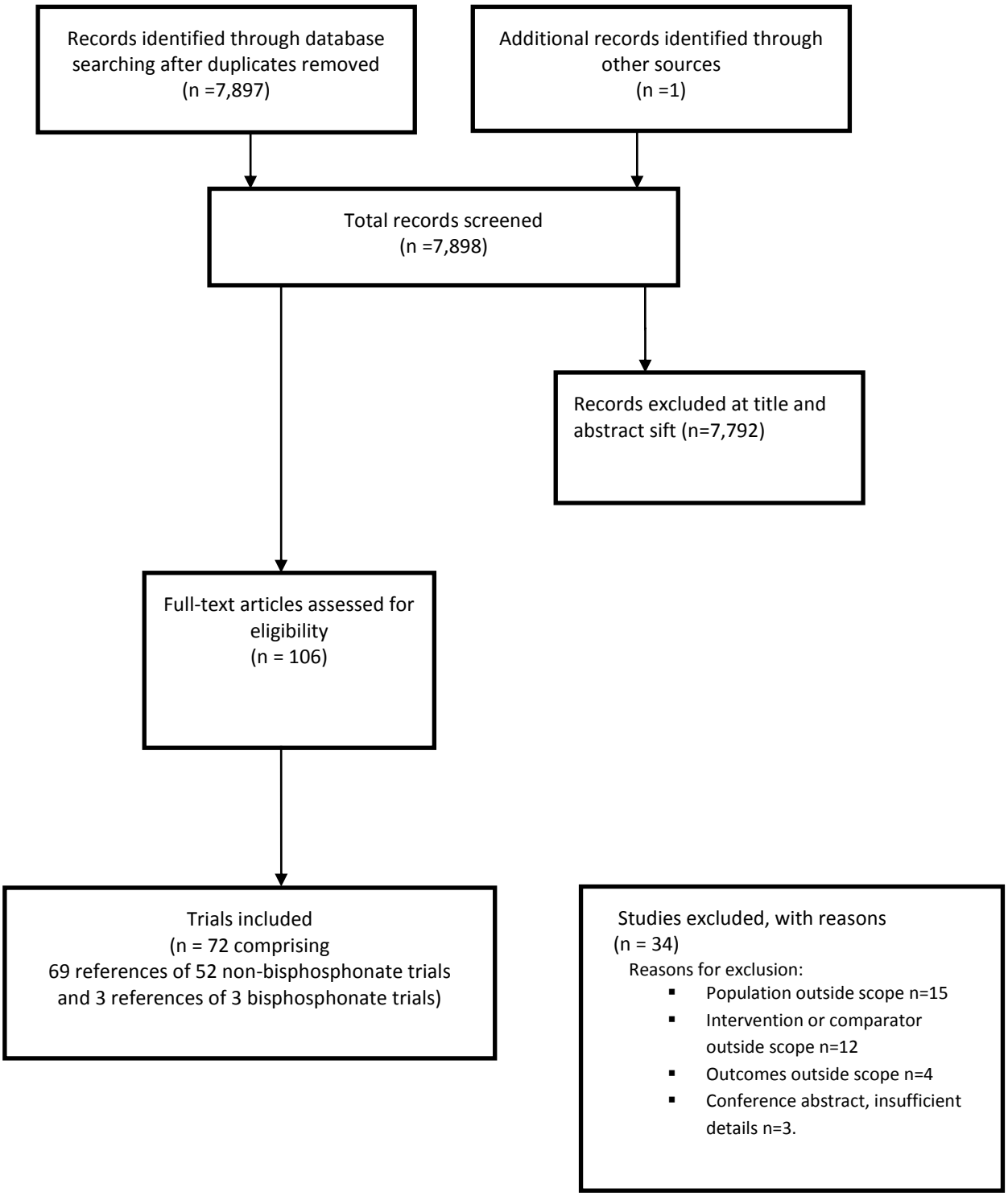

Figure 1: Flow diagram of study selection based

Randomised controlled trials included in the systematic review of clinical effectiveness and NMAs of fracture and FN BMD are presented in
Table **3**; only data from licensed dose arms are shown.

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

Table 3: Trials included in the review

Trial	**Intervention and comparators**	**Population**	**Included in vertebral fracture rate NMA?**	**Included in FN BMD NMA?**
DEN versus PBO				
FREEDOM[42]	DEN PBO	Postmenopausal Women with osteoporosis	Yes	Yes
ADAMO Orwoll 2012[43]	DEN PBO	Men with osteoporosis	Yes	Yes
DIRECT[44]	DEN followed by DEN PBO followed by DEN	Postmenopausal women and men with osteoporosis	Yes	Yes
Nakamura 2012[45]	DEN PBO	Postmenopausal Women with osteoporosis	Yes	
Koh 2016[46]	DEN PBO	Postmenopausal Women with osteoporosis		Yes
RLX versus PBO				
Adami 2008[47]	RLX PBO	Postmenopausal Women with osteoporosis		Yes
Morii *et al*	RLX	Postmenopausal	Yes	

2003[48]	PBO	Women with osteoporosis		
Liu 2004[49]	RLX PBO	Postmenopausal Women with osteoporosis	Yes	Yes
Gorai *et al* 2012[50]	RLX RLX plus alfacalcidol Alfacalcidol	Postmenopausal Women with osteoporosis		No, lumbar spine (LS) BMD
Silverman 2008[51]	RLX PBO	Postmenopausal Women with osteoporosis	Yes	Yes
MORE[52]	RLX PBO	Postmenopausal Women with osteoporosis	Yes	Yes
Lufkin 1998[53]	RLX Control	Postmenopausal Women with osteoporosis	Yes	
Mok, 2011[54]	RLX PBO	Postmenopausal Women with osteoporosis	Yes	Yes
ROMO versus PBO				
FRAME[55]	ROMO followed by DEN PBO followed by DEN	Postmenopausal Women with osteoporosis	Yes	Yes
Ishibashi 2017[56]	ROMO PBO	Postmenopausal Women with osteoporosis		Yes
BRIDGE[57]	ROMO	Men with osteoporosis		Yes

	PBO			
TPTD versus PBO				
Orwoll 2003[58]	TPTD PBO	Men with osteoporosis		Yes
Miyauchi *et al.* 2010[59]	TPTD PBO	Women and men with osteoporosis	Yes	Yes
Miyauchi *et al.* 2008[60]	TPTD PBO	Women with osteoporosis		Yes
ACTIVE[61]	TPTD PBO	Postmenopausal Women with osteoporosis	Yes	Yes
Leder 2015[62]	TPTD PBO	Postmenopausal Women with osteoporosis		Yes
Fracture prevention trial (FPT)[63]	TPTD PBO	Postmenopausal women with prior fractures	Yes	Yes
Sethi 2008[64]	TPTD Control	Postmenopausal Women with osteoporosis		Yes
Head-to-head non-bisphosphonates				
DATA[65] DATA-SWITCH[66]	DEN (then switch to TPTD) TPTD(then switch to DEN) Combined DEN and TPTD (then switch to DEN)	Postmenopausal Women with osteoporosis		Yes

EUROFORS[67]	TPTD followed by RLX TPTD	Postmenopausal Women with osteoporosis	Yes	Yes
STRUCTURE[68]	ROMO TPTD	Postmenopausal Women with osteoporosis	Yes	Yes
McClung 2014[69] [also bisphosphonate comparator]	ROMO TPTD ALN PBO	Postmenopausal Women with osteoporosis		Yes
DEN versus Bisphosphonates				
DECIDE[70]	DEN plus PBO ALN plus PBO	Postmenopausal Women with osteoporosis		Yes
STAND[71]	DEN ALN [after ALN]	Postmenopausal Women with osteoporosis		Yes
DAPS[72]	DEN followed by ALN ALN followed by DEN	Postmenopausal Women with osteoporosis		Yes
AMG 162 Bone Loss study[73]	DEN ALN PBO	Postmenopausal Women with osteoporosis		Yes
Recknor *et al.* 2013[74]	DEN	Postmenopausal Women with		Yes

	IBN (oral)	osteoporosis		
Saag 2018[75]	DEN RIS	Glucocorticoid-induced Osteoporosis (men and women)		Yes
Miller *et al.* 2016[76]	DEN plus PBO Zoledronic acid plus PBO	Postmenopausal Women with osteoporosis		Yes
RLX versus Bisphosphonates				
EFFECT (International)[77]	RLX plus PBO ALN plus PBO	Postmenopausal Women with osteoporosis	Yes	Yes
EFFECT (US)[78]	RLX plus PBO ALN plus PBO	Postmenopausal Women with osteoporosis		Yes
Johnell et al. 2002[79]	RLX ALN	Postmenopausal Women with osteoporosis		Yes
Muscoso 2004[80]	RLX ALN RIS	Postmenopausal Women with osteoporosis	Yes	
EVA[81]	RLX ALN	Postmenopausal Women with osteoporosis	Yes	Yes
Sanad 2011[82]	RLX ALN	Postmenopausal Women with osteoporosis		Yes

Michalska 2006[83]	RLX ALN PBO	Postmenopausal Women with osteoporosis		Yes
ROMO versus Bisphosphonates				
ARCH[84]	ROMO followed by ALN ALN	Postmenopausal Women with osteoporosis	Yes	Yes
TPTD versus Bisphosphonates				
FACT[85]	TPTD plus PBO ALN plus PBO	Postmenopausal Women with osteoporosis		Yes
Saag 2009[86]	TPTD ALN	Glucocorticoid-induced Osteoporosis (men and women)	Yes	Yes
Panico 2011[87]	TPTD ALN	Postmenopausal Women with osteoporosis	Yes	Yes
EuroGIOPs[88]	TPTD RIS	Glucocorticoid-induced Osteoporosis (men)		Yes
Anastasilakis 2008[89]	TPTD RIS	Postmenopausal Women with osteoporosis		No, LS BMD
Walker 2013[90]	TPTD RIS	Glucocorticoid-induced Osteoporosis (men)	Yes	Yes
VERO[91]	TPTD plus	Postmenopausal	Yes	

	PBO RIS plus PBO	Women with osteoporosis		
Hadji 2012[92]	TPTD plus PBO RIS plus PBO	Postmenopausal Women with osteoporosis	Yes	Yes
MOVE[93]	TPTD plus PBO RIS plus PBO	Post-surgery for osteoporotic hip fracture	Yes	Yes
Cosman 2011[94]	TPTD ZOL	Postmenopausal Women with osteoporosis	Yes	Yes

Listed treatment arms were all at licensed dose

Trial characteristics are shown in Appendix 4. All 52 included trials were RCTs, with the majority being multi-centre studies. All trials providing data for the NMAs had concomitant treatment with calcium and vitamin D. The most common primary outcome measure was percent 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-score and percent of participants with fractures at baseline. Within RCTs, population baseline characteristics were balanced between treatment arms.

5.2.1.2 Quality of research available

Results of the risk of bias assessment

Non-bisphosphonates vs. placebo

A summary of the Cochrane Risk of Bias assessment across the placebo-controlled non-bisphosphonate studies is presented in Figure 2.

DEN vs. placebo

None of the five studies comparing DEN to placebo[42-46] reported how the random sequence was generated, and only two reported that allocation to treatment groups was concealed.[42, 43]

Four of the five studies reported that participants and personnel were blinded to treatment allocation.[42-44, 46] Four studies reported that fracture assessment was blinded to treatment allocation.[43-46] However, only one reported that BMD assessment was blinded to treatment allocation.[43]

One study was considered at high risk of attrition bias for both fracture and BMD outcomes as ≥10% in both treatment groups did not complete the study.[42]

Only one study did not report the location of a study protocol to check reported outcomes against for selective reporting.[45] The remaining four studies of DEN vs. placebo were all considered at low risk of bias for this domain.[42-44, 46]

RLX vs. placebo

Of the eight studies comparing RLX with placebo,[47-49, 51-54, 95] only one reported how the random sequence was generated (computer generated), and was considered at low risk of bias for this domain.[51] Only three of the eight studies reported that allocation to treatment groups was concealed.[48, 51, 52]

Six of the studies reported that participants and personnel were blinded to treatment allocation.[48, 49, 51-54] One study was considered at high-risk of bias for this domain as it was described as open-label.[95]

Four of the studies comparing RLX to placebo reported that fracture assessment was blinded to treatment allocation,[48, 51, 52, 54] and three reported that BMD assessment was blinded to treatment allocation.[47, 48, 54] One study reported that BMD assessment was not blinded to treatment allocation and was therefore considered high risk for this domain.[95]

Four studies were considered at high risk of attrition bias for fracture and/or BMD outcomes as ≥10% participants did not complete the study.[48, 52, 54, 95]

Only three studies reported the location of a protocol to check outcomes against and were considered at low-risk of bias as all outcomes in the protocol had been reported.[51, 53, 54]

In one study not reporting a protocol, BMD was only reported for a subset of participants and adverse events were not reported by the different RLX doses.[52] This study was considered at high-risk of bias for selective reporting.

ROMO vs. placebo

All three of the studies comparing ROMO with placebo reported that allocation to treatment groups was concealed,[55-57] and two reported how the random sequence was generated (all adequate methods).[56, 57] All three reported that participants and personnel were blinded to treatment allocation.

All three studies assessed BMD,[55-57] but none reported if the assessment was blind or not. Only one of the two studies assessing fracture, reported that this outcome was blinded to treatment allocation.[55]

One study was considered to be at high risk of attrition bias (≥10% participants did not complete the study) for both BMD and fracture outcomes,[55] and one study was considered at low-risk of bias for BMD and fracture outcomes,[56] as was one study that only assessed BMD.[57]

One of the studies comparing ROMO with placebo did not report the location of a protocol and was therefore judged to have an unclear-risk of bias for selective reporting.[55]

All three studies reported the location of the protocol and all items in the protocol were reported in all three study publications.[55-57]

TPTD vs. placebo

Across the seven studies in TPTD vs. placebo,[58-60, 62-64, 96] four reported a method for the random sequence generation (all adequate)[58-60, 62] and three reported that allocation to treatment groups was concealed.[59, 60, 62]

Three of the studies were described as open-label, and were considered at high-risk of bias for blinding of participants and study personnel.[64, 66, 96] The other four trials were considered at low-risk of bias for this domain,[58-60, 63]

Where fractures and/or BMD was an outcome, only two of the studies reported that fracture assessment was blind,[63, 96] and only one reported that BMD assessment was blinded to treatment

allocation.[63] One study that reported that BMD assessment was unblinded (fractures not an outcome), was considered at high-risk of bias for this domain.[64]

Attrition bias of ≥10% was evident for reporting of fracture outcomes in three studies,[58, 63, 96] and evident for five studies reporting BMD outcomes, all of which were judged at high risk of attrition bias.[58, 60, 63, 64, 66]

Three studies reporting the location of a protocol were judged at low risk of selective reporting bias.[59, 64, 96] One study was judged at high risk of selective reporting bias[63] 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.[97]

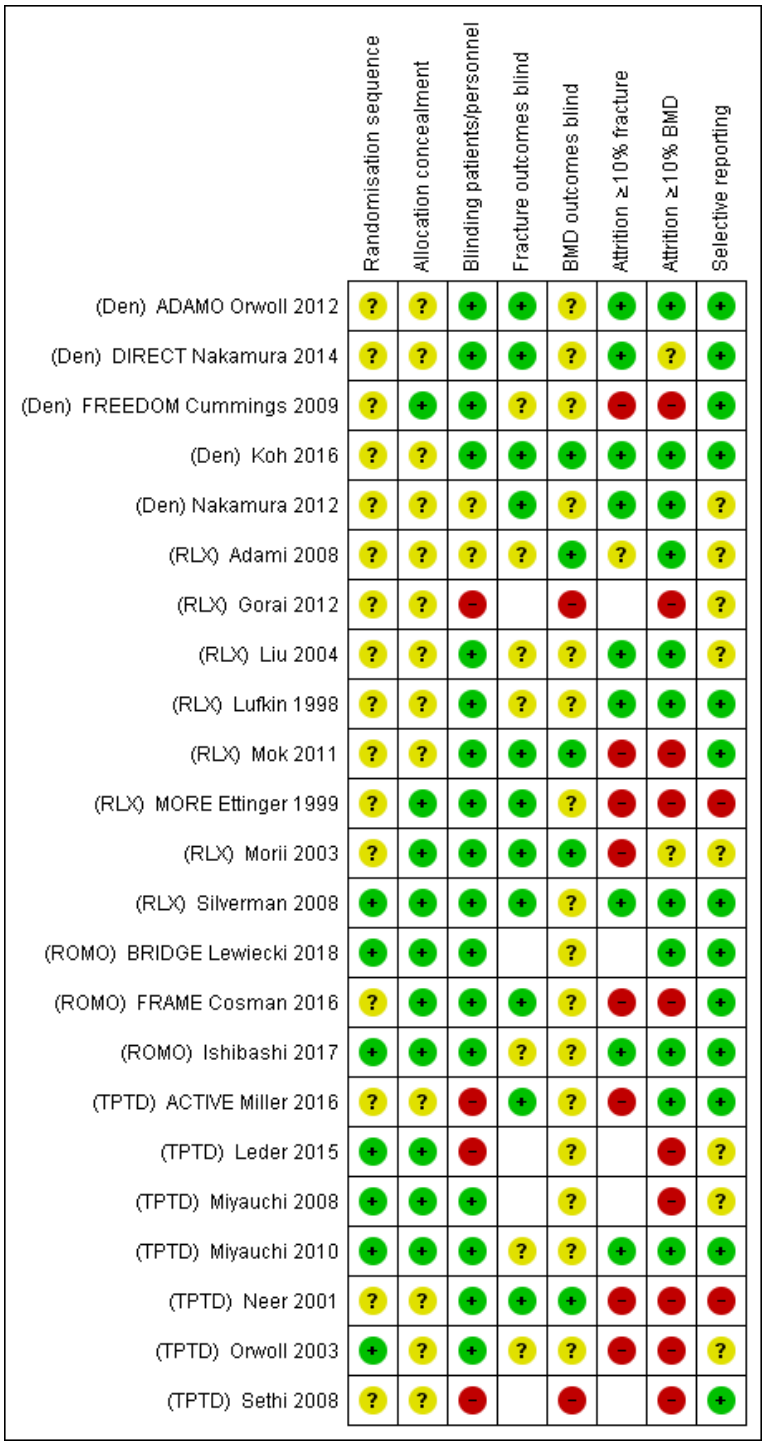

Figure 2: Cochrane Risk of Bias summary across placebo-controlled non-bisphosphonate studies

?, unclear-risk of bias; +, low-risk of bias; –, high-risk of bias; blank cells, not a study outcome

DEN, Denosumab, RLX, Raloxifene; ROMO, Romosozumab; TPTD, Teriparatide; ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ADAMO, DEN Versus Placebo in Males With Osteoporosis; BRIDGE, Phase 3 randomized placeBo-contRolled double-blind study evaluating the efficacy anD safety of ROMO in treatinG mEn with osteoporosis; DIRECT, DEN fracture Intervention RandomizEd placebo Controlled Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture Reduction Evaluation of DEN in Osteoporosis; MORE, European Study of Forsteo

Non-bisphosphonates head-to-head

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,[65, 67-69] three reported the method for the random sequence generation,[65, 67, 68] and three reported that allocation was concealed.[67-69]

All four studies were reported as open-label and considered at high-risk of bias for blinding of participants and personnel.

Where fractures were an outcome, two studies reported that fracture assessment was not blinded to treatment allocation.[67, 68] All four studies assessed BMD and three were considered at low-risk of bias for blinding of BMD assessment.[65, 67, 68]

Two of the three studies assessing fracture were considered at low risk of attrition bias (<10% withdrawing/not included in the analysis) for this domain.[65, 67, 68] All four studies reported BMD outcomes of which one was considered at high risk of attrition bias (≥10%) for this domain.[69] All other studies were considered at low risk.

Three studies reporting the location of a protocol were judged at low risk of selective reporting bias.[65, 68, 69]

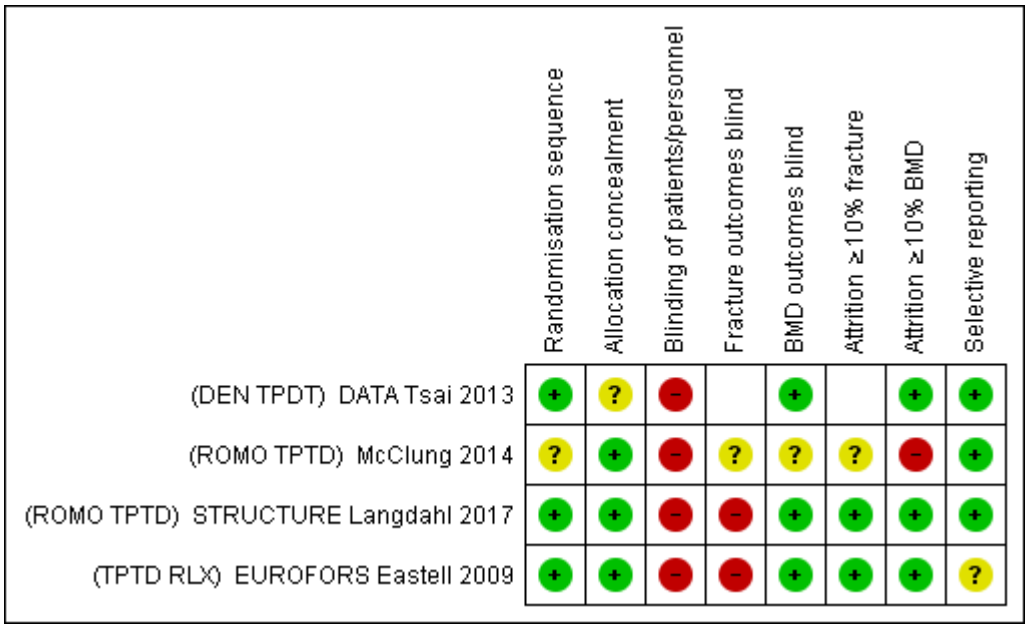

Figure 3: Cochrane Risk of Bias summary across non-bisphosphonate head-to-head studies

?, unclear-risk of bias; +, low-risk of bias; – high-risk of bias; blank cells, not a study outcome

DEN, Denosumab, RLX, Raloxifene; ROMO, Romosozumab; TPTD, Teriparatide; DATA, DEN and TPTD Administration; DIRECT, DEN fracture Intervention RandomizEd placebo Controlled Trial EUROFORS, European Study of Forsteo; EVA, Evista ALN Comparison trial; STRUCTURE, Study to Evaluate the Effect of Treatment With ROMO or TPTD in Postmenopausal Women

Non-bisphosphonates vs. bisphosphonates

The summary of the Cochrane Risk of Bias assessment across the non-bisphosphonate vs. non-bisphosphonate studies is presented in Figure 4.

DEN vs. bisphosphonates

Of the seven studies comparing DEN to a bisphosphonate,[70-76] only one reported the method for the random sequence generation,[72] and only three reported the method of treatment allocation concealment.[70, 74, 75]

Three studies comparing DEN to a bisphosphonate were reported as open-label and were considered at high-risk of bias for blinding of participants and personnel.[72-74]

All seven studies assessed BMD as an outcome, but only one reported that the assessment was blinded to treatment allocation.[76] The remaining six studies were considered at unclear-risk of bias for this domain.[70-75] Four of these studies were also considered at high risk of attrition bias (≥10%) for BMD outcomes.[72-75]

The six studies that assessed fracture as an outcome were all considered at unclear-risk of bias for blinded assessment.[71-76] All six studies were also considered at unclear risk of attrition bias (≥10%) for BMD outcomes.

Only one of the studies comparing DEN to a bisphosphonate reported the location of a protocol to check and was considered at low-risk of bias for selective reporting.[74]

For one study,[70] health related quality of life was reported as an outcome for the study in the manufacturer's company submission.[98] However, this outcome was not reported in the published study which was considered at high risk of selective reporting.[70]

RLX vs. bisphosphonates

Of the seven studies comparing RLX to a bisphosphonate,[77-83] four reported the method for the random sequence generation (all adequate).[77-79, 81] However, only three reported a method of treatment allocation concealment.[81]

Two of the studies comparing RLX to a bisphosphonate reported that participants and personnel were blinded to treatment allocation (low risk)[77, 81] and one study reported an open-label design (high risk).[83] All other studies comparing RLX to a bisphosphonate were considered at unclear-risk of bias for blinding of participants and study personnel.[78-80, 82]

Across studies comparing RLX to a bisphosphonate that assessed fracture and/or BMD, only one study reported that the fracture assessment was blinded to treatment allocation,[81] and only two reported that fracture assessment was blinded to treatment allocation.[77, 78]

One study comparing RLX to a bisphosphonate that reported fracture outcomes was considered at high risk of attrition bias (≥10%),[81] and four studies assessing BMD were considered at high risk of attrition bias (≥10%).[77-79, 81]

No study comparing RLX to a bisphosphonate reported the location of a study protocol. In one of the studies, adverse events were not fully reported in the study publication,[79] and one study reported that fractures was an assessed outcome, but did not report any results in the study publication.[82] These two studies were considered at high risk of selective reporting.

ROMO vs. bisphosphonates

In the one study that compared ROMO to a bisphosphonate,[84] 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 at 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 at high risk of attrition bias (≥10%). All outcomes in the study protocol were reported.

TPTD vs. bisphosphonates

Across the 11 studies that compared TPTD to a bisphosphonate,[85-90, 92-94, 99, 100] four reported an adequate method of random sequence generation and only one study reported an adequate method of treatment allocation concealment.[100] One study reported that unblinded pharmacists distributed the study drug, and was considered at high-risk of bias for allocation concealment.[94]

Three of the studies comparing TPTD to a bisphosphonate reported that participants and personnel were blinded to treatment allocation (low risk)[86, 99, 100] and five studies reported an open-label design (high risk).[87-89, 93, 94] The other three studies comparing TPTD to a bisphosphonate were considered at unclear-risk of bias for blinding of participants and study personnel.[85, 90, 92]

Four of the studies comparing TPTD to a bisphosphonate reported that fracture assessment was blinded to treatment allocation,[86, 90, 92, 100] and three reported that BMD assessment was blinded to treatment allocation.[88, 90, 93]

Five studies comparing TPTD to a bisphosphonate that reported fracture outcomes were considered at high risk of attrition bias (≥10%),[86, 92, 93, 99, 100] and five studies assessing BMD were considered at high risk of attrition bias (≥10%).[85, 86, 88, 92, 93]

Six studies comparing TPTD to a bisphosphonate that reported that location of a protocol to check were considered at low risk of selective reporting bias.[85, 86, 88, 93, 99, 100] One study reporting an intention-to-treat and per-protocol analysis stated in the study publication that the data from the per-protocol analysis were not reported.[90] This study was considered at high risk of selective reporting.[90]

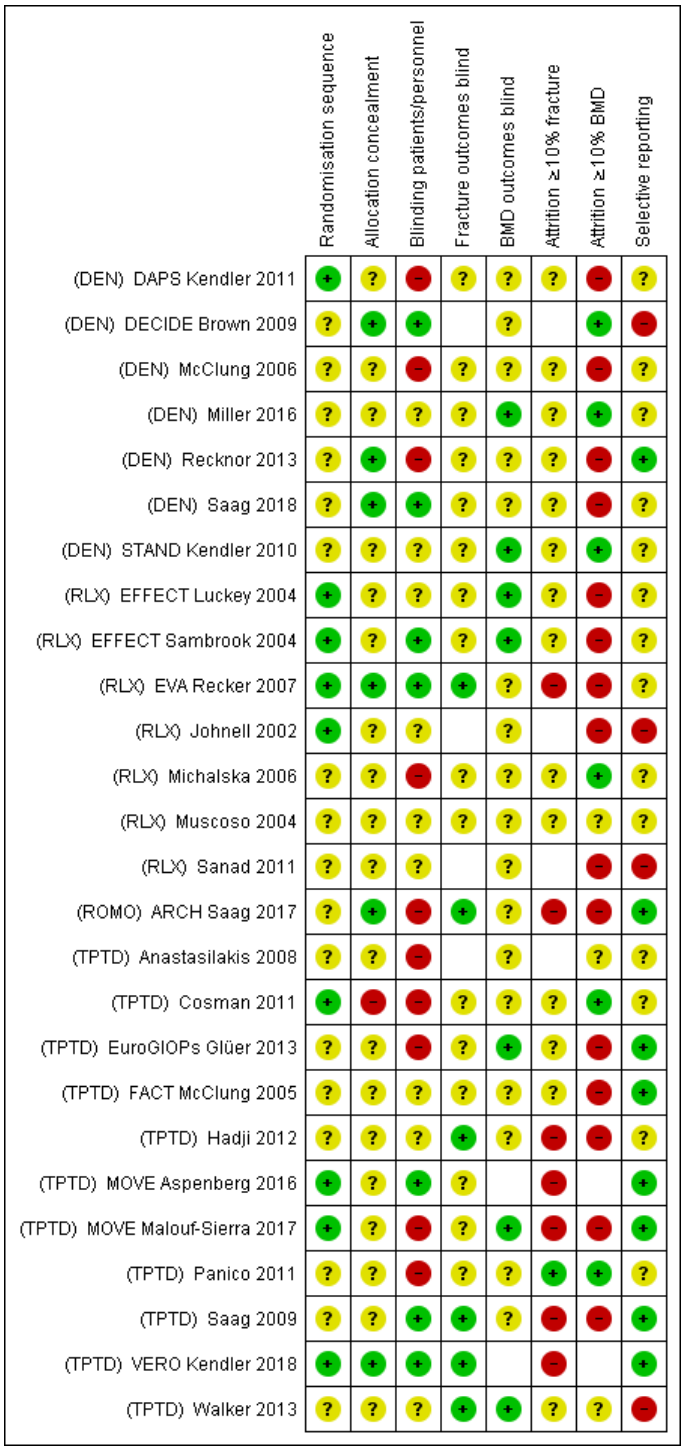

Figure 4: Cochrane Risk of Bias summary across non-bisphosphonate vs. bisphosphonate studies

?, unclear-risk of bias; +, low-risk of bias; -, high-risk of bias; blank cells, not a study outcome

DEN, Denosumab, RLX, Raloxifene; ROMO, Romosozumab; TPTD, Teriparatide; DATA, DEN and ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; DAPS, DEN Adherence Preference Satisfaction; DECIDE, Determining Efficacy: Comparison of Initiating DEN versus ALN; EFFECT, EFficacy of FOSAMAX versus EVISTA Comparison Trial; EuroGIOPS, acronym meaning not reported; EVA, Evista ALN Comparison trial; FACT, Forteo ALN Comparator Trial; MOVE, acronym meaning not reported; STAND, Study of Transitioning from ALN to DEN; VERO, VERtebral fracture treatment comparisons in Osteoporotic women

5.2.2 Assessment of effectiveness

5.2.2.1 Fractures

Here we summarise the fracture results for the individual non-bisphosphonate RCTs included in the review. The results of the network meta-analyses which include both the bisphosphonate and non-bisphosphonate studies are summarised in Section 5.3.3.

5.2.2.1.1 Vertebral Fractures

Results for vertebral fractures reported by the included studies are presented in Table 17 for the non-bisphosphonate treatments compared to placebo, non-bisphosphonate treatments compared head-to-head, and non-bisphosphonate treatments compared to bisphosphonates. Fracture data used in the NMAs are shown in Appendix 9.1.

Clinical vertebral fractures –efficacy

Non-bisphosphonates vs. placebo – clinical vertebral fractures

One study comparing DEN to placebo reported a statistically significant between-group difference in clinical vertebral fractures at 36 months in favour of DEN in postmenopausal women with osteoporosis ($p<0.001$).[42]

Three of the studies comparing RLX to placebo in postmenopausal women with osteoporosis reported on clinical vertebral fractures.[49, 51, 101] One of these reported a statistically significant between-group difference in favour of RLX at 12 months in postmenopausal women with osteoporosis ($p<0.001$).[101] In the other two studies comparing RLX to placebo the between-group difference was not statistically significant (RLX 0% vs. PBO 4.90%,$p>0.05$;[49] RLX 2.36% vs. PBO 4.10%, $p=0.89$[51]).

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

Only one study comparing TPTD prescribed open-label to placebo reported on clinical vertebral fractures at 18 months in postmenopausal women with osteoporosis.[96] The estimated between-group difference was not statistically significant (TPTD 0.40% vs. PBO 1.10%, $p=0.10$).

Non-bisphosphonates compared head-to-head – clinical vertebral fractures

One study comparing TPTD to 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).[67]

Non-bisphosphonates vs. bisphosphonates – clinical vertebral fractures

The estimated between-group difference in clinical vertebral fractures for one study comparing DEN to RIS in women and men receiving glucocorticoids was not statistically significant at 12 months (DEN 3.00% vs. RIS 4.00%, p=0.34).[75]

The estimated between-group difference in clinical vertebral fractures for one study comparing RLX to ALN in postmenopausal women with osteoporosis was not statistically significant after approximately 45 weeks of treatment (study stopped early due to difficulty in finding treatment-naïve women) (ALN 3.14% vs. RLX 1.93%, p=0.20).[81]

The reported between-group difference in clinical vertebral fractures for one study comparing ROMO to ALN in postmenopausal women with osteoporosis was not statistically significant at 12 months (ALN 0.9% vs. ROMO 0.50%, p=0.14).[84]

The reported between-group difference in clinical vertebral fractures for one study comparing TPTD to ALN in women and men receiving glucocorticoids was not statistically significant at 18 months (p=0.07).[102] However, the between-group difference at 36 months was statistically significant in favour of TPTD (p=0.037).[102]

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.[38]

Non-bisphosphonates vs. placebo – new morphometric vertebral fractures

One study comparing DEN to 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).[42] The estimated between-group differences for this study over zero to 12 months, 12 to 24 months, and 24 to 36 months, were also statistically significant in favour of DEN (p<0.05).[103] However, the estimated between-group difference at the end of the seven-year open-label extension to this study following treatment switching (all participants received DEN) was not statistically significant (PBO switched to DEN 7.30% vs. continued DEN 7.04%, p=0.76).[104]

In a single study comparing DEN to 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).[44] 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).[105] The estimated between-

group difference for the 12-month open-label extension alone was p=0.05 (PBO switched to DEN 2.00% vs. continued DEN 0.25%).[105]

Across two studies comparing RLX to 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).[51, 52] However, the between-group difference was not statistically significant in two studies in postmenopausal women with osteoporosis that reported this outcome at 12 months (PBO 2.30% vs. RLX 0%, estimated p=0.33[48] and PBO 40.00% vs. RLX 48.84%, estimated p=0.41[53]), and one study in postmenopausal women on long-term glucocorticoids that reported this outcome at 12 months (PBO 5.36% vs. RLX 0%, reported p=0.24).[54]

In the one study that compared ROMO to 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).[55] Following treatment switching to DEN (all participants), [redacted] between-group differences in new vertebral fracture [redacted] group were reported at 36 months [redacted][37]

In one study comparing TPTD to 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).[96] 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 (PBO 5.97% vs. TPTD 3.68%, p=0.46).[59]

Non-bisphosphonates compared head-to-head – new morphometric vertebral fractures

New morphometric vertebral fracture was not an outcome in the study comparing TPTD and RLX in postmenopausal women with osteoporosis.[67]

Non-bisphosphonates vs. bisphosphonates – new morphometric vertebral fractures

The estimated between-group difference in new morphometric vertebral fractures in one study comparing RLX to ALN in postmenopausal women with osteoporosis after approximately 45 weeks of treatment (study stopped early due to difficulty in finding treatment-naïve women) was not statistically significant (ALN 3.14% vs. RLX 1.93%, p=0.39).[81]

The reported between-group difference between new morphometric vertebral fractures for one study comparing ROMO to ALN in postmenopausal women with osteoporosis was statistically significant at 12 months (mITT, p=0.003; LOCF, p=0.008) and at 24 months following treatment switching to ALN, in favour of the ROMO switching to ALN group (mITT and LOCF, p<0.001).[84]

The reported between-group difference in new morphometric vertebral fractures for one study comparing TPTD to 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.[102] 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).[106] One open-label study in 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).[87]

Across studies comparing TPTD to 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),[90] or at six months in postmenopausal women with osteoporosis (RIS 5.10% vs. TPTD, reported p=0.6).[92] 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),[92] and at 24 months (p<0.0001).[100]

Vertebral fractures assessed as safety or where the efficacy assessment method was not reported

One study comparing DEN to 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 (PBO 0.83% vs. DEN 0%, p=0.50).[43]

One study comparing RLX to ALN in postmenopausal women with osteoporosis reported vertebral fractures as a safety outcome, but did not report the assessment method.[77] Zero events were reported in both treatment groups in this study.[77] One study comparing RLX, ALN and in postmenopausal women with osteoporosis reported vertebral fractures as an efficacy outcome, but did not report the assessment method.[80] Where 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).[80]

In one study comparing TPTD to RIS in women and men with low BMD following hip fracture surgery where clinical vertebral fractures were a safety outcome,[107] zero events were reported in both groups at six months. The between-group difference at 18 months was not statistically significant (RIS 1.00% vs. TPTD 0%, p=1.00).[93]

One study in postmenopausal women with osteoporosis comparing TPTD (plus a placebo for ZOL) to ZOL (without a placebo for TPTD) also reported vertebral fractures as a safety outcome (assessment

method not reported).[94] The estimated between-group difference at 12 months was not statistically significant (TPTD+PBO 0.70% vs. ZOL 3.70%, p=0.14).

Summary – clinical vertebral fractures

There is single study evidence that DEN is statistically more effective than placebo at 36 months reducing clinical vertebral fractures in postmenopausal women with osteoporosis. There is also single study evidence 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 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 single study evidence that there is no statistically significant difference between: DEN and RIS; between RLX and ALN; and between ROMO and ALN, in the reduction of clinical vertebral fractures at up to 12 months in postmenopausal women with osteoporosis.

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

Summary – new morphometric vertebral fractures

There is single study evidence 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 that RLX is statistically more effective than placebo at reducing new morphometric vertebral fractures at 36 months in postmenopausal women with osteoporosis. There is single study evidence 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 single study evidence that TPTD is statistically more effective than placebo at reducing new morphometric vertebral fractures at 18 months in postmenopausal women with osteoporosis.

There is single study evidence that there is no statistically significant difference in new morphometric vertebral fractures between: RLX and ALN at approximately 45 weeks (study stopped early due to difficulty in finding treatment-naïve women) in postmenopausal women with osteoporosis; between TPTD and ALN at 18 months in women with severe osteoporosis receiving treatment for osteoporosis; and between TPTD and RIS at 18 months in men with osteoporosis. However, there is single study evidence that ROMO is significantly more effective than ALN at reducing new

morphometric vertebral fractures at 12 months in postmenopausal women with osteoporosis, 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. There is also evidence from two studies that TPTD is significantly more effective than RIS at reducing new morphometric vertebral fractures at 18 and 24 months in postmenopausal women with osteoporosis.

5.2.2.1.2 Non-Vertebral Fractures

Non-vertebral fracture outcomes were reported in 28 RCTs and are shown in Table 18.Where reported separately, hip, wrist and proximal humerus fracture outcomes, reported in 22 RCTS, are shown in Table 19. These fractures are also counted among the non-vertebral total. Results of the network meta-analyses for these outcomes are shown in 5.3.3. Fracture data used in the NMAs are shown in Appendix 9.1.

Non-bisphosphonates versus placebo

FREEDOM[42] reported a significant (p=0.01) advantage in non-vertebral fractures for DEN (6.1%) over PBO (7.5%) at 36 months for postmenopausal women. FREEDOM also had a lower rate of non-vertebral fractures for DEN (7.3%) than PBO/DEN (9.9%) (significance not reported, estimated in RevMan as p=0.01) 84 months into the open label extension. At 36 months FREEDOM reported a significantly (p=0.04) lower rate of hip fracture for DEN (0.7%) compared with PBO (1.2%) (Table 19). DIRECT,[44] an RCT in postmenopausal women and men, did not find a difference in all non-vertebral fractures at 24 months between DEN and PBO groups (both 4.1%), although there was a trend (P=0.0577) toward fewer major non-vertebral fractures in the DEN (1.6%) than the PBO (3.7%) group. Rates of non-vertebral fractures in the DEN groups at 24 months were similar for the international population of FREEDOM, and Japanese population of DIRECT.[42 44] Following a further year in which all participants received DEN, DIRECT[105] reported non-vertebral fracture rates of 6.7% for PBO/DEN and 5.2% for DEN, with rates of major non-vertebral fractures of 5.4% and 2.0% respectively. At 24 months, DIRECT[44] reported 0% hip fractures for DEN, and 0.4% for PBO.

For the RLX versus PBO RCTs, Morii 2003[48] and Lufkin 1998[53] 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 2008[51] RCT there was no significant difference (estimated in RevMan as p=0.6409) in non-vertebral fractures at 36 months between RLX (6.3%) and PBO (5.7%) groups (Table 18), with rates of hip fracture 0.3% in both groups (Table 19).

FRAME[55] at 12 months reported a non-significant (p=0.096) difference between ROMO 1.6% and PBO 2.1% for non-vertebral fractures. At 24 months, FRAME[55] reported a significant advantage for

ROMO/DEN over PBO/DEN in non-vertebral fractures (2.7% versus 3.6%, p=0.029), with a trend (p=0.059) favouring ROMO/DEN in hip fractures, 0.3% compared with PBO/DEN 0.6%.

Miyauchi 2010,[59] 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 PBO (6.0%) at 12 months. In postmenopausal women, the ACTIVE[96] RCT did not find a significant difference (p=0.22) between TPTD (3.3%) and PBO (4.7%) non-vertebral fractures at 18 months. No hip fractures were reported in the TPTD group, with 0.2% in the PBO group of ACTIVE.[96] The FPT[63] RCT found a significant (p=0.04) advantage for TPTD (6.3%) over PBO (9.7%) in non-vertebral fractures. FPT[63] reported hip fracture rates of 0.4% in the TPTD group and 0.7% in the PBO group. The population in FPT[63] all had vertebral fracture at baseline, in contrast to ACTIVE[96] in which two-thirds had prior fractures at baseline. Whereas FPT was blinded, the TPTD arm in ACTIVE was open-label as the trial was designed compare abaloparatide with PBO.[96 63]

Studies reporting non-vertebral fracture rates as safety data reported, for postmenopausal women, 6 month rates of DEN 1.5% and PBO 1.5%,[46] and 12 month rates of ROMO 3.2% and PBO 1.6%,[56] and in men 12 month rates of DEN 0.8% and PBO 1.7%.[43]

Head-to-head non-bisphosphonates

EUROFORS[67] 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.

STRUCTURE[68] 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.[68]

Non-bisphosphonates versus bisphosphonates

Saag 2018[75] 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 0.3% for both groups.

Muscoso 2004[80] reported rates of non-vertebral fractures of 0% in both RLX and RIS group and 0.2% in the ALN group in both the first and second years of the RCT. The EVA[81] 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. EVA[81] reported hip fracture rates of RLX 0.3% and ALN 0.1%.

ARCH[84] reported a trend (p=0.057) favouring ROMO (3.4%) over ALN (4.6%) for non-vertebral fractures at 12 months, and for major non-vertebral fractures (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) there was a significant (p=0.019) difference (2.9% for ROMO, and 4.3% for ALN). There was no significant (p=0.19) difference in hip fracture rates at 12 months.[84] After a further year in which all participants received ALN, there was a significant (p=0.037) advantage in non-vertebral fractures for ROMO/ALN (8.7%) over ALN (10.6%), as well as for major non-vertebral fractures (p=0.004) and hip fractures (p=0.015).

Saag 2009[102] 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 in postmenopausal women comparing TPTD and RIS found no significant treatment difference for non-vertebral fractures; VERO Kendler 2018[100] at 24 months (TPTD 4.0%, RIS 6.0%, p=0.10) and Hadji 2012[92] at 6 months (TPTD 7.8%, RIS 8.3%, p=0.89). The population in Hadji 2012[92] were selected for having back pain due to vertebral fracture which may explain the higher rates in both groups than in VERO. Rates of hip fractures were TPTD 0.3% and RIS 0.7% for VERO,[100] and TPTD 1.4% and RIS 0.6% for Hadji 2012.[92]

For studies reporting fractures as safety data, non-vertebral fracture rates for postmenopausal women at 12 months were reported as DEN 0.8% and ALN 0.9%,[108] RLX 3.9% and ALN 2.5%,[78] TPTD 5.1%,[94] ZOL 5.8%[94] and for women pre-treated (with ALN) DEN 3.2% and ALN 1.6%.[71] At 24 months non-vertebral fracture rates were RLX 3.0%, ALN 3.0% and PBO 6.0% for women pre-treated (with ALN).[83] Hip fracture rates at 12 months were reported as RLX 0.4% and ALN 0.0%.[77] For men with glucocorticoid induced osteoporosis, non-vertebral fracture rates of TPTD 0.0% and RIS 10.6% (trend p=0.056) were reported at 18 months.[88] In a population following hip surgery, at 18 months follow-up non-vertebral fractures reported were TPTD 4.7% and RIS 9.1%, and hip fracture rates TPTD 1.9% and RIS 6.4%.[93]

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

5.2.2.2 BMD

Here we summarise the BMD results of the individual non-bisphosphonate RCTs included in the review. The results of the network meta-analyses which include both the bisphosphonate and non-bisphosphonate studies are summarised in Section 5.3.3.

Femoral neck BMD

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

Non-bisphosphonates vs. placebo – femoral neck BMD

Three studies comparing DEN to placebo reported a statistically significant between-group difference in femoral neck BMD in favour of DEN: at six months in postmenopausal women with osteoporosis ($p=0.0042$);[46] at 12 months in men with osteoporosis ($p<0.0001$);[43] and at 24 months in women and men with osteoporosis ($p<0.0001$).[44] 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 upon data extracted from graphs.

Statistically significant between-group differences in femoral neck BMD in favour of RLX compared to placebo were evident for two studies in postmenopausal women with osteoporosis, at 36 months ($p<0.00001$[51] and $p<0.001$[52]), and one study at 12 months in postmenopausal women with osteoporosis who were pre-treated with TPTD ($p<0.001$).[47] However, the between-group difference in the open-label extensions to the study in postmenopausal women with osteoporosis pre-treated with TPTD was not statistically significant (Table 20).[47] The estimated between-group difference in one study at 12 months in postmenopausal women with osteoporosis was not statistically significant,[49] nor was the between-group difference in one study at 12 months in postmenopausal women receiving long-term glucocorticoids (data from graph).[54]

Statistically significant between-group differences in femoral neck BMD in favour of ROMO compared to placebo were reported at 12 months for two studies in postmenopausal women with osteoporosis ($p<0.001$[55] and $p<0.00001$[56]), and at 12 months in one study in men with osteoporosis ($p<0.001$).[57] 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 compared to switching from placebo to DEN ($p<0.001$)[55] (Table 20).

Four studies comparing TPTD to placebo reported a statistically significant between-group difference in femoral neck BMD in favour of TPTD at six months in postmenopausal women with osteoporosis ($p<0.01$).[62] Statistically significant between-group difference in favour of TPTD were also reported by one study at 12 months ($p=0.015$),[59] by one study at 18 months ($p<0.0001$),[96] and by one study at 24 months ($p<0.001$).[63] 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 to placebo switching to TPTD at 18 months ($p=0.03$), but not at 24 months (Table 20).[59] The estimated between-

group difference for one study comparing TPTD to placebo at six months in postmenopausal women with osteoporosis was not statistically significant,[60] nor was one study at six months comparing TPTD plus calcium and vitamin D to calcium and vitamin D alone.[64]

Non-bisphosphonates compared head-to-head – femoral neck BMD

One study comparing TPTD to DEN in postmenopausal women with osteoporosis reported no statistically significant between group difference in femoral neck BMD at either 12[65] or at 24 months.[109] However, statistically significant differences were reported in the open-label extension following treatment switching, in favour of the TPTD switching to DEN group, at 24 and 48 months following switching.[66]

A statistically significant between-group difference in femoral neck BMD at 12 months in postmenopausal women with osteoporosis pre-treated with ALN prior to randomisation, was reported by one study comparing TPTD to ROMO, in favour of ROMO ($p<0.0001$).[68]

One study comparing TPTD, RLX, and a non-active control, in postmenopausal women with osteoporosis pre-treated with ALN, only reported on the between group difference in femoral neck BMD for TPTD compared to control, in favour of the non-active treatment ($p<0.05$).[67] No variance estimates were reported by this study. As such, the other between-group comparisons could not be estimated.

The estimated between-group difference in femoral neck BMD for one study at 12 months comparing TPTD to ROMO in postmenopausal women was not statistically significant.[69] In this study, the estimated between-group differences for both non-bisphosphonates compared to placebo were statistically significant in favour of the active treatment (TPTD, $p=0.0007$; ROMO, $p=0.0002$). However, for comparisons ROMO with ALN and for TPTD with ALN were not.

Non-bisphosphonates vs. bisphosphonates – femoral neck BMD

Across two open-label studies comparing DEN to ALN, statistically significant between-group differences in femoral neck BMD in favour of DEN were reported at 12 months in one study in postmenopausal women with osteoporosis ($p=0.0001$),[70] and at 12 months in one study in postmenopausal women with osteoporosis already receiving ALN($p<.0121$).[71] The estimated between-group difference for one study comparing DEN to ALN in postmenopausal women with osteoporosis, which was not powered for femoral neck BMD, was not statistically significant (Table 20).[72]

In one open-label study comparing DEN to 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 ($p<0.001$).[74]

Statistically significant between-group differences in femoral neck BMD in favour of DEN at 12 months were also reported by one study comparing DEN to RIS in women and men with osteoporosis who were continuing or initiating glucocorticoids (continuing, $p=0.004$; initiating, $p=0.020$),[75] and one study comparing DEN to ZOL at 12 months in postmenopausal women with osteoporosis previously treated with bisphosphonates ($p<0.0001$).[76]

Two studies comparing RLX to ALN in postmenopausal women with osteoporosis reported statistically significant between-group differences in femoral neck BMD in favour of RLX at 12 months ($p=0.0001$),[77] and at 24 months ($p=0.002$).[81] However, one study comparing RLX to ALN in postmenopausal women with osteoporosis,[78] and one study comparing RLX to ALN in postmenopausal women with osteoporosis previously treated with bisphosphonates,[83] reported that the between-group difference at 12 months was not statistically significant. In one of these studies, the estimated between-group difference following a 12-month open-label extension to 24 months (data from graph) was statistically significant in favour of ALN ($p=0.03$).[83] One other study comparing RLX to ALN in postmenopausal women with osteoporosis also reported statistically significant between-group difference in favour of ALN at 12 months ($p<0.05$).[79]

One study comparing TPTD to ALN in women and men with osteoporosis receiving glucocorticoids, reported a statistically significant between-group difference in femoral neck BMD at 36 months ($p<0.001$).[102] The between-group difference reported by one study comparing TPTD to ALN at 18 months in postmenopausal women with osteoporosis was $p=0.05$.[85]

Across three studies comparing TPTD to 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 ($p=0.026$);[88] in postmenopausal women with osteoporosis ($p=0.02$);[92] and in women and men with low BMD following hip fracture surgery ($p=0.003$).[93] However, one of these studies reported an imbalance in femoral neck BMD across study groups at baseline.[92] One study comparing TPTD to RIS in men with osteoporosis reported that the between-group difference at 18 months was not statistically significant.[90]

One study comparing TPTD (plus a placebo for ZOL) to 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 ($p<0.05$).[94]

Summary – femoral neck BMD

There is single study evidence that DEN is statistically more effective than placebo at increasing femoral neck BMD at six months in postmenopausal women with osteoporosis, at 12 months in men with osteoporosis, and at 24 months in women and men with osteoporosis.

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

There is single study evidence that ROMO is statistically more effective than placebo at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis (two studies) and at 12 months in men with osteoporosis.

The evidence for TPTD in increasing femoral neck BMD compared to placebo is mixed. There is single study evidence that TPTD is statistically more effective than placebo at six months, 12 months and 18 months, in postmenopausal women with osteoporosis. However, there is single study evidence that the between-group difference in TPTD compared to placebo, or TPTD plus calcium and vitamin D compared to calcium or vitamin D alone, is not statistically different at six months in postmenopausal women with osteoporosis.

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

There is single study evidence that ROMO is statistically more effective than TPTD at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis pre-treated with ALN.

There is single study evidence that DEN is statistically more effective than ALN at increasing femoral neck BMD at 12 months in postmenopausal women with osteoporosis and at 12 months in postmenopausal women with osteoporosis already receiving ALN. There is also single study evidence that DEN is statistically more effective than oral IBN at 12 months in postmenopausal women with

osteoporosis, that DEN is statistically more effective than RIS at 12 months in women and men with osteoporosis continuing or initiating glucocorticoids, and that DEN is statistically more effective than ZOL at 12 months in postmenopausal women with osteoporosis previously treated with bisphosphonates.

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

There is single study evidence 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).

The evidence for TPTD in increasing femoral neck BMD compared to placebo is mixed. 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 single study evidence 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 single study evidence that that the between-group difference in TPTD and RIS is not statistically different at 18 months in men with osteoporosis.

There is single study evidence 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.

Lumbar Spine BMD

Six RCTs did not report FN BMD but did report lumbar spine (LS) BMD (Appendix 5 Table 23). One RCT reported a significant increase in lumbar spine (LS) BMD for DEN versus placebo.[45] A placebo controlled trial reported a significant increase in LS BMD for RLX,[48] a small RCT reported an advantage for RLX plus Alfacalcidol (n=31) versus alfacalcidol alone (n=34),[50] whereas another small trial found no significant difference for RLX (n=48) versus a no active treatment control (n=48).[53]

One RCT of RLX versus bisphosphonates reported that ALN and RIS had a higher percentage increase in LS BMD at 24 months than RLX (estimated in RevMan p<0.001).[80] One small RCT did not find a significant difference between TPTD (n=22) and RIS (n=22) in the improvement of LS BMD.[89]

5.2.2.3 Adverse events

Adverse events - mortality

Mortality across the included studies is presented in Table 21for the non-bisphosphonate treatments compared to placebo, non-bisphosphonate treatments compared head-to-head and non-bisphosphonate treatments compared to 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 vs. placebo -mortality

Across the studies comparing DEN to placebo, six reported on mortality;[42-44, 46, 105, 110] across studies comparing RLX to placebo, two reported on mortality;[49, 51] and across studies comparing ROMO to placebo, three reported on mortality.[55, 57] Six studies comparing TPTD to placebo reported on numbers of mortality,[58,59,60, 62, 64, 96] and one reported that there was no statistically significant between-group difference (data not reported).[63]

Where mortality was reported across studies comparing non-bisphosphonates with placebo, event rates were low with active treatment (0% to 1.8%). Only one study reported a between group difference[42] which was not statistically significant (p=0.08). Where 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 DATA[65] and DATA-Switch study,[66] that compared DEN to TPTD did not report on mortality; neither did the EUROFORS study,[67] that compared TPTD to RLX. In the two studies that compared ROMO to TPTD and reported on mortality[68, 69] event rates for mortality were low with either treatment (0% to 2%). The estimated between-group differences were not statistically significant (p>0.05).

Non-bisphosphonates vs. bisphosphonates - mortality

Across studies in DEN compared to bisphosphonates, three studies comparing DEN to ALN;[70, 71, 73] one comparing DEN to oral IBN,[74] one comparing DEN to RIS,[75] and one comparing DEN to ZOL,[76] reported on mortality. 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).

Across studies in RLX compared to bisphosphonates, two studies comparing RLX to ALN reported on mortality.[77, 81] 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).

One study comparing ROMO to ALN reported mortality rates of <2% with either treatment at 12 months prior to treatment switching and <5% at 24 months following treatment switching.[84] The estimated between-group differences were not statistically significant (p>0.05).

Across studies in TPTD compared to bisphosphonates, one study comparing TPTD to ALN;[75] four comparing TPTD to RIS,[88, 92, 93, 99, 100] and one comparing TPTD to ZOL,[94] reported on mortality. Across these studies event rates ranged from 0% to 4.4% with TPTD and <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 across the included studies are presented in Table 22 for the non-bisphosphonate treatments compared to placebo, non-bisphosphonate treatments compared head-to-head and non-bisphosphonate treatments compared to bisphosphonates.

Non-bisphosphonates vs. placebo – adverse events

Five studies comparing DEN to placebo,[42-46, 105, 110] three studies comparing RLX to placebo,[48, 51, 95] three studies comparing ROMO to placebo,[55-57] and five studies comparing TPTD to placebo,[58,59,60, 62, 64, 96] reported on adverse events. Event rates ranged from 37% to 94.3% with DEN, 27.1% to 96% with RLX, 12.9% to 78.4% with ROMO, and 21.9% to 91.9% with TPTD. Where between-group differences were reported, these were not statistically significant, as were those that were estimated by ScHARR (p>0.05).

Non-bisphosphonates vs. placebo – serious adverse events

Five studies comparing DEN to placebo,[42-46, 105, 110] three studies comparing RLX with placebo,[48, 49, 51, 95] three studies comparing ROMO to placebo,[55-57] and six studies comparing TPTD to placebo,[58, 59,60, 62-64, 96] reported on serious adverse events. Event rates ranged from 2.0% to 25.8% with DEN, 2.0% to 18.6% with RLX, 3.2% to 12.9% with ROMO, and 0% to 10.0% with TPTD. Where between-group differences were reported, these were not statistically significant, as were those that were estimated (p>0.05).

Non-bisphosphonates compared head-to-head – adverse events

One study that compared TPTD to DEN,[65] one study that compared TPTD to RLX,[67] and two studies that compared TPTD to ROMO,[68, 69] reported on adverse events. Across these studies, events for TPTD ranged from 16.1% to 90%, and 75.0% to 82.0% for ROMO and were 12.1% for DEN and 54.6% 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[65] and DATA-SWITCH[66] studies that compared TPTD to DEN before and after treatment switching,[65] and two studies that compared TPTD to ROMO,[68, 69] reported on serious adverse events. Across these studies, events for TPTD ranged from 6.5% to 11.0% (22.0% following treatment switching to DEN[65]) and 8.0% to 10.0% for ROMO and was 3% for DEN. The estimated between-group differences were not statistically significant (p>0.05).

Non-bisphosphonates vs. bisphosphonates – adverse events

Across studies in DEN compared to bisphosphonates, three studies comparing DEN to ALN,[70, 72, 73, 111] one comparing DEN to oral IBN,[74] one comparing DEN to RIS,[75] and one comparing DEN to ZOL,[76] reported on adverse events. Across these studies event rates for DEN ranged from 59.6% to 80.9%, event rates for bisphosphonates, from 64.1% to 91.3% with ALN, and were 56.1% with IBN, 69.0% with RIS and 62.2% with ZOL. Across these studies, both the reported and estimated between-group differences were not statistically significant (p>0.05).

Across studies in RLX compared to bisphosphonates, four studies comparing RLX to ALN reported on adverse events.[77, 78, 81, 83] Across these studies 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 to ALN reported adverse events at 12 months prior to treatment switching (75.7% vs. 78.6%) and 24 months following treatment switching to ALN (86.6% vs. 88.6%).[84] 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.

Across studies in TPTD compared to bisphosphonates, one study comparing TPTD to ALN;[75] six comparing TPTD to RIS,[88, 89, 92, 93, 99, 100] and one comparing TPTD to ZOL,[94] reported on adverse events. Across these studies event rates with TPTD ranged from 31.9% to 79.1%, RIS from 33.3% to 81.4%, 86% for ALN, and 70.1% for ZOL. The estimated between-group difference for the study comparing TPTD and ZOL[94] was statistically in favour of TPTD (p=0.006). All other reported or estimated between-group differences were not statistically significant (p>0.05).

Non-bisphosphonates vs. bisphosphonates – serious adverse events

Across studies in DEN compared to bisphosphonates, three studies comparing DEN to ALN,[70, 72, 73, 111] one comparing DEN to oral IBN,[74] one comparing DEN to RIS,[75] and one comparing DEN to ZOL,[76] reported on serious adverse events. 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% with ALN, 5.4% with IBN, 17% with RIS, and 9.1% with ZOL. The study comparing DEN to IBN,[74] 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).

Across studies in RLX compared to bisphosphonates, four studies comparing RLX to ALN reported serious adverse events.[77, 78, 83] Across these studies event rates for RLX ranged from 24% to 75.2% and for ALN from 12% to 74.2%. Across these studies, both the reported and estimated between-group differences were not statistically significant (p>0.05).

One study comparing ROMO to ALN reported serious adverse events at 12 months prior to treatment switching (12.8% vs. 13.8%) and 24 months following treatment switching to ALN (28.7% vs. 30.0%).[84] The estimated between-group differences were not statistically significant (p>0.05).

Across studies in TPTD compared to bisphosphonates, one study comparing TPTD to ALN;[75] four comparing TPTD to RIS,[88, 92, 93, 99, 100] and one comparing TPTD to ZOL,[94] reported on serious adverse events. Across these studies event rates with TPTD ranged from 11% to 28.9%, from 16.6% to 46.8% for RIS, 30% for ALN, and 14.6% for ZOL. The estimated between-group difference for the study comparing TPTD to ZOL[94] 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 venous thromboembolism, stroke, ONJ, and atypical femoral fracture, reported by the included studies are presented in Appendix 7.

Other evidence on adverse events

DEN – NICE Technology Appraisal summary of adverse events evidence

The NICE Technology Appraisal for DEN for the prevention of osteoporotic fractures in postmenopausal women [TA204],[10] found that whilst the summary of product characteristics[112] indicates that conditions associated with DEN include: urinary tract infection, upper respiratory tract infection, sciatica, cataracts, constipation, rash, pain in extremity and skin infections, that 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. The

summary of product characteristics[112] 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.

The NICE Technology Appraisal 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.[10]

DEN – European Medicines Agency Assessment Report summary of adverse events evidence

The European Medicines Agency Assessment Report for DEN,[113] 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[113] found that in one study in postmenopausal women, more subjects receiving DEN developed an infection that required hospitalisation compared with subjects receiving placebo. The report[113] 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 six to 12 months after the initial administration of DEN.

The report[113] found that in the combined safety analysis across the four pivotal trials, the small differences noted in individual studies in certain serious adverse events were not evident across the postmenopausal women and hormone ablation therapy populations. Across other SAEs, the report found that fatalities in DEN and placebo occurred with the same frequencies. In one study in postmenopausal women, the report observed significantly more patients in the DEN group than in the placebo group reported SAEs, particularly osteoarthritis and pneumonia. However, in another study in postmenopausal women the report observed that there were no significant differences in SAEs between treatment groups.

The report[113] 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 compared with the control.

RLX – NICE Technology Appraisal summary of adverse events evidence

The NICE Technology Appraisal that included RLX for the secondary prevention of osteoporotic fragility fractures in postmenopausal women [TA161],[11] found that venous thromboembolism (VTE)

is the most serious adverse event reported with RLX with an approximate three-fold 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 compared with placebo. The report also found that whilst the impact of RLX 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.

RLX – European Medicines Agency Assessment Report summary of adverse events evidence

The European Medicines Agency Summary of Product Characteristics for RLX,[10] states that RLX is associated with an increased risk for venous thromboembolic events in postmenopausal women which occurred in <1.1% of treated patients.

RLX – European Medicines Agency SmPC summary of adverse events evidence

The European Medicines Agency Public Assessment Report for RLX,[114] states that the most common side effects (seen in more than 1 patient in 10) are vasodilation and flu-like symptoms.

ROMO – Draft Summary of Product characteristics

The draft Summary of Product Characteristics for ROMO,[115] notes under special precautions that

[redacted]

TPTD– NICE Technology Appraisal summary of adverse events evidence

The NICE Technology Appraisal that included TPTD for the secondary prevention of osteoporotic fragility fractures in postmenopausal women [TA161],[11] only reported on adverse events associated with TPTD at 40µg per day compared with placebo, which were nausea and headache.

TPTD– European Medicines Agency Scientific Discussion summary of adverse events evidence

The European Medicines Agency initial marketing Scientific Discussion for TPTD,[116] reported that in the clinical pharmacology studies, orthostatic hypotension was observed in healthy subjects following administration of TPTD at doses higher that 20 µg/day and at the proposed therapeutic dose of 20µg/day the most frequently reported adverse events were leg cramps, nausea and headache. The more recent European Medicines Agency variation on the Scientific Discussion,[117] concluded that no further safety issues had been identified from further studies. The European Medicines Agency SmPC,[117] states that the most commonly reported adverse reactions in patients treated with TPTD are nausea, pain in limb, headache and dizziness.

5.2.2.4 Health related quality of life

Five studies published results of reported health related quality of life (HRQoL) measured by a validated assessment tool (Appendix 6).

Non-bisphosphonates versus placebo- HRQoL

HRQoL was reported from the FREEDOM trial.[118, 119] At three 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) (Appendix 6).[118]

RLX and placebo groups did not differ significantly in change from baseline as measured by the Women's Health Questionnaire (WHQ), or the European Foundation for Osteoporosis Quality of Life Questionnaire (QUALEFFO), or the Euro Quality of Life-5 Dimensions (EQ-5D) Visual Analog Scale (VAS), or the Euro Quality of Life-5 Dimensions (EQ-5D) Health State Profile Utility Score (Appendix 6) at 36 months follow-up in the Silverman 2008 RCT.[51]

Non-bisphosphonates versus bisphosphonates- HRQoL

In the Panico 2011 RCT,[87] both ALN and TPTD groups were significantly improved at 18 months on the QUALEFFO-41 domains 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 was significantly improved (Appendix 6).

In the VERO RCT[91] there was no significant difference between TPTD and RIS groups, which both showed significant improvement in the EQ-5D-5L VAS. The MOVE RCT[99] also reported no significant difference between the TPTD and RIS groups, which both showed significant improvement in the physical component of the SF-36.

5.3 Network meta-analysis

5.3.1 Methods for the network meta-analysis

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

For consistency with NICE technology appraisal 464 (TA464),[9] 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 (RE) 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 (HR) relative to placebo, with a HR less than one reflecting a reduced risk of fracture relative to the comparator treatment. To account for different lengths of follow up across the trials, the model assumed an underlying Poisson process for each trial arm, with constant event rate.[120] 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 follow-up (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 (<0.1) moderate ($0.1 \leq HR < 0.5$), high ($0.5 \leq HR < 1$) or extremely high (≥ 1) and for femoral neck BMD characterisation was based on a conversion as described in *Ren et al*.[121] Where appropriate, heterogeneity in treatment effects was explored by considering potential treatment effect modifiers using meta-regression.[122] Baseline risk/response can be used as a proxy for differences in patient characteristics across trials that may be modifiers of treatment effect. Adjustment for baseline risk/response was assessed using the method of Achana *et al*.[123]

Potential inconsistency between direct and indirect evidence was assessed using node-splitting.[124]

All analyses were conducted in the freely available software package WinBUGS[125] and R,[126] using the R2Winbugs[127] interface package. Convergence to the target posterior distributions was assessed using the Gelman-Rubin statistic, as modified by Brooks and Gelman,[128] 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 to 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.[129] Lower values of DIC are favourable, suggesting a more parsimonious model.

Results are presented using the posterior median treatment effects, 95% credible intervals (CrI) and 95% prediction intervals (PrI). 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 to placebo together with the median rank and probability of being the highest-ranking treatment are displayed in forest plots.

5.3.2 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 Table 15 and vertebral fractures in 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 (S1) 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 (S2) was conducted restricting the analysis to studies that report outcomes at 12 months.

In order 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 (reported percentages, figures), however the exact numbers are subject to uncertainty.

Sensitivity was therefore assessed (S3) by excluding these studies, along with other studies that that raised concerns regarding risk of bias due to blinding issues and early study termination.

A sensitivity analysis was also conducted excluding studies for which prior treatment with bisphosphonates was permitted (S4).

In summary, the following four sensitivity analyses were conducted for vertebral fracture outcomes:
S1: Clinical assessment
S2: 12-month data
S3: Exclusion for quality issues
S4: Exclusion for prior bisphosphonate treatment

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

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

Where 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, while presenting MDs numerically in the text, MDs were selected. 6 RCTs that did not provide variance estimates (in any format) were excluded.

5.3.3 Results of the network meta-analysis

Network diagrams for fracture outcomes and femoral neck BMD are presented in Figure 5 and Figure 7 respectively. Study level data contributing to the NMAs are provided in Appendix 9.1: Data contributing to the network meta-analysis.

The effects of each treatment relative to placebo are presented in Figure 6 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 datapoints in the network.

For comparison, results using a standard RE model with unrelated treatment effects for all interventions are provided in Appendix 9.2 NMA results from random effects model. 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.

Vertebral fractures

Vertebral fracture data were available from 46 RCTs, each comparing two treatments with the exception of one three arm study.[80] Nineteen of these studies were included in TA464 (including one study[80] where an additional non-bisphosphonate treatment arm was added for the current review). Two further bisphosphonate studies not already in TA464,[130, 131] 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 6 and pairwise comparisons between treatments are provided in Appendix 9.4 Pairwise summary tables 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, 0.32), with the highest probability of being the best treatment (0.38), and was statistically significantly more effective than all active treatments apart from denosomab, ROMO, and ROMO/ALN (Table 34). The H for a randomly chosen study for a new bisphosphonate is 0.47 (95% PrI: 0.19, 1.16), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

Within the network there were 12 treatment pairs for which both direct and indirect comparison were available. None of the comparisons showed significant evidence of inconsistency (Table 40).

Four sensitivity analyses were conducted for the main vertebral fracture network. Treatment effects are provided in Appendix 9.3 Vertebral fracture sensitivity analyses(Figure 14) and a summary of model fit and heterogeneity is shown in Appendix 9.3 Vertebral fracture sensitivity analyses (Table 33).

S1 included outcomes assessed by clinical methods only. Data were available from 19 RCTs which assessed a total of 10 interventions, including four non-bisphosphonate treatments. It was concluded that the results are generally consistent with the primary analysis which includes both clinical and x-ray assessed outcomes. This supports the assumption that the treatment effect is not highly influenced by assessment method.

S2 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 is has a more beneficial treatment effect in the 12 month sensitivity (HR 0.44 95% CrI 0.32-0.60) compared with the primary analysis (HR 0.52 95% CrI 0.42-0.65). In both analyses, RIS has zero probability of being the best ranking treatments. It was concluded that the results are generally consistent with the primary analysis which included the longest duration of follow up for each study, and therefore supports the use of a constant HR.

S3 excluded studies for which there was a risk of bias in the reported outcomes. 4[94 87 93 96] studies were excluded due to blinding issues, 2[63 81] studies were terminated early, and for 10 studies[43 132 133 134 130 135 51 44 136, 137] 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 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.

S4 excluded studies for which prior treatment with bisphosphonates was permitted. 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 are consistent with the primary analysis.

Non-vertebral fractures

Non-vertebral fracture data were available from 42 RCTs, each comparing two treatments with the exception of two three arm studies.[80,83] Fifteen of these studies were included in TA464 (including one study[80] where an additional non-bisphosphonate treatment arm was added for the current review), and 27 non-bisphosphonate studies were included from the current review. A total of 11 interventions were assessed, including f non-bisphosphonate treatments.

Pairwise comparisons between treatments are provided in

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, 0.76), with the highest probability of being the best treatment (0.52), although there was insufficient evidence to differentiate between TPTD and the other active treatments apart from IBN daily, DEN and RLX (

Table 35). The HR for a randomly chosen study for a new bisphosphonate is 0.78 (95% PrI: 0.60, 1.08), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

Within the network there were 14 treatment pairs for which both direct and indirect comparison were available. None of the comparisons showed significant evidence of inconsistency (

Table 35).

Hip fractures

Hip fracture data were available from 23 RCTs, each comparing two treatments with the exception of one three arm study.[80] Eight of these studies were included in TA464 (including one study[80] where an additional non-bisphosphonate treatment arm was added for the current review), and 15 non-bisphosphonate studies were included from the current review. A total of nine interventions were assessed, including five non-bisphosphonate treatments.

Pairwise comparisons between treatments are provided in

Table 36. All treatments were associated with beneficial treatment effects relative to placebo, although the comparison to placebo was not statistically significant for ROMO or RLX. TPTD was associated with the greatest effect, HR 0.35 (95% CrI: 0.15, 0.73), with the highest probability of being the best treatment (0.50), although there was insufficient evidence to differentiate between reriparatide and the other active treatments (

Table 36). The HR for a randomly chosen study for a new bisphosphonate is 0.64 (95% PrI: 0.32, 1.29), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

Within the network there were 14 treatment pairs for which both direct and indirect comparison were available. None of the comparisons showed significant evidence of inconsistency (Table 42).

Wrist fractures

Wrist fracture data were available from 15 RCTs, each comparing two treatments with the exception of one three arm study.[80] Six of these studies were included in TA464 (including one study[80] where an additional non-bisphosphonate treatment arm was added for the current review), and eight non-bisphosphonate studies were included from the current review. A total of eight interventions were assessed, including four non-bisphosphonate treatments.

Pairwise comparisons between treatments are provided in

Table 37. All treatments were associated with beneficial treatment effects relative to placebo, apart from DEN, RLX and ROMO. Treatment effects for ROMO are based only on one small study[68] with zero events in the TPTD arm and one event in the ROMO arm. 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.[71] Treatment effects for these interventions are therefore highly uncertain.

TPTD was associated with the greatest effect, HR 0.75 (95% CrI: 0.38, 1.41), with the highest probability of being the best treatment (0.28), although there was insufficient evidence to differentiate between TPTD and the other active treatments (

Table 37). The HR for a randomly chosen study for a new bisphosphonate is 0.82 (95% PrI: 0.29, 2.19), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

Within the network there were eight treatment pairs for which both direct and indirect comparison were available. None of the comparisons showed significant evidence of inconsistency (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 and 11 non-bisphosphonate studies were included from the current review. A total of eight interventions were assessed, including two bisphosphonate treatments.

Pairwise comparisons between treatments are provided in Table 38. All treatments were associated with beneficial treatment effects relative to placebo, apart from RLX. Treatment effects for RLX are based only on one small study[78] 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 RCT's had zero counts in one of the treatments arms.

ROMO was associated with the greatest effect, HR 0.10 (95% CrI: 0.0, 3.66), with the highest probability of being the best treatment (0.77), although the treatment effect was highly uncertain and there was insufficient evidence to differentiate between ROMO and the other active treatments (

Table 38). Only RIS was associated with a HR that was statistically significant compared to placebo (HR 0.49, 95% CrI 0.23, 0.96). The HR for a randomly chosen study for a new bisphosphonate is 0.82 (95% PrI: 0.29, 2.19), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

Within the network there were five treatment pairs for which both direct and indirect comparison were available. None of the comparisons showed significant evidence of inconsistency (

Table 38).

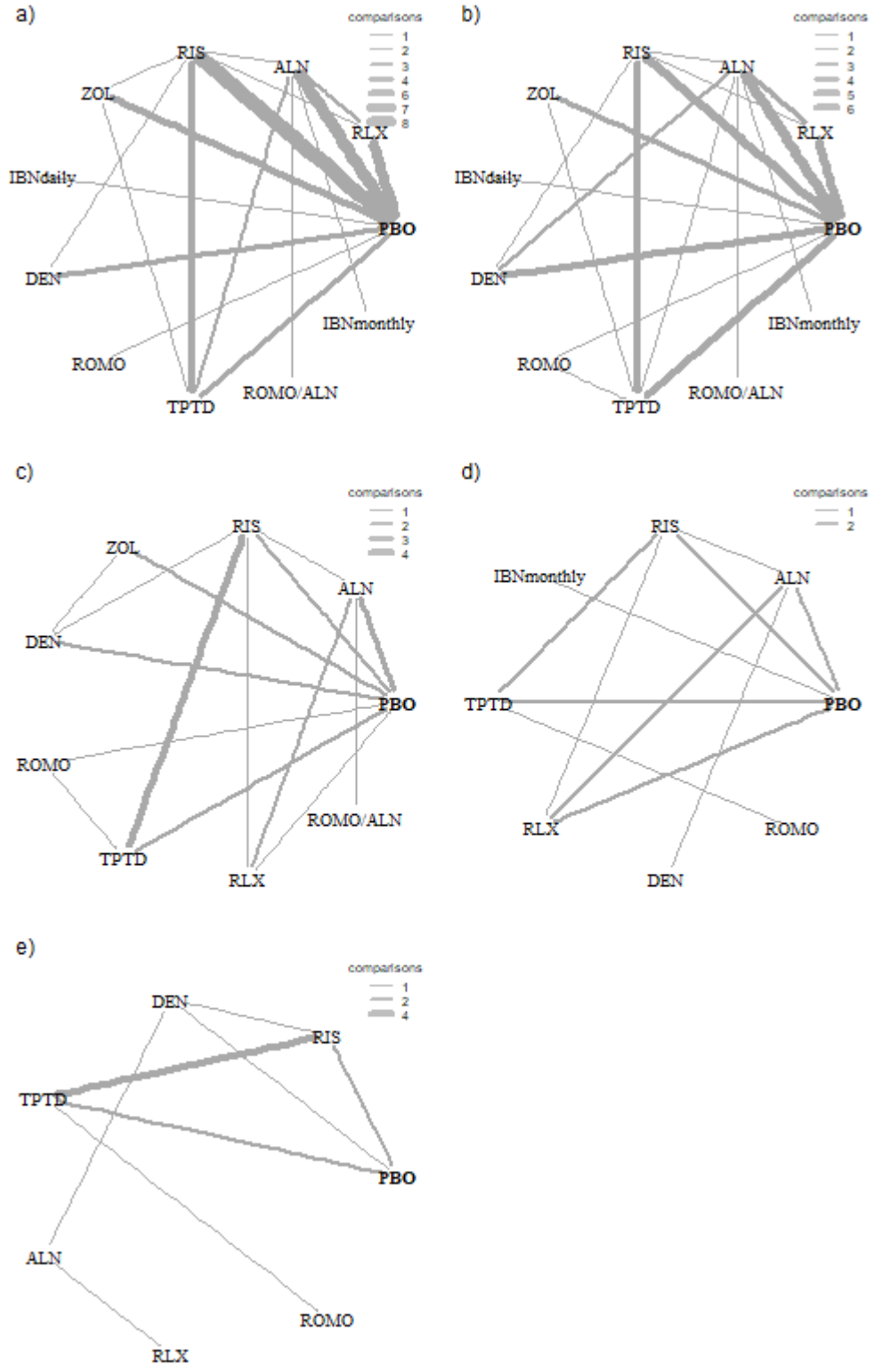

Figure 5: **Network diagrams for a) vertebral b) non-vertebral c) hip d) wrist e) proximal humerus fracture outcomes**

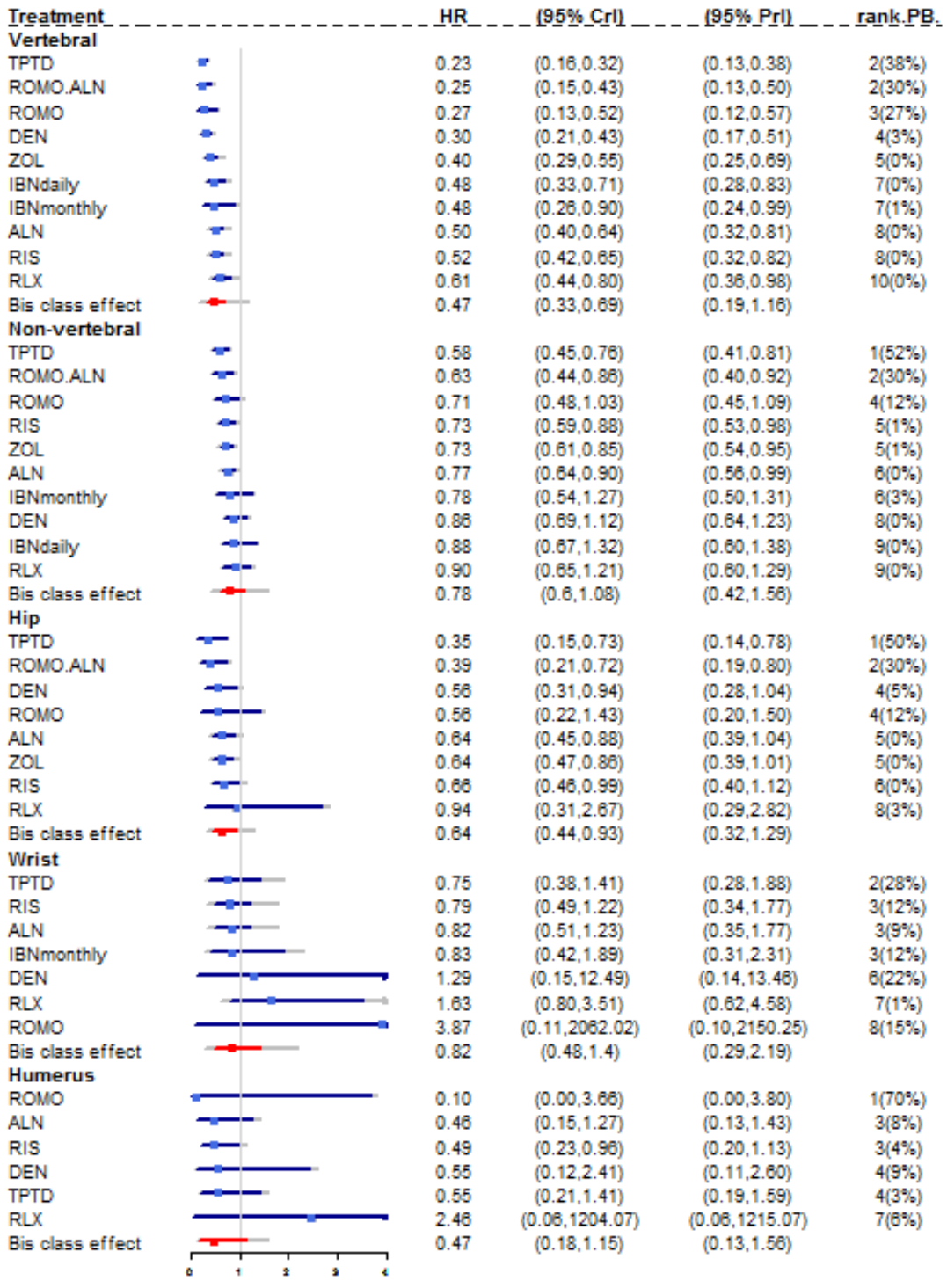

Figure 6: Forest plot for all fracture outcomes, main analysis

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

outcome	absolute model fit			Heterogeneity	
	D_{res}	DP	DIC	SD (95%CI)	SDt (95%CI)
vertebral	91.21	93	153.31	0.17 (0.02,0.37)	0.21 (0.01,0.90)
non-vertebral	74.05	86	128.40	0.08 (0,0.24)	0.15 (0.01,0.73)
hip*	38.63	47	70.23	0.12 (0.01,0.4)	0.13 (0.01,0.53)
wrist*	29.92	31	54.20	0.28 (0.04,0.62)	0.16 (0.01,0.61)
proximal humerus*	21.99	26	41.83	0.17 (0.01,0.57)	0.21 (0.01,0.7)
femoral neck BMD	144.70	137	258.86	0.85 (0.64,1.12)	0.74 (0.25,2.26)

D_{res}: Total residual deviance, DP: data points, DIC: deviance information criterion, SD: between study standard deviation, SDt: between bisphosphonate treatment standard deviation

* For hip, wrist and humerus fractures weakly informative priors were used for the between study and between treatment SD such that SD, SDt $\sim HN(0, 0.32^2)$

Heterogeneity in treatment effects between studies, and between bisphosphonates, is summarised in Table 4. The estimates of between-study standard deviation suggest mild (non-vertebral) and moderate (vertebral, hip, wrist, proximal humerus, femoral neck BMD) heterogeneity in treatment effects between RCTs, respectively. The estimates of between-treatment standard deviation 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.[122] Based on comparison of models with and without a covariate for mean age or mean percentage female, there was no evidence that treatment effect varied with age or gender. 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

Table **45**.

Baseline fracture risk 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. The effect of baseline fracture risk as a potential treatment effect modifier was explored using the method of Achana *et al.*,[123] assuming a common meta-regression coefficient for all treatments (as for age and gender), 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 (Appendix 9.6 NMA results of meta-regressions

Table **45**).

Femoral neck BMD

Femoral neck BMD data were available from 73 RCTs, each comparing two treatments with the exception of one four-arm study and three three-arm studies.[80] Thirty-two of these studies were included in TA464. Three further bisphosphonate studies not already in TA464,[130, 138, 139] 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 7.

The effects of each treatment relative to placebo are presented in Figure 8. Pairwise comparisons between treatments are provided in

Table 39. All treatments were associated with statistically significant beneficial treatment effects relative to placebo. ROMO/ALN was associated with the greatest treatment effect, mean difference 6.08 (95% CrI: 4.25, 7.91), with the highest probability of being the best treatment (0.96), and was statistically significantly more effective than all active treatments apart from ROMO (

Table 39). The treatment effect for a randomly chosen study for a new bisphosphonate is 2.34 (95% PrI: 1.26, 3.28), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

To account for differing trial lengths, study duration was included as a trial level covariate. The estimated impact of duration of study on treatment effect, assuming a common relationship for each treatment, was 1.09 (95% CrI: 0.73, 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, gender or baseline response

Table **45**).

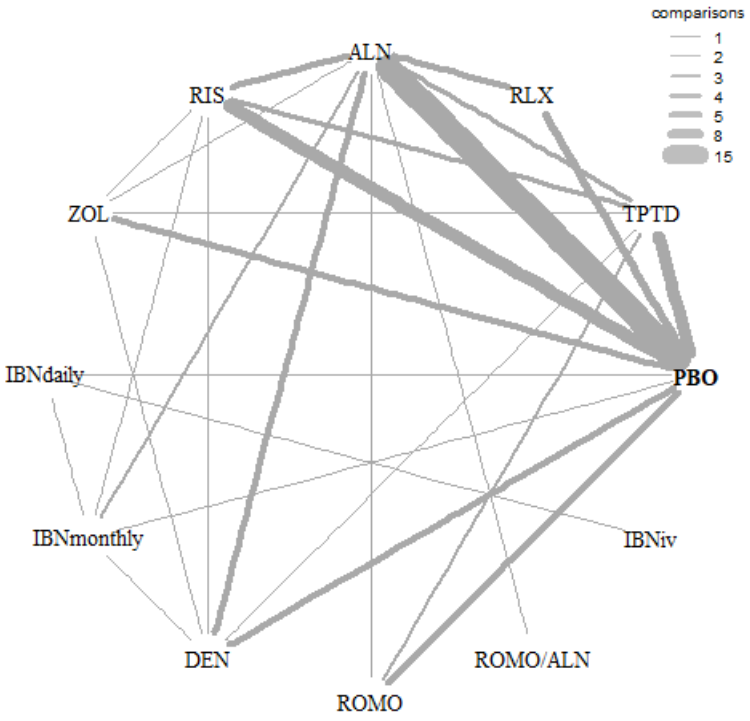

Figure 7: Network diagram for percentage change in femoral neck BMD

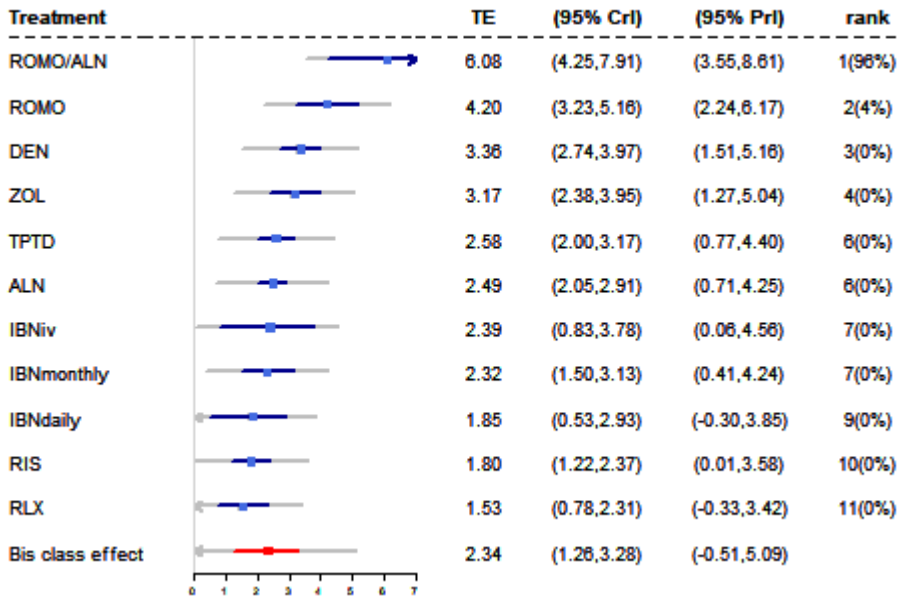

Figure 8: Forest plot for percentage change in femoral neck BMD

5.4 Discussion

Quantity and quality of RCT evidence

A systematic literature search identified 7,898 records. Fifty-two RCTs of non-bisphosphonates were included (published in 69 references). Of the 52 RCTs included, there were 23 RCTs comparing non-bisphosphonate to placebo, four head-to-head comparisons of non-bisphosphonates (of which one RCT also included a bisphosphonate arm), and 25 RCTs comparing a non-bisphosphonate to 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 the main analysis. Most of the included RCTs were conducted in postmenopausal women, although there were some trials of men and steroid induced osteoporosis for interventions where these were licensed indications. The majority of included trials typically excluded people with underlying conditions that influence bone metabolism, or receiving medications that influence bone metabolism.

Adverse events and HRQoL

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 for DEN ranged from 12.1% to 94.3%, for RLX ranged from 24.0% to 96%, and for ROMO ranged from 74.6% to 82% across non-treatment switch studies, and 86.6% in one study where ROMO was switched to ALN; and for TPTD from 16.1% to 91.9%. 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 where 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 and ZOL where the between-group difference was statistically in favour of TPTD (P=0.006).

Serious adverse event rates for DEN 2% to 25.8%; RLX 2% to 18.6%; ROMO 3.2% to 12.9%; TPTD 0% to 33%. 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 comparing DEN with oral IBN where 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 PBO, or RLX and PBO, but more improvement with TPTD than ALN, suggested by one RCT for each comparison. On generic measures of HRQoL, there was similarity for RLX and PBO (one RCT), or TPTD and RIS (two RCTs).

Discussion of NMA results

NMAs were conducted for vertebral fractures (46 RCTs, 11 interventions), non-vertebral fractures (42 RCTs, 11 interventions), hip fractures (23 RCTs, 9 interventions), wrist fractures (15 RCTs, 8 interventions), proximal humerus fractures (13 RCTs, 8 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: 0.16-0.32, Probability of being the best (PB): 0.38), non-vertebral (HR 0.58, 95%CrI: 0.45-0.76, PB: 0.52), hip (HR 0.35, 95%CrI: 0.15-0.73, PB: 0.50) and wrist (HR 0.75, 95%CrI: 0.38-1.41, PB: 0.28) fractures, while ROMO was the most effective for proximal humerus fractures, and ROMO/ALN (HR 0.10, 95%CrI: 0-3.66, PB: 0.77) 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 of vertebral fractures within the studies 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 impacted 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, but with the treatment effects for bisphosphonate interventions in the primary model shrunk towards the overall bisphosphonate class effect.

6 ASSESSMENT OF COST-EFFECTIVENESS

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Methods

A comprehensive search was undertaken with a cut-off date of 16th July 2018 to identify papers published in 2006 or later which 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 until 2018 to update the searches conducted for TA464.[140] In addition, for records between 2006 and 2013, each of the named non-bisphosphonate interventions (RLX, DEN, ROMO and TPTD) were 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, TA161[141] and TA204[142] and studies reporting the cost-effectiveness of ROMO are not expected prior to 2006. However, any relevant studies published prior to 2006 which were identified within these previous appraisals or within published systematic reviews were included.

The following databases were searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid) 1946 to 2018
- Embase (Ovid) 1974 to 2018
- Database of Abstract of Reviews of Effects (CRD Database) 1995 - 2015
- Health Technology Assessment Database (CRD Database) 1995 - 2016
- NHS Economic Evaluation Database (CRD Database) 1995 – 2015

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

6.1.1.2 Inclusions /exclusion criteria

Studies were included in the review if they reported full economic evaluations comparing DEN, RLX, ROMO or TPTD against each other, against bisphosphonates or against no treatment. Studies were included if any of the population considered would be eligible for risk assessment within CG146.[143] For example studies on post-menopausal women were included whether or not they specified that the women had risk factors as those aged over 65 would be eligible for risk assessment under CG146 even without risk factors being present.[143] Studies which did not assess outcomes using QALYs or

did not report the incremental cost per QALY of alternative treatment strategies were excluded. Studies which did not assess the cost-effectiveness within a UK setting were excluded to ensure consistency with the NICE reference case. Studies which assessed the cost-effectiveness of treatment at non-licensed doses were also excluded as were studies which 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 within existing NICE appraisals or published systematic reviews as described above. Studies were included only if they were reported as full papers with conference abstracts being excluded from the review as they present insufficient detail to allow for a rigorous assessment of study quality. Studies not reported in English language were also excluded. *De novo* economic analyses reported within the consultee submissions were included if they met the inclusion criteria of the review.

6.1.1.3 Review methods

The results of the economic searches described above were combined with the results of the searches conducted for the health related quality of life 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 which potentially met the inclusion criteria were retrieved for further inspection the same reviewer. Studies included in the systematic review were examined to determine whether they met the NICE reference case.[144] We stated in our protocol that we would critically appraise the included cost-effectiveness analyses using the checklist published by Philips *et al.,*[145] but this was not done due to time constraints.

6.1.2 Results

The study selection process is summarised in the form of a PRISMA diagram[34] in Figure 9, with the most common reason being that they were non-UK studies.

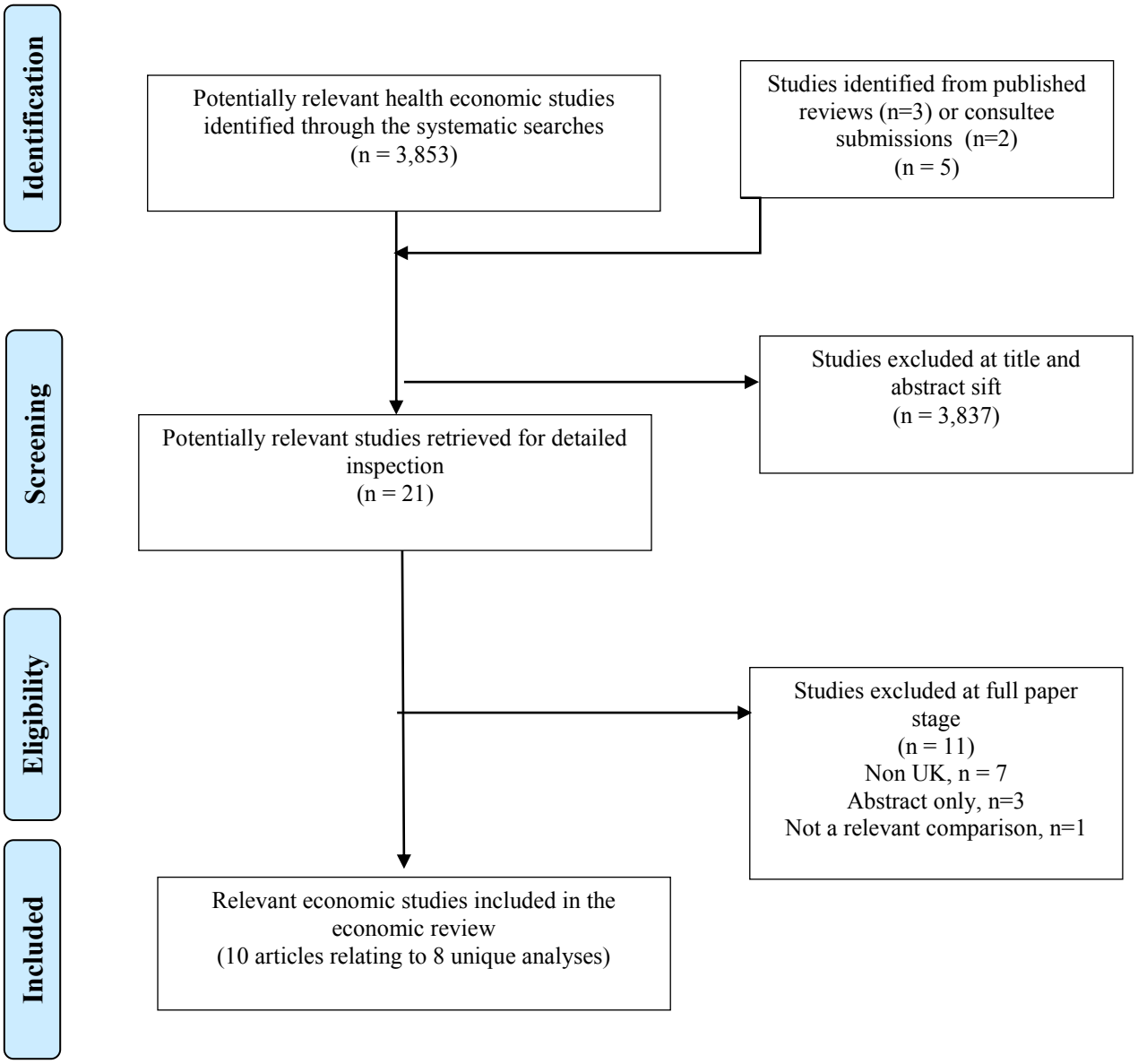

Figure 9: Flow diagram of study selection process (adapted from PRISMA) – cost-effectiveness review

6.1.2.1 Quantity of evidence identified

The database search identified 3,853 citations across the combined cost-effectiveness and health related quality of life searches. Three additional articles[146-148] were identified from the reference list of published reviews. None of the consultee submissions identified any published analyses not already picked up by through the systematic search but two reported *de novo* economic analyses which were included giving a total of 3,858 citations. Of these 3,837 were excluded at the title and abstract stage and a further 11 were excluded at the full paper stage with the most common reasons being that they were conference abstracts with limited data presented. Appendix 10 provides the reasons for exclusion for those papers which were not excluded based on title or abstract.

A total of 10 articles[20, 98, 140, 146-152] were included however, one paper (Kanis 2002)[147] reported a previous version the model reported by Stevenson *et al.*[148] and was therefore not separately extracted and two articles provided the ERG's summary of the company submission for TA204.[150, 152] Therefore, the review included 8 unique cost-effectiveness analyses. Additional documents related to TA204[142] were downloaded from the NICE website to allow a full examination of this model (NB: this model is referred to as Waugh 2011 to avoid confusion with the Amgen submission for the current MTA). The model described in the Amgen submission for the current MTA[98] was an adaptation of the model described in the company submission for TA204[150, 152] but these were separately extracted due to differences in the decision problem.

Although the assessment report for TA464 by Davis *et al.*[140] 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 in order to ensure consistency across related appraisals, the economic analysis conducted to inform TA464[9] 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 against relevant published analyses to identify any significant areas of difference.

6.1.2.2 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 [Kanis 2005, Stevenson 2005, Kanis 2008, Waugh 2011, Strom 2013, UCB 2018][20, 146, 148, 149, 151, 152] were in post-menopausal women. The CS by UCB restricted the population modelled to postmenopausal women at imminent risk of fracture, which it characterised as those with a recent major osteoporotic fracture.[20] Whilst no results were presented for men, UCB 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.*)[140] included all patients eligible for risk assessment under CG146,[143] therefore including both men and women, those with steroid induced osteoporosis and those with and without a prior fracture. However, Davis *et al*. examined subgroups according to absolute fracture risk rather than according to any of these specific patient characteristics. The submission by Amgen did not restrict the population to postmenopausal women and instead included people eligible for risk assessment under TA464 at varying levels of absolute fracture risk.[98] This was similar to the approach taken in TA464 except that the only risk cut-offs examined in the Amgen submission were 10 year risks of 10% and 20%, whereas Davis *et al*.

reported outcomes for 10 risk deciles and also used regression to estimate thresholds for cost-effective intervention when treating risk as continuous variable.

Several of the analyses presented results separately for those with and without a prior fracture (Kanis 2005, Kanis 2008, Stevenson 2005. Waugh 2011)[146, 148, 149, 152] or presented separate estimates for subgroups defined by combinations of age and T-Score, (Waugh 2011),[152] combinations of age and number of risk factors (Strom 2013)[151] or combinations of T-Score and risk factors (Waugh 2011).[152] Two studies estimated the threshold for cost-effective intervention and expressed this using 10-year risk of fracture (Davis 2016, Strom 2013).[140, 151] Two studies provided results for patients with a specific level of absolute fracture risk (Amgen and UCB)[20, 98] but explored alternative specified levels of absolute fracture risk in scenario analysis.

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 provided comparisons of RLX versus no treatment (Kanis 2005 and Kanis 2008).[146, 149] Strom *et al.* (2013)[151] compared DEN to bisphosphonates (ALN and RIS) and no treatment. Stevenson *et al.* (2005)[148] conducted an incremental analysis across multiple technologies but did not include DEN or ROMO. The submission by UCB[20] did not provide a comparison against oral or i.v. IBN but included all other comparators. The Amgen submission[98] stated that DEN was primarily used in primary care by patients unable to take an oral bisphosphonates and therefore the main comparators were RLX or no treatment. However, secondary analyses were provided comparing against i.v. ZOL and oral bisphosphonates. The company submission for TA204, described by Waugh *et a.,*[152] also restricted the decision problem to patients unable to take bisphosphonates. Their primary analysis compared DEN to RLX and no treatment, but they also included comparisons against i.v. IBN, i.v. ZOL, TPTD and oral bisphosphonates in secondary analyses. Davis *et al.*[140] included only bisphosphonates and no treatment in their incremental analysis, which was consistent with the scope of TA464.[140]

Model structure and outcomes modelled

Seven studies (Kanis 2005, Stevenson 2005, Kanis 2008, Waugh 2011, Strom 2013, Amgen 2018, UCB 2018)[20, 98, 146, 148, 149, 151, 152] used a Markov model framework with five using a cohort-level modelling approach and two (UCB 2018, Stevenson 2005)[20, 148] using a patient-level Markov simulation. Four of the Markov models employed a 6 monthly cycle length (Strom 2013, Waugh 2011, Amgen, UCB)[20, 98, 151, 152] whilst the other three (Kanis 2005, Kanis 2008, Stevenson 2005)[148] used an annual cycle length. The AG for TA464 used a discrete event framework which is a patient level simulation which 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 within a patient-level simulation. All studies included wrist fracture. All but one study (Kanis 2005)[146] included fractures at sites other than the hip, wrist and vertebrae, but some modelled wrist fractures separately from other fracture sites (Davis 2016, Stevenson 2005, Kanis 2005, Waugh 2011, Amgen 2018, Strom 2013).[98, 140, 146, 148, 151, 152] One study (UCB)[20] bundled wrist fracture together in a health state with fractures at other sites. Davis *et al.*[140] 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, spine 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 within 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 future fractures were restricted for patient experiencing a hip or vertebral fracture (Strom 2013, Kanis 2005, Kanis 2008, Waugh 2011)[146, 149, 151, 152] 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 (Amgen 2018)[98] 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 the individual's entire history. However, Davis *et al.*[140] 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 including breast cancer (Kanis 2005, Kanis 2008, Stevenson 2005),[146, 148, 149] two including coronary heart disease CHD (Kanis 2005 and Stevenson 2005)[146, 148] and two including either stroke or VTE (Kanis 2005, Kanis 2008).[146, 149] All except 1 study (Kanis 2005)[146] reported including an increased risk of nursing home admission after hip fracture (Stevenson 2005, UCB, Amgen, Strom 2013, Kanis 2008, Waugh 2011, Davis 2016).[20, 98, 140, 148, 149, 151, 152] None of the studies included an increased risk of nursing home admission following fractures at other sites but Davis *et al.*[140] presented a sensitivity analysis in which an equivalent rate of nursing home admission occurred for vertebral fracture and hip fracture.

Treatment duration

Four of the studies modelled a maximum treatment duration of 5-years for all treatments (Strom 2013, Kanis 2008, Kanis 2005, Waugh 2011).[146, 149, 151, 152] Davis *et al.*[140] assumed a 5-year intended treatment duration for all bisphosphonates except i.v. ZOL where a 3-year intended treatment duration was assumed. Stevenson *et al.*[148] assumed a 5-year treatment duration for all treatments except TPTD, where the treatment duration was assumed to be 18 months. One study (Amgen)[98] assumed a 10-year treatment duration of 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).[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.*)[140] 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 subcutaneous and i.v. therapies. The exact costs for administration and monitoring are discussed further in section 6.2.1.8, where we also describe the approach taken in the AG analysis.

Persistence

Persistence was included in either the basecase or sensitivity analysis within six of the models (Davis, UCB, Amgen, Waugh, Strom 2013, Kanis 2008).[20, 98, 140, 149, 151, 152] In TA464,[140] the persistence data applied in the model were identified from a review of systematic reviews. In the other models, one used published estimates but did not describe how they were identified (Strom 2013),[151] one used a mixture of published and unpublished data (UCB),[20] two used data on file from an unpublished study (Amgen, Waugh),[98, 152] and one applied the assumption made in the model that informed TA160 and TA161. 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 (CRPD/GPRD) (Amgen, UCB, Waugh).[20, 98, 152] A full discussion of the data sources used in these models and the choice of data source for the AG model is provided in Section 6.2.1.4.

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 (Strom 2013, Kanis 2005, Kanis 2008).[146, 149, 151] Davis *et al.*[140] and Stevenson *et al.*[148] made the same assumption for all but one intervention. Due to the shorter

treatment period for TPTD (18 months), Stevenson *et al.*[148] applied the full treatment effect was for 3.5 years after the end of treatment and this was noted as a very favourable assumption. Davis *et al.*[140] 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 basecase analysis where the treatment persistence was less than three years, the same ratio of offset period to treatment duration was applied by Davis *et al* (i.e. offset = 7/3 x treatment persistence). Two studies assumed a 1 year offset for all treatments (Waugh 2011 and Amgen 2018)[98, 152] and one study(UCB)[20] assumed an offset equal to treatment duration for all interventions except for DEN where 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 Section 6.2.1.6.

Adverse effects

All of the studies included some adverse effects (AEs) in either their basecase or their sensitivity analysis but there was considerable inconsistency between the studies in terms of the adverse events included. Three papers included gastrointestinal (GI) AEs in their basecase analysis (Davis 2015, UCB, Waugh 2011)[20, 140, 152] and two included them in a sensitivity analysis (Kanis 2008, Strom 2013).[149, 151] Amgen included GI AEs for oral bisphosphonates in the model reported in the company submission for TA204 (Waugh *et al*)[152] but did not include any in the model reported in the company submission for the current appraisal.[98] Stevenson *et al*. did not include any GI adverse effects for bisphosphonates in their analysis, but their model was later adapted to include AEs for GI bisphosphonates in an analysis by Stevenson and Davis[153] conducted to inform TA160 and TA161. There was some consistency in the assumptions regarding GI AEs across the various models with three using the assumptions from TA160 and TA161 (Waugh, Kanis 2008, Strom 2013)[149, 151, 152] and one (UCB)[20] using assumptions consistent with those applied in TA464 (Davis *et al*)[140] which themselves were very similar to those applied by Stevenson and Davis.[153] Davis *et al.*[140] included a one-off QALY loss to account for flu-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 for RLX (Kanis 2005, Kanis 2008).[146, 149] Amgen included cellulitis (a common bacterial skin infection) as an AEs for DEN in the model reported in the company submission for TA204 but did not include any AEs for DEN in the model reported in the company submission for the current appraisal.[98] Strom *et al.*[151] 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.*[140] incorporated post-hip fracture mortality by assuming that a fixed proportion (which was gender and age specific) of patients experiencing hip fracture would die 3 months after fracture. This

was based on evidence showing from a study by Tosteson *et al.*[154] 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 another study by Abrahamsen *et al.*[155] which found that approximately half of all excess mortality had occurred at 3 months. Davis *et al.*[140] incorporated an increased risk of fracture 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 (Amgen, UCB, Waugh 2010, Strom 2013)[20, 98, 151, 152] applied HRs to the general population mortality rate, with the hazard ratios for hip and vertebral fracture applied for 8 years following fracture and the HRs for non-hip non-vertebral fractures applied for 1 year. The data inputs appear to be consistent across these four models, with the primary source cited being Johnell *et al*. 2004[156] for clinical vertebral fractures, Jonsson *et al*.[157] for hip fractures and Barrett *et al*.[158] for "other fractures". These four models all assumed that only 30% of the increased risk was attributable to the fracture itself and down weighted the additional mortality risks accordingly. Kanis *et al*. (2005)[146] cited the same data source[156] 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*. (2008)[149] cited alternative sources (Parker and Anand, Kanis 2004, Kanis 2003)[159-161] and stated that 30% is assumed to be causally related, but does not describe the duration over which the HRs are applied. Stevenson *et al*.[148] used unpublished estimates from the Anglian audit of hip fracture,[162] which were reported for 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.[161] Stevenson *et al*.[148] based their risk of death following vertebral fracture on a study by Centre *et al*. (1999).[163] Stevenson *et al*.[148] included a 2-fold increase in mortality following proximal humerus fracture, citing Johnell *et al*.,[156] 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.

Table 5: Characteristics of included studies – cost-effectiveness review

First author **Location**	**Population Interventions**	**Type of evaluation**	**Perspective**	**Time Horizon**	**Cost year Cost discount rate**	**Cost source**	**Benefits population Benefits discount rate**	**Benefits source Benefits instrument**	**Effectiveness data**
Kanis 2005[146] (MORE)	Postmenopausal women – subgroups for with and 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[148] UK	Postmenopausal women Bisphosphonates, RLX; TPTD; no treatment*	Patient level Markov model	UK NHS & 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[149] (BONE)	Postmenopausal women Bisphosphonates, RLX,* no treatment	Cohort Markov model	UK NHS (includes nursing home admission)	Lifetime	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

First author **Location**	**Population Interventions**	**Type of evaluation**	**Perspective**	**Time Horizon**	**Cost year Cost discount rate**	**Cost source**	**Benefits population Benefits discount rate**	**Benefits source Benefits instrument**	**Effectiveness data**
Scotland /Waugh 2011/Amgen submission for TA204[152]	Postmenopausal women unable to take, comply with or tolerate bisphosphonates – 70 years, T-score -2.5; Subgroups with and without prior fracture. DEN, RLX, i.v. bisphosphonates, TPTD, oral bisphosphonates, no treatment*	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)
Strom 2013[151]	Postmenopausal women – subgroups by fracture risk DEN, ALN, RIS, no treatment*	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 Persistence incorporated Treatment effect after cessation incorporated

First author Location	Population Interventions	Type of evaluation	Perspective	Time Horizon	Cost year Cost discount rate	Cost source	Benefits population Benefits discount rate	Benefits source Benefits instrument	Effectiveness data
Davis 2016[140]	People eligible for risk assessment within CG146 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 network meta-analysis
UCB 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 network meta-analysis
Amgen 2018 [98]	People eligible for risk assessment under CG146 who cannot take oral bisphosphonates DEN, RLX, no treatment (i.v. ZOL, and oral bisphosphonates in	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 except changes in monitoring and administration costs)	Patient only 3.5%	Systematic review in TA464 EQ-5D using UK tariff	Published systematic review and network meta-analysis (TA464)

First author Location	Population Interventions	Type of evaluation	Perspective	Time Horizon	Cost year Cost discount rate	Cost source	Benefits population Benefits discount rate	Benefits source Benefits instrument	Effectiveness data
	secondary analysis)								

* other non-relevant interventions were also modelled e.g. oestrogen, strontium ranelate

6.1.2.3 Consistency with the NICE 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 reporting no additional disutility (Waugh 2011),[152] one study reporting using a value based on an expert panel (Stevenson 2005),[148] one study reporting a value based on EQ-5D (Davis *et al.*)[140] and several studies not reporting the approach taken to estimating utility values for nursing home admission (Strom 2013, Kanis 2005, Kanis 2008, UCB, Amgen).[20, 98, 146, 149, 151]

One study based its effectiveness estimate on a single RCT (Kanis 2005)[146] and only reported a comparison between the interventions included in the RCT (RLX versus no treatment). The other studies all sourced their effectiveness estimates from a systematic review and meta-analysis, although only the three most recent models used network meta-analysis to estimate the relative treatment between active comparators (Davis 2016, UCB, Amgen).[20, 98, 140] One study used the method published by Bucher *et al.* to conduct an indirect comparison (Waugh 2011).[152] Two studies (Strom 2013, Stevenson 2005)[148, 151] present incremental analyses that appear to be based on a naïve indirect comparisons based on equivalent outcomes for patients receiving placebo. The remaining study only provided comparisons against no treatment (Kanis 2008).[149]

Five studies explicitly reported using an NHS and personal social services (PSS) perspective (Stevenson 2005, Waugh 2011, Davis 2016, UCB and Amgen).[20, 98, 140, 148, 152] Three studies reported taking a healthcare perspective (Kanis 2005, Kanis 2008, Strom 2013)[146, 149, 151] but two of these (Kanis 2008 and Strom 2013)[149, 151] 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)[144] was applied in all but two studies (Stevenson 2005 and Kanis 2005)[146, 148] who applied discounting 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.* but otherwise, all of the included economic evaluations incorporated a lifetime horizon, although in the analysis by Stevenson *et al* (2005)[148] the Markov model was used for the first 10 years and then additional calculations were used to estimate QALYs gained over the remaining lifetime.

6.1.2.4 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[20] and Amgen[98] and the analysis by Davis *et al.* [140] which informed TA464. None of the other models provided an incremental analysis informed by a

systematic review and network meta-analysis, 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.*[140] was not relevant to the decision problem, and was included purely to allow comparisons to be made between the published models and the model we intended to adapt for this appraisal.

6.1.2.5 Study conclusions

Due to the concerns regarding applicability to the decision problem and consistency with the NICE reference case, for several of the studies[140, 146, 149-152] included in the review, results are only summarised here for the UCB[20] and Amgen[98] submission.

In the Amgen company submission,[98] which investigated the cost-effectiveness of DEN in a population of patients with a ten-year fracture risk of 20%, DEN was found to be associated with an ICER of £27,792 per QALY versus RLX and £27,363 per QALY versus no treatment. At the same risk of facture, DEN was also found to dominate ZOL.

In the UCB 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 post-menopausal women with a ten-year fracture risk of 30%, ROMO/ALN was found to be associated with an ICER of [redacted] per QALY versus ALN alone and [redacted] per QALY versus no treatment. The UCB submission also presented scenario analyses comparing ROMO/ALN to RIS, ZOL, RLX, DEN, TPTD (18 months and 24 months). The ICERs for ROMO/ALN when compared against these alternative comparators were [redacted] and dominating (ROMO/ALN had more QALY and less cost than TPTD for both 18 and 24 month treatment durations) respectively when using the PAS price for ROMO.

6.1.2.6 Review conclusions

The review has identified that there are no published cost-effectiveness studies which are 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. Whilst the Amgen and UCB submissions,[20, 98] provide an incremental analysis agaist the majority of the interventions and comparators specified in the scope (neither compared against 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 differed from the models included in the review. These are discussed further in section 6.2 where we describe the changes made to the model reported by Davis *et al.*[140]

6.2 Independent economic assessment

6.2.1 Methods

Having considered the review of published models and the models included within the company submissions, the AG decided to adapt the model used to inform TA464 (Davis *et al.*)[140] 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 the model should be updated or adapted. The areas identified for consideration were:

- 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 adverse events 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 within the published cost-effectiveness studies. This was supplemented by ad-hoc searches using google scholar 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.*[140]

In addition to these updates the AG also identified that changes to the VBA code would be needed to: (a) increase the number of treatment strategies that can be modelled, (b) allow for drug specific offset periods and (c) 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.* 2016),[140] with the additional change regarding nursing and residential care home costs described in the addendum provided before the second committee meeting (Davis *et al.* 2017). The other changes documented in the addendum are superseded by the updated NMA reported in section 5.3 and the need to update drug costs to reflect current prices.

6.2.1.1 Model structure

The ScHARR osteoporosis model (used in TA464) is a discrete event simulation (DES) which simulates the clinical events occuring over the life-times of individual patients with heterogenous

characteristics. A patient-level simulation approach was chosen to allow the future events expererinced 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. In this situation the cost-effectiveness for a patient with average characterisitcs is not the same as the average cost-effectiveness when taking into account the distribution of that characteristic across the population.

In general, within a DES model, the 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 within the patient's lifetime with the arrows showing which events can occur following other events. (N.B. 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 (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.

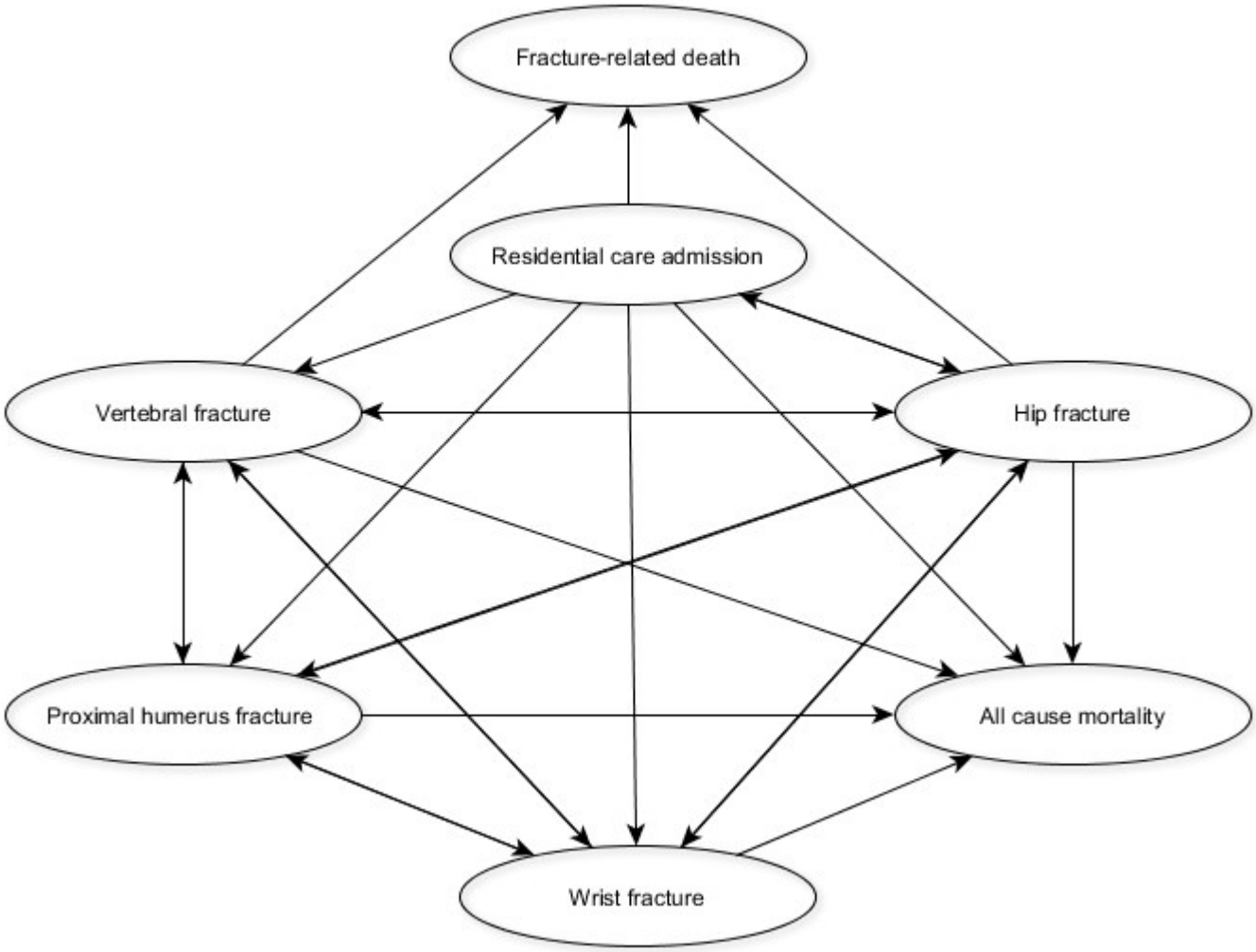

Figure 10: Clinical events that can occur during a patient's lifetime in the DES

In a DES no changes are made to the patient's attributes between events, but the event list which determines the future events experience, can be re-sampled 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 gender, 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 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 within 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 1 per bone (i.e. 2 hip fractures) with an additional limit of 4 vertebral fractures, 4 rib fractures and 2 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 less than one 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 only occur following fracture and 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 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 has been valued using the United States rather than the UK valuation set for EQ-5D.

Table 6: Overview of the modelling methodology and key data sources

Model feature	Description of model in TA464	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. The population is stratified into 10 risk categories and results presented for each risk category. This is done once using FRAX and once using QFracture.	No change (see section 6.2.1.2)
Interventions	ALN RIS oral IBN I.V. IBN I.V. ZOL	DEN RLX ROMO TPTD (see section 6.2.1.3)
Comparators	No treatment	No treamtment and the bisphosphonates listed as comparators for TA464 (see section 6.2.1.3)
Perspective	NHS and Person Social Services (PSS)	No change
Model type	Discrete event simulation with heterogeneous patient	No change

Model feature	Description of model in TA464	Description of revised model
	population	
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 one year after fracture and to update the fracture risks once treatment finishes.	No change (see description of model events in section 6.2.1.1)
Time horizon	Lifetime (up to age of 100)	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 section 6.2.1.4)
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 are 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

Model feature	Description of model in TA464	Description of revised model
Effectiveness	The hazard ratios from the systematic review and network meta-analysis 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 section 6.2.15) Data has been identified on the duration of treatment effect after treatment cessation for the non-bisphosphonates. (see section 6.2.1.6) No changes were made to offset assumptions for bisphosphonates. (see section 6.2.1.6)
Adverse events	Upper GI side-effects for oral bisphosphonates and flu-like symptoms for i.v. bisphosphonates are included by applying one-off cost and QALY deductions in the first month of treatment.	Additional adverse events have been incorporated for; • ONJ • VTE • Cellulitis (see section 6.2.1.9)
Mortality	All-cause mortality is based on UK life-tables. Fracture related mortality is based on estimates of excess mortality attributable to hip and vertebral from a case-control study 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 which used EQ-5D. Variation in baseline utility by age and gender was	The utility decrements for fracture have been updated to reflect new evidence identified in an updated systematic review. (see section 6.2.11) Utility estimates have been identified and incorpated for the AEs of ONJ, VTE and cellulitis (see section 6.2.1.9)

Model feature	Description of model in TA464	Description of revised model
	based on UK EQ-5D population estimates.	The incorporated utility estimates are all based on EQ-5D with valuation using the UK time-trade-off (TTO) data set, with the exception of ONJ where the estimates are based on the US valuation set for EQ-5D.
Resource use and unit costs	The analysis includes drug costs, administration costs and costs of fracture including those falling on primary care, secondary care and personal social services. Post-fracture costs were based on a case control study which 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 pounds sterling (£) Cost year is 2014.	Drug costs have been updated using the latest National Drug Tariff and eMIT database. (see section 6.2.1.7) Costs for monitoring (DXA scanning and annual physican review) have been incorporated. (see section 6.2.1.8) Administration costs for i.v. bisphosphonates have updated and administration costs for non-bisphosphonates have been incorporated. (see section 6.2.1.8) Other costs have been inflated using standard inflation indicies (see section 6.2.1.10) Costs are reported in pounds sterling (£) 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 basecase scenario to estimate the mean costs and benefits when taking into account parameter uncertainty. Structural uncertainty was assessed through scenario	No change

Model feature	Description of model in TA464	Description of revised model
	analysis where parameters were set to their midpoint values.	

*eMIT, electronic market information tool

6.2.1.2 Population

The population is patients eligible for risk assessment under CG146[143] as per the final NICE scope. CG146 recommends that either FRAX[32] or QFracture[33, 164, 165] be used to assess the absolute risk of fracture. In order to explore whether 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 two approaches. Firstly, we report outcomes for ten risk categories, based on deciles of absolute fracture risk. Secondly, 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 both FRAX and for absolute risk assessed by QFracture.

6.2.1.3 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 against a strategy of no treatment to estimate the incremental costs, incremental QALYs and incremental net monetary benefit (INMB) relative to no treatment. We note that in the basecase 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.[140] 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, but does not specify the duration for anti-resportive treatment. In the ARCH trial[166] patients in both arms received open-label ALN after the 1-year double blind phase. In the clinical study report (CSR)[166] for the ARCH trial, the mean duration of ALN exposure after the 1-year double blind phase is [redacted] in both arms, but the maximum treatment exposure is between [redacted] years across the

two trial arms. In order 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 submission[98] where it was argued that there is data from the FREEDOM study on the efficacy and safety of up to 10 years of DEN treatment.

6.2.1.4 Treatment persistence

In the AG model, we have assumed 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 assumption was found to be reasonable in sensitivity anslyses reported by Davis *et al*. 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.*[140] 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.*,[167] and i.v. bisphosphonates, based on a US study of Medicare patients (Curtis *et al.*).[168] Davis *et al.*[140] 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 submission[98] used persistence data from a retrospective analysis of a large UK primary care database (the Clinical Practice Research Dataline [CPRD]) (Amgen, 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 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[20] as the source for TPTD and ZOL persistence. For the sequence of ROMO followed by ALN, the model submitted by UCB[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.*[151] used persistence data for oral bisphosphonates from a UK CPRD study (Li *et al.* 2010,[169] similarities suggest this is the same study cited by UCB) 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.*[151] used a non-UK randomised crossover comparison study to model treatment persistence with DEN (Freemantle 2011).[108] Kanis *et al* (2008) 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.* (2008) regarding treatment

persistence for RLX. In the model based on the MORE study (Kanis *et al* 2005), patient compliance was not taken into account, but it was noted in the discussion that 92% of patients took more than 80% of their study medication. In the model submitted by Amgen for TA204 (Waugh 2011), treatment persistence was assumed to be 100% for all treatments in the basecase analysis but a lower rate of treatment persistence for oral bisphosphonates was applied in a sensitivity analysis based on data from the General Practice Research Database (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 submission).

Both of the company submissions used data from the same large UK primary care database (GPRD/ CPRD). The published analysis by Li *et al*. (2012)[170] gave a median durations of persistence for oral bisphosphonates ragning 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 submission[98] had a lower median persistence of 3.7 months for all oral bisphoshonates. However, the AG notes that the data from Li *et al*. 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.*[170] by crudely estimating the area under tha Kaplan-Meier curve assuming linear changes between the estiamtes reported. (The AG note that the data from Table 3 in the paper by Li *et al.*[170] do not match the data used in the UCB mdoel with the exception of the first two time points for RLX despite this being the cited souce.[20]) The data from the more recent analysis presented in the Amgen submission[98] were considered less mature than the data presented by Li *et al.*[170] 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 due 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.[140]

The AG was not convinced that data from a primary care database, as used in both the Amgen[98] and UCB models, would be generalisabel 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.[140]

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 (Hadji 2016,[171] Karlsson 2015,[172] Silverman 2018,[173] Freemantle [111]). It is difficult to estimate the mean or median duration of treatment from studies which 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 submission[98] presents data beyond 2 years but these were described as exploratory analyses only. The AG were concerned about whether the analysis of CPRD data presented by Amgen would accurately capture DEN persistence as whilst 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. Furthermore, the data in the Amgen spreadsheet model for DEN persistence do not match those provided in Table 4-2 of the Amgen submission. The persistence data used for DEN in the UCB submission[20] match the cited source (Karlsson *et al*)[172] up to 24 months but beyond that they have simply assumed a fixed proportional decrease in the numbers who are persistent based on a comparison between the 18 month and 24 months persistence rates, despite the proportional decrease from 24 months to 30 months being smaller in the Kaplan-Meier plot presented by Karlsson *et al.* The AG decided to estimate the mean treatment persistence from the CRPD data presented by Amgen 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 to 4 to estimate the proportionate decrease in persistence experienced thereafter. From this the mean treatment persistence over 10 years was estimated to be [redacted]). The AG notes that these estimates are uncertain due to the exclusive use of primary care records and need for an assumption to be made to extrapolate persistence up to 10 years due to the low proportion of patients captured in the analysis beyond 2 years ([redacted]).

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 were identified from ad hoc literature searches which described persistence in UK patients in real clinical practice based on data from the main homecare provider of TPTD in the UK (Arden 2006, Abhiskeh 2006).[174, 175] Both these studies were conducted before the maximum duration of treatment in the MA was extended from 18 to 24 months, but they show high levels of persistence at 18 months of 79%[174] and 74%,[175] 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 longest follow-up. Data from the ExFOS study, which was a large European real-life clinical practice study of TPTD use after the license was extended to 24 months, showed a mean treatment duration of 20.7 months despite 29% of patients residing in

countries where the license 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 months to 24 months based on the rate observed over 18 months by Arden *et al.*,[174] 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 SE 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 ther PSA, maximum number of doses was capped at 24 as per the SmPC for TPTD.[24]

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 to estimate mean persistence with treatment and found that this agreed with patients being treated for a mean of [redacted], although it noted that only [redacted] of patients received all 12 doses of ROMO. When sampling this parameter in the PSA, the maximum nmber of doses was capped at 12 as per the draft SmPC for ROMO provided in the UCB submission.[115] 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.

6.2.1.5 Effectiveness data

The HRs estimated in the NMA (see Figure 7) 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 and therefore it would not have been possible to generate separate estimates of treatment efficacy for the ROMO and ALN parts of the treatment sequence.

Where 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 otucomes translate into superior fracture prevention outcomes. However, this is consistent with the approach taken in TA464.

For vertebral fracture we have used the outputs of the basecase NMA which included studies reporting morphometric fractures. This is because the outcome of morphometric fracture was more

widely reported, and the NMA sensitivity analysis which excluded studies that only reported 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,[140] it was possible to use the bisphosphonate class effect estimate where data on individual bisphosphonates were lacking. In the updated networks described in section 5.3, there were no hip fracture data 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 where data were lacking for hip fracture. We note that the class effect for bisphosphonates was very similar to the estimates for ALN, RIS, ZOL and so this was not considered to unfairly bias the cost-effectiveness analysis.

In the analysis that informed TA464,[140] 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 basecase analysis, the CODA (convergence diagnosis and output analysis) 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.

6.2.1.6 Offset period

The AG used a review by Idolazzi *et al.* (2013)[176] 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 FLEX study as this provides comparative data on both fracture risk and BMD for patients remaining on, or stopping treatment with, ALN after 5 years of treatment (Schwartz 2010 and Black 2006).[177, 178] 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 to those stopping treatment. There was some evidence of a

continued treatment effect for LS BMD and a continued reduction in vertebral fracture risk was observed (RR 0.45, 95%CI 0.24-0.88) for patients who continued versus those who discontinued.

For RIS, two studies were identified (Watts 2008 and Eastell 2011).[179, 180] Watts *et al.* reported outcomes for patients randomised to either placebo or RIS in the year after discontinuing study drug. Eastell *et al.* reported outcomes in patients in the year after completing the VERT-MN study where 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 one year following treatment discontinuation, although Watts *et al.* observed smaller losses in LS BMD and reported a statistically significant reduction in vertebral fracture incidence between those previously treated with RIS and those previously treated with placebo and 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 (Ravn 1998)[181] which included the 2.5mg daily dose that has been shown in non-inferiority bridging studies to be equivalent to the 150mg monthly dose that is now licensed (Reginster 2006).[182] This study appears to show a similar patter to that seen for the RIS, in that hip BMD appears to return to pre-treatment levels in the year after treatment, with a slightly slower return for LS BMD. However, as the duration of treatment was only 1 year it is not clear if 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,[140] 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 HORIZON PFT extension study are provided by Black *et al.* (2012).[183] 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, FN BMD had declined in those 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 picture seen in the FLEX study, further gains were made in LS 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,[140] 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 Fracture Prevention Trial follow-up study (Lindsay 2004 and Prince 2005)[184, 185] which followed patients for a median duration of 30 months after the RCT phase of the study. The RCT phase was terminated early (due to concerns regarding the safety of long-term use) with a 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.* in the 18 months following discontinuations and not all of the LS 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 FN and total hip BMD appear to be lost by 18 months in the group not receiving other osteoporosis interventions. A second smaller study in men with shorter follow-up had similar findings (Kaufman 2005). 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 (Naylor 2010). Although there were some baseline differences in BMD the percentage change in LS BMD from baseline was no longer statistically significant at 144 weeks in the group who had discontinued at 96 weeks, whereas the benefit in LS BMD was maintained in those continuing RLX up to 192 weeks from baseline. A second RCT extension study 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 LS and FN BMD. Whilst these data are from a small study, they support a rapid loss of efficacy in the year after treatment even for patients

treated for longer than 2 years. Based on these two studies we decided to apply a 1-year offset period for RLX.

For DEN, two papers reporting outcomes from a single study were identified (Bone 2011, Bone 2008). 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 LS 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 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 1 year after discontinuation occurred even after treatment lasting 10 years (Popp *et al.*).[186] Whilst this analysis was limited to 12 women from a single site and therefore can only be considered to be 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 the treatment duration when this is less than 1 year).

For ROMO, no data were identified in the published literature on the treatment effect following discontinuation. In sequences where 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.[20]

6.2.1.7 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.[187] For drugs administered in secondary care, the eMIT database[188] was used for generic preparations (i.v. bisphosphonates) and the NHS Drug Tariff[187] price was used where no generic preparation was listed as being available (TPTD and DEN). For ROMO, the annual costs for both the list price and the patient access scheme (PAS) price were taken from the company submission. The PAS price was used in the AG's basecase analysis. Whilst the TPTD patent will expire in August 2019 and two biosimilars have already been approved (Movymia and Terrosa),[21, 22] their prices are currently unknown.

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
Intended treatment duration (years)	5	5	3	5	10	2	1 ROMO 4 ALN
Mean persistence (years)	1.60	1.1	1.7	1.38	[redacted]	1.72	[redacted] ROMO 1.60 ALN
Offset	1.60	1.10	1.70	1.00	1.00	1.72	[redacted]
Drug acquisition costs							
Dosing unit	70mg /35mg / 150mg	3mg in 3ml	5mg / 100ml	60mg	60mg	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 per 1	£271.88 per 30	Not provided
Total cost/year	£9.91 / £9.91 / £11.88	£31.56	£13.24	£42.63	£366	£3,307.87	[redacted]
Administration costs							
Route of administration	Oral	i.v.	i.v.	Oral	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Resource use for administrations	N/A	Outpatient	Day case	N/A	2 as outpatient then GP nurse	Self-administered	Self-administered
Cost per administration	N/A	£150.38	£253.32	N/A	£10.85 (£150.38 1st yr)	N/A	£0.00
No. administrations/year	N/A	4	1	N/A	2	N/A	12
Total costs/year	£0.00	£601.52	£253.32	£0.00	£21.70 (£300.76 1st yr)	N/A	£0.00
Monitoring costs							
Type of follow-up visit	GP	Outpatient	Outpatient	GP	GP with 1 in 4 as outpatient	Outpatient	Outpatient
Cost per follow-up visit (1 per annum)	£38	£150.38	£150.38	£38	£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/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 1st yr)**	**£3,492.40**	[redacted]

6.2.1.8 Treatment initiation, administration and monitoring

Six of the studies assumed that patients would receive DXA scans every other year whilst on treatment (Waugh, Kanis 2008, Kanis 2005, Strom 2013, Amgen, UCB).[20, 98, 146, 149, 151, 152] Stevenson *et al.*[148] assumed that patients would receive DXA scans at years 2 and 5 and Davis *et al.*[140] did not include any DXA scans to monitor treatment with bisphosphonates. Not all of the papers were explicit about whether patients were assumed to have had a DXA before starting treatment but in Davis *et al.*[140] all costs related to risk assessment, which may include DXA in some patients, were considered to be have already occurred prior to treatment choice as these were included in the cost-effectiveness analysis for risk assessment within CG146.[143] The AG considered that the inclusion of routine DXA scans 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 scans are performed routinely as part of the risk assessment of patients.[143] Therefore it is reasonable to assume that many patients may be started on the current first line therapy, which is oral bisphosphonates, without a DXA scan and this is consistent with the approach recommended in the NICE-accredited NOGG guideline.[13] 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 DXA scans are given when patients 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 here we assumed a DXA scan 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 one DXA at the end of the 1 year of ROMO and 1 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 DXA costs 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 a DXA is based on the NHS reference cost for a direct access DXA (£68.29 for RD50Z).[189]

Four of the studies assumed that patients would receive annual General Practitioner (GP) appointments to monitor treatment (UCB, Kanis 2005, Strom 2013, Waugh).[20, 146, 151, 152] Amgen 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.[98] Kanis *et al.* (2008) assumed 1 GP appointment to initiate treatment. Stevenson *et al.*[148] assumed 2 GP appointments per annum, whilst Davis *et al.*[140] did not include any GP appointments for monitoring. There is now a NICE quality standard[12] which states that patients having bone sparing treatments

should have medication reviews to discuss adverse effects 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 per 9.22 mins).[16] For DEN we were advised that patients would be reviewed in secondary care every 3 to 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 endocriniology outpatients has been applied (healthcare resource group [HRG] currency code, WF01A, service code 302).[189]

As noted previously, none of the studies identified in the review included any costs for the administration of oral therapies and this was the assumption applied in our model. UCB also assumed no administration costs for subcutaneous therapies (i.e. DEN, TPTD and ROMO).[20] In the Amgen submission for this MTA[98] it was assumed that DEN would be given by a GP nurse whereas in the Amgen submission for TA204 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 pe hour for GP 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.*[148] do not describe any additional administration costs for TPTD. Waugh *et al.*[152] 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.*[140] assumed that i.v. IBN is delivered during an outpatient endocrinology appointment and i.v. ZOL is delivered as a day case procedure using the HRG code for administration of a simple parenteral chemotherapy (SB12Z). UCB assumed administration of i.v. ZOL in secondary care but the exact source of the cost applied is unclear.[20] In the Amgen 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.*[140] for i.v. ZOL. However, in the Amgen submission for the current MTA,[98] it was argued

that the use of an oncology HRG was inappropriate and instead the cost was based on day case and elective inpatient spells averaged over 9 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.[190] In correspondence with the study author[191] 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 were likely to be too high and we decided to use the HRG codes applied in the model that informed TA464[140] but updated to the latest reference costs[189] 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. We therefore decided to assume the same resource use as in the model used to inform TA464[140] (one outpatient endocrinology follow-up appointment), but we updated the unit cost to reflect the latest reference costs[189] giving a cost of £150.

6.2.1.9 Adverse effects

For oral and i.v. bisphosphonates the AG decided not to change the approach to modelling AEs that was adopted in TA464[140] 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 which informed TA204. Although it was noted that the 10-year results of the FREEDOM study suggest that the incidence is low at 0.2% or less in each of the study years. The HRG cost for a non-elective inpatient spell for minor skin conditions with interventions ranges from £2,588 to £7,764 depending on the level of complications and comorbidities with a weighted average of £4,467.[189] Assuming an incidence 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 which had estimated the QALY loss of cellulitis as 0.005 QALYs (reduction in EQ-5D 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.[192] This is equivalent to a loss of INMB of £0.20 per annum. As the duration of treatment persistence with DEN in the model is [redacted] years, this would suggest that the total impact of cellulitis is a reduction in INMB for DEN of the order of [redacted]. Costs and QALY losses for cellulitis per year of exposure to DEN have been included in the basecase model.

The AG notes that the Medicines and Healthcare products Regulatory Agency/Commission on Human Medicines (MHRA/CHM) has issued advice regarding the risk of atyprical femoral fractures for both DEN and bisphosphonates[30] 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 within the model. This was firstly 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 within the model. The AG accepts that atypical femoral fractures may not have been captured within the trials if they only occur after long-term use of osteoporosis treatment. However, the AG notes that the basecase scenario incorporates real world treatment persistence which is much shorter than the intended treatment duration for both bisphosphonates and DEN making these adverse events which 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.[30] The advice states that the risk is considered to be substantially higher in those receiving IV bisphosphonates in the treatment of cancer and the risk is said to be related to cumulative dose. Similarly, the MHRA/CHM advice on DEN states that *"Osteonecrosis of the jaw is a well-known and common side-effect in patients receiving DEN 120 mg for cancer"* and recommends dental examination and preventative dentistry treatment in all patients starting DEN for cancer.[30] It should be noted that the dose for cancer is 120mg monthly rather than 60mg every 6 months and in the context of using DEN to prevent osteoporotic fracture, such precautions are only recommended by the MHRA/CHM only for those with risk factors.[30] The AG also notes that a systematic review by Boquete-Castro *et al.* (2016)[193] 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 antiresportives for osteoporosis than for cancer, the AG decided to incorporate this AE within the model to establish the likely impact on the cost-effectiveness estimates.

The AG examined a systematic review reported by Khan *et al.* (2015) which was conducted to inform an international consensus statement on osteonecrosis of the jaw.[194] Khan *et al.* conclude from their review that, *"the incidence of ONJ in the osteoporosis patient population appears to be very low, ranging from 0.15% to less than 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.* [194] identified a UK (Scotland) prospective case series that reported an incidence for ONJ of 1 case per 4,545 drug-patient-years (0.022%) for patients exposed to ALN (Malden 2012).[195] This was within the incidence range of 1.04 to 69 cases per 100,000 patient-years reported by the other

studies identified in the review by Khan *et al.* [194] It should be noted that Lo *et al.*[196] found in a cross-sectional survey conducted in the United States 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 <4 years and 4 years and over. For i.v. bisphosphonates, Khan *et al.* reported an incidence range of 0 to 90 per 100,000 patient-years. [194] The incidence estimated across 5 RCTs is given by Khan *et al.* as <1 in 14,200 patient years of exposure (<0.007%).[194] For DEN, Khan *et al.* reported that the estimates of incidence ranged from 0 to 30.2 per 100,000 patient years.[194] However, more recent data from the 10-year follow-up of the FREEDOM trial gave an exposure-adjusted incidence of ONJ of 5.2 per 10,000 participant years (0.052%). The SmPC for DEN stgates that the incidence is related to the duration of exposure.[197] Given that there is a lack of comparative data on the incidence of ONJ across the different forms of antiresportives, and that the estimates for the different antiresportive drugs all relate to different periods of exposure, we have decided to assume the same incidence per year of drug exposure across all antiresportives. This was based on the estimate from the prospective case series in Scotland. This was because this estimate fell within the range provided by Kahn *et al.* for each type of antiresportive (oral bisphosphonates, i.v. bisphosphonates and DEN) and was based on the average duration of use in clinical practice and therefore would be more applicable to the duration of treatment persistence modelled in this analysis.

A paper measuring health utility in patients with ONJ was identied using ad-hoc searches of google scholar (Miksad *et al.*).[198] It reported utility measured by the EQ-5D in 34 cancer patients with bisphosphonate-associated ONJ patients. However, it should be noted that it was not compliant with the reference case in several ways. Firstly, althought 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. Secondly, 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 to 3 (-0.33 and -0.61 respectively) and the distribution of ONJ stages (2 were stage 3 and 9 were stage 2) across the UK prospective case series reported by Malden *et al.*[195] 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[195] to given an average QALY loss of 0.206 QALYs per case of ONJ. The NHS reference cost for a minor outpatient oral surgical procedure was applied (HRG code, CD03A, £166),[189] to account for the cost of surgical management as most patients in the Malden *et al.,*[195] case series had some form of surgical management, with debridement being the most common procedure. We note that the Malden *et al.*[195] case series may have missed less severe cases of osteonecrosis of the jaw 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 cancer patients without ONJ (Miksad *et al.*),[198] and patients with stage 1 would be more likely to be managed

conservatively,[194] we felt that exclusion of this group was unlikely to significantly bias the estimates of costs and QALYs resulting from ONJ priovided 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 basecase analysis but we note that their impact is very small due to the extremely low incidence.

Kanis *et al.*[146] 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 that average discounted lifetime cost and QALY loss attributable to VTE using a published model (Pandor *et al*, In press).[199] 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 where 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 £1,890 and 0.77 QALYs for a patient with a starting age of 50.

The largest RCT reporting VTE as an adverse outcome for RLX was the MORE study (Ettinger *et al.,* 1999, Maricic *et al.,* 2002)[52, 101] which reported that 25 out of 2557 patients receiving RLX experience VTE, whereas 8 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*. did not report the proportion of these events that were PE but did say that a mixture of PE and DVT events were observed. The study by Silverman *et al.*[51] did repot the breakdown by type of VTE and reported that 4 of the 12 VTE events in the RLX treated arm were PE. It should be noted that in the model by Pandor *et al*.[199] 30% of symptomatic VTE events are PE which is reasonably consistent with the ratio of PE to DVT observed in the RLX arm in the study by Silverman *et al*. (2008).[51]

By applying the estimates of costs and QALYs per symptomatic VTE derived from Pandor *et al.*[199] 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 age 50). 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 lower for older patients experiencing VTE as much of the QALY loss is attributed to long-term sequelae that have a greater impact in patients with higher life-expectancy. However, when assuming a start age of 75, the INMB loss attributable to VTE per patient started on RLX was estimated to be £47 (compared with £53 for patients aged 50) so the error associated with applying costs and QALYas estimated for a 50 year-old was not considered likely to have resulted in a large bias. The average costs and QALYs 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 SA assuming full treatment persistence.

6.2.1.10 Disease costs

The costs of fracture in the TA464[140] model were based on a UK resource use study reported in two papers by Gutierrez *et al.*[200, 201] which used a GP database (The Health Improvement Network) to estimate resource use for those who fractured compared with matched controls. Unit costs from 2013/14 reference costs[202] and PSSRU unit costs[203] were then applied to this resource use to estimate 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 reported using costs based on Gutierrez *et al.* (UCB and Amgen)[20, 98] and five used estimates from the literature from less recent publications (Kanis 2005, Kanis 2008, Strom 2013, Stevenson 2005, Waugh 2011).[146, 148, 149, 151, 152]

The AG identified two additional relevant UK studies in the systematic database search conducted to identify published cost-effectiveness analyses. Lambrelli *et al.*[204] used a methodology similar to that employed by Gutierrez *et al.* but using an alternative primary care database (CPRD) with linkage to a secondary care database (Hospital Episode Statistics [HES]). Lambrelli *et al.*[204] reported costs in the year following hip fracture of £7,359. Leal *et al.*[205] 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[140] based on the data from Gutierrez *et al.* when excluding the costs of home help was £6,274. The AG decided to use the data from TA464[140] and to adjust it using PSSRU inflation indices,[16] as the two studies by Gutierrez *et al.* provided a consistent methodology for estimating both hip and non-hip fractures and they 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[140] using PSSRU inflation indices.[16]

The costs applied in the first and subsequent years following fracture are summarised in

Table 8.

6.2.1.11 Health-related quality of life

The systematic review of health-related quality of life studies conducted to for TA464[140] was updated. Further details on the review methods and findings can be found in Appendix 11. In summary, the review identified four papers[206-209] all reporting outcomes from the ICUROS study. This study was previously identified in the review conducted for TA464.[140] However, the four new papers identified reported additional data. ICUROS was an international multi-centre study and two of the papers[206, 207] reported outcomes from specific countries that formed subgroups of the overall ICUROS study population. The other two papers reported longer-term follow-up from the overall international dataset. One of these papers[209] restricted their 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 dataset.[208] 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 sub-population of ICUROS.[206] Although these data were specific to a different country, results were presented in an appendix using the UK TTO 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.

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

Parameter	Hip	Vertebrae	Proximal humerus	Wrist	New admission to residential care
Costs in year of fracture [a]	£8,568	£4,342	£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
Utility in subsequent years	0.86 [b]	0.85 [b]	1.00 [c]	0.99 [b]	0.625

[a] data applied in TA464[140] but inflated using PSSRU inflation indices[16]

[b] International ICUROS data reported by Svedbom *et al.* (2018) [208]

[c] Calculated from Australian ICUROS subgroup data reported by Abimanyi-Ochom *et al.* (2015)[206] and assumed fixed it the PSA

[d] data from Tidermark *et al.*[210] previously applied in TA464[140]

6.2.12 Model valudation

The model is designed to operate in several different modes which facilitate 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 12.

6.2.13 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 estiamtes 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 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 PSSRU; utility in the second year after proximal humerus fracture; life expectancy after fracture associated with excess mortality; unit costs for

prescriptions after fracture; and proportion of self-funders for residential care, costs and QALY decrements for adverse events.

Structural sensitivity analyses were conducted to explore whether the results were sensitive to different model assumptions. To reduce model computation time, the structural sensitivity analyses were conducted using midpoint parameter inputs rather than using the full PSA version of the model. Any structural sensitivity analyses conducted during TA464 which 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 adverse events.

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.], TPTD and offset period equal to treatment duration for ZOL, DEN, 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 and UCB submissions focused on high risk subgroups. In order 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 model as closely as possible, although an exact match was not possible as the AG model uses FRAX for unknown BMD whereas the UCB model specifies the T-Score of the patient. The patient characteristics selected were female, aged 75, with a previous fracture, a BMI of 21 and one additional risk factor which was chosen to be moderate alcohol consumption (3-6 units per day) to give a FRAX risk which was similar to the FRAX risk of 30% reported for the patient population in the UCB 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.

6.2.2 Basecase results

The basecase results are based on the average model outcomes across 2 million patients from the PSA version of the model run with 1 parameter sample per patient. As the cost-effectivenss is dependent on absolute risk of fracture, results are provided for 10 risk categories each containing approximately 200,000 patients. It should be noted that the patients within 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 to no treatment, when using QFracture to estimate fracture risk, are summarised in Table 9 along with the LYs gained (equivalent data when using FRAX to estimate fracture risk can be found in Appendix 13). It shoud 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 midpoint 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, where the HR for hip fracture was 0.93 (CrI of 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 midpoint HRs and therefore it clear that it is being caused by the distribution of CODA samples for the hip fracture HR for RLX.

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 LYs gained. This is because the LYs 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 and this results in a greater number of LYs gained.

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

	Adverse clinical outcomes <u>avoided</u> per 100,000 patients treated when compared to no treatment							**Total LYS 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

Table 10. We used a regression using a generalised additive model (GAM) 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 Figure 12 for FRAX. 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 acrosss the range of fracture risk observed in the population eligible for risk assessment. (A negative INMB in Figures 11 and 12 indicates an ICER over £20,000 per QALY compared to no treatment). For RLX, the relationship between fracture risk and INMB is less clear, particularly when using FRAX to estimate fracture risk. The INMB versus no treatment predicted by the regression does go above zero from a FRAX score of 32.6% to 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 over 30% and 0.2% of patients have a FRAX score less than 40%, which is why we do not present the INMB plots for FRAX scores higher than 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 over 30% when using QFracture. The plot of INMB versus risk for RLX may also be less well defined for RLX than 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.

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 below £30,000 compared to no treatment for FRAX scores above 45%; it remained under zero for the full range of QFracture scores. However, the AG notes the estimates of INMB at these very high levels of risk are uncertain as they are informed by less than 0.05% of the simulated population.

A full incremental analysis for each risk category is presented in Appendix 14 for QFracture and Appendix 15 for FRAX. The optimal treatment (i.e. the one with maximum INMB) when valuing a QALY at either £20,000 or £30,000 is summarised in Table 9 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 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 estimates 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 higher INMB than the oral bisphosphonates. However, ZOL has a positive INMB versus no treatment from a FRAX score of 31.1% for Qfracture and 22.5% for FRAX. Conversely, i.v. IBN is always dominated by i.v. ZOL due to the higher costs associated with quarterly administration and the poorer efficacy estimates.

RLX 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.

TPTD is consistently dominated by ROMO/ALN across all risk categories for both QFracture and FRAX. This is because [redacted], the efficacy is applied over a longer timeframe as the treatment duration is not limited to 2 years and the [redacted] benefits from the low cost of [redacted].

6.2.3 Sensitivity analyses results

The results for the structural sensitivity analyses (conducted using midpoint parameter estimates) are presented in Appendix 16. In broad terms the results for non-bisphosphonates were consistent with the basecase analysis in that none of the non-bisphosphonates had an ICER under £30,000 per QALY when compared to 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 versus no treatment (see Table 74). The ICER for ZOL versus 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 had an ICER of £26,977 versus ALN. However, this scenario analysis shows that the results may be more favourable when considering specific high risk groups, even though the ICER for DEN in the highest decile of FRAX risk scores where the average risk score was 25% was above £30,000 per QALY versus no treatment. 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 at 13.3%. In this scenario none of the non-bisphosphonates had ICERs under £30,000 versus no treatment (see Table 75) when using QFracture to estimate absolute fracture risk.

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

	Adverse clinical outcomes avoided per 100,000 patients treated when compared to no treatment							Total LYS 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

Table 10: ICERs versus no treatment (NT) and treatment with maximum INMB by risk deciles for QFracture and FRAX

Risk decile	**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	£5,622	Dominates	£31,200
RIS	£829,832	£319,027	£129,889	£100,618	£81,404	£64,979	£32,482	£17,119	£7,235	Dominates	£33,840
IBN (oral)	£948,571	£301,165	£119,370	£137,375	£93,736	£68,805	£34,713	£21,840	£9,443	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max INMB at £20K	NT	NT	NT	NT	NT	NT	NT	ALN	ALN	ALN	NT
at £30K	NT	NT	NT	NT	NT	NT	NT	ALN	ALN	ALN	NT
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	£8,951	£3,791	Dominates	Dominates	Dominates	£3,659
RIS	£32,429	£27,654	£15,575	£17,389	£11,265	£8,736	£4,572	Dominates	Dominates	Dominates	£4,181
IBN (oral)	£34,519	£27,349	£17,728	£16,459	£12,209	£12,389	£6,035	£734	Dominates	Dominates	£5,333
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max INMB at £20K	NT	NT	RIS	ALN	RIS	ALN	ALN	ALN	ALN	ALN	ALN
at £30K	ALN	ALN	RIS	ALN	RIS	ALN	ALN	ALN	ALN	ALN	ALN

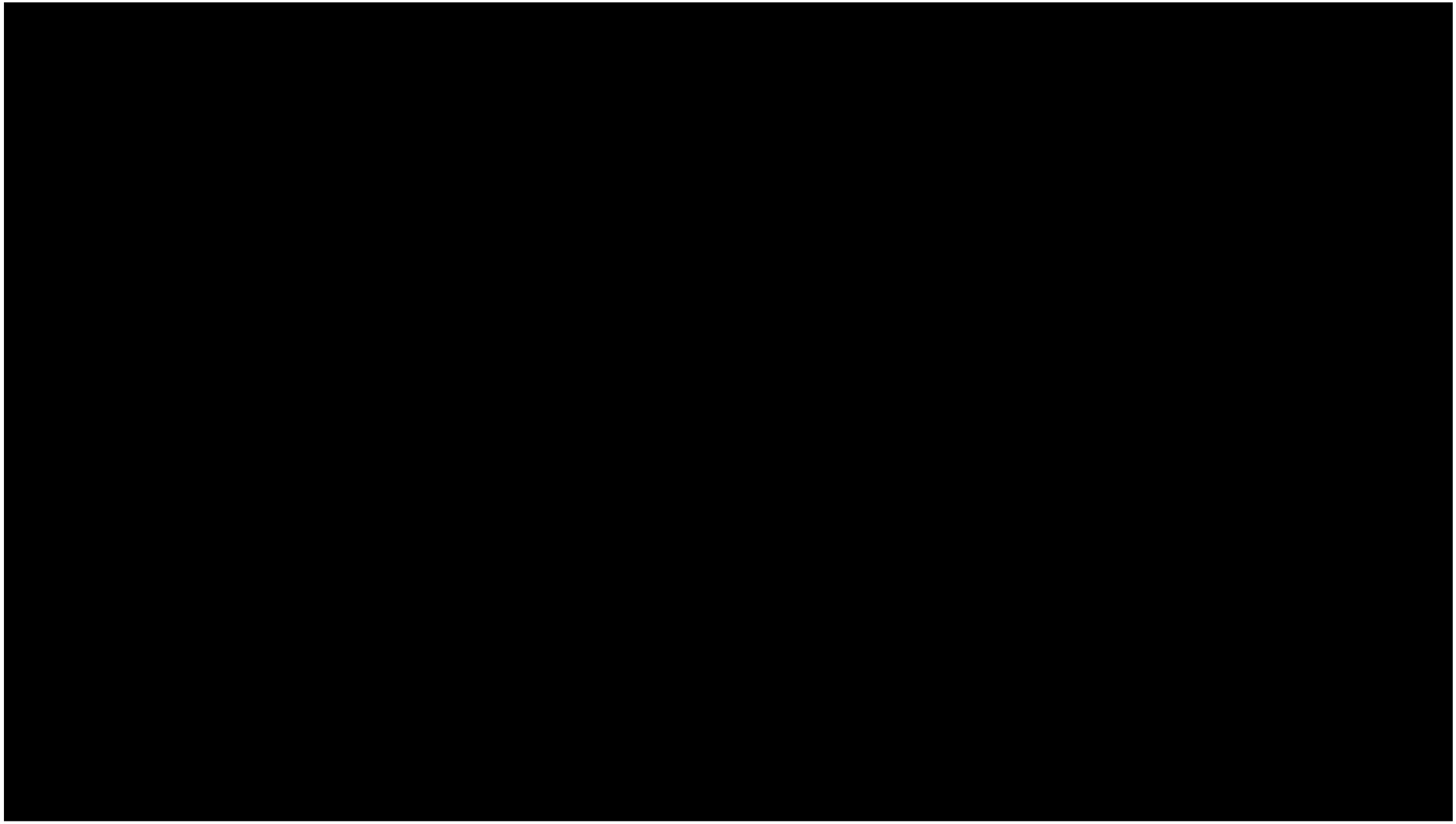

Figure 11: INMB as a function of absolute fracture risk as determined by QFracture

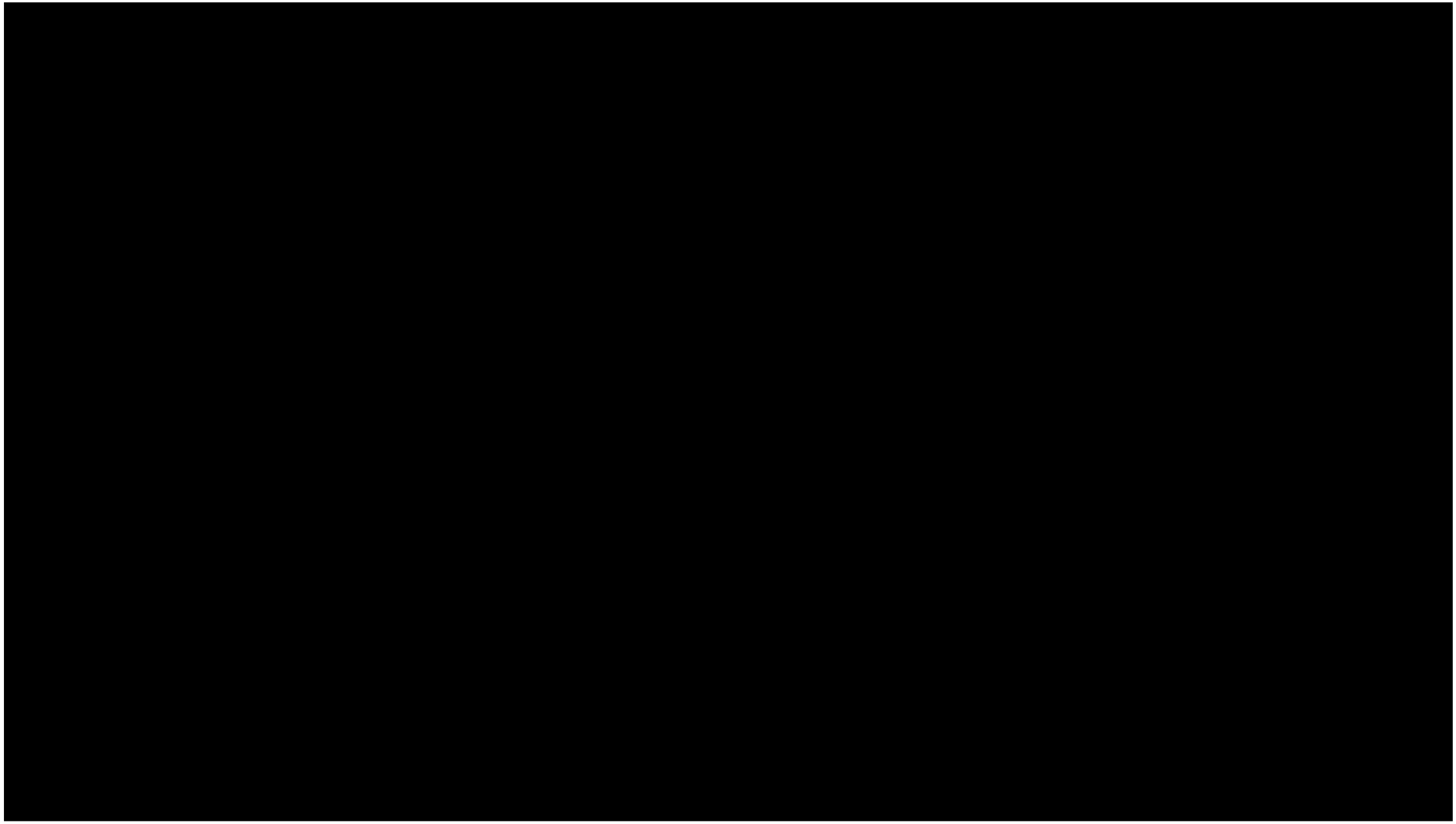

Figure 12: INMB as a function of absolute fracture risk as determined by FRAX

6.2.4 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, whilst the overall model structure and many of the data inputs have remained unchanged to maintain consistency, there are several areas of 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 company submission. This has increased the duration of treatment persistence for oral bisphosphonates 3-fold. We have incorporated monitoring costs for bisphosphonates consisting of annual follow-up appointments to encourage persistence and manage adverse events and DXA scans when completing treatment to assess need for continued treatment. We have applied the HRs from the NMA for each individual bisphosphonate, as per the original AG report for TA464, rather than the estimates based on the bisphosphonate class-effect as presented in the addendum which followed the original assessment report. However, this only impacts 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 prices 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 due to sparse 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 bisphosphonates become cost-effective is higher than in the analysis that informed TA464. 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 Quality Standard (QS14) which provide age-related intervention thresholds varying from a 10-year absolute risk level of 5.9% in patients aged 40 rising to 20% in patients aged ≥70.[12] In addition, it is noted that TA464 recommends i.v. bisphosphonates for patients with a risk of 10% or higher but i.v. IBN and ZOL had ICERs over £30,000 at this

risk level in the revised analysis. Again, this is likely to be as a results of the incorporation of additional costs for monitoring in secondary care and the correction to the administration costs for i.v. ibandronate.

The models in the UCB and Amgen submissions both focused their analysis only on higher risk subgroups of the population specified in the scope, whilst the AG model provides cost-effectiveness estimates for 10 risk categories covering the whole population eligible for risk assessment under CG146. 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 and Amgen 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 versus no treatment for DEN that was under £30,000 per QALY suggesting that the cost-effectiveness estimates for some non-bisphosphonates may be more favourable for specific high risk patients. The AG notes that this scenario analyses should be interpreted somewhat cautiously as other patients with a similar FRAX score may be more or less cost-effective.

There are several key differences between the AG analysis and the analyses presented in the UCB and Amgen submissions that should also be noted when interpreting these differences. The model in the Amgen submission incorporated a much higher cost of administration for i.v. ZOL (£559 vs £253) which resulted in a more favourable comparison of DEN versus ZOL. The model in the Amgen submission assumed that all DEN treatments would be administered in primary care whereas the AG model assumed that the first 2 DEN treatments would be given in secondary care which substantially increases the administration costs for DEN. The model in the Amgen submission 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 and UCB submissions which allowed for an increase risk of mortality that persisted beyond the 6-month timeframe assumed by the AG for excess mortality attributable to fracture. However, it was not possible to assses the impact of the different assumptions on mortality attributable to fracture within the AG model due to the different model structures employed. The model in the UCB submission 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 applied a short-term elevated risk for recent fracture in addition to the long-term elevated risk following fracture incorporated within 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, within the AG model, the increased risk incoporated within the QFracture and FRAX score 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 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 they had previously had 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 within 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 who have different treatment options which was not feasible. Whilst 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, whilst 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 within 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 antiresportives (ALN, RIS, IBN, ZOL, DEN). Alternatively, deleting the bisphosphonates rows from the tables would allow the optimal treatment to be identified for patients in 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 gender, 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,

gender 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[84] 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 less than 4 years in the basecase model due to the application of real-world persistence data for ALN so the need for extrapolation is minimised.

AEs 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 within 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 within the simulated population. The estimates of costs and QALY decrements attributable to AE 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 where the AE events 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 costs of treatment (discounted INMB decrement of £53 per patient started on treatment versus an annual drug cost of £43) meaning that this is likely to be a significant driver of cost-effectiveness for RLX. (Whilst 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 where there is more than one preparation we have assumed that the lowest cost preparation is used, which is often the generic form, where one is avaiable. We also note that the TPTD patent will expire in August 2019 and two biosimilars have already been approved (Movymia and Terrosa),[21, 22] but their prices are currently unknown. It is likely that these biosimilar preparations will have a lower cost and therefore the estimates of cost-effectiveness for TPTD may be overly pessimistic compared to 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 of the MTA stated that, "if evidence allows, treatment sequences will be considered." 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 submission 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. Whilst there was RCT evidence comparing the sequence of ROMO/DEN to placebo followed by DEN from the FRAME[55] 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) and 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 within the population eligible for risk assessment under CG146. 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 adderess 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.

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7 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

The only non-bisphosphonate not currently in use within the NHS in England is ROMO. The UCB 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.

8 DISCUSSION

8.1 Statement of principle findings

Fifty-two RCTs of non-bisphosphonates were included in the review. An additional fifty-one 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 serious adverse event rates were: DEN 2% to 25.8%; RLX 2% to 18.6%; ROMO 3.2% to 12.9%; TPTD 0% to 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: 0.16-0.32, Probability of being the best (PB): 0.38), non-vertebral (HR 0.58, 95% CrI: 0.45-0.76, PB: 0.52), hip (HR 0.35, 95%CrI: 0.15-0.73, PB: 0.50) and wrist (HR 0.75, 95% CrI: 0.38-1.41, PB: 0.28) fractures, while ROMO was the most effective for proximal humerus fractures, and ROMO/ALN (HR 0.10, 95% CrI: 0-3.66, PB: 0.77) for percentage change in femoral neck BMD. In general, the ranking of treatments varied for the different outcomes.

The ICERS compared with no treatment are above £20,000 per QALY for all non-bisphosphonate interventions across the range of QFracture and FRAX scores expected in the population eligible for fracture risk assessment. The ICER for DEN may fall below £30,000 at very high levels of risk (FRAX score >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 in high risk patients with specific characteristics.

8.2 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 FN BMD data. NMAs were used to synthesise the evidence, permiting 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 endpoint of BMD which is a surrogate endpoint, rather than fractures which are of clinical importance to patients.

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 this network as this was less sparse.

Due to the limitations of the evidence available, we were only able to model one treatment sequence within the economic analysis. Whilst we were able to estimate INMB as a function of absolute risk across the full range of risk scores expected within 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).

8.3 Uncertainties

Although statistically significant treatment effects were found when comparing interventions to 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.

8.4 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 whilst ROMO

was still being assessed by the European Medicines Agency and therefore it is based on the anticipated rather than the final licensed indication for ROMO.

9 CONCLUSIONS

RCTs were available for all non-bisphosphonate treatments of interest, reporting fracture data and FN BMD data. 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 compared with no treatment are above £20,000 per QALY for all non-bisphosphonate interventions across the range of QFracture and FRAX scores expected in the population eligible for fracture risk assessment. The ICER for DEN may fall below £30,000 at very high levels of risk (FRAX score >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 in high risk patients with specific characteristics.

9.1 Implications for service provision

As the majority of the non-bisphosphonates 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.

9.2 Suggested research priorities

Additional head-to-head studies 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 a treatment sequence of TPTD followed by ALN provides similar efficacy to the ROMO/ALN sequence.

There were not many trials with a follow-up of longer than 36 months. The reporting of long-term outcomes from the ARCH and FRAME studies for ROMO in particular would be useful to see if the treatment effectiveness persists during the following years of antiresportive 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 in men or 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.

10 REFERENCES

1. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of World Health Organization study group no. WHO Technical Report Series 843; 1994.
2. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F*, et al.* European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2008;19:399-428.
3. Online NCS. Osteoporosis Prevention, Diagnosis, and Therapy. 200011/12/2014).
4. Pasco JA, Seeman E, Henry MJ, Merriman EN, Nicholson GC, Kotowicz MA. The population burden of fractures originates in women with osteopenia, not osteoporosis. *Osteoporosis Int* 2006;17:1404-9.
5. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J*, et al.* Osteoporosis in the European Union: Medical management, epidemiology and economic burden: A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Archives of Osteoporosis* 2013;8 (1-2) (no pagination).
6. Svedbom A, Hernlund E, Ivergard M, Compston J, Cooper C, Stenmark J*, et al.* Osteoporosis in the European Union: A compendium of country-specific reports. *Archives of Osteoporosis* 2013;8 (1-2) (no pagination).
7. Gauthier A, Kanis J, Jiang Y, Martin M, Compston J, Borgstrom F*, et al.* Epidemiological burden of postmenopausal osteoporosis in the UK from 2010 to 2021: estimations from a disease model. Paper presented at: Archives of Osteoporosis2011.
8. National Institute for Health and Care Excellence. Osteoporosis: assessing the risk of fragility fracture. Clinical guideline [CG146]. *Journal* 2012. https://www.nice.org.uk/guidance/cg146/resources/osteoporosis-assessing-the-risk-of-fragility-fracture-pdf-35109574194373 [Accessed 20 November 2018]
9. National Institute for Health and Care Excellence. Bisphosphonates for treating osteoporosis. Technology Appraisal Guidance [TA464]. *Journal* 2017. https://www.nice.org.uk/guidance/ta464/resources/bisphosphonates-for-treating-osteoporosis-pdf-82604905556677 [Accessed 20 November 2018]
10. National Institute for Health and Care Excellence. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. Technology appraisal guidance [TA204]. 2010. https://www.nice.org.uk/guidance/ta70 [Accessed 31 October 2018] (Accessed 23 November 2016).
11. National Institute of Heath and Care Excellence (NICE). Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women [TA161]. 2008. https://www.nice.org.uk/Guidance/TA161 [Accessed 2 November 2018] (Accessed 22 March 2016).
12. National Institute for Health and Care Excellence. NICE quality standard 149 on osteoporosis. *Journal* 2017. https://www.nice.org.uk/guidance/qs149/resources/osteoporosis-pdf-75545487906757 [Accessed 20 November 2018]
13. National Osteoporosis Guideline Group. NGG 2017: Clinical guideline for the prevention and treatment of osteoporosis. *Journal* 2017. https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf [Accessed 20 November 2018]

14. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J*, et al.* Osteoporosis in the European Union: Medical management, epidemiology and economic burden: A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Journal* 2013. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2014029368 [Accessed 20 November 2018]
15. Stevenson M, Davis S. Analyses of the cost-effectiveness of pooled alendronate and risedronate, compared with strontium ranelate, raloxifene, etidronate and teriparatide. *Journal* 2006. https://www.nice.org.uk/guidance/TA160/documents/dsu-economic-evaluation-of-pooled-alendronate-and-risedronate-compared-with-strontium-ranelate-raloxifene-etidronate-and-teriparatide2 [Accessed 30 November 2018]
16. Curtis L, Burns A. Unit costs for health and social care 2017. *Journal* 2017. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/ [Accesed 20 November 2018]2014
17. National Institute for Health and Care Excellence. Osteoporosis Overview - NICE pathway. *Journal* 2018. https://pathways.nice.org.uk/pathways/osteoporosis#content=view-index [Accessed 20 November 2018]
18. National Institute for Health and Care Excellence. Fragility fracture risk assessment - NICE Pathway. *Journal* 2018. http://pathways.nice.org.uk/pathways/osteoporosis#path=view%3A/pathways/osteoporosis/fragility-fracture-risk-assessment.xml&content=view-index [Accessed 30 November 2018]
19. National Institute for Health and Clinical Excellence. Non-bisphosphonates for treating osteoporosis: Final Scope. London; 2018.
20. UCB Pharma. Company evidence submission for romosozumab.
21. Summary of opinion1 (initial authorisation) - Movymia. London: European Medicines Agency; 2016.
22. Summary of opinion1 (initial authorisation) - Terrosa. London: European Medicines Agency; 2016.
23. Summary of Product Characteristics for Evista 60 mg film coated tablets. *Journal* 2018. https://www.medicines.org.uk/emc/product/3778/smpc [Accessed 20 Novmebr 2018]
24. Summary of Product Characteristics for FORSTEO 20 micrograms/80 microlitres solution for injection in pre-filled pen. *Journal* 2018. https://www.medicines.org.uk/emc/product/2215 [Accessed 20 Novmebr 2018]
25. UCB Pharma Ltd. A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Compare the Efficacy and Safety of Romosozumab With Placebo in Men With Osteoporosis. Clinical Study Report.; 2016.
26. National Institute for Health and Care Excellence. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. Technology Appraisal Guidance [TA464]. *Journal* 2010. https://www.nice.org.uk/guidance/ta204/resources/denosumab-for-the-prevention-of-osteoporotic-fractures-in-postmenopausal-women-pdf-82600189194949 [Accessed 20 November 2018]

27. National Institute for Health and Care Excellence. Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal actures inpostmenopausal women. Technology Appraisal Guidance [TA161]. *Journal* 2010. https://www.nice.org.uk/guidance/ta161/resources/raloxifene-and-teriparatide-for-the-secondary-prevention-of-osteoporotic-fragility-fractures-in-postmenopausal-women-pdf-82598370170821 [Accessed 20 November 2018]
28. NHS Digital. Prescription Cost Analysis - England, 2017 [PAS]. *Journal* 2017. https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/prescription-cost-analysis-england-2017 [Accessed 21 November 2018]
29. NHS Digital. Prescribing Costs in Hospitals and the Community, England 2016/17. *Journal* 2017. https://digital.nhs.uk/data-and-information/publications/statistical/prescribing-costs-in-hospitals-and-the-community/2016-17 [Accessed 21 November 2018]
30. MedicinesComplete. British National Formulary (BNF). *Journal* 2018. https://www.medicinescomplete.com/#/ [Accessed 21 November 2018]
31. Compston J, Cooper A, Cooper C, Francis R, Kanis JA, Marsh D*, et al.* Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. National Osteoporosis Guideline Group; 2014.
32. World Health Organization Centre for Metabolic Bone Diseases. FRAX®. 2014. http://www.shef.ac.uk/FRAX/ (Accessed 11/12/2014).
33. ClinRisk. QFracture® - 2012 risk calculator. ClinRisk Ltd. 2012. http://qfracture.org (Accessed 11/12/2014).
34. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2009;339.
35. National Institute for Health and Clinical Excellence. Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161). London: National Institute for Health and Clinical Excellence (NICE); 2015.
36. National Institute for Health and Clinical Excellence. Non-bisphosphonates for treating osteoporosis: Final scope. London: National Institute for Health and Clinical Excellence (NICE); 20158.
37. UCB Pharma Ltd. A Multicenter, International, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Efficacy and Safety of Romosozumab Treatment in Postmenopausal Women With Osteoporosis. Clinical Study Report.; 2017.
38. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. 1993;8:1137-48.
39. Higgins J, Altman A, Sterne J, on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins J, Churchill R, Chandler J, Cumpston M, editors. *Cochrane Handbook for Systematic Reviews of Interventions version 520 (updated June 2017)*: Cochrane, 2017. Available from www.training.cochrane.org/handbook; 2017.
40. The Cochrane Collaboration. Review Manager (RevMan). In. 5.2 ed; 2014.
41. Wright CC, Sim J. Intention-to-treat approach to data from randomized controlled trials: a sensitivity analysis. *Journal of Clinical Epidemiology* 2003;56:833-42.

42. Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR*, et al.* Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756-65.
43. Orwoll E, Teglbjaerg CS, Langdahl BL, Chapurlat R, Czerwinski E, Kendler DL*, et al.* A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. *J Clin Endocrinol Metab* 2012;97:3161-9.
44. Nakamura T, Matsumoto T, Sugimoto T, Hosoi T, Miki T, Gorai I*, et al.* Clinical Trials Express: fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: denosumab fracture intervention randomized placebo controlled trial (DIRECT). *J Clin Endocrinol Metab* 2014;99:2599-607.
45. Nakamura T, Matsumoto T, Sugimoto T, Shiraki M. Dose-response study of denosumab on bone mineral density and bone turnover markers in Japanese postmenopausal women with osteoporosis. *Osteoporos Int* 2012;23:1131-40.
46. Koh JM, Chung DJ, Chung YS, Kang MI, Kim IJ, Min YK*, et al.* Assessment of Denosumab in Korean Postmenopausal Women with Osteoporosis: Randomized, Double-Blind, Placebo-Controlled Trial with Open-Label Extension. *Yonsei Medical Journal* 2016;57:905-14.
47. Adami S, San Martin J, Munoz-Torres M, Econs MJ, Xie L, Dalsky GP*, et al.* Effect of raloxifene after recombinant teriparatide [hPTH(1-34)] treatment in postmenopausal women with osteoporosis. *Osteoporos Int* 2008;19:87-94.
48. Morii H, Ohashi Y, Taketani Y, Fukunaga M, Nakamura T, Itabashi A*, et al.* Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. *Osteoporos Int* 2003;14:793-800.
49. Liu JL, Zhu HM, Huang QR, Zhang ZL, Li HL, Qin YJ*, et al.* Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in Chinese postmenopausal women with osteoporosis: a multi-center, randomized, placebo-controlled clinical trial. *Chin Med J* 2004;117:1029-35.
50. Gorai I, Hattori S, Tanaka Y, Iwaoki Y. Alfacalcidol-supplemented raloxifene therapy has greater bone-sparing effect than raloxifene-alone therapy in postmenopausal Japanese women with osteoporosis or osteopenia. *J Bone Miner Metab* 2012;30:349-58.
51. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ*, et al.* Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res* 2008;23:1923-34.
52. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK*, et al.* Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators.[Erratum appears in JAMA 1999 Dec 8;282(22):2124]. *Jama* 1999;282:637-45.
53. Lufkin EG, Whitaker MD, Nickelsen T, Argueta R, Caplan RH, Knickerbocker RK*, et al.* Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res* 1998;13:1747-54.

54. Mok CC, Ying KY, To CH, Ho LY, Yu KL, Lee HK*, et al.* Raloxifene for prevention of glucocorticoid-induced bone loss: a 12-month randomised double-blinded placebo-controlled trial. *Annals of the Rheumatic Diseases* 2011;70:778-84.
55. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S*, et al.* Romosozumab Treatment in Postmenopausal Women with Osteoporosis. *N Engl J Med* 2016;375:1532-43.
56. Ishibashi H, Crittenden DB, Miyauchi A, Libanati C, Maddox J, Fan M*, et al.* Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study. *Bone* 2017;103:209-15.
57. Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD*, et al.* A Phase 3 Randomized Placebo-controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis. *J Clin Endocrinol Metab* 2018;20:20.
58. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A*, et al.* The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003;18:9-17.
59. Miyauchi A, Matsumoto T, Sugimoto T, Tsujimoto M, Warner MR, Nakamura T. Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-month, randomized, placebo-controlled, double-blind and 12-month open-label phases. *Bone* 2010;47:493-502.
60. Miyauchi A, Matsumoto T, Shigeta H, Tsujimoto M, Thiebaud D, Nakamura T. Effect of teriparatide on bone mineral density and biochemical markers in Japanese women with postmenopausal osteoporosis: a 6-month dose-response study. *J Bone Miner Metab* 2008;26:624-34.
61. Miller PD, Leder BZ, Hattersley G, Lau E, Alexandersen P, Hala T*, et al.* Effects of abaloparatide on vertebral and non-vertebral fracture incidence in postmenopausal women with osteoporosis-results of the phase 3 active trial. *Endocrine Reviews Conference: 97th Annual Meeting and Expo of the Endocrine Society, ENDO* 2015;36.
62. Leder BZ, O'Dea LS, Zanchetta JR, Kumar P, Banks K, McKay K*, et al.* Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2015;100:697-706.
63. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY*, et al.* Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-41.
64. Sethi BK, Chadha M, Modi KD, Kumar KM, Mehrotra R, Sriram U. Efficacy of teriparatide in increasing bone mineral density in postmenopausal women with osteoporosis--an Indian experience. *Journal of the Association of Physicians of India* 2008;56:418-24.
65. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA*, et al.* Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet* 2013;382:50-6.
66. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM*, et al.* Denosumab and teriparatide transitions in postmenopausal osteoporosis (the

DATA-Switch study): extension of a randomised controlled trial. *Lancet* 2015;386:1147-55.
67. Eastell R, Nickelsen T, Marin F, Barker C, Hadji P, Farrerons J*, et al.* Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS). *J Bone Miner Res* 2009;24:726-36.
68. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS*, et al.* Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet* 2017;390:1585-94.
69. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A*, et al.* Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2014;370:412-20.
70. Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH*, et al.* Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res* 2009;24:153-61.
71. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S*, et al.* Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res* 2010;25:72-81.
72. Kendler DL, McClung MR, Freemantle N, Lillestol M, Moffett AH, Borenstein J*, et al.* Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. *Osteoporos Int* 2011;22:1725-35.
73. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH*, et al.* Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006;354:821-31.
74. Recknor C, Czerwinski E, Bone HG, Bonnick SL, Binkley N, Palacios S*, et al.* Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. *Obstet Gynecol* 2013;121:1291-9.
75. Saag KG, Wagman RB, Geusens P, Adachi JD, Messina OD, Emkey R*, et al.* Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diabetes Endocrinol* 2018;6:445-54.
76. Miller PD, Pannacciulli N, Brown JP, Czerwinski E, Nedergaard BS, Bolognese MA*, et al.* Denosumab or Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates. *J Clin Endocrinol Metab* 2016;101:3163-70.
77. Sambrook PN, Geusens P, Ribot C, Solimano JA, Ferrer-Barriendos J, Gaines K*, et al.* Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) International. *J Intern Med* 2004;255:503-11.
78. Luckey M, Kagan R, Greenspan S, Bone H, Kiel RD, Simon J*, et al.* Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. *Menopause* 2004;11:405-15.

79. Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;87:985-92.
80. Muscoso E, Puglisi N, Mamazza C, Lo Giudice F, Testai M, Abbate S*, et al.* Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study. *Eur Rev Med Pharmacol Sci* 2004;8:97-102.
81. Recker RR, Kendler D, Recknor CP, Rooney TW, Lewiecki EM, Utian WH*, et al.* Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone* 2007;40:843-51.
82. Sanad Z, Ellakwa H, Desouky B. Comparison of alendronate and raloxifene in postmenopausal women with osteoporosis. *Climacteric* 2011;14:369-77.
83. Michalska D, Stepan JJ, Basson BR, Pavo I. The effect of raloxifene after discontinuation of long-term alendronate treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2006;91:870-7.
84. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T*, et al.* Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *N Engl J Med* 2017;377:1417-27.
85. McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M*, et al.* Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass.[Erratum appears in Arch Intern Med. 2005 Oct 10;165(18):2120]. *Arch Intern Med* 2005;165:1762-8.
86. Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K*, et al.* Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum* 2009;60:3346-55.
87. Panico A, Lupoli GA, Marciello F, Lupoli R, Cacciapuoti M, Martinelli A*, et al.* Teriparatide vs. alendronate as a treatment for osteoporosis: changes in biochemical markers of bone turnover, BMD and quality of life. *Medical Science Monitor* 2011;17:CR442-8.
88. Gluer CC, Marin F, Ringe JD, Hawkins F, Moricke R, Papaioannu N*, et al.* Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. *J Bone Miner Res* 2013;28:1355-68.
89. Anastasilakis AD, Goulis DG, Polyzos SA, Gerou S, Koukoulis GN, Efstathiadou Z*, et al.* Head-to-head comparison of risedronate vs. teriparatide on bone turnover markers in women with postmenopausal osteoporosis: a randomised trial. *Int J Clin Pract* 2008;62:919-24.
90. Walker MD, Cusano NE, Sliney J, Jr., Romano M, Zhang C, McMahon DJ*, et al.* Combination therapy with risedronate and teriparatide in male osteoporosis. *Endocrine* 2013;44:237-46.
91. Geusens P, Marin F, Kendler DL, Russo LA, Zerbini CA, Minisola S*, et al.* Effects of Teriparatide Compared with Risedronate on the Risk of Fractures in Subgroups of Postmenopausal Women with Severe Osteoporosis: The VERO Trial. *J Bone Miner Res* 2018;33:783-94.
92. Hadji P, Zanchetta JR, Russo L, Recknor CP, Saag KG, McKiernan FE*, et al.* The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporos Int* 2012;23:2141-50.

93. Malouf-Sierra J, Tarantino U, Garcia-Hernandez PA, Corradini C, Overgaard S, Stepan JJ, *et al.* Effect of Teriparatide or Risedronate in Elderly Patients With a Recent Pertrochanteric Hip Fracture: Final Results of a 78-Week Randomized Clinical Trial. *J Bone Miner Res* 2017;32:1040-51.
94. Cosman F, Eriksen EF, Recknor C, Miller PD, Guanabens N, Kasperk C, *et al.* Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res* 2011;26:503-11.
95. Gorai I, Tanaka Y, Hattori S, Iwaoki Y. Assessment of adherence to treatment of postmenopausal osteoporosis with raloxifene and/or alfacalcidol in postmenopausal Japanese women. *J Bone Miner Metab* 2010;28:176-84.
96. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, *et al.* Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial.[Erratum appears in JAMA. 2017 Jan 24;317(4):442; PMID: 28118431]. *Jama* 2016;316:722-33.
97. NCT00670501. Effects of Teriparatide in the Treatment of Postmenopausal Women With Osteoporosis. *Journal* 2008. http://clinicaltrials.gov/show/NCT00670501 [Accesed 06 November 2018]
98. Amgen. Company evidence submission for denosumab.
99. Abtahi J, Henefalk G, Aspenberg P. Randomised trial of bisphosphonate-coated dental implants: Radiographic follow-up after five years of loading. *International Journal of Oral and Maxillofacial Surgery* 2016;45:1564-9.
100. Kendler DL, Marin F, Zerbini CAF. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial (vol 391, pg 230, 2017). *Lancet* 2018;391:204-.
101. Maricic M, Adachi JD, Sarkar S, Wu W, Wong M, Harper KD. Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. *Arch Intern Med* 2002;162:1140-3.
102. Saag KG, Shane E, Boonen S, Marin F, Donley DW, Taylor KA, *et al.* Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med* 2007;357:2028-39.
103. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, *et al.* 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol* 2017;5:513-23.
104. NCT00523341. Extension Study to Evaluate the Long Term Safety and Efficacy of Denosumab in the Treatment of Osteoporosis. 2007. https://clinicaltrials.gov/ct2/show/NCT00523341 (Accessed 20 October 2018).
105. Sugimoto T, Matsumoto T, Hosoi T, Miki T, Gorai I, Yoshikawa H, *et al.* Three-year denosumab treatment in postmenopausal Japanese women and men with osteoporosis: results from a 1-year open-label extension of the Denosumab Fracture Intervention Randomized Placebo Controlled Trial (DIRECT). *Osteoporos Int* 2015;26:765-74.
106. Langdahl BL, Marin F, Shane E, Dobnig H, Zanchetta JR, Maricic M, *et al.* Teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. *Osteoporos Int* 2009;20:2095-104.
107. Aspenberg P, Tarantino U, Corradini C, Overgaard S, Borris L, Frihagen F, *et al.* Teriparatide seems to improve recovery after pertrochanteric hip fracture:

Comparison with risedronate in a randomized, controlled trial. *HIP International* 2016;26 (Supplement 2):S14.
108. Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S*, et al.* Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int* 2011; http://dx.doi.org/10.1007/s00198-011-1780-1:1-10.
109. Leder BZ, Tsai JN, Uihlein AV, Burnett-Bowie SA, Zhu Y, Foley K*, et al.* Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab* 2014;99:1694-700.
110. Langdahl BL, Teglbjaerg CS, Ho PR, Chapurlat R, Czerwinski E, Kendler DL*, et al.* A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. *J Clin Endocrinol Metab* 2015;100:1335-42.
111. Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S*, et al.* Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int* 2012;23:317-26.
112. Curtis L, Burns A. Unit Costs of Health and Social Care 2017. *University of Kent* 2017.
113. European Medicines Agency. CHMP Assessment Report for Prolia. *Journal* 2010. https://www.ema.europa.eu/documents/assessment-report/prolia-epar-public-assessment-report_en.pdf [Accessed 31 October 2018]
114. European Medicines Agency. CHMP Assessment Report for Prolia. *Journal* 2009. https://www.ema.europa.eu/documents/assessment-report/prolia-epar-public-assessment-report_en.pdf [Accessed 31 October 2018]
115. National Institute of Heath and Care Excellence (NICE). Alendronate, Etidronate, Risedronate, Raloxifene and Strontium Ranelate for the Primary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women (Amended) [TA160]. 2011. http://www.laalamedilla.org/GUIAS/Guia%20NICE%20osteoporosis%20P12011.pdf (Accessed 31 October 2018).
116. European Medicines Agency. EPAR Scientific Discussion for Forsteo. *Journal* 2005. https://www.ema.europa.eu/documents/scientific-discussion/forsteo-epar-scientific-discussion_en.pdf [Accessed on 2 November 2018]
117. European Medicines Agency. Summary of Product Characteristics for Forsteo. *Journal* 2016. https://www.ema.europa.eu/documents/product-information/forsteo-epar-product-information_en.pdf [Accessed on 2 November 2018]
118. Silverman S, Viswanathan H, Wang A, Ragi-Eis S, Fardellone P, Gilchrist N*, et al.* Evaluation of health-related quality of life in postmenopausal women with osteoporosis who participated in the freedom trial. *Osteoporos Int* 2010;1):S14-S5.
119. Silverman S, Viswanathan HN, Yang YC, Wang A, Boonen S, Ragi-Eis S*, et al.* Impact of clinical fractures on health-related quality of life is dependent on time of assessment since fracture: results from the FREEDOM trial. *Osteoporos Int* 2012;23:1361-9.

120. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013;33:607-17.
121. Ren SJ, Oakley JE, Stevens JW. Incorporating Genuine Prior Information about Between-Study Heterogeneity in Random Effects Pairwise and Network Meta-analyses. *Med Decis Making* 2018;38:531-42.
122. Dias S., Sutton A. J., Welton N. J., Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. . *Med Decis Making* 2013;33:618-40.
123. Achana FA, Cooper NJ, Dias S, Lu G, Rice SJ, Kendrick D*, et al.* Extending methods for investigating the relationship between treatment effect and baseline risk from pairwise meta-analysis to network meta-analysis. *Stat Med* 2013;32:752-71.
124. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932-44.
125. Lunn DJ, Thomas A, Best N, Spiegelhalter DJS, Computing. WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. 2000;10:325-37.
126. R CORE TEAM. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. 2017.
127. Sturtz S., Ligges U., A. G. R2WinBUGS: A package for running WinBUGS from R. *Journal of Statistical Software* 2005;12:1-16.
128. Brooks S. P., A. G. General methods for monitoring convergence of iterative simulations. *Journal of Computational and Graphical Statistics* 1998;7:434-55.
129. Spiegelhalter DJ, Best NG, Carlin BR, Van Der Linde A. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society Series B-Statistical Methodology* 2002;64:583-616.
130. Miller PD, Schnitzer T, Emkey R, Orwoll E, Rosen C, Ettinger M*, et al.* Weekly oral alendronic Acid in male osteoporosis. *Clin Drug Investig* 2004;24:333-41.
131. Nakamura T, Fukunaga M, Nakano T, Kishimoto H, Ito M, Hagino H*, et al.* Efficacy and safety of once-yearly zoledronic acid in Japanese patients with primary osteoporosis: two-year results from a randomized placebo-controlled double-blind study (ZOledroNate treatment in Efficacy to osteoporosis; ZONE study). *Osteoporos Int* 2017;28:389-98.
132. Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. *Int J Clin Pract* 2001;55:505-9.
133. Hooper MJ, Ebeling PR, Roberts AP, Graham JJ, Nicholson GC, D'Emden M*, et al.* Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. *Climacteric* 2005;8:251-62.
134. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA*, et al.* Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. Paper presented at: N Engl J Med5/3/2007.
135. Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH*, et al.* Effect of Oral Alendronate on Bone Mineral Density and the Incidence of Fractures in Postmenopausal Osteoporosis. Paper presented at: N Engl J Med11/30/1995.

136. Carfora E, Sergio F, Bellini P. Effect of treatment of postmenopausal osteoporosis with continuous daily oral alendronate and the incidence of fractures. *Gazzetta Medica Italiana - Archivio Per Le Scienze Mediche* 1998;157:106-9.
137. Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, *et al.* Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004;19:1241-9.
138. Tan W, Sun J, Zhou L, Li Y, Wu X. Randomized trial comparing efficacies of zoledronate and alendronate for improving bone mineral density and inhibiting bone remodelling in women with post-menopausal osteoporosis. *J Clin Pharm Ther* 2016;41:519-23.
139. Paggiosi MA, Peel N, McCloskey E, Walsh JS, Eastell R. Comparison of the effects of three oral bisphosphonate therapies on the peripheral skeleton in postmenopausal osteoporosis: the TRIO study. *Osteoporos Int* 2014;25:2729-41.
140. Davis S, Martyn-St James M, Sanderson J, Stevens J, Goka E, Rawdin A, *et al.* A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. *Health Technol Assess* 2016;20:1-406.
141. National Institute for Health and Care Excellence. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. London: NICE; 2008.
142. National Institute for Health and Care Excellence. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. London: NICE; 2010.
143. National Institute for Health and Care Excellence. Osteoporosis: assessing the risk of fragility fracture. *Journal* 2018. https://pathways.nice.org.uk/pathways/osteoporosis#content=view-index&path=view%3A/pathways/osteoporosis/osteoporosis-assessing-the-risk-of-fragility-fracture.xml [Accessed 20 November 2018]
144. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. London: NICE; 2013.
145. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;8:iii-iv, ix-xi, 1-158.
146. Kanis JA, Borgstrom F, Johnell O, Oden A, Sykes D, Jonsson B. Cost-effectiveness of raloxifene in the UK: an economic evaluation based on the MORE study. *Osteoporos Int* 2005;16:15-25.
147. Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M. Treatment of established osteoporosis: a systematic review and cost-utility analysis. *Health Technol Assess* 2002;6:1-146.
148. Stevenson M, Jones ML, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess* 2005;9:1-160.
149. Kanis JA, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, *et al.* The cost-effectiveness of alendronate in the management of osteoporosis. *Bone* 2008;42:4-15.

150. Scotland G, Waugh N, Royle P, McNamee P, Henderson R, Hollick R. Denosumab for the prevention of osteoporotic fractures in post-menopausal women: a NICE single technology appraisal. *Pharmacoeconomics* 2011;29:951-61.
151. Strom O, Jonsson B, Kanis JA. Intervention thresholds for denosumab in the UK using a FRAX-based cost-effectiveness analysis. *Osteoporos Int* 2013;24:1491-502.
152. Waugh N, Royle P, Scotland G, Henderson R, Hollick R, McNamee P. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. *Health Technol Assess* 2011;15 Suppl 1:51-9.
153. Stevenson M, Davis S. Analyses of the Cost Effectiveness of Pooled Alendronate and Risedronate, Compared with Strontium Ranelate, Raloxifene, Etidronate and Teriparatide. Sheffield: University of Sheffield; 2006.
154. Tosteson AN, Gottlieb DJ, Radley DC, Fisher ES, Melton LJ, 3rd. Excess mortality following hip fracture: the role of underlying health status. *Osteoporos Int* 2007;18:1463-72.
155. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int* 2009;20:1633-50.
156. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C*, et al.* Mortality after osteoporotic fractures. *Osteoporos Int* 2004;15:38-42.
157. Jonsson B, Strom O, Eisman JA, Papaioannou A, Siris ES, Tosteson A*, et al.* Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 2011;22:967-82.
158. Barrett JA, Baron JA, Beach ML. Mortality and pulmonary embolism after fracture in the elderly. *Osteoporos Int* 2003;14:889-94.
159. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int* 2004;15:108-12.
160. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. *Bone* 2003;32:468-73.
161. Parker MJ, Anand JK. What is the true mortality of hip fractures? *Public Health* 1991;105:443-6.
162. Todd CJ, Freeman C, Camilleri-Ferrante C, Laxton C, Murrell P, Palmer C*, et al.* Anglian Audit of Hip Fracture 2. Cambridge: Unviersity of Cambridge; 1999.
163. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 1999;353:878-82.
164. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. *Bmj* 2009;339.
165. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *Bmj* 2012;344.
166. UCB Pharma Ltd. A Multicenter, International, Randomized, Double-blind, Alendronate-controlled Study to Determine the Efficacy and Safety of Romosozumab in the Treatment of Postmenopausal Women With Osteoporosis. Clinical Study Report.; 2017.

167. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: Systematic review and meta-analysis. *Osteoporos Int* 2010;21:1943-51.
168. Curtis JR, Yun H, Matthews R, Saag KG, Delzell E, Curtis JR*, et al.* Adherence with intravenous zoledronate and intravenous ibandronate in the United States Medicare population. *Arthritis care & research* 2012;64:1054-60.
169. Li L, Roddam A, Gitlin M, Taylor A, Shepherd S, Jick S. Non-Persistence to Anti-Osteoporosis Medications in the UK using the General Practice Research Database (GPRD). *Rheumatology* 2010;49:i23-i5.
170. Li L, Roddam A, Gitlin M, Taylor A, Shepherd S, Shearer A*, et al.* Persistence with osteoporosis medications among postmenopausal women in the UK General Practice Research Database. *Menopause* 2012;19:33-40.
171. Hadji P, Papaioannou N, Gielen E, Feudjo Tepie M, Zhang E, Frieling I*, et al.* Persistence, adherence, and medication-taking behavior in women with postmenopausal osteoporosis receiving denosumab in routine practice in Germany, Austria, Greece, and Belgium: 12-month results from a European non-interventional study. *Osteoporos Int* 2015;26:2479-89.
172. Karlsson L, Lundkvist J, Psachoulia E, Intorcia M, Strom O. Persistence with denosumab and persistence with oral bisphosphonates for the treatment of postmenopausal osteoporosis: a retrospective, observational study, and a meta-analysis. *Osteoporos Int* 2015;26:2401-11.
173. Silverman SL, Siris E, Belazi D, Recknor C, Papaioannou A, Brown JP*, et al.* Persistence at 24 months with denosumab among postmenopausal women with osteoporosis: results of a prospective cohort study. *Arch Osteoporos* 2018;13:85.
174. Arden NK, Earl S, Fisher DJ, Cooper C, Carruthers S, Goater M. Persistence with teriparatide in patients with osteoporosis: the UK experience. *Osteoporos Int* 2006;17:1626-9.
175. Abhishek A, Pande I. Teriparatide in men: persistence and geographical variation in the UK. *Osteoporos Int* 2009;20:1453-4.
176. Idolazzi L, Fassio A, Gatti D, Tamanini S, Viapiana O, Rossini M*, et al.* Duration of treatment for osteoporosis. *Reumatismo* 2013;65:22-35.
177. Schwartz AV, Bauer DC, Cummings SR, Cauley JA, Ensrud KE, Palermo L*, et al.* Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. *J Bone Miner Res* 2010;25:976-82.
178. Black D, Schwartz A, Ensrud K, Cauley J, Levis S, Quandt S*, et al.* Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *Journal of American Medical Association* 2006;296:2927-38.
179. Eastell R, Hannon RA, Wenderoth D, Rodriguez-Moreno J, Sawicki A. Effect of stopping risedronate after long-term treatment on bone turnover. *J Clin Endocrinol Metab* 2011;96:3367-73.
180. Watts NB, Chines A, Olszynski WP, McKeever CD, McClung MR, Zhou X*, et al.* Fracture risk remains reduced one year after discontinuation of risedronate. *Osteoporos Int* 2008;19:365-72.
181. Ravn P, Christensen JO, Baumann M, Clemmesen B. Changes in biochemical markers and bone mass after withdrawal of ibandronate treatment: prediction of bone mass changes during treatment. *Bone* 1998;22:559-64.

182. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL*, et al.* Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. *Annals of the Rheumatic Diseases* 2006;65:654-61.
183. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F*, et al.* The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT).[Erratum appears in J Bone Miner Res. 2012 Dec;27(12):2612]. *J Bone Miner Res* 2012;27:243-54.
184. Lindsay R, Scheele WH, Neer R, Pohl G, Adami S, Mautalen C*, et al.* Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med* 2004;164:2024-30.
185. Prince R, Sipos A, Hossain A, Syversen U, Ish-Shalom S, Marcinowska E*, et al.* Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. *J Bone Miner Res* 2005;20:1507-13.
186. Popp AW, Varathan N, Buffat H, Senn C, Perrelet R, Lippuner K. Bone Mineral Density Changes After 1 Year of Denosumab Discontinuation in Postmenopausal Women with Long-Term Denosumab Treatment for Osteoporosis. *Calcif Tissue Int* 2018;103:50-4.
187. NHS Prescription Servcies. The electronic Drug Tariff. Online: The Department of Health; 2018.
188. Commercial Medicines Unit. eMit national database. Online: Department of Health and Social Care; 2017.
189. Department of Health. National Schedule of Reference Costs - Year 2015/16 - NHS trusts and NHS foundation trusts. London: The Department of Health; 2016.
190. Wong M, Pacey S, Sahota O. Setting up a homecare service for zoledronic acid treatment of osteoporosis. *European Journal of Hospital Pharmacy* 2016;23:364-5.
191. Opinder S. Near final version of "Setting up a homecare service for zoledronic acid treatment of osteoporosis". In: Davis S, ed.; 2018.
192. Mason JM, Thomas KS, Crook AM, Foster KA, Chalmers JR, Nunn AJ*, et al.* Prophylactic antibiotics to prevent cellulitis of the leg: economic analysis of the PATCH I & II trials. *PLoS One* 2014;9:e82694.
193. Boquete-Castro A, Gomez-Moreno G, Calvo-Guirado JL, Aguilar-Salvatierra A, Delgado-Ruiz RA. Denosumab and osteonecrosis of the jaw. A systematic analysis of events reported in clinical trials. *Clinical Oral Implants Research* 2016;27:367-75.
194. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F*, et al.* Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015;30:3-23.
195. Malden N, Lopes V. An epidemiological study of alendronate-related osteonecrosis of the jaws. A case series from the south-east of Scotland with attention given to case definition and prevalence. *J Bone Miner Metab* 2012;30:171-82.
196. Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D*, et al.* Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *J Oral Maxillofac Surg* 2010;68:243-53.

197. Summary of Product Characteristics for Prolia 60 mg solution for injection in pre-filled syringe. Electronic Medicines Compendium. https://www.medicines.org.uk/emc/product/568/smpc [Accessed 31 October 2018] (Accessed
198. Miksad RA, Lai KC, Dodson TB, Woo SB, Treister NS, Akinyemi O*, et al.* Quality of life implications of bisphosphonate-associated osteonecrosis of the jaw. *Oncologist* 2011;16:121-32.
199. Pandor A, Horner D, Davis S, Goodacre S, Stevens JW, Clowes M*, et al.* Thromboprophylaxis for lower limb immobilisation: Systematic review and economic evaluation. *Health Technology Assessment* In press.
200. Gutierrez L RN, Castellsague J, Beard S, Rycroft C, Abeysinghe S, Shannon P, Robbins S, Gitlin M,. Study of the incremental cost and clinical burden of hip fractures in postmenopausal women in the United Kingdom. *J Med Econ* 2011;14:99-107.
201. Gutierrez L, Roskell N, Castellsague J, Beard S, Rycroft C, Abeysinghe S*, et al.* Clinical burden and incremental cost of fractures in postmenopausal women in the United Kingdom. *Bone* 2012;51:324-31.
202. Department of Health. National Schedule of Reference Costs - Year 2013-14. Department of Health, London: NHS Trusts and NHS Foundation Trusts; 2015.
203. Curtis L. Unit costs for health and social care 2014. Canterbury: PSSRU, University of Kent; 2014.
204. Lambrelli D, Burge R, Raluy-Callado M, Chen SY, Wu N, Schoenfeld MJ. Retrospective database study to assess the economic impact of hip fracture in the United Kingdom. *Journal of Medical Economics* 2014;17:817-25.
205. Leal J, Gray AM, Prieto-Alhambra D, Arden NK, Cooper C, Javaid MK*, et al.* Impact of hip fracture on hospital care costs: a population-based study. *Osteoporos Int* 2016;27:549-58.
206. Abimanyi-Ochom J, Watts JJ, Borgstrom F, Nicholson GC, Shore-Lorenti C, Stuart AL*, et al.* Changes in quality of life associated with fragility fractures: Australian arm of the International Cost and Utility Related to Osteoporotic Fractures Study (AusICUROS). *Osteoporos Int* 2015;26:1781-90.
207. Jurisson M, Pisarev H, Kanis J, Borgstrom F, Svedbom A, Kallikorm R*, et al.* Quality of life, resource use, and costs related to hip fracture in Estonia. *Osteoporos Int* 2016;27:2555-66.
208. Svedbom A, Borgstom F, Hernlund E, Strom O, Alekna V, Bianchi ML*, et al.* Quality of life for up to 18 months after low-energy hip, vertebral, and distal forearm fractures-results from the ICUROS. *Osteoporos Int* 2018;29:557-66.
209. Svedbom A, Borgstrom F, Hernlund E, Strom O, Alekna V, Bianchi ML*, et al.* Quality of life after hip, vertebral, and distal forearm fragility fractures measured using the EQ-5D-3L, EQ-VAS, and time-trade-off: results from the ICUROS. *Quality of Life Research* 2018;27:707-16.
210. Tidermark J, Zethraeus N, Svensson O, Tornkvist H, Ponzer S. Femoral neck fractures in the elderly: functional outcome and quality of life according to EuroQol. *Qual Life Res* 2002;11:473-81.
211. Tsourdi E, Langdahl B, Cohen-Solal M, Aubry-Rozier B, Eriksen EF, Guanabens N*, et al.* Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. *Bone* 2017;105:11-7.
212. Nayak S, Greenspan SL. Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc* 2017;65:490-5.

213. Kim SM, Kang KC, Kim JW, Lim SJ, Hahn MH. Current Role and Application of Teriparatide in Fracture Healing of Osteoporotic Patients: A Systematic Review. *Journal of Bone Metabolism* 2017;24:65-73.
214. Shi Z, Zhou H, Pan B, Lu L, Liu J, Kang Y*, et al.* Effectiveness of Teriparatide on Fracture Healing: A Systematic Review and Meta-Analysis. *PLoS ONE [Electronic Resource]* 2016;11:e0168691.
215. Beaudoin C, Jean S, Bessette L, Ste-Marie LG, Moore L, Brown JP. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. *Osteoporos Int* 2016;27:2835-44.
216. Chen JF, Yang KH, Zhang ZL, Chang HC, Chen Y, Sowa H*, et al.* A systematic review on the use of daily subcutaneous administration of teriparatide for treatment of patients with osteoporosis at high risk for fracture in Asia. *Osteoporos Int* 2015;26:11-28.
217. Diedhiou D, Cuny T, Sarr A, Norou Diop S, Klein M, Weryha G. Efficacy and safety of denosumab for the treatment of osteoporosis: A systematic review. *Ann Endocrinol (Paris)* 2015;76:650-7.
218. Fujiwara S, Hamaya E, Sato M, Graham-Clarke P, Flynn JA, Burge R. Systematic review of raloxifene in postmenopausal Japanese women with osteoporosis or low bone mass (osteopenia). *Clinical Interventions In Aging* 2014;9:1879-93.
219. Trevisani VF, Riera R, Imoto AM, Saconato H, Atallah AN. Teriparatide (recombinant human parathyroid hormone 1-34) in postmenopausal women with osteoporosis: systematic review. *Sao Paulo Med J* 2008;126:279-84.
220. Brandao CM, Lima MG, Silva AL, Silva GD, Guerra AA, Jr., Acurcio Fde A. Treatment of postmenopausal osteoporosis in women: a systematic review. *Cadernos de Saude Publica* 2008;24 Suppl 4:s592-606.
221. Gallacher SJ, Dixon T. Impact of treatments for postmenopausal osteoporosis (bisphosphonates, parathyroid hormone, strontium ranelate, and denosumab) on bone quality: a systematic review. *Calcif Tissue Int* 2010;87:469-84.
222. Lin T, Yan SG, Cai XZ, Ying ZM, Yuan FZ, Zuo X. Alendronate versus Raloxifene for Postmenopausal Women: A Meta-Analysis of Seven Head-to-Head Randomized Controlled Trials. *International Journal of Endocrinology Print* 2014;2014:796510.
223. MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M*, et al.* Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 2008;148:197-213.
224. Liu CL, Lee HC, Chen CC, Cho DY. Head-to-head comparisons of bisphosphonates and teriparatide in osteoporosis: a meta-analysis. *Clin Invest Med* 2017;40:E146-E57.
225. Liu GF, Wang ZQ, Liu L, Zhang BT, Miao YY, Yu SN. A network meta-analysis on the short-term efficacy and adverse events of different anti-osteoporosis drugs for the treatment of postmenopausal osteoporosis. *Journal of Cellular Biochemistry* 2018;119:4469-81.
226. Murad MH, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA*, et al.* Comparative Effectiveness of Drug Treatments to Prevent Fragility Fractures: A Systematic Review and Network Meta-Analysis. *J Clin Endocrinol Metab* 2012;97:1871-80.

227. Saito T, Sterbenz JM, Malay S, Zhong L, MacEachern MP, Chung KC. Effectiveness of anti-osteoporotic drugs to prevent secondary fragility fractures: systematic review and meta-analysis. *Osteoporos Int* 2017;28:3289-300.
228. Liu Y, Cao Y, Zhang S, Zhang W, Zhang B, Tang Q*, et al.* Romosozumab treatment in postmenopausal women with osteoporosis: a meta-analysis of randomized controlled trials. *Climacteric* 2018;21:189-95.
229. Wang YK, Qin SQ, Ma T, Song W, Jiang RQ, Guo JB*, et al.* Effects of teriparatide versus alendronate for treatment of postmenopausal osteoporosis: A meta-analysis of randomized controlled trials. *Medicine* 2017;96:e6970.
230. Wang G, Sui L, Gai P, Li G, Qi X, Jiang X. The efficacy and safety of vertebral fracture prevention therapies in post-menopausal osteoporosis treatment: Which therapies work best? a network meta-analysis. *Bone & Joint Research* 2017;6:452-63.
231. Lou S, Lv H, Wang G, Li Z, Li M, Zhang L*, et al.* The effect of sequential therapy for postmenopausal women with osteoporosis A PRISMA-compliant meta-analysis of randomized controlled trials. *Medicine (United States)* 2016;95:e5496.
232. Amiche MA, Albaum JM, Tadrous M, Pechlivanoglou P, Levesque LE, Adachi JD*, et al.* Efficacy of osteoporosis pharmacotherapies in preventing fracture among oral glucocorticoid users: a network meta-analysis. *Osteoporos Int* 2016;27:1989-98.
233. Chen LX, Zhou ZR, Li YL, Ning GZ, Zhang TS, Zhang D*, et al.* Comparison of Bone Mineral Density in Lumbar Spine and Fracture Rate among Eight Drugs in Treatments of Osteoporosis in Men: A Network Meta-Analysis. *PLoS ONE [Electronic Resource]* 2015;10:e0128032.
234. Freemantle N, Cooper C, Diez-Perez A, Gitlin M, Radcliffe H, Shepherd S*, et al.* Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. *Osteoporos Int* 2013;24:209-17.
235. Bolland MJ, Grey AB, Gamble GD, Reid IR. Effect of osteoporosis treatment on mortality: a meta-analysis. *J Clin Endocrinol Metab* 2010;95:1174-81.
236. Gu HF, Gu LJ, Wu Y, Zhao XH, Zhang Q, Xu ZR*, et al.* Efficacy and Safety of Denosumab in Postmenopausal Women With Osteoporosis: A Meta-Analysis. *Medicine* 2015;94:e1674.
237. Han SL, Wan SL. Effect of teriparatide on bone mineral density and fracture in postmenopausal osteoporosis: meta-analysis of randomised controlled trials. *Int J Clin Pract* 2012;66:199-209.
238. Lin T, Wang C, Cai XZ, Zhao X, Shi MM, Ying ZM*, et al.* Comparison of clinical efficacy and safety between denosumab and alendronate in postmenopausal women with osteoporosis: a meta-analysis. *Int J Clin Pract* 2012;66:399-408.
239. Nakamura T, Tsujimoto M, Hamaya E, Sowa H, Chen P. Consistency of fracture risk reduction in Japanese and Caucasian osteoporosis patients treated with teriparatide: a meta-analysis. *J Bone Miner Metab* 2012;30:321-5.
240. Schwarz P, Jorgensen NR, Mosekilde L, Vestergaard P. Effects of increasing age, dosage, and duration of PTH treatment on BMD increase--a meta-analysis. *Calcif Tissue Int* 2012;90:165-73.
241. von Keyserlingk C, Hopkins R, Anastasilakis A, Toulis K, Goeree R, Tarride JE*, et al.* Clinical efficacy and safety of denosumab in postmenopausal women

with low bone mineral density and osteoporosis: a meta-analysis. *Semin Arthritis Rheum* 2011;41:178-86.
242. Benjamin B, Benjamin MA, Swe M, Sugathan S. Review on the comparison of effectiveness between denosumab and bisphosphonates in post-menopausal osteoporosis. *Osteoporosis and Sarcopenia* 2016;2:77-81.
243. Sutton EE, Riche DM. Denosumab, a RANK ligand inhibitor, for postmenopausal women with osteoporosis. *Ann Pharmacother* 2012;46:1000-9.
244. Whelan AM, Raman-Wilms L. Denosumab: A new injectable treatment for postmenopausal osteoporosis. *Canadian Pharmacists Journal* 2011;144:72-8.
245. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y*, et al.* Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab* 2008;93:2149-57.
246. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC*, et al.* Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab* 2011;96:972-80.
247. Naylor KE, Clowes JA, Finigan J, Paggiosi MA, Peel NF, Eastell R. The effect of cessation of raloxifene treatment on bone turnover in postmenopausal women. *Bone* 2010;46:592-7.
248. Dore RK, Cohen SB, Lane NE, Palmer W, Shergy W, Zhou L*, et al.* Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. *Annals of the Rheumatic Diseases* 2010;69:872-5.
249. Cosman F, Wermers RA, Recknor C, Mauck KF, Xie L, Glass EV*, et al.* Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. *J Clin Endocrinol Metab* 2009;94:3772-80.
250. Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F*, et al.* Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009;361:745-55.
251. Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J*, et al.* Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol* 2008;26:4875-82.
252. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R*, et al.* Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:433-43.
253. Klotz L, Smith MR, Coleman RE, Pittman KB, Milecki P, Wei R*, et al.* Symptomatic skeletal events (SSE) in patients with advanced prostate cancer: Results from a phase III trial of denosumab for the prevention of skeletal-related events. *Journal of Clinical Oncology Conference* 2014;32.
254. Raje N, Terpos E, Willenbacher W, Shimizu K, Garcia-Sanz R, Durie B*, et al.* Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol* 2018;19:370-81.
255. Henry DH, Von Moos R, Hungria V, Costa L, Woll PJ, Scagliotti G*, et al.* Delaying skeletal-related events in a randomized phase III study of denosumab versus zoledronic acid in patients with advanced cancer. *Journal of Clinical Oncology Conference* 2010;28.

256. Fazeli PK, Wang IS, Miller KK, Herzog DB, Misra M, Lee H, *et al.* Teriparatide increases bone formation and bone mineral density in adult women with anorexia nervosa. *J Clin Endocrinol Metab* 2014;99:1322-9.
257. Ensrud KE, Stock JL, Barrett-Connor E, Grady D, Mosca L, Khaw KT, *et al.* Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. *J Bone Miner Res* 2008;23:112-20.
258. Bonani M, Brockmann J, Cohen CD, Fehr T, Nocito A, Schiesser M, *et al.* A randomized open-label clinical trial examining the effect of denosumab on the prevention of 1st-year bone mineral density loss after renal transplantation (POSTOP study; NCT01377467). *Nephrology Dialysis Transplantation* 2012;2):ii304.
259. Haghverdi F, Farbodara T, Mortaji S, Soltani P, Saidi N. Effect of raloxifene on parathyroid hormone in osteopenic and osteoporotic postmenopausal women with chronic kidney disease stage 5.[Erratum appears in Iran J Kidney Dis. 2015 Jan;9(1):76; PMID: 25599744]. *Iranian journal of Kidney Diseases* 2014;8:461-6.
260. Szczepanek K, Pedziwiatr M, Klek S. Denosumab Improves Bone Mineral Density in Patients With Intestinal Failure Receiving Home Parenteral Nutrition: Results From a Randomized, Controlled Clinical Trial. *JPEN J Parenter Enteral Nutr* 2017; https://dx.doi.org/10.1177/0148607117695247:148607117695247.
261. Zhu H, Tang H, Cheng Q, He L, Li P, Xue Q, *et al.* Efficacy and safety of denosumab in Chinese postmenopausal women with osteoporosis at increased risk of fracture: results from a 12-month, randomized, double-blind, placebo-controlled phase III study. *Journal* 2017. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/241/CN-01462241/frame.html
262. Thomas T, Cheung AM, Shane E, Zanchetta JR, Kearns A, Hans D, *et al.* Changes in lumbar spine QCT, DXA and TBS following treatment with denosumab (DMAB), alendronate (ALN), or placebo (PBO) in postmenopausalwomen with low bone mass. *Osteoporos Int* 2014;2):S123.
263. Galesanu C, Lisnic N, Moisii L. Denosumab significantly increases BMD compared with alendronate in postmenopausal women. *Journal* 2015. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/035/CN-01080035/frame.html https://link.springer.com/content/pdf/10.1007%2Fs00198-015-3068-3.pdf
264. Nakano T, Shiraki M, Sugimoto T, Kishimoto H, Ito M, Fukunaga M, *et al.* Once-weekly teriparatide reduces the risk of vertebral fracture in patients with various fracture risks: subgroup analysis of the Teriparatide Once-Weekly Efficacy Research (TOWER) trial. *J Bone Miner Metab* 2014;32:441-6.
265. Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Effect of prior and ongoing raloxifene therapy on response to PTH and maintenance of BMD after PTH therapy. *Osteoporos Int* 2008;19:529-35.
266. Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, *et al.* A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;87:4528-35.
267. Finkelstein JS, Wyland JJ, Lee H, Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2010;95:1838-45.

268. Iseri K, Iyoda M, Watanabe M, Matsumoto K, Sanada D, Inoue T*, et al.* Comparison of the efficacy of denosumab and alendronate in glucocorticoid-induced osteoporosis. *Nephrology Dialysis Transplantation* 2017;32 (Supplement 3):iii235.
269. Iwamoto J, Sato Y, Uzawa M, Takeda T, Matsumoto H. Comparison of effects of alendronate and raloxifene on lumbar bone mineral density, bone turnover, and lipid metabolism in elderly women with osteoporosis.[Retraction in Yonsei Med J. 2018 Jan;59(1):167; PMID: 29214794]. *Yonsei Medical Journal* 2008;49:119-28.
270. Roux C, Hofbauer LC, Ho PR, Wark JD, Zillikens MC, Fahrleitner-Pammer A*, et al.* Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. *Bone* 2014;58:48-54.
271. Mok CC, Ho LY, Ma KM. Denosumab for patients receiving long-term glucocorticoids who do not have adequate response to bisphosphonate treatment: A randomized controlled trial. *Annals of the Rheumatic Diseases Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR* 2014;73.
272. Gonnelli S, Martini G, Caffarelli C, Salvadori S, Cadirni A, Montagnani A*, et al.* Teriparatide's effects on quantitative ultrasound parameters and bone density in women with established osteoporosis. *Osteoporos Int* 2006;17:1524-31.
273. Siris ES, Harris ST, Eastell R, Zanchetta JR, Goemaere S, Diez-Perez A*, et al.* Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. *J Bone Miner Res* 2005;20:1514-24.
274. Majima T, Komatsu Y, Shimatsu A, Satoh N, Fukao A, Ninomiya K*, et al.* Efficacy of combined treatment with raloxifene and alfacalcidol on bone density and biochemical markers of bone turnover in postmenopausal osteoporosis. *Endocr J* 2008;55:127-34.
275. Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E*, et al.* Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. *J Bone Miner Res* 2010;25:1886-94.
276. Dempster DW, Zhou H, Recker RR, Brown JP, Bolognese MA, Recknor CP*, et al.* Skeletal histomorphometry in subjects on teriparatide or zoledronic acid therapy (SHOTZ) study: a randomized controlled trial. *J Clin Endocrinol Metab* 2012;97:2799-808.
277. Bai H, Jing D, Guo A, Yin S. Randomized controlled trial of zoledronic acid for treatment of osteoporosis in women. 2013;41:697-704.
278. Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM*, et al.* Differential Effects of Teriparatide and Denosumab on Intact PTH and Bone Formation Indices: AVA Osteoporosis Study. *J Clin Endocrinol Metab* 2016;101:1353-63.
279. Adami S, Passeri M, Ortolani S, Broggini M, Carratelli L, Caruso I*, et al.* Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *Bone* 1995;17:383-90.
280. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC*, et al.* Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *The Lancet* 1996;348:1535-41.

281. Cummings S, Black D, Thompson D, Applegate W, Barrett-Connor E, Musliner T*, et al.* Effect of Alendronate on Risk of Fracture in Women With Low Bone Density but Without Vertebral Fractures. *Journal of American Medical Association* 1998;280:2077-82.
282. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW*, et al.* Alendronate and estrogen effects in postmenopausal women with low bone mineral density. *Journal of Clinical Endocrinology and Metabolism* 2000;85:720-6.
283. Greenspan SL, Schneider DL, McClung MR, Miller PD, Schnitzer TJ, Bonin R*, et al.* Alendronate Improves Bone Mineral Density in Elderly Women with Osteoporosis Residing in Long-Term Care Facilities: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Intern Med* 2002;136:742-6.
284. Greenspan SL, Resnick NM, Parker RA. Combination Therapy With Hormone Replacement and Alendronate for Prevention of Bone Loss in Elderly Women: A Randomized Controlled Trial. *Journal of American Medical Association* 2003;289:2525-33.
285. Ho A, Kung A. Efficacy and tolerability of alendronate once weekly in Asian postmenopausal osteoporotic women. *Ann Pharmacother* 2005;39:1428-33.
286. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J*, et al.* Alendronate for the Treatment of Osteoporosis in Men. Paper presented at: N Engl J Med8/31/2000.
287. Pols HAP, Felsenberg D, Hanley DA, Štepán J, Munoz-Torres M, lkin TJ*, et al.* Multinational, Placebo-Controlled, Randomized Trial of the Effects of Alendronate on Bone Density and Fracture Risk in Postmenopausal Women with Low Bone Mass: Results of the FOSIT Study. Paper presented at: Osteoporos International1999.
288. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S*, et al.* Alendronate for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Paper presented at: N Engl J Med7/30/1998.
289. Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E*, et al.* Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: A randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum* 2001;44:202-11.
290. Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST*, et al.* Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. *Curr Med Res Opin* 2005;21:391-401.
291. McClung MR, Bolognese MA, Sedarati F, Recker RR, Miller PD, McClung MR*, et al.* Efficacy and safety of monthly oral ibandronate in the prevention of postmenopausal bone loss. *Bone* 2009;44:418-22.
292. Delmas PD, Adami S, Strugala C, Stakkestad JA, Reginster JY, Felsenberg D*, et al.* Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 2006;54:1838-46.
293. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R*, et al.* Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol* 2008;35:488-97.
294. Miller PD, McClung MR, Macovei L, Stakkestad JA, Luckey M, Bonvoisin B*, et al.* Monthly Oral Ibandronate Therapy in Postmenopausal Osteoporosis: 1-

Year Results From the MOBILE Study. *Journal of Bone and Mineral Research* 2005;20:1315-22.
295. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD*, et al.* Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. *J Bone Miner Res* 2009;24:719-25.
296. Cohen S, Levy RM, Keller M, Boling EP, Emkey RD, Greenwald M*, et al.* Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 1999;42:2309-18.
297. Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster for the bmd-mn Study Group J-Y. Risedronate Reverses Bone Loss in Postmenopausal Women with Low Bone Mass: Results From a Multinational, Double-Blind, Placebo-Controlled Trial. Paper presented at: The Journal of Clinical Endocrinology & Metabolism5/1/2000.
298. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M*, et al.* Effects of Risedronate Treatment on Vertebral and Nonvertebral Fractures in Women With Postmenopausal Osteoporosis: A Randomized Controlled Trial. *Journal of American Medical Association* 1999;282:1344-52.
299. Ste-Marie LG, Sod E, Johnson T, Chines A. Five Years of Treatment with Risedronate and its Effects on Bone Safety in Women with Postmenopausal Osteoporosis. Paper presented at: Calcified Tissue International2004.
300. Reginster JY, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML*, et al.* Randomized Trial of the Effects of Risedronate on Vertebral Fractures in Women with Established Postmenopausal Osteoporosis. Paper presented at: Osteoporosis International2000.
301. Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D*, et al.* Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003;32:120-6.
302. Leung JYY, Ho AYY, Ip TP, Lee G, Kung AWC. The efficacy and tolerability of risedronate on bone mineral density and bone turnover markers in osteoporotic Chinese women: a randomized placebo-controlled study. *Bone* 2005;36:358-64.
303. Reid DM, Hughes RA, Laan RFJM, Sacco-Gibson NA, Wenderoth DH, Adami S*, et al.* Efficacy and Safety of Daily Risedronate in the Treatment of Corticosteroid-Induced Osteoporosis in Men and Women: A Randomized Trial. *Journal of Bone and Mineral Research* 2000;15:1006-13.
304. Ringe JD, Faber H, Farahmand P, Dorst A. Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. Paper presented at: Rheumatology International2006.
305. Ringe JD, Farahmand P, Faber H, Dorst A, Ringe JD, Farahmand P*, et al.* Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. *Rheumatology International* 2009;29:311-5.
306. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM, Reid IR*, et al.* Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab* 2010;95:4380-7.
307. Lyles KW, Cólon-Emeric C, Magaziner JS, Adachi JD, Pieper CF, Mautalen C*, et al.* Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture. Paper presented at: N Engl J Med11/1/2007.

308. Adachi JD, Lyles KW, Colon-Emeric CS, Boonen S, Pieper CF, Mautalen C*, et al.* Zoledronic acid results in better health-related quality of life following hip fracture: the HORIZON-Recurrent Fracture Trial. *Osteoporos Int* 2011;22:2539-49.
309. Boonen S, Eastell R, Su G, Mesenbrink P, Cosman F, Cauley JA*, et al.* Time to onset of antifracture efficacy and year-by-year persistence of effect of zoledronic acid in women with osteoporosis. *J Bone Miner Res* 2012;27:1487-93.
310. McClung M, Miller P, Recknor C, Mesenbrink P, Bucci-Rechtweg C, Benhamou CL*, et al.* Zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass: a randomized controlled trial. *Obstet Gynecol* 2009;114:999-1007.
311. Miller PD, Epstein S, Sedarati F, Reginster JY, Miller PD, Epstein S*, et al.* Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study. *Curr Med Res Opin* 2008;24:207-13.
312. Sarioglu M, Tuzun C, Unlu Z, Tikiz C, Taneli F, Uyanik BS. Comparison of the effects of alendronate and risedronate on bone mineral density and bone turnover markers in postmenopausal osteoporosis. Paper presented at: Rheumatology International2006.
313. Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S*, et al.* Treatment With Once-Weekly Alendronate 70 mg Compared With Once-Weekly Risedronate 35 mg in Women With Postmenopausal Osteoporosis: A Randomized Double-Blind Study. *Journal of Bone and Mineral Research* 2005;20:141-51.
314. Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SA*, et al.* Comparison of Weekly Treatment of Postmenopausal Osteoporosis with Alendronate Versus Risedronate Over Two Years. Paper presented at: The Journal of Clinical Endocrinology & Metabolism7/1/2006.
315. Reid DM, Hosking D, Kendler D, Brandi ML, Wark JD, Weryha G*, et al.* Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis: results of FACTS-international. *Clinical Drug Investigation* 2006;26:63-74.
316. Reid DM, Hosking D, Kendler D, Brandi ML, Wark JD, Marques-Neto JF*, et al.* A comparison of the effect of alendronate and risedronate on bone mineral density in postmenopausal women with osteoporosis: 24-month results from FACTS-International. *Int J Clin Pract* 2008;62:575-84.
317. Reid I, Boonen S, Black DM, Colon-Emeric C, Eastell R, Magaziner J*, et al.* Once-yearly treatment with zoledronic acid continues to be effective in old age. *Bone* 2009;44:S94.
318. Chesnut III CH, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST*, et al.* Alendronate treatment of the postmenopausal osteoporotic woman: Effect of multiple dosages on bone mass and bone remodeling. *The American Journal of Medicine* 1995;99:144-52.
319. Klotz LH, McNeill IY, Kebabdjian M, Zhang L, Chin JL, Consortium. CUR*, et al.* A phase 3, double-blind, randomised, parallel-group, placebo-controlled study of oral weekly alendronate for the prevention of androgen deprivation bone loss in nonmetastatic prostate cancer: the Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) study. *European Urology* 2013;63:927-35.

320. Shilbayeh S, S-Zumeili A, Hilow HM. The efficacy and safety of Calidron tablets for management of osteoporosis in Jordanian women: A randomised clinical trial. *Saudi Pharmaceutical Journal* 2004;12:86-95.
321. Smith BJ, Laslett LL, Pile KD, Phillips PJ, Phillipov G, Evans SM*, et al.* Randomized controlled trial of alendronate in airways disease and low bone mineral density. *Chronic Respiratory Disease* 2004;1:131-7.
322. Lester JE, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R*, et al.* Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. *Clin Cancer Res* 2008;14:6336-42.
323. Choo C, Lukka H, Kiss A, Danjoux C. Double-blinded, placebo-controlled randomized study evaluating the efficacy of risedronate to prevent the loss of bone mineral density in non-metastatic prostate cancer patients undergoing radiotherapy plus 2-3 years of androgen ablation therapy. *Journal* 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70648453
324. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C*, et al.* Effect of Risedronate on the Risk of Hip Fracture in Elderly Women. Paper presented at: N Engl J Med2/1/2001.
325. Taxel P, Dowsett R, Richter L, Fall P, Klepinger A, Albertsen P*, et al.* Risedronate prevents early bone loss and increased bone turnover in the first 6 months of luteinizing hormone-releasing hormone-agonist therapy for prostate cancer. *BJU International* 2010;106:1473-6.
326. Atmaca A, Gedik O. Effects of alendronate and risedronate on bone mineral density and bone turnover markers in late postmenopausal women with osteoporosis. *Advances in Therapy* 2006;23:842-53.
327. Hadji P, Gamerdinger D, Spieler W, Kann P, Loeffler H, Articus K*, et al.* The Rapid Onset and Sustained Efficacy (ROSE) study: Zoledronic acid vs. alendronate. *Journal* 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70226012
328. Hadji P, Gamerdinger D, Spieler W, Kann PH, Loeffler H, Articus K*, et al.* Rapid Onset and Sustained Efficacy (ROSE) study: results of a randomised, multicentre trial comparing the effect of zoledronic acid or alendronate on bone metabolism in postmenopausal women with low bone mass. *Osteoporos Int* 2012;23:625-33.
329. NCT00205777. Study Evaluating Bazedoxifene Acetate In Osteoporosis In Postmenopausal Women. 2005. https://clinicaltrials.gov/ct2/show/NCT00205777 (Accessed 20 October 2018).
330. Silverman SLJQoLR. The Osteoporosis Assessment Questionnaire (OPAQ): A reliable and valid disease-targeted measure of health-related quality of life (HRQOL) in osteoporosis. 2000;9:767-74.
331. Hunter MS. The Women's Health Questionnaire (WHQ): Frequently Asked Questions (FAQ). *Health and quality of life outcomes* 2003;1:41-.
332. Lips P, Cooper C, Agnusdei D, Caulin F, Egger P, Johnell O*, et al.* Quality of life in patients with vertebral fractures: validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Working Party for Quality of Life of the European Foundation for Osteoporosis. *Osteoporos Int* 1999;10:150-60.

333. EuroQol group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
334. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T*, et al.* Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ (Clinical research ed)* 1992;305:160-4.
335. Aspenberg P, Malouf J, Tarantino U, Garcia-Hernandez PA, Corradini C, Overgaard S*, et al.* Effects of Teriparatide Compared with Risedronate on Recovery After Pertrochanteric Hip Fracture: Results of a Randomized, Active-Controlled, Double-Blind Clinical Trial at 26 Weeks. *J Bone Joint Surg Am* 2016;98:1868-78.
336. NCT00680953. Denosumab Fracture Intervention Randomized Placebo Controlled Trial in Japanese Patients With Osteoporosis. In; 2008.
337. Chapurlat R, Papapoulos S, Brown JP, Franchimont N, Brandi ML, Czerwinski E*, et al.* Treatment of postmenopausal women with osteoporosis for six years with denosumab: Three-year results from the freedom extension. *Annals of the Rheumatic Disease Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR* 2012;71.
338. NCT00542425. Phase 2 Dose-finding Study to Evaluate the Effects of BA058 in the Treatment of Postmenopausal Women With Osteoporosis. In; 2007.
339. NCT00043186. Determine the Efficacy, Safety and Tolerability of Denosumab (AMG 162) in the Treatment of Postmenopausal Women With Low Bone Mineral Density. 2007.
340. NCT01575873. Efficacy and Safety of Denosumab Compared With Risedronate in Individuals Taking Glucocorticoids (GIOP). *Journal* 2012. https://clinicaltrials.gov/ct2/show/NCT01575873 [Accessed 28 November 2018]
341. NCT01732770. Safety and Efficacy Study to Evaluate Denosumab Compared With Zoledronic Acid in Postmenopausal Women With Osteoporosis. 2012. https://clinicaltrials.gov/ct2/show/NCT00523341 (Accessed 20 October 2018).
342. NCT00051558. Comparison of Teriparatide With Alendronate for Treating Glucocorticoid-Induced Osteoporosis. In; 2003.
343. NCT00887354. A Study That Will Compare the Effect of Two Drugs on Participants With Low Bone Mass and a Recent Hip Fracture (MOVE). *Journal* 2015. https://clinicaltrials.gov/ct2/show/NCT00887354 [Accessed 28 November 2018]
344. Saag KG, Shane E, Boonen S, Marin F, Donley DW, Taylor KA*, et al.* Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *Obstetrical and Gynecological Survey* 2008;63:232-3.
345. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making* 2013;33:618-40.
346. Griffin XL, Parsons N, Achten J, Fernandez M, Costa ML. Recovery of health-related quality of life in a United Kingdom hip fracture population: The warwick hip trauma evaluation - A prospective cohort study. *Bone and Joint Journal* 2015;97-B:372-82.

11 APPENDICES

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 to 2018

11th 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
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)
72	68 or 71
73	64 not 72
74	26 and 73
75	45 or 74

Embase 1974 to 2018

11th 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.
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.
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)

11th 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))
# 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 (CDR): Wiley Interscience. 1996-2018

Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Interscience. 1898-2018

Health Technology Assessment Database (HTA): Wiley Interscience. 1995-2016

Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-2015

11th 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
#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

WHOICTRP

11th 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.
211-216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244

COST-EFFECTIVENESS STUDIES OF OSTEOPOROSIS

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily, and Versions(R) 1946 to 2018
16th 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	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 to 2018
16th 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	*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 (HTA): Centre for Reviews and Dissemination. 1995-2016
NHS Economic Evaluation Database (NHS EED): Centre for Reviews and Dissemination. 1995-2015
Database of Abstracts of Reviews of Effects (DARE): Centre for Reviews and Dissemination. 1995-2015
16th 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

EQ-5D AND OSTEOPOROSIS

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily, and Versions(R) 1946 to 2018
19th 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 to 2018
19th 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.
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: Thirty-four studies of non-bisphosphonates were excluded

Table 11: Excluded studies

Trial	Reason for exclusion
Bone 2008 [245] and extension [246]	Population outside scope Low BMD not osteoporosis (and mean age under 65)
Naylor 2010 [247]	Population outside scope Low BMD not osteoporosis (and mean age under 65)
Dore 2010 [248]	Population outside scope Low BMD not osteoporosis (and mean age under 65)
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
Fazelli 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
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
Majima 2008 [274]	Comparison outside scope RLX versus RLX plus alfacalcidol
Seeman *et al.* 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

Appendix 3: Bisphosphonate studies

Of 48 RCTs (reported in 59 references) included in TA464,[35] 38 RCTs (reported in 48 references) were included in the NMAs of fracture and/or FN BMD data in this report.

Three additional bisphosphonate RCTs were identified by the searches in this report (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 FN BMD data. Additionally, three RCTs of bisphosphonates from TA464 were excluded for being conducted in a cancer population.

Table 12: Included bisphosphonate RCTs from TA 464[35]

Trial	Population	Intervention and comparator(s)	Vertebral fracture NMA	FN BMD NMA
Adami 1995[279]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d		Yes
FIT I Black 1996[280]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d	Yes	Yes
FIT II Cummings 1998[281]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d	Yes	Yes
Bone 2000[282]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d		Yes
Carfora 1998[136]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d	Yes	
Dursun 2001[132]	Postmenopausal women with osteoporosis	Calcium ALN 10mg/d+calcium	Yes	Yes
Greenspan 2002[283]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d		Yes
Greenspan 2003[284]	Postmenopausal aged 65 or older	Placebo ALN 10mg/d		Yes
Ho 2005[285]	Postmenopausal women with osteoporosis	Calcium ALN 10mg/d+calcium		Yes

Trial	Population	Intervention and comparator(s)	Vertebral fracture NMA	FN BMD NMA
Liberman 1995[135]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d	Yes	Yes
Orwoll 2000[286]	Men with osteoporosis	Placebo ALN 10mg/d	Yes	Yes
Miller 2004 [130]	Men with osteoporosis	Placebo ALN 70mg/w	Yes	
FOSIT Pols 1999[287]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d		Yes
Saag 1998[288] Adachi 2001[289]	Men and women with glucocorticoid induced osteoporosis	Placebo ALN 10mg/d		Yes
BONE Chesnut 2004[137]; Chesnut 2005[290]	Postmenopausal women with osteoporosis	Placebo IBN 2.5mg/d IBN 20mg eod,	Yes	Yes
McClung 2009[291]	Postmenopausal women with osteoporosis	Placebo IBN 150mg/m		Yes
DIVA Delmas 2006[292] Eisman 2008[293]	Postmenopausal women with osteoporosis	IBN 2.5mg/d IBN 2mg/iv, 2/m IBN3mg/iv, 3/m		Yes
MOBILE Miller 2005[294] Reginster 2006[182]	Postmenopausal women with osteoporosis	IBN 2.5mg IBN 50mg. 2 doses/m IBN100mg/m IBN 150mg/m		Yes
Boonen 2009[295]	Men with osteoporosis	Placebo RIS 35mg/w	Yes	Yes
Cohen 1999[296]	Men and women 18-85 years receiving glucocorticoids	Placebo RIS 5mg/d	Yes	Yes
BMD-MN Fogelman 2000[297]	Postmenopausal women with osteoporosis	Placebo RIS 5mg/d	Yes	Yes
Hooper 2005[133]	Postmenopausal women with osteoporosis	Placebo RIS 5mg/d	Yes	Yes

Trial	Population	Intervention and comparator(s)	Vertebral fracture NMA	FN BMD NMA
VERT-NA Harris 1999,[298] Ste-Marie (2004)[299]	Postmenopausal women with osteoporosis	Placebo RIS 5mg/d	Yes	Yes
VERT-MN Reginster 2000,[300] Sorensen 2003[301]	Postmenopausal women with osteoporosis	Placebo RIS 5mg/d	Yes	Yes
Leung 2005[302]	Postmenopausal women with osteoporosis	Placebo RIS 5mg/d		Yes
Reid 2000[303]	Men and women taking glucocorticoids for ≥6 months	Placebo RIS 5mg/d	Yes	Yes
Ringe 2006,[304] Ringe 2009[305]	Men with osteoporosis	Placebo RIS 5mg/d	Yes	
HORIZON-PFT Black 2007,[134] Reid 2010[306]	Postmenopausal women with osteoporosis	Placebo ZOL 5mg/y	Yes	Yes
HORIZON-RFT Lyles 2007[307] Adachi 2011[308]	Men and women 50 years of age or older within 90 days after surgical repair of a hip fracture	Placebo ZOL 5mg/y	Yes	Yes
Boonen 2012[309]	Men with osteoporosis	Placebo ZOL 5mg/y	Yes	Yes
McClung 2009[310]	Postmenopausal women with osteoporosis	Placebo ZOL 5mg/y		Yes
MOTION Miller 2008[311]	Postmenopausal women with osteoporosis	ALN 70mg/w IBN150mg/m	Yes	Yes
Muscoso 2004[80]	Postmenopausal women with osteoporosis	RIS 5mg/d ALN 10mg/d	Yes	
Sarioglu 2006[312]	Postmenopausal women with osteoporosis	RIS 5mg/d ALN 10mg/d		Yes
FACT Rosen 2005,[313] Bonnick 2006[314]	Postmenopausal women with osteoporosis	ALN 70mg/w RIS 35mg/w		Yes

Trial	Population	Intervention and comparator(s)	Vertebral fracture NMA	FN BMD NMA
FACTS Reid 2006,[315] Reid 2008[316]	Postmenopausal women with osteoporosis	ALN 70mg/w RIS 35mg/w		Yes
HORIZON Reid 2009[317]	Men and women taking glucocorticoids<3mo or ≥3mo	ZOL 5mg/y RIS 5mg/d	Yes	Yes

eod every other day, /d per day, /w per week , /y per year

Table 13: Included bisphosphonate RCTs from update review (additional to the NICE TA464)

Trial	Population	Intervention and comparators	Included in fracture rate NMA?	Included in FN BMD NMA?
TRIO [139]	Postmenopausal Women with osteoporosis	ALN IBN RIS	No	Yes
Tan 2016 [138]	Postmenopausal Women with osteoporosis	ALN ZOL	No	Yes
ZONE [131]	Women and men with osteoporosis	Placebo ZOL	Yes	No

Table 14: Excluded bisphosphonate RCTs from TA 464

Trial	Population	Intervention and comparators	Reason for exclusion
Chesnut 1995[318]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d	Outcome outside scope
CORAL Klotz 2013[319]	Men with androgen deprivation bone loss in non-metastatic prostate cancer	Placebo ALN 70mg/w	Population outside scope, cancer
Shilbayeh 2004[320]	Postmenopausal women with osteoporosis	Placebo ALN 10mg/d	Outcome outside scope
Smith 2004[321]	Men and women with asthma and/or chronic obstructive airways disease	Placebo ALN 10mg/d	Outcome outside scope
ARIBON Lester 2008[322]	Postmenopausal women with breast cancer	Placebo IBN150mg/m	Outcome outside scope
Choo 2011[323]	Men with androgen deprivation bone loss in non-metastatic prostate cancer	Placebo RIS 35mg/w	Population outside scope, cancer
McClung 2001[324]	Postmenopausal women with osteoporosis	Placebo RIS 5mg/d	Outcome outside scope
Taxel 2010[325]	Men aged >55 years and within a month of receiving an initial injection of ADT for prostate cancer	Placebo RIS 35mg/w	Population outside scope, cancer
Atmaca 2006[326]	Postmenopausal women with osteoporosis	RIS 5mg/d ALN 10mg/d	Outcome outside scope
ROSE Hadji 2010 [327] Hadji 2012 [328]	Postmenopausal women with osteoporosis	ZOL 5mg/y ALN 70mg/d	Outcome outside scope

ADT, androgen deprivation therapy; eod, every other day; mg/d, milligrams per day; mg/m, milligrams per month; mg/iv, milligrams intravenous; mg/y, milligrams per year; 2/m, twice per month; 3/m, three times per month

Trial acronyms: ARIBON, reversal of anastrozole (ARImidex) induced bone loss with oral monthly IBN (BONdronat) treatment during adjuvant therapy for breast cancer; BONE, IBN 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; HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial; HORIZON-RFT, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Recurrent Fracture Trial; ROSE, Rapid Onset and Sustained Efficacy; MOBILE, Monthly Oral IBN In LadiEs; MOTION, Monthly Oral Therapy with IBN for Osteoporosis iNtervention; VERT-NA, Vertebral efficacy with RIS Therapy-North American; VERT-MN, Vertebral efficacy with RIS Therapy-Multi National

Appendix 4: Trial and Population characteristics

Table 15: Trial characteristics

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
DEN versus Placebo						
FREEDOM Cummings 2009[42] Bone 2017[103]	International, randomised, placebo-controlled trial -21 centres in the United States and Canada	Women between the ages of 60 and 90 years with a lumbar spine or total hip T-score of less than −2.5 Excluded if they had conditions that influence bone metabolism or had taken oral bisphosphonates for more than 3 years	Placebo, 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[43]	Randomised placebo-controlled phase III trial, International, multi-centre Belgium, Canada,	Men with low bone mineral density LS or FN BMD T-score ≤-2.0 ≥-3.5;	Placebo for one year, then open label DEN for 1 year	Daily calcium (≥1000 mg) and vitamin D (≥800 IU)	24 months	LS BMD % change from baseline at 12 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
	Denmark, France, Poland, Sweden, United States	or previous major osteoporotic fracture and BMD-score ≤-1.0 ≥-3.5 Excluded if severe, or multiple, vertebral fracture(s), conditions that influence bone metabolism, or prior bisphosphonate treatment (3 months+ in past 2 years or 1 month+ in past year or within 3-months of randomisation	N=121 DEN 60 mg of DEN every 6 months for 2 years (1 year blinded, then 1 year open label) N=121			
DIRECT NCT00680953	Randomised placebo-controlled phase III trial,	Postmenopausal women and men aged 50+ with	Placebo 2 years followed by	Daily calcium ≥600 mg and	36 months	Incidence of new or worsening

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Nakamura 2014[44]	multi-centre, Japan, open-label extension	osteoporosis. 1-4 vertebral fractures and LS BMD T-score <-1.7 (Young Adult Mean in Japan 80%), or total hip BMD-T-score <-1.6. Excluded if severe, or 2+ moderate, vertebral fractures, conditions that influence bone metabolism, or prior bisphosphonate Treatment (3+ years, or with 6 months of randomisation), prior hormonal treatments, calcitonin o TPTD	open label DEN 1 year N=511 DEN 60 mg every 6 months 2 years followed by open label DEN 1 year N=500	vitamin D ≥400 IU		vertebral fracture by X-ray at 24-months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		within 6 weeks of enrolment.				
Nakamura 2012[45]	Randomised placebo-controlled phase II trial, multi-centre, Japan	Postmenopausal women aged 80 or under, ambulatory, osteoporosis, LS BMD T-score (for Japanese subjects) ≤-2.5≥-4.0 or FN or total hip ≤-2.5≥-3.5 Excluded if any severe or 2+ moderate vertebral fracture, hypocalcaemia, prior bisphosphonates or parathyroid hormone within 12 months, or hormonal or calcium	Placebo N=55 DEN 60mg every 6 months N=54 For 1 year	Daily calcium ≥600 mg and vitamin D ≥400 IU	12 months	LS BMD % change from baseline at 12 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		treatment within 3 months prior to randomisation.				
Koh 2016 NCT01457950[46]	Randomised placebo-controlled phase III trial, multi-centre, Korea, open-label extension	Postmenopausal women aged 60-90, Korean-born, LS or total hip BMD <-2.5≥-4.0 Excluded if conditions that influence bone metabolism, increased risk of ONJ, hypo-hyper-calcaemic, vitamin D deficiency, prior treatment with bone metabolism drugs	Placebo 6months then open label DEN 6 months N=66 DEN 60mg 6 months then open label DEN 6months N=69	Daily calcium ≥1000 mg and vitamin D ≥400 IU	12 months	LS BMD % change from baseline at 6 months
RLX versus Placebo						
Adami 2008[47]	International, randomised-controlled trial - 32 clinical	Postmenopausal women, aged 50 to 80,	Placebo, 172 RLX 60 mg, 157	All participants received oral	12 months from randomisation	Lumbar spine BMD

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
	centres in seven countries (the United States, France, Germany, Spain, Italy, Canada, and Australia).	BMD T-score below -2.5 at the lumbar spine. Exclude if had condition or receiving treatment affecting BMD.	Both daily All pre-treated for 12 months with TPTD 20 µg s.c. daily prior to randomisation	supplements of at least 500 mg/day of elemental calcium and 400 to 800 IU/day of vitamin D		
Morii *et al* 2003[48] Japan Clinical Trial Research Group	Randomised placebo-controlled, multicentre, Japan	Postmenopausal (2+ years) women, aged ≤80, LS BMD ≤-2.5 YAM Excluded if conditions that influence bone metabolism, hormonal therapy, pathologic fractures or LS BMD unevaluable,	Placebo N=100 RLX 60mg daily N=100	Daily Calcium 500mg and vitamin D 200 ID	12 months	LS BMD % change from baseline at 12 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		bisphosphonates within 6months				
Liu 2004[49]	Randomised placebo-controlled, multicentre, China	Postmenopausal (2+ years) women, aged 50-80, LS or FN BMD T-score ≤-2.5 Excluded if conditions or treatments that influence bone metabolism	Placebo N=102 RLX 60mg daily N=102	Daily Calcium 500mg and vitamin D 200 ID	12 months	LS BMD % change from baseline at 12 months
Gorai *et al* 2012[50]	Randomised controlled trial, open label, two centres, Japan	Postmenopausal (2+ years) women, LS BMD ≤-2.0 YAM Excluded if conditions or treatments that influence bone metabolism, bisphosphonates within	Alfacalcidol 1microgram/day N=46 RLX 60mg/day N=42 RLX 60mg/day		24 months	LS BMD % change from baseline and bone turnover

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		18 months	plus alfacalcidol 1microgram/day N=45			
Silverman 2008 NCT00205777[51]	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, Netherlands, New Zealand, Norway, Poland, Romania, Russian Federation,	Postmenopausal (2+ years) women, aged 55-85, LS or FN BMD T-score ≤-2.0 ≥-4.0; or 1+ mild vertebral fracture and LS or FN BMD T-score ≥-4.0 Excluded if conditions that influence bone metabolism, history of thrombosis, hormonal or bisphosphonate treatment within 6 months	Placebo N=1885 RLX 60mg/day N=1849	Daily Calcium ≤1200mg and vitamin D 400-800 ID	36 months	% new vertebral fractures by X-ray at 36 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
	Slovakia, South Africa, Spain, United States					
MORE[52,101]	Randomised controlled trial, multicentre, Canada, Europe, South America, USA	Postmenopausal (2+ years) women, FN or LS BMD T-score <-2.5; Or 1+ moderate or severe or 2+ mild or moderate vertebral fractures. Excluded if conditions that influence bone metabolism, history of thrombosis, hormonal therapy 2/6 months, bisphosphonates with 6 months, pathologic fractures, unevaluable	Placebo N=2576 RLX 60mg/day N=2557	Daily Calcium 500mg and vitamin D 400-600 ID	36 months	Incident vertebral fractures and BMD

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		by thoracic/lumbar X-ray				
Lufkin 1998[53]	Randomised controlled trial, two centres, USA	Postmenopausal (5+ years) women, aged 45-75, ambulatory, LS or FN BMD $\leq 10^{th}$ percentile of normal and 1+ non-traumatic vertebral fracture. Excluded if conditions that influence bone metabolism, history of thrombosis, prior bisphosphonates, hormonal therapy within 6months	Control N=48 RLX 60mg/day N=48	Daily Calcium 750mg and vitamin D 800 ID	12 months	Biochemical markers of bone turnover
Mok 2011 NCT00371956[54]	Randomised placebo controlled trial, phase IV,	Postmenopausal (1+ year) women receiving	Placebo N=57	Daily calcium 1000mg/day and	12 months	LS and hip BMD % change from

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
	two sites, China	long-tern glucocorticoid treatment (prednisone ≤10mg/d or equivalent) ≥6 months. Excluded if history of thrombosis or hypercoagulability, prior bisphosphonates or PTH	RLX 60mg/day N=57	calcitrol 0.25 microgram/day		baseline at 12 months
ROMO versus Placebo						
FRAME Cosman 2016[55]	International, randomised-controlled trial – 25 countries across Latin America, Central or Eastern Europe, Western Europe, Australia, or New Zealand, Asia Pacific and the US	Women aged 55 to 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	Placebo, 3591 ROMO 210 mg s.c., 3589 Both once monthly for 12 months then DEN 60 mg s.c. every 6 months	daily calcium (500 to 1000 mg) and vitamin D_3 or D_2 (600 to 800 IU) For patients with low screening vitamin D blood	12 months from randomisation then a further 12 months open-label following treatment switching	New vertebral fractures

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		affecting BMD, osteonecrosis of the jaw, and low 25-hydroxyvitamin D level.	for 12 months open-label (both groups)	test, a loading dose of 50,000 to 60,000 IU of vitamin D was given		
Ishibashi (2017) NCT01992159[56]	Randomised placebo controlled trial, phase II, multicentre, Japan	Postmenopausal women, aged 55-85, ambulatory, LS FN or total hip BMD T-score ≤-2.5, LS BMD >-4.0, FN or total hip BMD >-3.5. Excluded if condition or prior treatment influencing bone metabolism, including i.v. bisphosphonates within 5 years, oral	Placebo N=63 ROMO 210 mg per month N=63 For 12 months	Daily calcium ≥500mg and vitamin D ≥ 600IU	15 months	LS BMD % change from baseline at 12 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		bisphosphonates within 6 months or 1+ months within 1year, or >3years, or prior DEN within 18 months, or PTH within 1year, history of vertebral or hip fracture				
BRIDGE NCT02186171[57]	Randomised placebo controlled trial, phase III, multicentre, Europe, Latin America, Japan, North America	Men aged 55-90, LS total hip or FN BMD T-score ≤-2.5, Or ≤-1.5 with fragility fracture, evaluable for LS and hip DXA. Excluded if condition or current treatment influencing bone metabolism, hip or FN	Placebo N=82 ROMO 210mg/month N=163 For 12 months	Daily calcium 500-1000mg and vitamin D 600-800 IU	15 months	LS BMD % change from baseline at 12 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		T-score ≤-3.5, hip fracture				
TPTD versus Placebo						
Orwoll 2003[58]	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, 147 TPTD 20 µg s.c., 151 Both daily	All subjects also received supplemental calcium and vitamin D	The study was stopped after a median duration of 11 months	LS BMD % change from baseline
Miyauchi *et al.* 2010 NCT00433160[59]	Randomised placebo-controlled phase III trial, multicentre, Japan	Postmenopausal (≥5 years) women and men, ambulatory, aged 55+, LS BMD <80% young adult mean for Japanese subjects (approx. T-	Placebo 12months then option of open label TPTD for 12months N=70	Daily calcium 610mg and vitamin D 400IU	24 months	LS BMD % change from baseline at 12 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		score -2.6) and 1+ vertebral fragility fracture; or age 65+ approx. LS BMD T-score -1.7; or age 55+ with LS BMD <65% YAM	TPTD 12months then open label TPTD for 12months N=137			
Miyauchi *et al.* 2008[60]	Randomised placebo-controlled phase II trial, multicentre, Japan	Postmenopausal (≥5 years) women, ambulatory, aged 55+, LS BMD <80% YAM for Japanese subjects (approx. T-score -2.6) and 1+ moderate or 2+ mild vertebral fragility fracture; or age 65+ and <70% YAM; or LS BMD <60% YAM	Placebo 6months n=38 TPTD 20microg daily for 6 months N=39	Daily calcium 610mg and vitamin D 400IU	6 months	LS BMD % change from baseline at 24 weeks

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		Excluded if conditions that influence bone metabolism, treatment influencing bone metabolism within 24 months of randomisation				
ACTIVE NCT01343004[96]	Randomised placebo-controlled phase III trial, multicentre, Argentina, Brazil, Czech Republic, Denmark, Estonia, Hong Kong, Lithuania, Poland, Romania, United States	Postmenopausal women, age 49-86, FN or LS BMD T-score ≤-2.5>-5.0 and 2+ mild or 1+ moderate vertebral fracture, or other low trauma fracture within 5 years; Or age 65+ and T-score ≤-2.0>-5.0; Or age 65+ without	Placebo 18months (blinded against abaloparatide) n=821 TPTD 20microg daily for 18 months, open label N=818	Adequate calcium and vitamin D (25-hydroxyvitamin D concentrations in serum greater than 37.5 nmol/L)	18 months	% with 1+ new vertebral fracture (X-ray)

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		fracture if and T-score ≤-3.0>-5.0. Excluded if severe, or 4+ mild/moderate, vertebral fractures, <2 evaluable lumbar vertebrae, hip BMD unevaluable, conditions that influence bone metabolism, treatment influencing bone metabolism, bisphosphonates (3months+) within 5 years, DEN within 1 year				
Leder 2015[62]	Randomised, parallel-group, multicentre, dose-	Postmenopausal women, 55–85 years	Open-label Placebo, 45	All subjects received	6 months plus a further 6-month	BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
	finding, double-blind, placebo-controlled trial - 30 centres in the US, Argentina, India, and UK	old, with T-score ≤ -2.5 at the lumbar spine or femoral neck or total hip, or T-score ≤ -2.0 plus low trauma fracture, or T-score ≤ -2.0 plus risk factor for osteoporosis. Treatments and conditions affecting BMD were excluded	TPTD 20 µg, 45 Both daily	supplemental calcium (500–1000 mg) and vitamin D (400–800 IU)	extension to 12 months	and bone turnover markers
FPT NCT00670501[63]	Randomised placebo-controlled phase III trial, multicentre, Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, Hungary,	Postmenopausal (5+ years) women, ambulatory, 1+ moderate or 2+ mild atraumatic vertebral fractures ; or fewer than two	Placebo n=544 TPTD 20microg daily N=541 Study halted at	Daily calcium 1000mg and vitamin D 400-1200IU	Median 21 months	% with 1+ new vertebral fracture (X-ray) [planned at 3 years but study halted]

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
	Israel, Italy, Netherlands, New Zealand, Norway, Poland, Sweden, United States	moderate fractures, T-score BMD hip or LS ≤-1. Excluded if conditions that influence bone metabolism, bisphosphonates within 3months or within 24 months if 60 days+, other prior treatment that influenced bone metabolism within 6months	median 21 months			
Sethi 2008 NCT00500409[64]	Randomised placebo-controlled, open-label, phase III trial, multicentre, India	Postmenopausal (3+ years) women, aged 45-75, LS or FN BMD T-score ≤-2.5 Excluded if conditions	Control N=41 TPTD 20microg daily	Daily calcium 1000mg and vitamin D	180 days	LS BMD % change from baseline at 6 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		that influence bone metabolism, LS BMD unevaluable, prior treatment that influenced bone metabolism within 6months, current steroids, anticoagulants or anticonvulsants	N=41			
Head-to-head non-bisphosphonates						
DATA NCT00926380[65] DATA-SWITCH[66]	Randomised controlled phase II trial, open-label single centre, USA	Postmenopausal women, aged 45+, LS, FN or hip T-score ≤-2.5; Or T-score ≤-2.5 plus risk factor for fracture; Or T-score ≤-1.0 plus fragility fracture.	TPTD 20microg daily 24 months N=36 DATA-SWITCH TPTD followed by 24 months DEN	Daily calcium 1200mg and vitamin D (25-hydroxyvitamin D concentrations in serum greater than 50 nmol/L)	24	LS BMD % change from baseline at 12 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		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.	DEN 60mg every 6months for 24 months N=27 DATA-SWITCH DEN followed by 24 months TPTD N=27			
EUROFORS[67]	Randomised controlled open-label trial, multicentre, Austria, Belgium,	Postmenopausal (2+ years) women, aged 55+, LS or FN or total hip BMD T-score ≤-2.5,	Control 12months N=102	Daily Calcium ≥500mg and vitamin D 400-800 ID	12 months post randomisation (24 months total)	LS BMD % change from baseline at 24 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
	Denmark, France, Germany, Greece, Iceland, Portugal, Spain, United Kingdom	1+ vertebral or non-vertebral fragility fracture within 3years, 2+ BMD evaluable lumbar vertebrae. Excluded if conditions or treatments that influence bone metabolism	RLX 60mg daily N=100 TPTD 20microg daily N=305 All following 12months TPTD			
STRUCTURE NCT01796301[68]	Randomised controlled trial, open label, phase III, multicentre, North America, Latin America, Europe	Postmenopausal osteoporosis (3+ years), aged 55 to 90, vertebral fracture or non-vertebral after age 50, LS FN or total hip BMD T-score ≤-2.5, 3+ years of bisphosphonate therapy, evaluable for	TPTD 20 micrograms/day N=218 ROMO 210mg/month N=218 For 12 months	Daily calcium 500-1000mg and vitamin D 600-800 IU	12 months	Hip BMD % change from baseline at 12 months

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		hip and LS BMD Excluded if condition, or non-bisphosphonate treatment, influencing bone metabolism	Following 12 months of ALN			
McClung 2014[69]	Phase III, multicentre, international, randomised, placebo-controlled, parallel-group, eight-group study - 28 centres in Argentina, Austria, Belgium, Canada, Denmark, Spain, and the US	Postmenopausal women, 55 to 85 years old with a T score of −2.0 or less at the lumbar spine, total hip, or femoral neck and −3.5 or more at each of these sites. Treatments and conditions affecting BMD were excluded	Open-label ALN 70 mg weekly, 51 TPTD 20 µg daily, 55 Blind Pooled placebo (mix of administrations), 52 ROMO 210 mg s.c. monthly, 55	All the participants were required to take at least 1000 mg of elemental calcium and 800 IU of vitamin D daily	12 months	LS BMD % change from baseline
DEN versus Bisphosphonates						

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
DECIDE[70]	Randomised controlled trial, phase III, non-inferiority, multicentre, Australia, Europe, North America, South America	Postmenopausal women, ambulatory, LS or total hip BMD T-score ≤-2.0, evaluable for hip and LS BMD. Excluded if condition influencing bone metabolism, prior i.v. bisphosphonates, other treatments influencing bone metabolism within 3 months	DEN 60mg every six months plus placebo N=594 ALN 70mg/week plus placebo N=595	Daily calcium ≥500mg and vitamin D 400-800 IU	12 months	LS BMD % change from baseline at 12 months
STAND Kendler 2010[71]	Phase III 1- international, multicentre, randomised, double-blind, double-dummy, parallel-group. Countries NR	Women ≥ 55 years of age with a lumbar spine or total hip T-scores between −4.0 and −2.0 receiving ALN equivalent to	Open-label ALN 70 mg weekly for 1 month then: ALN 70 mg weekly, 251 DEN 60 mg s.c.,	daily 1000mg calcium and at least 400 IU vitamin D.	12 months	Total hip BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		70mg/week for at least 6 months. Treatments and conditions affecting BMD were excluded	every 6 months, 253 Both with placebo			
DAPS Kendler 2011[72,111]	Multicentre, randomised, open-label, 2-year, crossover - 20 centres in the USA and 5 centres in Canada	Postmenopausal women with low BMD who had not received prior bisphosphonate or DEN therapy with T-scores 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, 124 DEN 60 mg s.c., every 6 months, 126 Open-label	daily calcium (1,000 mg) and vitamin D (≥400 IU) supplementation.	12 months prior to crossover	Treatment adherence in the first 12 months
AMG 162 Bone Loss study McClung 2006[73]	Randomised, placebo-controlled, dose-ranging study - 29 study centres in	Osteopenic and osteoporotic postmenopausal women	Placebo s.c. every 3 months, 46	daily calcium (1 g) and vitamin D (400 IU).	12 months	LS BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
	the US	≤ 80 years of age 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	ALN 70 mg weekly, 47 (open-label) DEN 60 mg s.c., every 6 months, 47			
Recknor 2013[74]	Randomised, open-label, parallel-group study - 74 centres in the US and Europe	Postmenopausal women ≥ 55 years of age with T-score of ≤-2 or ≥-4 at the total hip who had either discontinued or had insufficient adherence to bisphosphonates ≥1 month before screening Treatments and	IBN 150 mg every month, 416 DEN 60 mg s.c., every 6 months, 417	daily calcium (500 mg or more) and vitamin D (800+ IU)	12 months	Total hip BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		conditions affecting BMD were excluded				
Saag 2018[75]	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 US	Women and men aged 18 years or older and were either continuing or initiating glucocorticoids (≥7.5 mg prednisone, or its equivalent daily) Patients younger than 50 years had to have a history of osteoporosis-related fracture. Continuing patients had to have total hip, femoral neck of lumbar spine T-score ≤2.0 or ≤1.0 with a history of	RIS 5 mg daily, 397 DEN 60 mg s.c., every 6 months, 398 Both groups received a placebo	at least 1000 mg calcium and at least 800 IU vitamin D daily	12 months	LS BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		fracture				
Miller 2016[76]	International, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group study - 37 study centres in Belgium, Denmark, Poland, Spain, Canada, the US, and Australia	Postmenopausal women ≥ 55 years of age who received oral bisphosphonate therapy for ≥2 years with a T-score of ≤2.5 or less at the lumbar spine, total hip, or femoral neck. Treatments and conditions affecting BMD were excluded	ZOL 5 mg iv annually, 322 DEN 60 mg s.c., every 6 months, 321 Both groups received a placebo	1000 mg or greater elemental calcium and 800 IU or greater vitamin D daily.	12 months	LS BMD % change from baseline
RLX versus Bisphosphonates						

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
EFFECT (International) Sambrook 2004[77]	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, 246 RLX 60 mg, 241 Both daily	Calcium and vitamin D	12 months	LS BMD % change from baseline
EFFECT (US) Luckey 2004[78]	Double-blind, randomised, active-controlled, multicentre study – 52 centres US	Postmenopausal women >40 years old 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, 223 RLX 60 mg daily, 233 Both groups received a placebo	500-1000 mg calcium and 200 IU Vitamin D daily	12 months	LS BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Johnell 2002[79]	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), 82 ALN 10 mg and RLX PBO, 83 RLX 60 mg and ALN PBO, 82 All daily	500 mg/d elemental calcium and vitamin D 400–600 IU/d.	12 months	LS BMD and FN BMD % change from baseline
Muscoso 2004[80]	Randomised trial – centres and countries NR	Women with osteoporosis. No further details of inclusion or exclusion criteria reported	ALN 10mg, 1000 RIS 5 mg, 100 RLX 60 mg, 100 All daily	1 gram of calcium and 800 IU of Vitamin D daily	24 months	NR Lumbar spine BMD and incidence fractures reported
EVA Recker 2007[81]	Randomised double-blind study – 13 centres in Canada and US (NCT00035971)	Postmenopausal women 50-80 years old with femoral neck T-score −2.5 to −4.0 and no	ALN 10mg, 716 RLX 60 mg, 717 Both daily	calcium (500 mg/day) and vitamin D (400 IU/day)	24 months Assessments also planned at 3 and 5 years, but trial was	Number of women with ≥1 new osteoporotic vertebral or non-

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		prevalent vertebral fractures. Treatments and conditions affecting BMD were excluded			stopped early	vertebral fracture
Sanad 2011[82]	Randomised clinical study – single centre, Egypt	Postmenopausal women 50-70 years old with BMD at lumbar spine or femoral neck -2.5 standard deviations below a reference population of young postmenopausal women. Treatments and conditions affecting BMD were excluded	ALN 10mg, 44 RLX 60 mg, 46 Both daily	1500 mg calcium carbonate and 400 IU vitamin D3	12 months	NR Lumbar spine, femoral neck and total hip BMD; bone turnover, and lipid metabolism reported
Michalska 2006[83]	Placebo-controlled, randomised trial – single centre, Austria	Postmenopausal women 50–80 years old with previous treatment with	Open-label ALN 10 mg, 33 Blind	calcium (500 mg/d) and vitamin D (800	12 months followed by 12 months open-label	LS BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		ALN (10 mg/d) for more than 3 years and lumbar spine or femoral neck T-score less than -2.5	Placebo, 33 RLX 60 mg, 33 All daily	IU/d)	extension	
ROMO versus Bisphosphonates						
ARCH Saag 2017[84]	Phase III, multicentre, international, randomised, double-blind trial – 137 centres (NCT01631214)	Postmenopausal women 55 to 90 years old with either T score of –2.5 or less at the total hip or femoral neck plus ≥1 moderate/severe or ≥2 mild vertebral fractures; or T score of –2.0 or less with ≥2 moderate/severe vertebral or proximal femur fracture	ALN 70 mg weekly, 2047 ROMO 210 mg s.c. monthly, 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

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
TPTD versus Bisphosphonates						
FACT McClung 2005[85]	Randomised, double-blind, active comparator study - 19 clinical sites globally	Postmenopausal women aged 45 to 84 years, with lumbar spine or femoral neck T-score between -2.5 and -4.0. Treatments and conditions affecting BMD were excluded.	ALN 10 mg, 101 TPTD 20 µg s.c., 102 Both daily Both groups received a placebo	daily supplementation of calcium (1000 mg) and vitamin D (400-800 IU)	18 months	LS and hip BMD % change from baseline
Saag 2009[86]	Randomised, double-blind, double-dummy, active comparator–controlled -13 countries at 76 centres	Women ≥21 years old who had taken prednisone or its equivalent at a dosage of ≥5 mg/day for ≥3 months with lumbar spine, femoral neck, or total hip BMD T score of ≤-2 or of ≤-1 plus a	ALN 10 mg, 214 TPTD 20 µg s.c., 214 Both daily Both groups received a placebo	calcium (1,000 mg/day) and vitamin D (800 IU/day) were provided	36 months	LS BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		prevalent fracture				
Panico 2011[87]	Randomised controlled trial, single centre, Italy	Postmenopausal women, LS or FN BMD T-score ≤-2.5, 2+ fractures, back pain, prior treatment for osteoporosis. Excluded if condition influencing bone metabolism, increased risk of osteosarcoma	TPTD 20micrograms daily N=42 ALN 70mg/week N=39	Daily calcium 1000mg and vitamin D 800 IU	18 months	% change from baseline in biochemical markers of bone turnover
EuroGIOPs Glüer 2013[88]	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	Open label RIS 35 mg weekly, 47 TPTD 20 µg s.c. daily, 45	1 g calcium and 800 to 1200 IU of vitamin D per day	18 months	LS BMD % change from baseline measured by QCT

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		mg prednisone, or its equivalent daily) ≥3 months. Treatments and conditions affecting BMD were excluded.				
Anastasilakis 2008[89]	Randomised, open-label trial - Greece.	Postmenopausal women with osteoporosis and T-score < -2.5 (site NR). Treatments and conditions affecting BMD were excluded.	Open label RIS 35 mg weekly, 22 TPTD 20 µg s.c. daily, 22	500 mg of elemental calcium and 400 IU vitamin D daily	12 months	Bone turnover markers
Walker 2013[90]	Randomised, double-blind, placebo-controlled trial - US	Men aged 30–85 years with low BMD secondary to idiopathic OP and lumbar spine, femoral neck or total hip T-score <-2.0. Treatments and	RIS 35 mg weekly, 10 TPTD 20 µg s.c. daily, 9 Both groups received a placebo	500 mg of calcium and 400 IU of vitamin D daily.	18 months	LS BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		conditions affecting BMD were excluded.				
VERO Kendler 2018[100]	Randomised, double-blind, active-controlled, parallel-group trial - 123 centres 14 countries in Europe, South America, and US	Postmenopausal women > 45 years of age and lumbar spine, femoral neck or total hip T-score ≥ −1·50 with prevalent vertebral fragility fracture. Treatments and conditions affecting BMD were excluded.	RIS 35 mg weekly, 683 TPTD 20 µg s.c. daily, 683 Both groups received a placebo 680 in each group started treatment	daily supplements of 500–1000 mg calcium and 400–800 IU of vitamin D3 or D2, or 2000 IU per day, if low screening vitamin D blood test	24 months	New radiographic vertebral fractures
Hadji 2012[92]	Randomised, parallel, double-blind, double-dummy, active-controlled trial – 72 international study locations (NCT00343252)	Postmenopausal women ≥45 years with a history of back pain likely to be caused by osteoporotic vertebral fracture, with lumbar spine, femoral	RIS 35 mg weekly, 350 TPTD 20 µg s.c. daily, 360 Both groups received a	1,000 mg/day calcium and 800 IU/day vitamin D	18 months	Proportion of patients experiencing ≥30% reduction in worst back pain at 6 months.

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
		neck, or total hip T-score of ≤−2; and a minimum of one moderate vertebral fracture. Treatments and conditions affecting BMD were excluded	placebo			
MOVE Aspenberg 2016[99] Malouf-Sierra 2017[93]	Multinational, multicentre, prospective, randomised, active-controlled study - 17 countries in US, Mexico, and Europe	Men and postmenopausal women with low bone mass (T-score <–2.0 s at the total hip, femoral neck, or lumbar spine who had sustained a recent unilateral pertrochanteric fracture	RIS 35 mg weekly, 113 TPTD 20 µg s.c. daily, 111 Both groups received a placebo Blind until 6 months then open label	calcium (500 to 1000 mg/day) and vitamin D (800 IU/day). For patients with low screening vitamin D blood test, loading dose of 100,000 IU of vitamin D2 or D3.	6 months[99] 18 months[93]	LS BMD % change from baseline

Trial name /Author/date	Trial design	Population eligibility	Intervention and comparators Numbers randomised to each group	Concomitant treatment	Follow-up duration	Primary outcome
Cosman 2011[94]	Partial double-blinded, randomised, multicentre, multinational – centres and countries NR	Women aged 45 to 89 years with BMD T-scores of -2.5 or less at the femoral neck, total hip, or lumbar spine or a BMD T-score of -2.0 or less at any site plus one or more documented vertebral or non-vertebral fractures. Treatments and conditions affecting BMD were excluded	ZOL 5 mg iv annually, 137 TPTD 20 µg s.c. daily, 138 Only TPTD received a placebo	daily calcium (1000 to 1200 mg) and vitamin D (400 to 800 IU).	12 months	LS BMD % change from baseline

Table 16: Population baseline characteristics

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
DEN versus Placebo							
FREEDOM[42,103]	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[43]	Placebo for one 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[44]	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[45]	Placebo N=55	64.6 (7.0)	100	LS -3.02 (0.34)	LS 0.652 (0.040)	7 (12.7)	NR
	DEN 60mg every 6 months N=54	65.1 (6.3)	100	LS -3.10 (0.44)	LS 0.642 (0.051)	7 (13.0)	NR
Koh 2016 NCT01457950[46]	Placebo 6months then open label DEN 6 months N=66	66.0 (4.77)	100	-2.4 (0.61)	NR	15 (23)	NR
	DEN 60mg 6 months then open label DEN 6months N=69	67.0 (4.86)	100	-2.5 (0.56)	NR	21 (30)	NR
RLX versus Placebo							
Adami 2008[47]	Placebo 172	67.1 (6.5)	100	NR	0.62 (0.10)	NR	0
	RLX 60 mg daily 157	66.7 (6.4)	100	NR	0.64 (0.10)	NR	0
Morii *et al* 2003[48]	Placebo N=97	64.3 (6.5)	100	NR	0.64 (0.05)	26 (26.8)	NR

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	RLX 60mg/d N=90	65.2 (6.2)	100	NR	0.66 (0.5)	22 (24.4)	NR
Liu 2004[49]	Placebo N=102	65.1 (5.4)	100	NR	NR	Thoracic 10 (9.8) Lumbar 6 (5.9)	0
	RLX N=102	65.5 (6.5)	100	NR	NR	Thoracic 11 (10.8) Lumbar 9 (8.8)	0
Gorai *et al* 2012[50]	Alfacalcidol N=46	65.2 (6.5)	100	NR	LS 0.663 (0.082)	NR	NR
	RLX N=42	64.4 (6.6)	100	NR	LS 0.678 (0.083)	NR	NR
	Alfacalcidol plus RLX N=45	65.1 (7.6)	100	NR	LS 0.670 (0.067)	NR	NR
Silverman 2008 NCT00205777[51]	Placebo N=1885	66.5 (6.8)	100	-1.8 (0.9)	NR	981 (56.4)	NR

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	RLX N=1849	66.4 (6.7)	100	-1.7 (0.9)	NR	954 (56.3)	NR
MORE[52,101]	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
Lufkin 1998[53]	Control	68.2 (0.7)	100	NR	LS 0.54	NR	NR

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	N=48				(0.01)		
	RLX N=48	69.9 (0.5)	100	NR	LS 0.52 (0.01)	NR	NR
Mok 2011 NCT00371956[54]	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 versus Placebo							
FRAME Cosman 2016[55]	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/ 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

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
Ishibashi (2017) NCT01992159[56]	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 NCT02186171[57]	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)
TPTD versus Placebo							
Orwoll 2003[58]	Placebo 147	59 (13)	0	-2.7 (0.8)	LS BMD 0.85 (0.14)	NR	8.16%
	TPTD 20 µg s.c. daily	59 (13)	0	-2.6 (0.8)	0.89 (0.15)	NR	7.95%

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	151						
Miyauchi *et al.* 2010[59]	Placebo 12months then option of open label TPTD for 12months N=67	70.4 (5.4)	92.5	NR	LS 0.638 (0.079)	29 (43.3)	34.3%
	TPTD 12months then open label TPTD for 12months N=136	69.2 (6.3)	93.4	NR	LS 0.639 (0.069)	54 (39.7)	36.8
Miyauchi *et al.* 2008[60]	Placebo N=38	69.9 (3.6)	100	NR	0.5068 (0.0802)	17 (44.7)	21.1
	TPTD 20microg daily N=39	71.5 (5.1)	100	NR	0.5168 (0.0927) (n=38)	16 (41.0)	25.6
ACTIVE NCT01343004[96]	Placebo N=821	68.7 (6.5)	100	-2.2 (0.7)	0.732 (0.099)	514 (62.6)	NR
	TPTD 20microg daily	68.8 (6.6)	100	-2.1 (0.7)	0.737 (0.096)	510 (62.3)	NR

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	N=818						
Leder 2015[62]	Placebo 45	65.0 (7.1)	100	-2.26 (0.72)	0.65 (0.11)	NR	0
	TPTD 20 µg daily 45	64.5 (7.5)	100	-2.09 (0.75)	0.66 (0.11)	NR	0
FPT NCT00670501[63]	Placebo n=448	69 (7)	100	NR	LS 0.82 (0.17)	448 (100)	15
	TPTD 20microg daily N=444	69 (7)	100	NR	LS 0.82 (0.17)	444 (100)	16
Sethi 2008 NCT00500409[64]	Control N=41	63.0 (6.3)	100	-2.34 (0.73)	0.62 (0.09)	NR	NR
	TPTD 20microg daily N=41	61.0 (6.3)	100	-2.49 (0.55)	0.62 (0.08)	NR	NR
Head-to-head non-bisphosphonates							
DATA[65]	TPTD	65.5 (7.9)	100	-1.9 (0.5)	0·643	16 (52)	Bisphosphonates

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	20microg daily N=36				(0·061)		42
	DEN 60mg every 6months N=34	66.3 (8.3)	100	-1.9 (0.8)	0·641 (0·086)	12 (36)	Bisphosphonates 36
EUROFORS[67]	Control 12months N=102 following 12months TPTD	69.1 (8.6)	100	LS -3.1 (0.89)	LS 0.75 (0.11)	102 (100)	Antiresorptive 62.7
	RLX 12months N=97 following 12months TPTD	69.4 (7.0)	100	LS -3.2 (0.85)	LS 0.75 (0.12)	97 (100)	Antiresorptive 64.9
	TPTD 12months N=304 following 12months TPTD	69.2 (7.2)	100	LS -3.2 (0.87)	LS 0.74 (0.11)	304 (100)	Antiresorptive 72.4
STRUCTURE[68]	TPTD N=218	71.2 (7.7)	100	-2.43 (0.66)	NR	(99.5)	Bisphosphonates 100
	ROMO	71.8 (7.4)	100	-2.49 (0.67)	NR	(100)	Bisphosphonates

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	N=218						100
McClung 2014[69]	Pooled placebo (mix of administrations), 52	67.0 (6.5)	100	-1.76 (0.56)	NR	NR	0
	Open-label ALN 70 mg weekly, 51	67.1 (5.8)	100	-1.91 (0.61)	NR	NR	0
	TPTD 20 µg daily, 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
DEN versus Bisphosphonates							
DECIDE[70]	DEN plus placebo N=594	64.1 (8.6)	100	LS -2.57 (0.75)	NR	(40)	Any 23 Bisphosphonates 13
	ALN plus placebo N=595	64.6 (8.3)	100	LS -2.57 (0.75)	NR	(41)	Any 24 Bisphosphonates 11
STAND Kendler 2010[71]	ALN 70 mg/week plus PBO 251	68.2 (7.7)	100	LS T-score -2.62 (0.79)	NR	NR	0

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	DEN 60 mg s.c., every 6 months plus PBO 253	66.9 (7.8)	100	-2.64 (0.75)	NR	NR	0
DAPS Kendler 2011[72, 111]	ALN 70 mg/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[73]	Placebo s.c. every 3 months, 46	63.7 (9.1)	100	-1.9 (0.6)	NR	0	0
	ALN 70 mg/week 47 (open-label)	62.8 (8.2)	100	-1.9 (0.7)	NR	0	0
	DEN 60 mg s.c., every 6 months, 47	63.1 (8.1)	100	-1.9 (0.7)	NR	0	0
Recknor 2013[74]	IBN 150 mg every month, 416	66.2 (7.8)	100	-2.1 (0.7)	NR	NR	Prior bisphosphonate 374 (89.9)

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	DEN 60 mg s.c., every 6 months, 417	67.2 (8.1)	100	-2.1 (0.7)	NR	NR	Prior bisphosphonate 377 (90.4)
Saag 2018[75]	RIS 5 mg daily plus PBO 397	Continuing GCC RIS, 61·3 (11·1) Initiating GCC 64·4 (10·0)	Continuing GCC, 73% Initiating GCC, 64%	LS 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 PBO 398	Continuing GCC 61·5 (11·6) Initiating GCC	Continuing GCC, 73% Initiating GCC, 64%	LS T-score Continuing GCC DEN–1.9 (1.4) Initiating	NR	Continuing GCC 67/253 (26) Initiating GCC 21/145 (14)	0

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
		67·5 (10·1)		GCC –0.9 (1.9)			
Miller 2016[76]	ZOL 5 mg iv annually plus PBO 322	69.5 (7.7)	100	LS T-score -2.64 (0.86)	NR	159 (49.4)	Prior oral bisphosphonates, mean years (SD) 6.4 (3.7)
	DEN 60 mg s.c., every 6 months plus PBO 321	68.5 (7.1)	100	-2.74 (0.83)	NR	169 (52.6)	Prior oral bisphosphonates, mean years (SD) 6.2 (3.8)
RLX versus Bisphosphonates							
EFFECT Sambrook 2004[77]	ALN 10 mg plus PBO 246	61.5 (8.2)	100	LS T-score -2.89 (0.78)	NR	NR	0
	RLX 60 mg daily plus PBO 241	61.8 (7.7)	100	LS T-score -2.86 (0.76)	NR	NR	0
EFFECT Luckey 2004[78]	ALN 70 mg weekly plus PBO 223	63.8 (9.9)	100	LS T-score -2.43 (0.78)	NR	NR	0

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	RLX 60 mg daily plus PBO 233	64.7 (9.8)	100	LS T-score -2.5 (0.69)	NR	NR	0
Johnell 2002[79]	Placebo (ALN and RLX), 82	63.8 (5.3)	100	NR	0.62 (0.09)	NR	0
	ALN 10 mg daily and RLX PBO, 83	63.7 (6.0)	100	NR	0.62 (0.08)	NR	0
	RLX 60 mg daily and ALN PBO, 82	63.4 (6.3)	100	NR	0.62 (0.07)	NR	0
Muscoso 2004[80]	ALN 10mg daily 1000	71 (8)	100	NR	NR	NR	NR
	RIS 5 mg daily 100	66 (9)	100	NR	NR	NR	NR
	RLX 60 mg daily 100	64 (3)	100	NR	NR	NR	NR
EVA Recker 2007[81]	ALN 10mg daily 716	65.7 (7.8)	100	−2.39 (0.56)	0.61 (0.09)	0	0
	RLX 60 mg daily 717	65.5 (7.7)	100	−2.39 (0.54)	0.61 (0.09)	0	0
Sanad 2011[82]	ALN 10mg daily	61.7 (4.3)	100	NR	0.63 (0.03)	NR	0

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	31						
	RLX 60 mg daily 35	62.5 (3.9)	100	NR	0.63 (0.05);	NR	0
Michalska 2006[83]	Blind Placebo 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 33	65.4 (6.8)	100	NR	0.609 (0.063)	9/33 (27.3)	100 (3+ years ALN)
	RLX 60 mg daily 33	65.6 (7.1)	100	NR	0.633 (0.087)	16/33 (48.5)	100 (3+ years ALN)
ROMO versus Bisphosphonates							
ARCH Saag 2017[84]	ALN 70 mg weekly N=2047 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	74.4 (7.5)	100	–2.89 (0.49)	NR	1969/2046	0

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	N=2046 12 months then ALN 70 mg weekly open-label for 12 months					(96.2)	
TPTD versus Bisphosphonates							
FACT McClung 2005[85]	ALN 10 mg daily plus PBO N= 101	66.6 (8.5)	100	−2.3 (0.8)	NR	NR	0
	TPTD 20 µg s.c. daily plus PBO N= 102	65.3 (8.4)	100	−2.3 (0.6)	NR	NR	0
Saag 2009[86 102]	ALN 10 mg daily plus PBO 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 PBO N= 214	56.1 (13.4)	100	-2.2 (0.10)	0.705 (0.013)	X-ray confirmed 63/214 (30)	0
Panico 2011[87]	TPTD N=42	65 (9.0)	100	-3.07 (0.60)	NR	42 (100)	100
	ALN	60 (14.4)	100	-3.02 (0.61)	NR	38 (97)	97

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
	N=39						
EuroGIOPs Glüer 2013[88]	Open label RIS 35 mg weekly, 47	55.1 (15.5)	0	–1.82 (0.91)	NR	17/47 (36.2)	0
	TPTD 20 µg s.c. daily 45	57.5 (12.8)	0	–1.95 (0.78)	NR	19/45 (42.2)	0
Anastasilakis 2008[89]	Open label RIS 35 mg weekly 22	64.7 (7.0)	100	NR	LS BMD 0.757 (0.08)	NR	0
	TPTD 20 µg s.c. daily 22	65.4 (7.5)	100	NR	LS BMD 0.764 (0.11)	NR	0
Walker 2013[90]	RIS 35 mg weekly plus PBO 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 PBO N= 9	51.6 (11.7)	100	-2.0 (0.9)	0.659 (0.12)	33	bisphosphonates 33
VERO Kendler	RIS 35 mg weekly plus PBO	71.6	100	–2.24 (0.74)	0.67 (0.11)	(100)	71

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
2018[100]	N=680	(8.58)					
	TPTD 20 µg s.c. daily plus PBO N= 680	72.6 (8.77)	100	−2.27 (0.76)	0.66 (0.11)	(100)	73
Hadji 2012[92]	RIS 35 mg weekly plus PBO 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 PBO 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	74.2

Trial name /Author/date	Treatment arms (n=)	Mean age in years (SD)	Sex % female	T-score FN (or LS if FN not reported) Mean (SD)	BMD at FN (or LS if FN not reported) (g/cm^2) Mean (SD)	Fractures (at baseline) n (%)	Prior treatment for osteoporosis %
						vertebral fracture)	
MOVE Aspenberg 2016[99] Malouf-Sierra 2017[93]	RIS 35 mg weekly plus PBO 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 PBO N= 86	77.2 (8.0)	76.7	–2.63 (0.519)	0.603 (0.098)	(100)	14.0
Cosman 2011[94]	ZOL 5 mg iv annually n=137	66.1 (9.0)	100	LS T-score -2.88 (0.883)	NR	21 (15.3)	0
	TPTD 20 µg s.c. daily plus PBO N= 138	63.8 (9.1)	100	LS T-score -2.87 (0.807)	NR	22 (15.9)	0

Appendix 5: Clinical effectiveness results

Table 17: Vertebral fracture data reported by the included studies

Trial name /Author date/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. PBO						
FREEDOM Cummings 2009[42] PM women with OP	Efficacy	Morphometric, new. Definition: increase of at least Genant[38] grade 1, 20% or more reduction in anterior, middle, and/or posterior height and a reduction of area 10-20%	PBO, 3906 DEN, 3902	PBO, 3691 DEN, 3702	36	PBO, 264/3691 (7.15%) DEN, 86/3702 (2.32%) (RD to 4.8 [95%CI, to 3.9 to 5.8]; RR, 0.32 [95%CI, to 0.26 to 0.41]; p<0.001)

Trial name /Author date/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 Cummings 2009[42] PM women with OP	Efficacy	Clinical	PBO, 3906 DEN, 3902	PBO, 3906 DEN, 3902	36	PBO, 92/3906 (2.36%) DEN, 29/3902 (0.74%) (RD to 1.7 [95%CI, to 1.1 to 2.3]; RR, 0.31 [95%CI, to 0.20 to 0.47]; p<0.001)
FREEDOM Cummings 2009[42] PM women with OP	Efficacy	Morphometric Multiple (>2)	PBO, 3906 DEN, 3902	PBO, 3691 DEN, 3702	36	PBO, 59/3691 (1.60%) DEN, 23/3702 (0.62%) (RD to 1.0 [95%CI, to 0.5 to 1.5]; RR, 0.39 [95%CI, to 0.24 to 0.63]; p <0.001)
FREEDOM Bone 2017[103] PM women with OP	Efficacy	Morphometric new	PBO, 3906 DEN, 3902	PBO, 3691 DEN, 3702	0-12 months	PBO, 82/3691 (2.22%) DEN, 32/3702 (0.86%) Values Estimated RR, from graph Estimated RR, 0.39 [95%CI, 0.26 to 0.58], p<0.00001

Trial name /Author date/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[103] PM women with OP	Efficacy	Morphometric new	As above	PBO, 3691 DEN, 3702	12-24 months	PBO, 116/3691 (3.14%) DEN, 26/3702 (0.70%) Values Estimated RR, from graph Estimated RR, 0.22 [95%CI, 0.15 to 0.34], p<0.00001
FREEDOM Bone 2017[103] PM women with OP	Efficacy	Morphometric new	As above	PBO, 3691 DEN, 3702	24-36 months	PBO, 114/3691 (3.09%) DEN, 40/3702 (1.08%) Values Estimated RR, from graph Estimated RR, 0.35 [95%CI, 0.24 to 0.50], p<0.00001
FREEDOM Bone 2017 OLE[104] PM women with OP)	Efficacy	Morphometric new	Entered OLE PBO to DEN, 2207 DEN to DEN, 2343	PBO/DEN, 1991 DEN/DEN, 2116	84 months from OLE	PBO/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

Trial name /Author date/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)**
ADAMO Orwoll 2012[43] Men with OP	Safety	Clinical	PBO, 121 DEN, 121	Safety Ns PBO, 120 DEN, 120	12	PBO, 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[44] Women and men with OP	Efficacy	Morphometric, new. Definition: increase of at least Genant[38] grade 1, 20% or more reduction in anterior, posterior, or central vertebra height	PBO, 511 DEN, 500	PBO, 480 DEN, 472	24	PBO, 41/480 (8.60%) DEN, 10/472 (2.20%) (HR to 0.260 [95%CI, to 0.129 to 0.521]; p<0.0001)

Trial name /Author date/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 Nakamura 2014[44] Women and men with OP	Efficacy	Morphometric new or worsening	As above	PBO, 480 DEN, 472	24	PBO, 49/480 (10.30%) DEN, 17/472 (3.60%) (HR 0.343 [95%CI, to 0.194 to 0.606], p=0.0001)
DIRECT Sugimoto 2015[105] Women and men with OP	Efficacy	Morphometric new	PBO to DEN, 406 DEN to DEN, 404 12 months open-label	PBO/DEN, 406 DEN/DEN, 404	36 including 12 OLE	PBO/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[105] Women and men with OP	Efficacy	Morphometric new or worsening	As above	PBO/DEN, 406 DEN/DEN, 404	36 including 12 OLE	PBO/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[105] Women and men with OP	Efficacy	Morphometric new	As above	PBO/DEN, 406 DEN/DEN, 404	12 OLE	PBO/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

Trial name /Author date/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[105] Women and men with OP	Efficacy	Morphometric new or worsening	As above	PBO/DEN, 406 DEN/DEN, 404	12 OLE	PBO/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 PM women with OP	Efficacy	Morphometric new or worsening	PBO, 55 DEN, 54	PBO, 55 DEN, 54	12	PBO, 0/55 (0%) DEN, 0/54 (0%) NE
RLX. vs PBO						
Morii 2003[48] PM women with OP	Efficacy	Morphometric, new. Definition: Genant[38] method	PBO, 97 RLX, 90	PBO, 87 RLX, 79	12	PBO, 2/87 (2.30%) RLX, 0/79 (0%) Estimated RR, 0.22 [95%CI, 0.01 to 4.51], p=0.33
Liu 2004[49] PM women with OP	Efficacy	Clinical	PBO, 102 RLX, 102	PBO,102 RLX, 102	12	PBO, 5/102 (4.90%) RLX, 0/102 (0%) (RR, 0.09 [95%CI, to 0.005 to 1.580]; p>0.05)

Trial name /Author date/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)**
Silverman 2008[51] PM women with OP	Efficacy	Morphometric, new Definition: Genant[38] method	PBO, 1855 RLX, 1849	PBO,1741 RLX, 1696	36	PBO, 71/1741 (4.10%) RLX, 40/1696 (2.36%) (HR to 0.58 [95%CI, 95% CI to 0.38 to 0.89]; p<0.05)
Silverman 2008[51, 329] PM women with OP	Efficacy	Clinical	As above	PBO, 1741 RLX, 1696	36	PBO, 16/1741 (0.92%) RLX, 15/1696 (0.88%) (p=0.89)
MORE Ettinger 1999[52] Women with OP	Efficacy	Morphometric new Definition: Genant[38] method	PBO, NR RLX, NR	PBO, 1522 RLX, 1490	36	PBO, 68/1522 (4.50%) RLX, 35/1490 (2.30%) (RR, 0.5 [95%CI, to 0.4 to 0.9]) Estimated p=0.002
MORE Ettinger 1999[52] Women with low BMD + fracture	Efficacy	Morphometric new	PBO, NR RLX, NR	PBO, 770 RLX, 769	36	PBO, 163/770 (21.20%) RLX, 113/769 (14.70%) (RR, 0.7 [95%CI, to 0.6 to 0.9]) Estimated p=0.001

Trial name /Author date/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[101] PM women with OP	Efficacy	Clinical	PBO, 2576 RLX, 2557	PBO, 2292 RLX, 2259	0-12 months	PBO, 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[101] PM women with OP	Efficacy	Clinical	As above	PBO, 2292 RLX, 2259	12-24 months	PBO, 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[101] PM women with OP	Efficacy	Clinical	As above	PBO, 2292 RLX, 2259	24-36 months	PBO, 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[101] PM women with OP	Efficacy	Clinical	As above	PBO, 2292 RLX, 2259	36	PBO, 81/2292 (3.50%) RLX, 47/2259 (2.10%) Estimated RR, 0.59 [95%CI, 0.41 to 0.84], p=0.003

Trial name /Author date/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[101] PM women with OP	Efficacy	Clinical	As above	PBO, 2292 RLX, 2259	24	PBO, 35/2292 (1.54%) RLX, 22/2259 (0.97%) Estimated RR, from graph Estimated RR, 0.64 [95%CI, 0.38 to 1.08], p=0.10
Lufkin 1998[53] PM women with OP	Efficacy	Morphometric new Definition: 15% decrease in the same vertebra	PBO, 48 RLX, 48	PBO, 45 RLX, 43	12	PBO, 18/45 (40.00%) RLX, 21/43 (48.84%) Estimated RR, 1.22 [95%CI, 0.76 to 1.96], p=0.41

Trial name /Author date/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)
Mok 2011[54] PM women on long-term GC	Efficacy	Morphometric new Definition: loss of at least 25% of vertebral height in previously normal vertebrae	PBO, 57 RLX, 57	PBO, 56 RLX, 51	12	PBO, 3/56 (5.36%) RLX, 0/51 (0%) (p=0.24)
ROMO. vs PBO						
FRAME Cosman 2016[55] PM women with OP	Efficacy	Morphometric new Definition: Genant[38] method	PBO, 3591 ROMO, 3589	PBO, 3322 ROMO, 3321	12	PBO, 59/3322 (1.78%) ROMO, 16/3321 (0.48%) (RR, 0.27 [95%CI, to 0.16 to 0.47]; Nominal p<0.001; Adjusted p<0.001)
FRAME Cosman 2016[55] PM women with OP	Efficacy	Morphometric Multiple or worsening	As above	PBO, 3322 ROMO, 3321	12	PBO, 9/3322 (0.27%) ROMO, 1/3321 (0.03%) (RR, 0.11 [95%CI, to 0.01 to 0.87]; Nominal p=0.011)

Trial name /Author date/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)
FRAME Cosman 2016[55] PM women with OP	Efficacy	Morphometric new	PBO to DEN, 3591 ROMO to DEN, 3589 12 months open-label	PBO, 3327 ROMO, 3325	24	PBO/DEN, 84/3327 (2.52%) ROMO/DEN, 21/3325 (0.63%) (RR, 0.25 [95%CI, to 0.16 to 0.40]; Nominal p<0.001; Adjusted p<0.001)
FRAME Cosman 2016[55] PM women with OP	Efficacy	Morphometric Multiple or worsening	As above	PBO, 3327 ROMO, 3325	24	PBO/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[37] PM women with OP	Efficacy	Morphometric new	PBO to DEN, 3591 ROMO to DEN, 3589 12 months open-label	PBO, 3327 ROMO, 3325	36	PBO/DEN, 94/3327 (2.8%) ROMO/DEN, 32/3327 (1.0%) (RR reduction 66% [95%CI, 95% CI: 49 to 77]; RR=0.34; Nominal p<0.001)

Trial name /Author date/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)**
FRAME Cosman 2016[37] PM women with OP	Efficacy	Morphometric Multiple or worsening	As above	PBO, 3327 ROMO, 3325	36	PBO/DEN, 94/3327 (2.8%) ROMO/DEN, 33/3327 (1.0%) (RR reduction 65% [95%CI, to 48 to 76] RR=0.35; Nominal p<0.001)
TPTD. vs PBO						
ACTIVE Miller 2016[96] PM women with OP	Efficacy	Morphometric new Definition: Genant[38] method	PBO, 821 TPTD, 818	PBO, 821 TPTD, 818	18	PBO, 30/711 (4.20%) TPTD, 6/717 (0.80%) (RD to −3.38 [95%CI, to −5.18 to −1.80]; RR, 0.20 [95%CI, to 0.08 to 0.47]; p<0.001)
ACTIVE Miller 2016[96] PM women with OP	Efficacy	Clinical	As above	PBO, 821 TPTD, 818	18	PBO, 9/821 (1.10%) TPTD, 3/818 (0.40%) Estimated RR, 0.59 [95%CI, 0.29 to 1.17], p=0.10

Trial name /Author date/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)
Miyauchi 2010[59] Women and men with OP	Efficacy	Morphometric any	PBO, 70 TPTD, 137	PBO, 67 TPTD, 136	12	PBO, 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[59] Women and men with OP	Efficacy	Morphometric new Definition: deterioration of at least one grade by Genant[38] method	As above	PBO, 67 TPTD, 136	12	PBO, 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[59] Women and men with OP	Efficacy	Morphometric worsening Definition: deterioration of at least one grade by Genant[38] method	As above	PBO, 67 TPTD, 136	12	PBO, 0/67 (0%) TPTD, 2/136 (1.47%) Estimated RR, 0.62 [95%CI, 0.17 to 2.22], p=0.56

Trial name /Author date/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)**
Neer 2001[63] PM women with OP	Efficacy	Morphometric ≥ 1 fracture Definition: Genant[38] method	PBO, 544 TPTD, 541	PBO, 448 TPTD, 444	24	PBO, 64/448 (14.00%) TPTD,22/444 (5.00%) (RR, 0.35 [95%CI, to 0.22 to 0.55]; Reduction in absolute risk to 9%; P≤0.001)
Neer 2001[63] PM women with OP	Efficacy	Morphometric > 1 fracture	As above	As above	24	PBO, 22/448 (5.00%) TPTD,5/444 (1.00%) (RR, 0.23 [95%CI, to 0.09 to 0.60]; Reduction in absolute risk to 4%; P≤0.001)
Neer 2001[63] PM women with OP	Efficacy	Morphometric ≥ 1 moderate or severe	As above	As above	24	PBO, 42/448 (9.00%) to 4/444 (0.90%) (RR, 0.10 [95%CI, to 0.04 to 0.27]; Reduction in absolute risk to 9%; P≤0.001)

Trial name /Author date/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)
Head-to-head non-bisphosphonates						
EUROFORS Eastell 2009[67] PM women with OP pre-treated with TPTD	Efficacy	Clinical	TPTD, 304 RLX, 97 CON[1], 102	TPTD, 304 RLX, 97 CON, 102	12	TPTD, 4/304 (1.32%) RLX, 0/97 (0%) CON, 0/102 (0%) (Not significant, P value NR)
DEN vs. Bisphosphonates						
Saag 2018[75] Women and men on GC with OP or low BMD+fracture	Efficacy	Clinical	RIS, 397 DEN, 398 Both with PBO	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[76]	Safety	NR	ZOL, 322 DEN, 321 Both with PBO	ZOL, 320 DEN, 320	12	ZOL, 4 fractures DEN, 0 fractures n participants NR

Trial name /Author date/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						
EFFCT Sambrook 2004[77] (International not including US) PM women with OP	Safety	Not reported	ALN, 246 RLX, 241 Both with PBO	ALN, 246 RLX, 241	12	ALN, 0/246 (0%) RLX, 0/241 (0%) NE
Muscoso 2004[80] PM women with OP	Efficacy	Not reported	ALN, 1000 RLX, 100 RIS, 100 All daily open-label	ALN, 1000 RLX, 100 RIS, 100	0-12 months	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

Trial name /Author date/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)**
Muscoso 2004[80] PM women with OP	Efficacy	Not reported	As above	ALN, 1000 RLX, 100 RIS, 100	12-24 months	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[81] PM women with OP	Efficacy	Morphometric new Definition: Genant[38] method	ALN, 716 RLX, 707 Both with PBO	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[81] PM women with OP	Efficacy	Morphometric moderate/ severe Definition: Genant[38] method >25% loss of height	ALN, 716 RLX, 707 Both with PBO	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

Trial name /Author date/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)**
EVA Recker 2007[81] PM women with OP	Efficacy	Clinical	As above	716/707	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
ROMO vs. Bisphosphonates						
ARCH Saag 2017[84] PM women with OP	Efficacy	Morphometric new ITT MI Definition: Genant[38] method	ALN, 2047 ROMO, 2046 Both with PBO	ALN, 2047 ROMO, 2046	12	ALN, 128/2047 (6.3%) ROMO, 82/2046 (4.00%) (RR, 0.63 [95%CI, to 0.47 to 0.85]; p=0.003)
ARCH Saag 2017[84] PM women with OP	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, (%%CI to 0.46 to 0.89]; p=0.008)

Trial name /Author date/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)
ARCH Saag 2017[84] PM women with OP	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, to 0.49 to 0.89]; p=0.006)
ARCH Saag 2017[84] PM women with OP	Efficacy	Clinical	As above	ALN, 2047 ROMO, 2046	12	ALN, 18/2047 (0.90%) ROMO, 10/2046 (0.50%) (HR 0.56 [95%CI, to 0.26 to 1.22]; p=0.14)
ARCH Saag 2017[84] PM women with OP	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, to 0.40 to 0.66]; p<0.001)
ARCH Saag 2017[84] PM women with OP	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, to 0.38 to 0.66]; p<0.001)

Trial name /Author date/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)**
ARCH Saag 2017[84] PM women with OP	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, [95%CI, to 0.52 0.40 to 0.66]; p<0.001)
TPTD vs. Bisphosphonates						
Saag 2009[102] Women and men on GC with OP or low BMD+fracture	Efficacy	Morphometric new Definition: Genant[38] method	Women and men ALN, 214 TPTD, 214 Both with PBO	ALN, 165 TPTD, 171	18	ALN, 10/165 (6.10%) TPTD, 1/171 (0.6%) (p=0.004)
Saag 2009[102] Women and men on GC with OP 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[102] Women and men on GC with OP 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)

Trial name /Author date/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)**
Saag 2009[86]	Efficacy	Clinical	As above	ALN, 169 TPTD, 173	36	ALN, 4/169 (2.40%) TPTD, 0/173 (0%) (p=0.037)
Langdahl 2009[106] Women and men on GC with OP or low BMD+fracture	Efficacy	Morphometric new	Women ALN, 173 TPTD, 171 Both with PBO	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[106] Women and men on GC with OP or low BMD+fracture	Efficacy	Morphometric new	Men ALN, 41 TPTD, 42 Both with PBO	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[87] PM women with severe OP+fracture and on treatment for OP	Efficacy	Morphometric new	ALN weekly,39 TPTD,42 Without PBO	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

Trial name /Author date/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[90] Men with OP	Efficacy	Morphometric new Definition: Genant[38] method	RIS weekly, 10 TPTD, 9 Both with PBO	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[92] PM women with OP	Efficacy	Morphometric new Definition: Genant[38] method	RIS weekly, 350 TPTD, 360 Both with PBO	RIS, 350 TPTD, 360	6	RIS, 18/350 (5.10%) TPTD, 15/360 (4.20%) (p=0.6)
Hadji 2012[92] PM women with OP	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[92] PM women with OP	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[92] PM women with OP	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)

Trial name /Author date/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)
VERO Kendler 2018[100] PM women with OP	Efficacy	Morphometric new Definition: Genant[38] method	RIS weekly, 680 TPTD, 680 Both with PBO	RIS, 533 TPTD, 516	24	RIS, 64/533 (12.00%) TPTD, 28/516 (5.00%) (RR, 0·44 [95%CI, to 0·29 to 0·68]; p<0.0001)
VERO Kendler 2018[100] PM women with OP	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, to 0·31 to 0·68]; p<0.0001)
VERO Kendler 2018[100] PM women with OP	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, to 0·04 to 0·74]; p=0.007)
VERO Kendler 2018[100] PM women with OP	Efficacy	Morphometric multiple	As above	RIS, 533 TPTD, 516	12	RIS, 11/533 (2.10%) TPTD, 4/516 (0.78%) Estimated RR, from graph Estimated RR, 0.38 [95%CI, 0.12 to 1.17], p=0.09

Trial name /Author date/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[107] Women and men with low BMD + recent hip fracture surgery	Safety	Clinical	RIS daily, 113 TPTD, 111 Both with PBO	RIS, 113 TPTD, 111	6	RIS, 0/110 (0%) TPTD, 0/116 (0%) NE
MOVE Malouf-Sierra 2017[93] 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[94] PM women with OP	Safety	Adverse event	ZOL[2], 137 TPTD + ZOL PBO, 138	ZOL, 137 TPTD+PBO, 138	12	ZOL, 5/137 (3.70%) TPTD+PBO, 1/137 (0.70%) Estimated RR, 0.20 [95%CI, 0.02 to 1.69], p=0.14

Definition of morphometric not provided in all studies.

ALN, Alendronate 10 mg daily or 70 mg weekly; BMD, bone mineral density; ; CON, control; DEN, Denosumab 60 mg s.c. every 6 months; HR, hazard ratio; GC, glucocorticoids; IBN, Ibandronate 150 mg oral every month; ITT LOCF, intention-to-treat last observation carried forward; ITT MI, intention-to-treat multiple imputation; NE. not estimable; PBO, placebo; RLX, RLX 60 mg daily; PM, postmenopausal; OLE, open-label extension; OP, osteoporosis; ROMO, Romosozumab 210 mg s.c. monthly; RR, risk ratio; NR, not reported; SD, standard deviation; TPTD, Teriparatide 20 ug s.c. daily; ZOL, ZOL 5 mg iv annually

ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ADAMO, DEN Versus Placebo in Males With Osteoporosis; ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BRIDGE, Phase 3 randomized placeBo-contRolled double-blind study evaluatIng the efficacy anD safety of ROMO in treatinG mEn with osteoporosis; DATA, DEN and TPTD Administration; DECIDE, Determining Efficacy: Comparison of Initiating DEN versus ALN; DIRECT, DEN fracture Intervention RandomizEd placebo Controlled Trial; EFFECT, EFficacy of FOSAMAX versus EVISTA Comparison Trial;

EUROFORS, European Study of Forsteo; EVA, Evista ALN Comparison trial; FACT, Forteo ALN Comparator Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture Reduction Evaluation of DEN in Osteoporosis; MORE, European Study of Forsteo; MOVE, acronym meaning not reported; VERO, VERtebral fracture treatment comparisons in Osteoporotic women.
[1]No active treatment, [2]Not placebo controlled for TPTD

Table 18: Non-vertebral fracture outcomes

Trial name /Author/date	Efficacy or safety outcome	Treatments n randomised	Follow-up months	Non-vertebral n/N (%) (reported between group difference)
DEN versus Placebo				
FREEDOM[42]	Efficacy	Placebo 3906 DEN 3902	36	PBO, 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[103]	Efficacy	Placebo 3906 DEN 3902	0-12 months	PBO, 120/3906 (3.06%), DEN, 101/3902 (2.59%) Values estimated from graph
FREEDOM[103]	Efficacy	Placebo 3906 DEN 3902	12-24 months	PBO, 113/3906 (2.89%) DEN, 82/3902 (2.09%) Values estimated from graph
FREEDOM[103]	Efficacy	Placebo 3906 DEN 3902	24-36 months	PBO, 98/3906 (2.50%) DEN, 84/3902 (2.15%) Values estimated from graph

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
FREEDOM OLE (NCT00523341)	Efficacy	Entered OLE Placebo/DEN2207 DEN/DEN 2343	84 months from OLE	PBO/DEN, 219/ 2207 (9.92%) DEN/DEN, 172/ 2343 (7.34%)
ADAMO[43]	Safety	Placebo 121 DEN 121	12	PBO 2/120 (1.67%) DEN 1/120 (0.83%)
DIRECT[44]	Efficacy	Placebo 511 DEN 500	24	All PBO 20/480 (4.10%) DEN 19/472 (4.10%) (HR 1.002 [95%CI 0.521to 1.926]; p=0.9951) Major (proximal humerus, forearm, ribs/clavicle, pelvis, hip, distal femur, and proximal tibia) PBO 18/480 (3.70%) DEN 8/472 (1.60%) (HR 0.434 [95%CI 0.178 to 1.055]; p=0.0577) Non-major PBO 2/480 (0.40%) DEN 12/472 (2.50%) (HR 5.552 [95%CI 1.231 to 25.042]; p=0.0120)

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
DIRECT[105]	Efficacy	PBO to DEN 406 DEN to DEN 404	36 including 12 OLE	All PBO/DEN 27/406 (6.65%) DEN/DEN 21/404 (5.20%) Major (proximal humerus forearm ribs/clavicle pelvis hip distal femur and proximal tibia) PBO/DEN 22/406 (5.42%) DEN/DEN 8/404 (1.98%)
Koh 2016[46]	Safety	Placebo 66 DEN 69	6	PBO 1/66 (1.52%) DEN 1/69 (1.45%)
Koh 2016 OLE[46]	Safety	PBO to DEN 66 DEN to DEN 69	6-12 months OLE	PBO 1/63 (1.60%) DEN 0/60 (0%)
RLX versus Placebo				
Morii 2003[48]	Efficacy	Placebo 97 RLX 90	12	PBO 4/97 (4.12%) RLX 0/88 (0%)

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
Silverman 2008[51] clinicaltrials.gov NCT00205777	Efficacy	Placebo 1855 RLX 1849	36	PBO 118/1885 (5.70%) RLX 109/1849 (6.30%) Non-significant p-value NR
Lufkin 1998[53]	Efficacy	Placebo 48 RLX 48	12	PBO 3/45 (6.67%) RLX 0/43 (0%)
ROMO versus Placebo				
FRAME[55]	Efficacy	Placebo 3591 ROMO 3589	12	PBO, 75/3591 (2.1%) ROMO, 56/3589 (1.6%) (HR, 0.75 [95%CI, 0.53 to 1.05]; p=0.096
FRAME[55]	Efficacy	PBO to DEN 3591 ROMO to DEN 3589	24	PBO, 129/3591 (3.6%), ROMO, 96/3589 (2.7%) (HR, 75 [95%CI, 0.57 to 0.97]; p=0.029
Ishibashi 2017[56]	Safety	Placebo 63 ROMO 63	12	PBO 1/63 (1.59%) ROMO 2/63 (3.17%)
TPTD versus Placebo				

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
Miyauchi 2010[59]	Efficacy	Placebo 70 TPTD 137	12	PBO 4/67 (6.00%) TPTD 3/136 (2.20%) Fragility PBO 1/67 (1.50%) TPTD 1/136 (0.70%)
Miyauchi 2010[59]	Efficacy	Entered extension PBO to TPTD 59 TPTD to TPTD 119	12-18 months OLE	PBO/TPTD 4/59 (6.78%) TPTD/TPTD 3/119 (2.52%) Estimated from graph
Miyauchi 2010[59]	Efficacy	Entered extension PBO to TPTD 59 TPTD to TPTD 119	18-24 months OLE	PBO/TPTD 4/50 (8.0%) TPTD/TPTD 3/102 (2.94%) Estimated from graph
ACTIVE[96]	Efficacy	Placebo 821 TPTD 818	18	PBO 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)

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
FPT[63]	Efficacy	Placebo 544 TPTD 541	19	PBO 53/544 (9.74%) TPTD34/541 (6.28%) (p=0.04) Fragility PBO 30/544 (5.51%) TPTD14/541 (2.59%) (p=0.02)
Head-to-head non-bisphosphonates				
EUROFORS[67]	Efficacy	TPTD 304 RLX 97 Control 102	12	TPTD 9/304 (2.96%) RLX 2/97 (2.06%) NT 1/102 (0.98%) Non-significant p value NR
STRUCTURE[68]	Safety	ROMO 218 TPTD 218	12	ROMO 7/218 (3.21%) TPTD 8/214 (3.67%)
Non-bisphosphonates versus Bisphosphonates				

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
STAND[71]	Safety	ALN 251 DEN 253	12	ALN 4/249 (1.61%) DEN 8/253 (3.16%)
DAPS[108]	Safety	ALN 124 DEN 126	12	ALN 1/118 (0.85%) DEN 1/125 (0.80%)
DAPS[108]	Safety	ALN to DEN 106 DEN to ALN 115	12-24mo	ALN/DEN 3/106 (2.83%) DEN/ALN 1/110 (0.90%)
Saag 2018[75]	Efficacy	RIS plus PBO 397 DEN plus PBO 398	12	RIS 10/397 (3.0%) DEN 17/398 (4.0%)
EFFECT (US)[78]	Safety	ALN 223 RLX 233	12	ALN 5/199 (2.51%) RLX 8/206 (3.88%)
Muscoso 2004[80]	Efficacy	ALN 1000 RLX 100 RIS 100	0-12 months	ALN 2/1000 (0.2%) RLX 0/100 (0%) RIS 0/100 (0%)
Muscoso 2004[80]	Efficacy	ALN 1000 RLX 100 RIS 100	12-24 months	ALN 2/1000 (0.2%) RLX 0/100 (0%) RIS 0/100 (0%)

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
EVA[81]	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[83]	Safety	Placebo 33 RLX 33 Open-label ALN 33	24	PBO 2/33 (6.06%) RLX 1/33 (3.03%) ALN 1/33 (3.03%)
ARCH[84]	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[84]	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[84]	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)

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
ARCH[84]	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[102]	Efficacy	Men and women ALN 214 TPTD 214	18	ALN 8/214 (3.70%) TPTD 12/214 (5.60%) (p=0.36)
Saag 2009[102]	Efficacy	Men and women ALN 214 TPTD 214	36	ALN 15/214 (7.00%) TPTD 16/214 (7.50%) (p=0.843)
Saag 2009[106]	Efficacy	Men ALN 41 TPTD 42	18	ALN 2/71 (2.82%) TPTD 1/42 (2.38%) (p=0.58)
Saag 2009[106]	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[88]	Safety	RIS 47 TPTD 45	18	RIS 5/47 (10.60%) TPTD 0/45 (0%) (p=0.056)

Trial name /Author/date	**Efficacy or safety outcome**	**Treatments n randomised**	**Follow-up months**	**Non-vertebral n/N (%) (reported between group difference)**
VERO[100]	Efficacy	RIS plus PBO 680 TPTD plus PBO 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[100]	Efficacy	RIS plus PBO 680 TPTD plus PBO 680	12	RIS 23/680 (3.32%) TPTD 15/680 (2.21%) Estimated from graph
Hadji 2012[92]	Efficacy	RIS 350 TPTD 360	6	RIS 29/350 (8.30%) TPTD 28/360 (7.80%) (p=0.89)
MOVE[93]	Safety	RIS 350 TPTD 360	18	RIS 10/110 (9.10%) TPTD 5/116 (4.70%) (p=0.286)
Cosman 2011[94]	Safety	ZOL (no PBO) 137 TPTD plus PBO 138	12	ZOL 8/137 (5.84%) TPTD+PBO 7/137 (5.11%)

All reported treatment arms at licensed dose. ALN Alendronate; BMD bone mineral density; DEN Denosumab; HR hazard ratio; IBN ibandronate; ITT LOCF intention-to-treat last observation carried forward; ITT MI intention-to-treat multiple imputation; ROMO Romosozumab; RD risk difference; RR risk ratio; NR not reported; PBO placebo; OLE=open label extension; RAL RLX; s.c. subcutaneous; SD standard deviation; TPTD Teriparatide; ZOL Zoledronate

Table 19: Fractures hip, wrist or proximal humerus

Trial name /Author/date	**Treatment arms**	**Follow-up Months**	**Hip fracture n/N (%) (reported between group difference)**	**Wrist fracture n/N (%) (reported between group difference)**	**Proximal humerus fracture n/N (%) (reported between group difference)**
DEN versus Placebo					
FREEDOM[42]	Placebo	0-36	43/3906 (1.2)	NR	NR
	DEN		26/3902 (0.7) Difference 0.3 (95%CI -0.1, 0.7) HR 0.60 (95%CI 0.37, 0.97) P=0.04	NR	NR
FREEDOM[103]	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)	NR	NR

Trial name /Author/date	**Treatment arms**	**Follow-up Months**	**Hip fracture n/N (%) (reported between group difference)**	**Wrist fracture n/N (%) (reported between group difference)**	**Proximal humerus fracture n/N (%) (reported between group difference)**
			Non-significant (p value NR)		
	Placebo	24-36	11/3906 (0.27)	NR	NR
	DEN		12/3902 (0.32) Non-significant (p value NR)	NR	NR
ADAMO[43]	Placebo	12	NR	NR	1/120 (0.8)
	DEN		NR	NR	0/120 (0)
DIRECT[44]	Placebo	24	2/480 (0.4)	NR	NR
	DEN		0/472 (0)	NR	NR
RLX versus placebo					
Silverman 2008[51 329]	Placebo	36	PBO 6/1885 (0.3)	PBO 31/1885 (1.6)	NR
	RLX		RLX 5/1849 (0.3)	RLX 46/1849 (2.5)[329]	NR
Lufkin 1998[53]	Placebo	12	0/45 (0)	0/45 (0)	NR
	RLX		0/43 (0)	0/43 (0)	NR
ROMO versus Placebo					
FRAME[55]	Placebo	12	13/3591 (0.4)	NR	NR
	ROMO		7/3589 (0.2)	NR	NR

Trial name /Author/date	**Treatment arms**	**Follow-up Months**	**Hip fracture n/N (%) (reported between group difference)**	**Wrist fracture n/N (%) (reported between group difference)**	**Proximal humerus fracture n/N (%) (reported between group difference)**
			HR 0.54 (95%CI 0.22, 1.35) p=0.18		
FRAME[55]	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, 1.04) p=0.059	NR	NR
Ishibashi 2017[56]	Placebo	12	NR	0/63 (0)	NR
	ROMO		NR	1/63 (1.6)	NR
TPTD versus Placebo					
ACTIVE[96]	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[63]	Placebo	19	All	All	All

Trial name /Author/date	**Treatment arms**	**Follow-up Months**	**Hip fracture n/N (%) (reported between group difference)**	**Wrist fracture n/N (%) (reported between group difference)**	**Proximal humerus fracture n/N (%) (reported between group difference)**
			4/544 (0.7) Fragility 4/544 (0.7)	13/544 (2.4) Fragility 7/544 (1.3)	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[67]	No active treatment [12months] (following pre-randomisation TPTD [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 [12 months] (following 12months		1/304 (0.3)	3/304 (1.0)	0/304 (0)

Trial name /Author/date	**Treatment arms**	**Follow-up Months**	**Hip fracture n/N (%) (reported between group difference)**	**Wrist fracture n/N (%) (reported between group difference)**	**Proximal humerus fracture n/N (%) (reported between group difference)**
	pre-random TPTD)				
STRUCTURE[68]	TPTD	12	0/218 (0)	0/218 (0)	1/218 (0.5)
	ROMO		1/218 (0.5)	1/218 (0.5)	0/218 (0)
Non-bisphosphonates versus Bisphosphonates					
STAND[71]	ALN	12	NR	2/249 (0.8)	0/249 (0)
	DEN		NR	3/253 (1.2)	1/253 (0.4)
Saag 2018[75]	RIS	12	1/397 (0.3)	NR	3/397 (0.8)
	DEN		1/398 (0.3)	NR	3/398 (0.8)
EFFECT (International)[77]	RLX plus placebo	12	1/241 (0.4)	NR	NR
	ALN plus placebo		0/246 (0)	NR	NR
EFFECT (US)[78]	RLX plus placebo	12	NR	1/206 (0.5)	1/206 (0.5)
	ALN plus placebo		NR	0/199 (0)	0/199 (0)
Muscoso 2004[80]	ALN	12	1/1000 (0.1)	1/1000 (0.1)	NR
	RLX		0/100 (0)	0/100 (0)	NR

Trial name /Author/date	**Treatment arms**	**Follow-up Months**	**Hip fracture n/N (%) (reported between group difference)**	**Wrist fracture n/N (%) (reported between group difference)**	**Proximal humerus fracture n/N (%) (reported between group difference)**
	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[81]	RLX	24	2/699 (0.3)	8/699 (1.1)	NR
	ALN		1/713 (0.1) RR 0.49 (95%CI 0.04, 3.77)	6/713 (0.8) RR 0.74 (95%CI 0.27, 2.02)	NR
ARCH[84]	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 year	41/2046 (2.0)	NR	NR
	ALN followed by ALN		66/2047 (3.2) P=0.015	NR	NR
EUROGIOPs[88]	RIS	18	1/47 (2.1)	NR	1/47 (2.1)
	TPTD		0/45 (0)	NR	0/45(0)

Trial name /Author/date	**Treatment arms**	**Follow-up Months**	**Hip fracture n/N (%) (reported between group difference)**	**Wrist fracture n/N (%) (reported between group difference)**	**Proximal humerus fracture n/N (%) (reported between group difference)**
VERO[100]	RIS	24	5/680 (0.7)	10/680 (1.5)	2/680 (0.3)
	TPTD		2/680 (0.3)	6/680 (0.9)	4/680 (0.6)
Hadji 2012[92]	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[99]	RIS	6	5/110 (4.5)	NR	1/110 (0.9)
	TPTD		2/106 (1.9)	NR	1/106 (0.9)
MOVE[93]	RIS	18	7/110 (6.4)	NR	1/110 (0.9)
	TPTD		2/106 (1.9)	NR	1/106 (0.9)

All reported arms at licensed dose; NR= not reported; NA=not applicable

Table 20: Femoral neck BMD data reported by the included studies

Trial name /Author date/Population	**Treatments, n randomised**	**Treatments, n analysed**	**Follow-up months**	FN BMD Percent change from baseline Mean (SD)	Estimated from graph	FN BMD Reported (estimated) between group difference
DEN vs. PBO						
FREEDOM Bone 2017[103] PM women with OP	PBO, 3906 DEN, 3902	PBO, 3906 DEN, 3902	36	PBO, +7.1 (NR) DEN, +9.0 (NR)	Nothing	NR (NE)
FREEDOM Bone 2017 OLE[104] PM women with OP	Entered OLE PBO to DEN, 2207 DEN to DEN, 2343	PBO/DEN, 2809 DEN/DEN, 2210	84 months from OLE	PBO/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[43] Men with OP	PBO, 121 DEN, 121	PBO, 117 DEN, 111	12	PBO, 0.00 (3.31[1]) DEN, +2.10 (3.35[1])	95%CIs	p<0.0001

DIRECT Nakamura 2014[44] Women and men with OP	PBO, 511 DEN, 500	PBO, 480 DEN, 472	24	PBO, -1.10 (4.30[1]) DEN, +4.00 (4.82[1])	95%CIs	p<0.0001
DIRECT Sugimoto 2015[105] Women and men with OP	PBO to DEN, 406 DEN to DEN, 404	PBO/DEN, 406 DEN/DEN, 404	36 including 12 OLE	PBO/DEN, +1.1 (4.32[1]) DEN/DEN, +4.8 (4.61[1])	95%CIs	NR (MD, +3.70 [95%Ci, 3.08 to 4.32], P0<0.00001)
DIRECT Sugimoto 2015[105] Women and men with OP	PBO to DEN, 406 DEN to DEN, 404	PBO/DEN, 406 DEN/DEN, 404	24-36 OLE	PBO/DEN, +0.8 (NR) DEN/DEN, +2.30 (NR)	Nothing	NR (NE)
Koh 2016[46] PM women with OP	PBO, 66 DEN, 69	PBO, 66 DEN, 68	6	PBO, +0.73 (2.88[1]) DEN, +4.37 (4.50[1])	Means and 95%CIs	Mean difference between groups in % change 1.4% (95% CI, 0.4%, 2.3%); p=0.0042
Koh 2016[46] PM women with OP	Entered OLE PBO to DEN, 63 DEN to DEN, 60	OLE PBO/DEN, 59 DEN/DEN, 59	6-12 OLE	PBO/DEN, +3.48 (3.29[1]) DEN/DEN, +5.59 (4.04[1])	Means and 95%CIs	NR (MD, +2.11 [95%CI, 0.78 to 3.44], p=0.002)
RLX. vs PBO						

Adami 2008[47] PM women with OP pre-treated with TPTD	PBO, 172 RLX, 157	PBO, 154 RLX, 145	12	PBO, +0.20 (3.72^2) RLX, +2.30 (4.82^2)	Nothing	p<0.001
Adami 2008[47] PM women with OP pre-treated with TPTD	OLE PBO to RLX, 172 RLX to RLX, 157	PBO/RLX, 146 RLX/RLX, 139	36 including 24 OLE	PBO, 1.70 (4.83^2) RLX, 2.20 (5.89^2)	Nothing	NR (MD, +0.50 [95%CI, -0.75 to 1.75], p=0.43)
Liu 2004[49] PM women with OP	PBO, 102 RLX, 102	PBO, 102 RLX, 102	12	PBO, -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[51] PM women with OP	PBO, 1855 RLX, 1849	PBO, 1711 RLX, 1662	36	PBO, -1.30 (6.20^2) RLX, 0.80 (6.11^2)	Nothing	NR (MD, +2.10 [1.68 to 2.52], p<0.00001)
MORE Ettinger 1999[52] Women with OP	PBO, NR RLX, NR	PBO, 1522 RLX, 1490	36	NR	Nothing	RLX group increased by 2.1% compared to placebo, p<0.001
Mok 2011[54] PM women on long-term GC	PBO, 57 RLX, 57	PBO, 56 RLX, 51	12	PBO, -0.45 (4.71^2) RLX, -0.59 (3.86^2)	Mean and SEMs	NR (MD, -0.14 [95%CI, -1.77 to 1.49], p=0.87)
ROMO. vs PBO						

FRAME Cosman 2016[55] PM women with OP	PBO, 3591 ROMO, 3589	Substudy PBO, 62 ROMO, 66	12	PBO, -0.70 (8.60[1]) ROMO, +5.20 (8.10[1])	95%CIs	ROMO group compared to placebo 5.9% (95%CI 4.3, 7.4) p<0.001
FRAME Cosman 2016[55] PM women with OP	PBO to DEN, 3591 ROMO to DEN, 3589 12 months open-label	PBO/DEN, 62 ROMO/DEN, 66	24	PBO/DEN, +0.60 (8.30[1]) ROMO/DEN, +6.60 (8.70[1])	95%CIs	ROMO group compared to placebo 6.0% (95%CI 4.4, 7.7) p<0.001
Ishibashi 2017[56] PM women with OP	PBO, 63 ROMO, 63	PBO, 59 ROMO, 59	12	PBO, +0.30 (3.53[1]) ROMO, +3.80 (4.31[1])	Nothing	ROMO group compared to placebo 3.5% (1-sided 95%CI 2.3%, NA) (p<0.00001)
BRIDGE[57] Men with OP	PBO, 82 ROMO, 63	PBO, 79 ROMO, 158	12	PBO, -0.20 (4.00[1]) ROMO, +2.20 (4.60[1])	95%CIs	p<0.001

TPTD. vs PBO						
ACTIVE Miller 2016[96] PM women with OP	PBO, 821 TPTD, 818	PBO, 821 TPTD, 818	18	PBO, -0.44 (3.57) TPTD, +2.26 (3.57)	Nothing	p<0.0001
Orwoll 2003[58] Men with OP	PBO, 147 TPTD, 151	PBO, 147 TPTD, 151	12	PBO, +0.31 (4.1) TPTD, +1.53 (3.95)	Nothing	p=0.029
Miyauchi 2010[59] Women and men with OP	PBO, 70 TPTD, 137	PBO, 67 TPTD, 136	12	PBO, +0.46 (3.89) TPTD, +2.24 (6.01)	Nothing	p=0.015
Miyauchi 2010[59] Women and men with OP	PBO to TPTD, 59 TPTD to TPTD, 119	PBO/TPTD, 58 TPTD/TPTD, 117	12-18 OLE	PBO, +1.22 (4.72) TPTD, +2.92 (4.83)	Nothing	NR (MD, +1.70 [95%CI, 0.20 to 3.20], p=0.03)
Miyauchi 2010[59] Women and men with OP	PBO to TPTD, 50 TPTD, to TPTD 102	PBO/TPTD, 48 TPTD/TPTD, 95	18-24 OLE	PBO, +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[60] PM women with OP	PBO, 39 TPTD, 39	PBO, 34 TPTD, 36	6	PBO, -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[62] PM women with OP	PBO, 45 TPTD, 45	PBO, 41 TPTD, 38	6	PBO, +0.8 (4.8) TPTD, +1.1 (4.6)	Nothing	p<0.01
Leder 2015[62] PM women with OP	Entered extension PBO, 11 TPTD, 14	PBO, 11 TPTD, 14	12 months	PBO, +1.0 (NR) TPTD, +2.2 (NR)	Nothing	NR (NE)
Neer 2001[63] PM women with OP	PBO, 544 TPTD, 541	PBO, 479 TPTD, 479	24	PBO, -0.7 (5.4) TPTD, +2.8 (5.7)	Nothing	p<0.001
Sethi 2008[64] PM women with OP	Ca+Vit D, 41 41	Ca+Vit D, 35 TPTD Ca+Vit D, 38	6	Ca+Vit D, +2.12 (5.92) TPTD Ca+Vit D, +1.97 (4.25)	Nothing	NR (MD, -0.15 [95%CI, -2.53 to 2.23], p=0.90)
Head-to-head non-bisphosphonates						
DATA Tsai 2013[65] PM women with OP	TPTD, 36 DEN, 34 Without PBO open-label	TPTD, 31 DEN, 33	12	TPTD, +0.80 (4.10 DEN, +2.10 (3.80)	Nothing	p=0.1939

DATA Leder 2014[109] PM women with OP	As above	TPTD, 31 DEN, 33	24	TPTD, +2.80 (3.90) DEN, +4.10 (3.80)	Nothing	p=0.23
DATA-SWITCH[66]	OLE TPTD to DEN, 27 DEN to TPTD, 27	TPTD/DEN, 27 DEN/TPTD, 27	0-24	TPTD/DEN, +8.30 (5.83[1]) DEN/TPTD, +4.90 (7.02[1])	Nothing	p<0.0005
DATA-SWITCH[66]	OLE TPTD to DEN, 27 DEN to TPTD, 27	TPTD/DEN, 27 DEN/TPTD, 27	24-48	TPTD/DEN, +5.60 (4.77[1]) DEN/TPTD, +1.20 (5.83[1]) From cis	Nothing	p<0.0005
EUROFORS Eastell 2009[67] PM women with OP pre-treated with TPTD	TPTD, 304 RLX, 97 CON[3], 102	TPTD, 304 RLX, 97 CON, 102	24	TPTD, +1.30 (NR) RLX, +3.10 (NR) CON, +3.50 (NR)	Nothing	p<0.05 TPTD vs no active treatment, other comparisons NR (NE)
STRUCTURE[68] PM women with OP pre-treated with ALN	TPTD, 218 ROMO, 218 Without PBO open-label	TPTD, 209 ROMO, 206	12	TPTD, -0.20 (4.43[1]) ROMO, +3.20, (3.30[1])	Nothing	p<0.0001

McClung 2014[69] PM women with OP	PBO, 52 TPTD, 55 ROMO, 52 ALN, 51	PBO, 47 TPTD,46 ROMO, 50 ALN, 47	12	PBO, +1.10 (3.15[1]) TPTD, +1.10 (3.11[1]) ROMO, +1.40 (3.25[1]) ALN, +1.2 (3.15[1])	Nothing	NR (TPTD vs. ROMO - MD, -0.30 [95%CI, -1.59 to 0.99], p=0.65) (ROMO vs. PBO, p=0.0002) (TPTD vs. PBO, p=0.0007) (ROMO vs. ALN, p=0.73) (TPTD vs. ALN, p=0.88)
DEN vs. Bisphosphonates						
DECIDE[70] PM women with OP	ALN, 595 DEN, 594 Both with PBO	ALN, 586 DEN, 593	12	ALN, +1.80 (3.77[1]) DEN, +2.40 (3.17[1])	95%CIs	Absolute treatment difference 0.6% (95%CI 0.3, 1.0) p=0.0001
STAND[71] PM women with OP already on ALN	ALN, 251 DEN, 253 Without PBO	ALN, 233 DEN, 241	12	ALN, +0.41 (3.81[1]) DEN, +1.40 (3.34[1])	Means and 95%CIs	p<0.0121
DAPS[72] PM women with OP	ALN, 124 DEN, 126 Without PBO	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) [note BMD not powered]

DAPS[108] PM women with OP	Cross-over ALN to DEN, 92 DEN to ALN, 102	ALN/DEN, 92 DEN/ALN, 102	12-24 months (post crossover)	ALN/DEN, -0.10 (NR) DEN/ALN, +1.70 (NR)	Nothing	NR (NE) [note BMD not powered]
McClung 2006[73] PM women with OP or osteopenia	PBO for DEN, 46 ALN, 47 DEN, 47	PBO, 40 ALN, 45 DEN, 42	12	PBO, -0.30 (3.16^2) ALN, +2.10 (3.35^2) DEN, +2.10 (3.24^2)	Nothing	ALN and DEN vs. PBO, both p<0.001 (ALN vs. DEN MD, 0.00 [95%CI, -1.38 to 1.38], p=1.00)
Recknor *et al.* 2013[74] PM women with OP	IBN, 416 DEN,414 Without PBO	IBN, 368 DEN,399	12	IBN, +0.70 (4.79^1) DEN, +1.70 (3.96^1)	95%CIs	p<0.001
Saag 2018[75] Women and men continuing GC with OP or low BMD+fracture	RIS,252 DEN, 145 Both with PBO	RIS, 215 DEN,217	12	RIS, +0.60 (3.37^1) DEN, +1.60 (3.76^1)	95%CIs	p=0.004

Saag 2018[75] Women and men initiating GC with OP or low BMD+fracture	RIS,253 DEN, 145 Both with PBO	RIS, 128 DEN, 119	12	RIS, -0.20 (4.33[1]) DEN, +0.90 (4.17[1])	95%CIs	p=0.020
Miller *et al.* 2016[76] PM women with OP previously treated with bisphosphonates	ZOL, 322 DEN, 321 Both with PBO	ZOL, 309 DEN, 311	12	ZOL, -0.10 (3.34[1]) DEN, +1.20 (3.96[1])	Nothing	p<0.0001
RLX vs. Bisphosphonates						
EFFCT Sambrook 2004[77] (International not including US) PM women with OP	ALN, 246 RLX, 241 Both with placebo	ALN, 246 RLX, 241	12	ALN, +2.20 (5.02[2]) RLX, +1.00 (4.66[2])	SEMs	1.3%; 95%CI, 0.5 to 2.1; p=0.0001
EFFECT (US)[78] PM women with OP	ALN, 223 RLX, 233 Both with placebo	ALN, 199 RLX, 206	12	ALN, +1.72 (4.23[2]) RLX, +1.35 (4.59[2])	Means and SEMs	p=0.396

Johnell 2002[79] PM women with OP	PBO, 82 ALN, 83 RLX, 82	PBO, 77 ALN, 77 RLX, 77	12	PBO, +0.20 (3.51^2) RLX, +1.70 (3.51^2) ALN, +2.70 (4.39^2)	Nothing	ALN and RLX both significantly different from PBO ($p<0.05$) ALN significantly different from RLX ($p<0.05$)
EVA Recker 2007[81] PM women with OP	ALN, 716 RLX, 707 Both with PBO	ALN, 64 RLX, 58	24	ALN, +3.88 (4.96^2) RLX, +2.31 (3.96^2)	SEMs	p=0.002
Sanad 2011[82] PM women with OP	ALN weekly, 46 RLX, 44 Without PBO	ALN, 31 RLX, 35	12	ALN, +3.11 (NR) RLX, +3.48 (NR)	Means	NR (NE)
Michalska 2006[83] PM women with OP previously treated with bisphosphonates	PBO, 33 RLX, 33 ALN, 33	PBO, 33 RLX, 33 ALN, 33	12	PBO, +1.11 (NR) RLX, +2.07 (NR) ALN, +2.32 (NR)	Means (SEMs in graph overlap – unable to extract)	$P\geq0.05$ (NE)

Michalska 2006[83] PM women with OP previously treated with bisphosphonates	OLE No treatment, 33 RLX, 33 ALN, 33	No treatment, 33 RLX, 33 ALN, 33	24 including 12 months OLE	No treatment, +0.89 (3.27[2]) RLX, +1.14 (2.81[2]) ALN, +2.86 (3.73[2])	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[84] PM women with OP	ALN, 2047 ROMO, 2046 Both with PBO	ALN, 1826 ROMO, 1829	12	ALN, +1.70 (5.67[1]) ROMO, +4.90 (6.33[1]) ITT LOCF	Nothing	p<0.001
ARCH Saag 2017[84] PM women with OP	ALN to ALN, 2047 ROMO to ALN, 2046 Open-label	ALN/ALN, 1826 ROMO/ALN, 1829	24	ALN/ALN, +2.30 (6.65[1]) ROMO/ALN, +6.00 (7.42[1]) ITT LOCF	Nothing	p<0.001
ARCH Saag 2017[84] PM women with OP	As above	ALN/ALN, 1826 ROMO/ALN, 1829	36	ALN/ALN, +2.40 (7.19[1]) ROMO/ALN, +6.00 (7.90[1]) ITT LOCF	Nothing	p<0.001

TPTD vs. Bisphosphonates						
FACT[85] PM women with OP	ALN, 101 TPTD, 102 Both with PBO	ALN, 101 TPTD, 102	18	ALN, +3.50 (3.18[1]) TPTD, +3.90 (4.51[1])	95%CIs	p=0.05
Saag 2009[102] Women and men on GC with OP or low BMD+fracture	ALN, 214 TPTD, 214 Both with PBO	ALN, 113 TPTD, 120	36	ALN, +3.40 (4.93[1]) TPTD, +6.29 (5.03[1])	95%CIs	p<0.001
EUROGIOPs[88] Men on GC with OP	RIS, 47 TPTD, 45 Without PBO Open label	RIS, 37 TPTD, 38	18	RIS, -1.10 (7.00[2]) TPTD, +1.52 (6.66[2])	SEMs	p=0.026
Walker 2013[90] Men with OP	RIS weekly, 10 TPTD, 9 Both with PBO	RIS, 10 TPTD, 9	18	RIS, +0.5 (5.38[2]) TPTD, +3.89 (5.10[2])	Nothing	P≥0.05
Hadji 2012[92] PM women with OP	RIS weekly, 350 TPTD, 360 Both with PBO	RIS, 338 TPTD, 351	18	RIS, +0.77 (7.35[2]) TPTD, +2.11 (7.58[2])	Nothing	p=0.02

MOVE Malouf-Sierra 2017[93] Women and men with low BMD + recent hip fracture surgery	RIS daily, 113 TPTD, 111 Both with PBO	RIS, 81 TPTD, 80	18	RIS, -1.19 (NR) TPTD, +1.96 (NR)	Nothing	p=0.003
Cosman 2011[94] PM women with OP	ZOL[4], 137 TPTD + ZOL PBO, 138	ZOL, 129 TPTD+PBO, 129	12	ZOL, +1.90 (5.22[2]) TPTD+PBO, +0.09 (4.20[2])	Nothing	p<0.05

ALN, Alendronate 10 mg daily or 70 mg weekly; BMD, bone mineral density; Ca, calcium; CON, control; DEN, Denosumab 60 mg s.c. every 6 months; hazard ratio; GC, glucocorticoids; IBN, Ibandronate 150 mg oral every month; ITT LOCF, intention-to-treat last observation carried forward; MD, mean difference; NE, not estimable; PBO, placebo; RLX, Raloxifene 60 mg daily; PM, postmenopausal; OLE, open-label extension; OP, osteoporosis; ROMO, Romosozumab 210 mg s.c. monthly; RR, risk ratio; NR, not reported; SD, standard deviation; SEM, standard error of the mean; tmt, treatment; TPTD, Teriparatide 20 ug s.c. daily; Vit, vitamin; ZOL, ZOL 5 mg iv annually

ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ADAMO, DEN Versus Placebo in Males With Osteoporosis; ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BRIDGE, Phase 3 randomized placeBo-contRolled double-blind study evaluatIng the efficacy anD safety of ROMO in treatinG mEn with osteoporosis; DATA, DEN and TPTD Administration; DECIDE, Determining Efficacy: Comparison of Initiating DEN versus ALN; DIRECT, DEN fracture Intervention RandomizEd placebo Controlled Trial; EFFECT, EFficacy of FOSAMAX versus EVISTA Comparison Trial; EUROFORS, European Study of Forsteo; EVA, Evista ALN Comparison trial; EuroGIOPS, acronym meaning not reported; FACT, Forteo ALN Comparator Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture Reduction Evaluation of DEN in Osteoporosis; MORE, European Study of Forsteo; MOVE, acronym meaning not reported; VERO, VERtebral fracture treatment comparisons in Osteoporotic women

[1]Estimated from 95%CI

[2]Estimated from standard error

[3]No active treatment

[4]Not placebo controlled for TPTD

Table 21: Adverse events: mortality

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
DEN vs. PBO				
FREEDOM Cummings 2009[42] Bone 2017[103]	PBO, 3876 DEN, 3882	36 months	PBO, 90/3876 (2.3%) DEN, 70/3886 (1.8%)[42]	p=0.08
ADAMO Orwoll 2012[43]	PBO, 120 DEN, 120 Both for 12 months then DEN open-label (both groups) for 12 months	12 months	1/120 (0.8%) 1/120 (0.8%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
ADAMO Langdahl 2015[110]	PBO, 116 DEN, 111 Both for 12 months then DEN open-label (both groups) for 12 months	12-24 months	0/116 (0%) 1/111 (1%)	NR
DIRECT Nakamura 2014[44]	PBO,481 DEN, 475	24 months	5/481 (1.0%) 5/475 (1.1%)	NR
DIRECT Sugimoto 2015[105]	PBO, 406 DEN, 404 Both for 24 months then DEN open-label (both groups) for 12 months	24-36 months	2/406 (0.5%) 4/404 (1.0%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
Nakamura 2012[45]	PBO, 55 DEN, 54	12 months	NR	NR
Koh 2016[46] NCT01457950	PBO, 66 DEN, 69	6 months	0/66 (0%) 1/69 (<1%)	NR
Koh 2016[46] NCT01457950	PBO, 63 DEN, 60 Both for 6 months then DEN open-label (both groups) for 12 months	6-12 months	0/63 (0%) 0/60 (0%)	NR
RLX vs. PBO				
Adami 2008[47]	All TPTD for 12 months then: PBO, 172 RLX, 157	12 months	NR	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
Morii *et al* 2003[48]	PBO,97 RLX, 90	12 months	NR	NR
Liu 2004[49]	PBO,102 RLX, 102	12 months	0/102 (0%) 0/102 (0%)	NR
Gorai *et al* 2012[95]	Alfacalcidol , 44 RLX, 45 Alfacalcidol plus RLX, 48	12 months	NR	NR
Silverman 2008 NCT00205777[51]	PBO,1885 RLX, 1849	36 months	11/1885 (0.6%) 19/1849 (1.0%)	NR
MORE Ettinger 1999/Muscoso 2002[52, 101]	PBO,2576 RLX, 2557	36 months	NR	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
Lufkin 1998[53]	Control (no active treatment), 48 RLX, 48	12 months	NR	NR
Mok 2011[54] NCT00371956	PBO,57 RLX, 57	12 months	NR	NR
ROM vs. PBO				
BRIDGE Lewiecki 2018[57] NCT02186171	PBO,82 ROM, 163	12 months	PBO, 1/81 (1.2%) ROM, 2/163 (1.2%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
FRAME Cosman 2016[55]	PBO, 3591 ROM, 3589 For 12 months then DEN for 12 months open-label (both groups)	12 and 24 months	12 months PBO, 23/3576 (0.6%) ROM, 29/3581 (0.8%) 24 months PBO-DEN, 47/3576 (1.3%) ROM-DEN, 52/3581 (1.5%)	NR
Ishibashi (2017)[56] NCT01992159	PBO,63 ROM, 63	12 months	PBO, 0/63 (0%) ROM, 0/63 (0%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
TPTD vs. PBO				
Orwoll 2003[58]	PBO, 147 TPTD, 151	Median 11 months	PBO, 0/147 (0%) TPTD, 2/151 (1.3%)	NR
Miyauchi *et al.* 2010[59]	PBO, 67 TPTD, 136 Both for 12 months then TPTD open-label (both groups) for 12 months	24 months	0/67 (0%) 0/136 (0%)	NR
Miyauchi *et al.* 2008[60]	PBO,38 TPTD, 39	6 months	0/38 (0%) 0/39 (0%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
ACTIVE[96] NCT01343004	PBO,820 TPTD, 818	18 months	5/820 (0.6%) 3/818 (0.4%)	NR
Leder 2015[62]	PBO, 45 TPTD, 45 Open-label	6 months plus a further 6-month extension to 12 months	6 months PBO, 0/45 (0%) TPTD, 0/45 (0%) 12 months NR	NR
Neer 2001[63] NCT00670501	PBO, 544 TPTD months, 541	21 months (stopped early)	NR	Reports no significant difference. Data NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
Sethi 2008[64] NCT00500409	Control (Calcium + Vitamin D), 41 TPTD and Calcium + Vitamin D, 41	6 months	0/41 (0%) 0/41 (0%)	Reports no significant difference.
Head-to-head non-bisphosphonates				
DATA[65]	DEN, 34 TPTD, 36	12 months	NR	NR
DATA[65] NCT00926380	DEN, 34 TPTD, 36	24 months	NR	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
DATA-SWITCH[66]	DEN, 27 TPTD, 27 Both for 24 months then DEN switched to TPTD and TPTD switched to DEN open-label for 12 months	24 to 48 months	NR	NR
EUROFORS Eastell 2009[67]	All TPDT for 12 months then: Control (no active treatment), 102 TPTD, 304 RLX, 97	24 months	NR	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
STRUCTURE[68]	ROM, 218 TPTD, 214	12 months	1/218 (0.5%) 1/214 (0.5%)	NR
McClung 2014[69]	ROM, 51 (blind) TPTD, 55 (open-label) Pooled PBO (mix of ALN, TPTD and ROM administrations), 50 (blind) ALN, 51 (open-label)	12 months	ROM, 0/51 (0%) TPTD, 0/54 (0%) PBO, 1/50 (2%) ALN, 0/51 (0%)	NR
DEN vs. Bisphosphonates				
DECIDE[70]	ALN, 586 DEN,593 Both plus PBO	12 months	1/593 (0.2%) 1/586 (0.2%)	NR (not significant)

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
STAND Kendler 2010[71]	ALN, 251 DEN, 253	12 months	ALN, 0/249 (0%) DEN, 1/253 (0.4%)	p=1.0000
DAPS Kendler 2011[72, 111]	ALN, 124 DEN, 126 Open-label	12 months	NR	NR
McClung 2006[73]	PBO for abaloparatide s.c. every 3 months, 46 ALN open-label, 47 DEN, 47	12 months	PBO, 0/46 (0%) ALN, 0/46 (0%) DEN, 0/47 (0%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
Recknor 2013[74]	IBN, 416 DEN, 417	12 months	IBN, 1/410 (0.2%) DEN, 0/411 (0%)	p=0.299
Saag 2018[75]	RIS, 384 DEN, 394 Both with PBO	12 months	RIS, 9/384 (2.34%) DEN, 13/394 (3.30%) NCT01575873	NR
Miller 2016[76]	ZOL, 322 DEN, 321 Both with PBO	12 months	Fatal AEs ZOL, 1/320 (0.3%) DEN, 0/320 (0.0%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
RLX vs. Bisphosphonates				
EFFECT (International excluding US) Sambrook 2004[77]	ALN, 246 RLX, 241	12 months	ALN, 0/246 (0%) RLX, 1/241 (<1%)	NR (not significant)
EFFECT (US) Luckey 2004[78]	ALN, 223 RLX, 233 Both groups received PBO	12 months	NR	NR
Johnell 2002[79]	PBO (ALN and RLX), 82 ALN, 83 RLX, 82 ALN and RLX received PBO	12 months	NR	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
Muscoso 2004[80]	ALN, 1000 RIS, 100 RLX, 100 All daily	24 months	NR	NR
EVA Recker 2007[81]	ALN, 716 RLX, 707	24 months	ALN, 1/716 (<1%) RLX, 1/707 (<1%)	NR (not significant)
Sanad 2011[82]	ALN, 44 RLX, 46	12 months	NR	NR
Michalska 2006[83]	Open-label ALN, 33 Blind PBO, 33 RLX, 33	12 months followed by 12 months open-label extension	NR	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
ROM vs. Bisphosphonates				
ARCH Saag 2017[84]	ALN, 2014 ROM, 2040 Both for 12 months then ALN open-label (both groups) for 12 months	12 months from randomisation then a further 12 months open-label following treatment switching	0-12 months ALN, 21/2014 (1.0%) ROM, 30/2040 (1.5%) 0-24 months ALN/ALN, 90/2014 (4.5%) ROM/ALN, 90/2040 (4.4%)	NR
TPTD vs. Bisphosphonates				

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
FACT McClung 2005[85]	ALN, 101 TPTD, 102 Both with PBO	18 months	NR	NR
Saag 2009[86]	ALN, 214 TPTD, 214 Both with PBO	36 months	ALN, 4/214 (1.87%) TPTD 2/214 (0.93%) NCT00051558	NR (not significant)
Panico 2011[87]	ALN, 39 TPTD, 42 Open-label	18 months	NR	NR
EuroGIOPs Glüer 2013[88]	RIS, 47 TPTD, 45 Open-label	18 months	RIS, 1/47 (2.1%) TPTD, 2/45 (4.4%)	p=0.613

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
Anastasilakis 2008[89]	RIS, 22 TPTD, 22 Open-label	12 months	NR	NR
Walker 2013[90]	RIS, 10 TPTD, 9 Both with PBO	18 months	NR	NR
Hadji 2012[92]	RIS, 350 TPTD, 360 Both with PBO	18 months	RIS, 5/350 (1.4%) TPTD, 4/360 (1.1%)	p=0.75
VERO Kendler 2018[100]	RIS, 680 TPTD, 680 Both with PBO	24 months	RIS, 7/680 (1.0%) TPTD, 15/690 (2.2%)	p=0.13

Trial name /Author/date	Treatment arms (n=)	Follow-up	Overall Mortality n/N (%)	Reported between group difference
MOVE Aspenberg 2016[99]	RIS, 110 TPTD, 106 Both with PBO Blind until 6 months then open-label	6 months	RIS, 5/110 (4.5%) TPTD, 2/106 (1.9%)	p= 0.446
MOVE Malouf-Sierra 2017[93]		24 months	RIS, 7/110 (6.4%) TPTD, 2/106 (1.9%)	p=0.171
Cosman 2011[94]	ZOL, 137 TPTD, 137 Only TPTD received PBO	12 months	ZOL, 1/137 (<1%) TPTD, 0/137 (0%)	NR

ALN, Alendronate 10 mg daily or 70 mg weekly; CON, control; DEN, Denosumab 60 mg s.c. every 6 months; IBN, Ibandronate 150 mg oral every month; NR, not reported; PBO, placebo; RLX, Raloxifene 60 mg daily; ROMO, Romosozumab 210 mg s.c. monthly; RIS, Risedronate 5mg daily or 35 mg weekly; s.c., subcutaneous; TPTD, Teriparatide 20 ug s.c. daily; ZOL, Zoledronate 5 mg iv annually. ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ADAMO, DEN Versus Placebo in Males With Osteoporosis; ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BRIDGE, Phase 3 randomized placeBo-contRolled double-blind study evaluatIng the efficacy anD safety of ROMO in treatinG mEn with osteoporosis; DAPS, DEN Adherence Preference Satisfaction; DATA, DEN and TPTD Administration; DECIDE, Determining Efficacy: Comparison of Initiating DEN versus ALN; DIRECT, DEN fracture Intervention RandomizEd placebo Controlled Trial; EFFECT, EFficacy of FOSAMAX versus EVISTA Comparison Trial; EuroGIOPS, acronym meaning not reported; EUROFORS, European Study of Forsteo; EVA, Evista ALN Comparison trial; FACT, Forteo ALN Comparator Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture Reduction Evaluation of DEN in Osteoporosis; MORE, European Study of Forsteo; MOVE, acronym meaning not reported; STAND, Study of Transitioning from ALN to DEN; STRUCTURE, Study to Evaluate the Effect of Treatment With ROMO or TPTD in Postmenopausal Women; VERO, VERtebral fracture treatment comparisons in Osteoporotic women

Table 22: Adverse events and serious adverse events

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
DEN vs. PBO						
FREEDOM Cummings 2009[42] Bone 2017[103]	PBO, 3876 DEN, 3886 Both every 6 months	36 months	PBO, 972/3876 (25.1%) DEN, 1004/3886 (25.8%)[42]	p=0.61	PBO, 3607/3876 (93.1%) DEN, 3605/3886 (92.8%)[42]	p=0.91
ADAMO Orwoll 2012[43]	PBO, 120 DEN, 120 Both for 12 months then DEN open-label (both groups) for 12 months	12 months	PBO, 10/120 (8.3%) DEN, 11/120 (9.2%)	NR	PBO, 84/120 (70.0%) DEN, 86/120 (71.7%)	NR
ADAMO Langdahl 2015[110]	PBO, 116 DEN, 111 Both for 12 months then DEN open-label (both groups) for 12 months	12-24 months	PBO, 5/116 (4%) DEN, 9/111 (8%)	NR	PBO, 60/116 (52%) DEN 70/111 (63%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
DIRECT Nakamura 2014[44]	PBO,481 DEN, 475	24 months	PBO, 68/481 (14.1%) DEN, 66/475 (13.9%)	NR	PBO, 446/481 (92.7%) DEN, 448/475 (94.3%)	NR
DIRECT[105]	PBO, 406 DEN, 404 Both for 24 months then DEN open-label (both groups) for 12 months	24-36 months	PBO, 27/406 (6.7%) DEN, 30/404 (7.4%)	NR	PBO, 339/406 (83.5%) DEN, 343/404 (84.9%)	NR
Nakamura 2012[45]	PBO, 55 DEN, 54	12 months	PBO, 4/54 (7.4%) DEN, 6/53 (11.3%)	NR	PBO, 49/54 (90.7%) DEN, 47/54 (87.0%)	NR
Koh 2016[46] NCT01457950	PBO, 66 DEN, 69	6 months	PBO, 1/66 (2%) DEN, 2/69 (3%)	NR	PBO, 32/66 (48%) DEN, 38/69 (55%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
Koh 2016[46] NCT01457950	PBO, 63 DEN, 60 Both for 6 months then DEN open-label (both groups) for 12 months	6-12 months	PBO/DEN, 3/63 (5%) DEN, 1/60 (2%)	NR	PBO/DEN, 29/63 (46%) DEN, 22/60 (37%)	NR
RLX vs. PBO						
Adami 2008[47]	All TPTD for 12 months then: PBO, 172 RLX, 157	12 months	NR	NR	NR	NR
Morii *et al* 2003[48]	PBO,97 RLX, 90	12 months	PBO, 7 (7.2%) RLX, 5 (5.4%)	p=0.452	PBO, TEAE 33 (34.0%) RLX, TEAE 32 (34.8%)	p=0.444 (all AEs [number NR] p=0.851)
Liu 2004[49]	PBO,102 RLX, 102	12 months	PBO, 5/102 (4.9%) RLX, 2/102 (2.0%)	Not significant at p<0.05	NR	

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
Gorai *et al* 2012[95]	Alfacalcidol , 44 RLX, 45 Alfacalcidol plus RLX, 48	12 months	NR	NR	Alfacalcidol 11/44 (25.0%) RLX, 17/45 (37.8%) Alfacalcidol plus RLX 13/48 (27.1%)	NR
Silverman 2008 NCT00205777[51]	PBO,1885 RLX, 1849	36 months	PBO, 353/1885 (18.7%) RLX, 344/1849 (18.6%)	NR	PBO, 1813/1885 (96.2%) RLX, 1775/1885 (96.0%)	NR
MORE Ettinger 1999/Muscoso 2002[52, 101]	PBO,2576 RLX, 2557	36 months	NR	NR	NR	NR
Lufkin 1998[53]	Control (no active treatment), 48 RLX, 48	12 months	NR			

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
Mok 2011[54] NCT00371956	PBO,57 RLX, 57	12 months	NR			
ROMO vs. PBO						
BRIDGE NCT02186171[57]	PBO,82 ROMO, 163	12 months	TEAE PBO, 10/81 (12.3%) ROMO, TEAE 21/163 (12.9%)	NR	TEAE PBO, 65/81 (80.2%) TEAE ROMO 123/163 (75.5%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
FRAME Cosman 2016[55]	PBO, 3591 ROMO, 3589 For 12 months then DEN for 12 months open-label (both groups)	12 months from randomisation then a further 12 months following treatment switching	12 months PBO, 312/3576 (8.7%) ROMO, 344/3581 (9.6%) 24 months PBO-DEN, 550/3576 (15.1%) ROMO-DEN, 565/3581 (15.8%)	NR	12 months PBO, 2850/3576 (79.7%) ROMO, 2806/3581 (78.4%) 24 months PBO-DEN, 3069/3576 (85.8%) ROMO-DEN, 3053/3581 (85.3%)	NR
Ishibashi (2017)[56] NCT01992159	PBO,63 ROMO, 63	12 months	PBO, 4/63 (6.3%) ROMO, 2/63 (3.2%)	NR	PBO, 43/63 (68.3%) ROMO, 47/63 (74.6%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
TPTD vs. PBO						
Orwoll 2003[58]	PBO, 147 TPTD, 151 Both daily	Median 11 months	NR	NR	Reports that the overall incidence of adverse events was similar across groups. No data	NR
Miyauchi *et al.* 2010[59]	PBO, 67 TPTD, 136 Both for 12 months then TPTD open-label (both groups) for 12 months	24 months	PBO,13/67 (19.4%) TPTD, 12/136 (8.8%)	Reported as not significant. p-value NR	PBO, 64/67 (95.5%) TPTD, 125/136 (91.9%)	Reported as not significant. p-value NR
Miyauchi *et al.* 2008[60]	PBO,38 TPTD, 39	6 months	[not reported as number of participants with SAE]		PBO, TEAE 29 (76.3%) TPTD, TEAE 33 (84.6%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
ACTIVE[96] NCT01343004	PBO,820 TPTD, 818	18 months	PBO, 90/820 (11.0%) TPTD, 82/818 (10.0%)	NR	PBO, 718/820 (87.6%) TPTD, 727/818 (88.9%)	NR
Leder 2015[62]	PBO, 45 TPTD, 45 Open-label	6 months plus a further 6-month extension to 12 months	6 months PBO, 1/45 (2.2%) TPTD, 0/45 (0%) 12 months PBO, 1/45 (2.2%) TPTD, 0/45 (0%)	NR	6 months PBO, 32/45 (71.1%) TPTD, 35/45 (77.8%) 12 months PBO, 16/45 (36%) TPTD, 14/45 (30%)	NR
Neer 2001[63] NCT00670501	PBO, 544 TPTD months, 541	21 months (stopped early)	PBO, NR [withdrew due to AE 32 (6%)] TPTD, NR			

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
Sethi 2008[64] NCT00500409	Control (Calcium + Vitamin D), 41 TPTD and Calcium + Vitamin D, 41	6 months	CON, 0/41 (0% TPTD, 0/41 (0%)	Reported as not significant. p-value NR	CON, 9/41 (21.9%) TPTD, 9/41 (21.9%)	Reported as not significant. p-value NR
Head-to-head non-bisphosphonates						
DATA[65]	DEN, 34 TPTD, 36	12 months	DEN, 1/34 (2.9%) TPTD, NR – 3 events		NR	
DATA[65] NCT00926380	DEN, 34 TPTD, 36	24 months	DEN, 1/33 (3.0%) TPTD, 2/31 (6.5%)	NR	TPTD, 5/31 (16.1%) DEN, 4/33 (12.1%)	NR

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
DATA-SWITCH[66]	DEN, 27 TPTD, 27 Both for 24 months then DEN switched to TPTD and TPTD switched to DEN open-label for 12 months	24 to 48 months	DEN/TPTD, 4/27 (14.8%) TPTD/DEN, 6/27 (22.2%)	NR	NR	NR
STRUCTURE[68]	ROMO, 218 TPTD, 214	12 months	TPTD, 23/214 (11%) ROMO, 17/218 (8%)	NR	TPTD, 148/214 (69%) ROMO, 164/218 (75%)	NR
EUROFORS[67]	All TPDT for 12 months then: Control (no active treatment), 102 TPTD, 304 RLX, 97	24 months	NR	NR	CON, 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 /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
McClung 2014[69]	ROMO, 51 (blind) TPTD, 55 (open-label) Pooled PBO (mix of ALN, TPTD and ROMO administrations), 50 (blind) ALN, 51 (open-label)	12 months	ROMO, 5/51 (10%) TPTD, 5/54 (9%) PBO, 7/50 (14%) ALN, 4/51 (8%)	NR	ROMO, 42/51 (82%) TPTD, 37/54 (69%) PBO, 45/50 (90%) ALN, 44/51 (86%)	NR
DEN vs. Bisphosphonates						
DECIDE[70]	ALN, 586 DEN,593 Both plus PBO	12 months	ALN, 37/586 (6.3%) DEN, 34/593 (5.7%)	0.71	ALN, 482/586 (82.3%) DEN, 480/593 (80.9%)	Nonsig p=0.60
STAND Kendler 2010[71]	ALN, 251 DEN, 253	12 months	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

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
DAPS Kendler 2011[72, 111]	ALN, 124 DEN, 126 Open-label	12 months	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[73]	PBO for abaloparatide s.c. every 3 months, 46 ALN open-label, 47 DEN, 47	12 months	PBO, 2/46 (4.3%) ALN, 1/46 (2.2%) DEN, NR 18/314 (5.7%) across all DEN dosing arms	NR	PBO, 41/46 (89.1%) ALN, 42/46 (91.3%) DEN, NR 274/314 (87.3%) across all DEN dosing arms	NR
Recknor 2013[74]	IBN, 416 DEN, 417	12 months	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

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
Saag 2018[75]	RIS, 384 DEN, 394 Both with PBO	12 months	RIS, 65/384 (17%) DEN, 63/394 (16%)	NR	RIS, 265/384 (69%) DEN, 285/394 (72%)	NR
Miller 2016[76]	ZOL, 322 DEN, 321 Both with PBO	12 months	ZOL 29/320 (9.1%) DEN, 25/320 (7.8%)	NR	ZOL, 199/320 (62.2%) DEN, 199/320 (62.2%)	NR
RLX vs. Bisphosphonates						
EFFECT (International excluding US) Sambrook 2004[77]	ALN, 246 RLX, 241	12 months	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

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
EFFECT (US) Luckey 2004[78]	ALN, 223 RLX, 233 Both groups received PBO	12 months	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[79]	PBO (ALN and RLX), 82 ALN, 83 RLX, 82 ALN and RLX received PBO	12 months	NR	NR	NR	NR
Muscoso 2004[80]	ALN, 1000 RIS, 100 RLX, 100 All daily	24 months	NR	NR	NR	NR
EVA Recker 2007[81]	ALN, 716 RLX, 707	24 months	NR	NR	ALN, 397/716 (55.5%) RLX, 390/707 (55.2%)	p=0.92

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
Sanad 2011[82]	ALN, 44 RLX, 46	12 months	NR	NR	NR	NR
Michalska 2006[83]	Open-label ALN, 33 Blind PBO, 33 RLX, 33	12 months followed by 12 months open-label extension	NR	NR	PBO, 2/33 (6%) ALN, 4/33 (12%) RLX, 8/33 (24%)	p=0.126

Trial name /Author/date	Treatment arms (n=)	Follow-up	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[84]	ALN, 2014 ROMO, 2040 Both for 12 months then ALN open-label (both groups) for 12 months	12 months from randomisation then a further 12 months 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

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
TPTD vs. Bisphosphonates						
FACT McClung 2005[85]	ALN, 101 TPTD, 102 Both with PBO	18 months	NR	NR	NR	NR
Saag 2009[86]	ALN, 214 TPTD, 214 Both with PBO	36 months	ALN, 64/214 (30%) TPTD, 70/214 (33%)	p=0.518	ALN, 184/214 (86%) TPTD, 194/214 (91%)	p=0.116
Panico 2011[87]	ALN, 39 TPTD, 42 Open-label	18 months	NR	NR	NR	NR
EuroGIOPs Glüer 2013[88]	RIS, 47 TPTD, 45 Open-label	12 months	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

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
Anastasilakis 2008[89]	RIS, 22 TPTD, 22 Open-label	12 months	NR	NR	RIS, 7/22 (33.3%) TPTD, 11/22 (39.1%)	Not significant at p<0.05
Walker 2013[90]	RIS, 10 TPTD, 9 Both with PBO	18 months	NR	NR	NR	NR
Hadji 2012[92]	RIS, 350 TPTD, 360 Both with PBO	18 months	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[100]	RIS, 680 TPTD, 680 Both with PBO	24 months	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

Trial name /Author/date	Treatment arms (n=)	Follow-up	One or more SAE(s) n/N (%)	Reported between group difference	One or more AE(s) n/N (%)	Reported between group difference
MOVE Aspenberg 2016[99]	RIS, 110 TPTD, 106 Both with PBO Blind until 6 months then open-label	6 months	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[93]		24 months	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[94]	ZOL, 137 TPTD, 137 Only TPTD received PBO	12 months	ZOL, 20/137 (14.60%) TPTD, 15/137 (10.95%) NCT00439244	NR	ZOL, 115/137 (83.94%) TPTD, 96/137 (70.07%) NCT00439244	NR

ALN, Alendronate; DEN, Denosumab; NR, not reported; PBO, placebo; RLX, Raloxifene; s.c., subcutaneous; TPTD, Teriparatide; ZOL< Zoledronate 5 mg iv
ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ADAMO, DEN Versus Placebo in Males With Osteoporosis; ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BRIDGE, Phase 3 randomized placeBo-contRolled double-blind study evaluatIng the efficacy anD safety of ROMO in treatinG mEn with osteoporosis; DAPS DEN Adherence Preference Satisfaction; DATA, DEN and TPTD Administration; DIRECT, DEN fracture Intervention RandomizEd placebo Controlled Trial; EFFECT, EFficacy of FOSAMAX versus EVISTA Comparison Trial; EuroGIOPS, acronym meaning not reported; EUROFORS, European Study of Forsteo; EVA, Evista ALN Comparison trial; FACT, Forteo ALN Comparator Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture Reduction Evaluation of DEN in Osteoporosis; MORE, European Study of Forsteo; MOVE, acronym meaning not reported; STAND, Study of Transitioning from ALN to DEN; STRUCTURE, Study to Evaluate the Effect of Treatment With ROMO or TPTD in Postmenopausal Women; VERO, VERtebral fracture treatment comparisons in Osteoporotic women.

Table 23: LS BMD for studies not reporting FN BMD

Trial	Intervention and comparators (n)	Follow-up duration Months	LS BMD change from baseline Mean (SD) reported between-group difference
Nakamura 2012[45]	Placebo N=55	12	3.2 (NR) (estimated from graph) P<0.0001
	DEN N=54		6.73 (NR)
Morii *et al* 2003[48]	Placebo N=97	12	0.0 (SE0.3) Estimated from graph P<0.001
	RLX N=90		3.5 (SE0.3) Estimated from graph
Gorai *et al* 2012[50]	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[53]	Control N=48	12	1.44 (0.74) Non-significant P value NR
	RLX N=48		1.34 (1.02)
Muscoso 2004[80]	ALN N=1000	24	7.2% (1.9)
	RIS N=100		6.2% (2.0)
	RLX N=100		2.4% (1.1)
Anastasilakis 2008[89]	RIS N=22	12	3.3 (NR) Calculated Non-significant p value NR
	TPTD N=22		5.9 (NR) Calculated

NR= not reported; SD= standard deviation

Appendix 6: Health-related Quality of Life

Table 24: Published results of validated HRQoL measures

Trial	Measure	Follow-up	Treatment group	Results
FREEDOM [118, 119]	Osteoporosis Assessment Questionnaire-Short Version (OPAQ-SV) [330]	36 months	PBO N=NR	Change from baseline 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) [118]	Change from baseline Mean Physical function -1.3 Emotional status -1.4 Back pain 4.1 Non-significant between groups P value NR
Silverman 2008 NCT00205777 Clinicaltrials.gov	Women's Health Questionnaire (WHQ) [331]	36 months	PBO N=1179	Change from baseline Least squares mean (SE) 0.005 (0.005)
			RLX N=1168	Change from baseline Least squares mean (SE) 0.005 (0.005) Non-significant between groups 0.98
	European Foundation for Osteoporosis Quality of Life	36 months	PBO N=1176	Change from baseline Least squares mean (SE) -0.35 (0.3)

Trial	Measure	Follow-up	Treatment group	Results
	Questionnaire (QUALEFFO)[332]			
			RLX N=1168	Change from baseline Least squares mean (SE) 0.26 (0.3) Non-significant between groups P=0.11
	Euro Quality of Life-5 Dimensions (EQ-5D) Visual Analog Scale (VAS)[333]	36 months	PBO N=1120	Change from baseline Least squares mean (SE) 4.66 (1.70)
			RLX N=1092	Change from baseline Least squares mean (SE) 1.60 (1.71) Non-significant between groups P=0.16
	Euro Quality of Life-5 Dimensions (EQ-5D)- Health State Profile Utility Score[333]	36 months	PBO N=1128	Change from baseline Least squares mean (SE) -0.00 (0.01)
			RLX N=1111	Change from baseline Least squares mean (SE) -0.01 (0.01) Non-significant between groups

Trial	Measure	Follow-up	Treatment group	Results
				P=0.92
Panico 2011[87]	QUALEFFO-41[332]	18 months	ALN N=39	Change from baseline 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	Change from baseline 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%
VERO[91] Clinicaltrials .gov	Euro Quality of Life-5 Dimensions (EQ-5D) Visual Analog Scale (VAS) UK[333]	24 months	RIS plus placebo	Change from baseline Least squares mean 0.04 Baseline 0.62 (SD 0.228); 24months 0.68 (SD 0.205)
			TPTD plus placebo	Change from baseline Least squares mean 0.06 Baseline 0.59 (SD 0.243); 24months 0.65 (SD 0.249) Between groups -0.0 (95%CI -0.03, 0.02) p=0.757
MOVE[99]	SF-36	26 weeks	RIS plus placebo	Mean (SD)

Trial	Measure	Follow-up	Treatment group	Results
	Questionnaire Physical Function Component (post-surgery)[334]			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; SE = standard error

The UCB CS reported that in both the FRAME (ROMO vs. PBO) and the ARCH (ROMO vs. ALN) studies there was [redacted] between treatment groups in HRQoL, [37] [redacted]

The Amgen CS [98] reported that DECIDE found [redacted] difference between DEN and ALN as measured by EQ-5D.

Appendix 7: Specific adverse events

Bisphosphonate studies - specific adverse events

Three additional bisphosphonate RCTs 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 ALN[138] or ZOL compared with placebo.[131] One study assessed osteonecrosis of the jaw and found no incidences in participants treated with ZOL or placebo.[131]

Table 25: Specific AEs Additional bisphosphonate trials

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
TRIO Paggiosi 2014[139]	ALN, 57 IBN, 57 RIS, 58	24 months	NR	NR	NR	NR
Tan 2016 [138]	ALN, 53 ZOL, 52	36 months	NR	NR	NR	ALN, 0/53 (0%) ZOL, 0/52 (0%)
ZONE [131]	PBO, 331 ZOL, 330	24 months	NR	NR	PBO, 0/331 ZOL, 0/330	PBO, 0/331 (0%) ZOL, 0/330 (0%)

ALN, ALN; PBO, placebo; RIS, RIS; VTE, venous thromboembolism; ZOL, zoledronic acid

Non-bisphosphonate studies– specific adverse events

Venous thromboembolism

Across the studies comparing a non-bisphosphonate to placebo, five reported thrombotic events of venous origin,[44, 47, 48, 51, 52] and one study reported on arterial limb thrombosis.[43] Across these studies event rates were ≤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 to placebo at 36 months in postmenopausal women with osteoporosis, in favour of placebo (estimated $p=0.005$).[52]

None of the bisphosphonates compared head-to-head studies reported on venous thromboembolism.

Across the studies comparing a non-bisphosphonate to a bisphosphonate, two studies reported on thrombosis but did not specify whether this was venous or arterial in origin,[73, 75] eight reported on thrombotic events of venous origin,[75, 78, 81, 82, 92, 100, 102, 335] and one reported on Peripheral artery thrombosis.[76] Across these studies event rates were ≤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 to placebo, four reported on stroke.[42, 51, 57, 110] Across these studies, event rates were ≤2% and no statistically significant between-group differences were evident (reported or estimated).

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

Across the studies comparing a non-bisphosphonate to placebo, eight reported on stroke.[73, 75, 84, 92, 94, 100, 102, 335] 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 between in stoke for one of these studies comparing ROMO to ALN in postmenopausal women with osteoporosis was statistically significant at 24 months following treatment switching to ALN, in favour of the continued ALN group ($p=0.004$).[84]

Osteonecrosis of the jaw

Osteonecrosis of the jaw was reported by nine studies comparing a non-bisphosphonate to placebo,[42, 43, 45, 46, 55-57, 110] one study comparing non-bisphosphonates head-to-head,[68] and three studies comparing a non-bisphosphonate with a bisphosphonate.[72, 75, 84] 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 to placebo,[42, 43, 46, 55-57, 105, 110, 336] one study comparing non-bisphosphonates head-to-head,[68] and three studies comparing a non-bisphosphonate with a bisphosphonate.[75, 76, 84, 108] 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 /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
DEN vs. PBO						
FREEDOM Cummings 2009[42] PM women with OP	PBO, 3607 DEN, 3886	36 months	NR	PBO, 54/3607 (1.4%) DEN, 56/3886 (1.4%) p=0.89[42]	PBO, 0/3607 (0%) DEN, 0/3886 (0%)[42]	PBO, 0/3607 (0%) DEN, 0/3886 (0%)[337]
ADAMO Orwoll 2012[43] Men with OP	PBO, 120 DEN, 120	12 months	Arterial limb thrombosis PBO, 0/120 (0%) DEN, 1/120 (1.7%)	NR	PBO, 0/120 (0%) DEN, 0/120 (0%)	PBO, 0/120 (0%) DEN, 0/120 (0%)
ADAMO Langdahl 2015[110] Men with OP	PBO to DEN, 120 DEN to DEN, 120	24 months including 12 OLE	NR	Transient ischemic attack PBO/DEN, 1/120 (<1%) DEN/DEN, 0/120 (0%)	PBO/DEN, 0/120 (0%) DEN/DEN, 0/120 (0%)	PBO/DEN, 0/120 (0%) DEN/DEN, 0/120 (0%)
DIRECT Nakamura 2014[336] Women and men with OP	PBO, 481 DEN, 475	24 months	1/481 (0.21%) 0/475 (0%) NCT00680953.	NR	PBO, 0/481 (0%) DEN, 0/475 (0%)	PBO, 0/481 (0%) DEN, 0/475 (0%)
DIRECT Sugimoto 2015[105] Women and men with OP	PBO to DEN, 406 DEN to DEN, 404 12 months open-label	24-36 months	NR	NR	PBO/DEN, 1/406 (0.2%) (0%) DEN/DEN, 0/404 (0%)	PBO/DEN, 0/406 (0%) DEN/DEN, 0/404 (0%)

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
Nakamura 2012[45] PM women with OP	PBO, 54 DEN, 54	12	NR	NR	PBO, 0/54 (0%) DEN, 0/54 (0%)	NR
Koh 2016[46] PM women with OP	PBO, 66 DEN, 69	6	NR	NR	PBO, 0/69 (0%) DEN, 0/69 (0%)	PBO, 0/69 (0%) DEN, 0/69 (0%)
Koh 2016[46] PM women with OP	Entered OLE PBO to DEN, 63 DEN to DEN, 60	6-12 OLE	NR	NR	PBO/DEN, 0/63 (0%) DEN/DEN, 0/60 (0%)	PBO/DEN, 0/63 (0%) DEN/DEN, 0/60 (0%)
RLX. vs PBO						
Adami 2008[47] PM women with OP pre-treated with TPTD	PBO, 172 RLX, 157	12 months	PBO, 0/172 (0%) RLX, 1/157 (<1%) retinal vein thrombosis	NR	NR	NR
Morii 2003[48] PM women with OP	PBO, 97 RLX, 90	12	PBO, 0/97 (0%) RLX, 0/90 (0%)	NR	NR	NR
Liu 2004[49] PM women with OP	PBO, 102 RLX, 102	12	PBO, 0/102 (0%) RLX, 0/102 (0%)	NR	NR	NR
Gorai *et al* 2012[95] PM women with low osteopenia	Alfacalcidol, 44 RLX, 45 Alfacalcidol+RLX, 48	12	NR	NR	NR	NR

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
Silverman 2008[51, 329] PM women with OP	PBO, 1855 RLX, 1849	36	DVT PBO, 1/1855 (0.1%) RLX, 8/1849 (0.4%) PE PBO, 4/1855 (0.2%) RLX, 4/1849 (0.2%) Retinal PBO, 3/1855 (0.2%) RLX, 0/1849 (0%)	PBO, 20/1855 (1.1%) RLX, 15/1849 (0.8%)	NR	NR
MORE Ettinger 1999[52] Women with OP	PBO, 2576 RLX, 2557	36	8/2576 (0.3%) 25/2557 (1.0%) Estimated p=0.005	NR	NR	NR
Lufkin 1998[53] PM women with OP	PBO, 48 RLX, 48	12	PBO, 0/48 (0%) RLX, 0/48 (0%)	NR	NR	NR
Mok 2011[54] PM women on long-term GC	PBO, 57 RLX, 57	12	PBO, 0/57 (0%) RLX, 0/57 (0%	NR	NR	NR
ROMO. vs PBO						
FRAME Cosman 2016[55] PM women with OP	PBO, 3591 ROMO, 3589	12	NR	NR	PBO, 0/3576 (0%) ROMO, 1/3581 (<0.1%)	PBO, 0/3576 (0%) ROMO, 1/3581 (<0.1%)

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
FRAME Cosman 2016[55] PM women with OP	PBO to DEN, 3591 ROMO to DEN, 3589 12 months open-label	24	NR	NR	PBO-DEN, 0/3576 (0%) ROMO-DEN, 2/3581 (<0.1%)	PBO-DEN, 0/3576 (0%) ROMO-DEN, 1/3581 (<0.1%)
Ishibashi 2017[56] PM women with OP	PBO, 63 ROMO, 63	12	NR	NR	PBO, 0/63 (0%) ROMO, 0/63 (0%	PBO, 0/63 (0%) ROMO, 0/63 (0%
BRIDGE[57] Men with OP	PBO, 82 ROMO, 163	12	NR	PBO, 1/82 (1.2%) ROMO, 3/163 (1.8%)	PBO, 0/82 (0%) ROMO, 0/163 (0%)	PBO, 0/82 (0%) ROMO, 0/163 (0%)
TPTD. vs PBO						
ACTIVE Miller 2016[96] PM women with OP	PBO, 820 TPTD, 818	18 months	NR	NR	NR	NR
Orwoll 2003[58] Men with OP	PBO, 147 TPTD, 151	The study was stopped after a median duration of 11 months	NR	NR	NR	NR
Miyauchi 2010[59] Women and men with OP	PBO, 67 TPTD, 136	12	NR	NR	NR	NR
Miyauchi 2010[59] Women and men with OP	PBO to TPTD, 59 TPTD to TPTD, 119	24 months including 12 OLE	NR	NR	NR	NR
Miyauchi 2008[60] PM women with OP	PBO, 38 TPTD, 39	6 months	NR	NR	NR	NR

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
Leder 2015[62, 338] PM women with OP	PBO, 45 TPTD, 45	6 months	NR	NR	NR	NR
Neer 2001[63] PM women with OP	PBO, 544 TPTD, 541	24	NR	NR	NR	NR
Sethi 2008[64] PM women with OP	Ca+Vit D, 41 TPTD Ca+Vit D, 41	6	NR	NR	NR	NR
Head-to-head non-bisphosphonates						
DATA Tsai 2013[65] PM women with OP	TPTD, 36 DEN, 34 Without PBO open-label	12	NR	NR	NR	NR
DATA Leder 2014[109] PM women with OP	TPTD, 36 DEN, 34 Without PBO open-label	24	NR	NR	NR	NR
EUROFORS Eastell 2009[67] PM women with OP pre-treated with TPTD	TPTD, 304 RLX, 97 CON[1], 102	24	NR	NR	NR	NR
STRUCTURE[68] PM women with OP pre-treated with ALN	TPTD, 218 ROMO, 218 Without PBO open-label	12	NR	NR	TPTD, 0/218 (0%) ROMO, 0/218 (0%)	TPTD, 0/218 (0%) ROMO, 0/218 (0%)
McClung 2014[69] PM women with OP	PBO, 52 TPTD, 55 ROMO, 52 ALN, 51	12	NR	NR	NR	NR

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
DEN vs. Bisphosphonates						
DECIDE[70] PM women with OP	ALN, 586 DEN, 593 Both with PBO	12	NR	NR	NR	NR
STAND[71] PM women with OP already on ALN	ALN, 251 DEN, 253 Both with PBO	12 months	NR	NR	NR	NR
DAPS[72] PM women with OP	ALN, 124 DEN, 126 Without PBO	12 months	NR	NR	ALN, 0/117 (0%) DEN, 0/125 (0%)	NR
DAPS[108] PM women with OP	Cross-over ALN to DEN, 92 DEN to ALN, 102	24 months	NR	NR	ALN, 0/228 (0%) DEN, 0/230 (0%)	ALN, 0/228 (0%) DEN, 0/230 (0%)
McClung 2006[73, 339] PM women with OP or osteopenia	PBO for DEN, 46 ALN, 47 DEN, 47	12 months	Thrombosis PBO, 0/46 (0.00%) ALN, 0/46 (0.00%) DEN, 0/47 (0.00%)	PBO, 0/46 (0.00%) ALN, 0/46 (0.00%) DEN, 0/47 (0.00%)	NR	NR
Recknor *et al*. 2013[74] PM women with OP	IBN, 416 DEN,417 Without PBO	12 months	NR	NR	NR	NR

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
Saag 2018[75, 340] Women and men on GC with OP or low BMD+fracture	RIS, 384 DEN, 394 Both with PBO	12 months	DVT RIS, 2/385 (0.52%) DEN, 0/394 (0.00%) Thrombosis RIS, 1/385 (0.26%) DEN, 0/394 (0.00%) NCT01575873	RIS, 1/384 (0.26%) DEN, 3/394 (0.76%) NCT01575873	RIS, 0/384 (0%) DEN, 0/394 (0%)	RIS, 0/384 (0%) DEN, 1/394 (<1%)
Miller *et al*. 2016[76, 341] PM women with OP previously treated with bisphosphonates	ZOL, 322 DEN, 321 Both with PBO	12 months	Peripheral artery thrombosis ZOL, 1/320 (0.31%) DEN, 0/320 (0.00%) NCT01732770	NR	NR	ZOL, 1/320 (0.3%) DEN, 2/320 (0.6%)
RLX vs. Bisphosphonates						
EFFCT Sambrook 2004[77] (International not including US) PM women with OP	ALN, 246 RLX, 241 Both with PBO	12 months	NR	NR	NR	NR
EFFECT (US)[78] PM women with OP	ALN, 223 RLX, 233 Both with placebo	12 months	ALN, 0/221 (0%) RLX, 1/230 (<1%)	NR	NR	NR

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
Johnell 2002[79] PM women with OP	PBO, 82 ALN, 83 RLX, 82	12 months	NR	NR	NR	NR
Muscoso 2004[80] PM women with OP	ALN, 1000 RLX, 100 RIS, 100 All daily open-label	24 months	NR	NR	NR	NR
EVA Recker 2007[81] PM women with OP	ALN, 716 RLX, 707 Both with PBO	24 months	DVT ALN, 1/716 (<1%) Pulmonary embolism RLX, 1/707 (<1%)	NR	NR	NR
Sanad 2011[82] PM women with OP	ALN weekly, 31 RLX, 35 Without PBO	12 months	DVT, 0/31 (0%) ALN, 1/35 (2.9%)	NR	NR	NR
Michalska 2006[83] PM women with OP previously treated with bisphosphonates	PBO, 33 RLX, 33 ALN, 33	12 months	NR	NR	NR	NR
ROMO vs. Bisphosphonates						
ARCH Saag 2017[84] PM women with OP	ALN, 2047 ROMO, 2046 Both with PBO	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%)

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
ARCH Saag 2017 [84] PM women with OP	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[85] PM women with OP	ALN, 101 TPTD, 102 Both with PBO	18 months	NR	NR	NR	NR
Saag 2009 [102] Langdahl 2009 [106, 342] Women and men on GC with OP or low BMD+fracture	ALN, 214 TPTD, 214 Both with PBO	36	DVT ALN, 1/214 (0.47%) TPTD. 2/214 (0.93%) Venous thrombosis ALN, 0/214 (0%) TPTD, 1/214 (0.47%) NCT01732770	ALN, 1/214 (0.47%) TPTD. 0/214 (0%) NCT01732770	NR	NR
Panico 2011[87] PM women with severe OP+fracture and on treatment for OP	ALN weekly,39 TPTD,42 Without PBO	18	NR	NR	NR	NR
Anastasilakis 2008[89]	RIS, 22 TPTD, 22 Without PBO open-label	12 months	NR	NR	NR	NR

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
EUROGIOPs[88] Men on GC with OP	RIS, 47 TPTD, 45 Without PBO Open label	18 months	NR	NR	NR	NR
Walker 2013[90] Men with OP	RIS weekly, 10 TPTD, 9 Both with PBO	18 months	NR	NR	NR	NR
Hadji 2012[92] PM women with OP	RIS weekly, 350 TPTD, 360 Both with PBO	18 months	DVT 1/350 (0.29%) 0/360 (0.00%) Pulmonary thrombosis 1/350 (0.29%) 0/360 (0.00%) NCT00343252	RIS, 6/350 (1.71%) TPTD, 1/360 (0.28%) NCT00343252	NR	NR
VERO Kendler 2018[100] PM women with OP	RIS weekly, 680 TPTD, 680 Both with PBO	24 months	DVT RIS, 3/683 (0.44%) TPTD, 2/683 (0.29%) Vena cava thrombosis RIS, 1/683 (0.15%) TPTD, 0/683 (0.00%) NCT01709110	RIS, 1/683 (0.15%) TPTD, 2/683 (0.29%) NCT01709110	NR	NR

Trial name /Author/date	Treatment arms (N=)	Follow-up	VTE(s) n/N (%)	Stroke n/N (%)	Osteonecrosis of jaw n/N (%)	Atypical femoral fractures n/N (%)
MOVE Aspenberg 2016,[335] Malouf-Sierra 2017[343]	RIS, 110 TPTD, 106 Both with PBO to 6 months then OLE to 12 months	NR	Venous thrombosis RIS, 1/110 (0.91%) TPTD, 0/106 (0.00%) NCT00887354	RIS, 2/110 (1.82%) TPTD, 0/106 (0.00%) NCT00887354	NR	NR
Cosman 2011[94] PM women with OP	ZOL[2], 137 TPTD + ZOL PBO, 138	12 months	NR	ZOL, 0/137 (0.00%) TPTD, 0/137 (0.00%) NCT00439244	NR	NR

ALN, ALN 10 mg daily or 70 mg weekly; BMD, bone mineral density; Ca, calcium; CON, control; DEN, DEN 60 mg s.c. every 6 months; DVT, deep vein thrombosis; GC, glucocorticoids; IBN, Ibandronate 150 mg oral every month; PBO, placebo; PE, pulmonary embolism; RLX, RLX 60 mg daily; PM, postmenopausal; OLE, open-label extension; OP, osteoporosis; ROMO, ROMO 210 mg sc. monthly; RR, risk ratio; NR, not reported; TPTD, TPTD 20 ug sc daily; Vit, vitamin; VTE, venous thromboembolism; ZOL, ZOL 5 mg iv annually

ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ADAMO, DEN Versus Placebo in Males With Osteoporosis; ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BRIDGE, Phase 3 randomized placeBo-contRolled double-blind study evaluatIng the efficacy anD safety of ROMO in treatinG mEn with osteoporosis; DATA, DEN and TPTD Administration; DECIDE, Determining Efficacy: Comparison of Initiating DEN versus ALN; DIRECT, DEN fracture Intervention RandomizEd placebo Controlled Trial; EFFECT, EFficacy of FOSAMAX versus EVISTA Comparison Trial; EUROFORS, European Study of Forsteo; EVA, Evista ALN Comparison trial; EuroGIOPS, acronym meaning not reported; FACT, Forteo ALN Comparator Trial; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FREEDOM, Fracture Reduction Evaluation of DEN in Osteoporosis; MORE, European Study of Forsteo; MOVE, acronym meaning not reported; VERO, VERtebral fracture treatment comparisons in Osteoporotic women

[1]No active treatment

[2]Not placebo controlled for TPTD

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

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

where $p_{i,k}$ represents the probability of an event in arm k of trial i $(i = 1 \dots ns, k = 1 \dots na)$ after follow up time f_i. For all RCTs, the number of arms included in the analysis is 2 (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

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

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:

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

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 below, two different modelling strategies were considered for the treatment effects; i) standard independent random (treatment) effects model ii) 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 ii) while the results for the standard independent random effects model are provided in the appendix 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

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

where $d_{t_{i1}t_{ik}}$ represents the mean effect of the treatment in arm k of study i (t_{ik}) compared to 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. Where 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 standard deviation 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 standard deviation. 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 standard deviation 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 <u>for bisphosphonate treatments only</u>. 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:

$$d_{t_{i1}\,t_{ik}} \sim N(D, \tau_D^2) \quad (5)$$

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

- Mean bisphosphonate effect, $D \sim N(0, 100^2)$,
- Between treatment standard deviation, $\tau_D \sim U(0,2)$.

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

Predicting effects in new RCTs

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

$$\delta_{i,j} = d_{1j} + \varepsilon_{ij}, \quad (6)$$

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:

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

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

$$d_{1j} = D + \xi_j, \quad (8)$$

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

$$\delta_{ij} = D + \zeta_j + \varepsilon_{ij}, \quad (9)$$

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

$$V[\delta_{ij}] = V[D + \zeta_j + \varepsilon_{ij}] = \tau^2 + \tau_D^2 \quad (10)$$

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

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

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 was 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 BMD

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

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

where the population variance of the mean, se_{ik}^2, is assume 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 lengths, study duration was included as a trial level covariate. The link function is given by:

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

where $\beta_{11} = 0$, and β_{1k} $(k = 2,..,na)$ 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 BMD

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, $v_{i,1k}$, 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:

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

where the population standard error of the difference, v^2_{i1k}, 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 the equation (13) and thus 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, $d_{1k} \sim N(0, 100^2)$,
- Between study standard deviation of treatment effects, $\tau \sim U(0,100)$.
- Mean of related treatment effects, $D \sim N(0, 100^2)$,
- Between treatment standard deviation, $\tau_D \sim U(0,100)$.

Meta-regression

Where 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.*.

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

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

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 below), 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.

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, $(t_{i1} \neq P)$, 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

$$\tilde{\delta}_{i,1k} = (d_{pt_{ik}} - d_{pt_{i1}}) + (\beta_{pt_{ik}} - \beta_{pt_{i1}})(\mu_{ip} - \bar{\mu}_p). \tag{22}$$

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: Additional results for the network meta-analysis

Appendix 9.1: Data contributing to the network meta-analysis

Table 27: Data contributing to the NMA of vertebral fractures

study	t1	t2	t3	t	n1	r1	n2	r2	n3	r3	M	S1
Liberman (1995)	PBO	ALN	-	36	355	22	175	5	-	-	1	0
Orwoll (2000)	PBO	ALN	-	24	94	7	146	1	-	-	1	0
FIT I Black (1996)	PBO	ALN	-	36	965	192	981	83	-	-	1	0
FIT I Black (1996)	PBO	ALN	-	36	1000	50	1000	23	-	-	0	0
FIT II Cumming (1998)	PBO	ALN	-	48	2077	78	2057	43	-	-	1	0
Dursun (2001)	PBO	ALN	-	12	35	14	38	12	-	-	1	1
Carfora (1998)	PBO	ALN	-	30	34	4	34	1	-	-	1	0
Cohen (1999)	PBO	RIS	-	12	35	5	34	2	-	-	1	1
Fogelman (2000)	PBO	RIS	-	24	125	17	112	8	-	-	1	0
VERT-USA Harris (1999)	PBO	RIS	-	36	678	93	696	61	-	-	1	0
VERT-USA Harris (1999)	PBO	RIS	-	12	660	42	669	16	-	-	0	1
VERT-EU Reginster (2000)	PBO	RIS	-	36	346	89	344	53	-	-	1	0
VERT-EU Reginster (2000)	PBO	RIS	-	12	334	45	333	19	-	-	0	1
Hooper (2005)	PBO	RIS	-	24	125	10	129	10	-	-	1	0
Reid (2000)	PBO	RIS	-	12	60	9	60	3	-	-	1	1
Boonen (2009)	PBO	RIS	-	24	80	0	179	2	-	-	1	0
Ringe (2006)	PBO	RIS	-	12	158	20	158	8	-	-	1	1
Boonen (2012)	PBO	ZOL	-	24	574	28	533	9	-	-	1	0
Boonen (2012)	PBO	ZOL	-	12	574	16	553	5	-	-	0	1
HORIZON-PFT Black (2007)	PBO	ZOL	-	36	3861	84	3875	19	-	-	0	0
HORIZON-PFT Black (2007)	PBO	ZOL	-	12	3861	143	3875	58	-	-	0	1
HORIZON-PFT Black (2007)	PBO	ZOL	-	36	3861	310	3875	92	-	-	1	0
HORIZON-RFT Lyles (2007)	PBO	ZOL	-	36	1062	39	1065	21	-	-	1	0
HORIZON-RFT Lyles (2007)	PBO	ZOL	-	12	1057	21	1054	13	-	-	0	1
BONE Chestnut (2004)	PBO	IBN daily	-	36	975	73	977	37	-	-	1	0
BONE Chestnut (2004)	PBO	IBN daily	-	12	889	24	929	13	-	-	0	1
BONE Chestnut (2004)	PBO	IBN daily	-	36	975	41	977	22	-	-	0	0
HORIZON-SIO Reid (2009)	RIS	ZOL	-	12	381	3	378	5	-	-	1	1
MOTION Miller (2008)	ALN	IBN monthly	-	12	859	5	874	5	-	-	1	1
ZONE Nakamura (2017)	PBO	ZOL	-	24	327	29	330	10	-	-	1	0
ZONE Nakamura (2017)	PBO	ZOL	-	24	331	17	330	5	-	-	0	0
ZONE Nakamura (2017)	PBO	ZOL	-	12	331	6	330	4	-	-	0	1
FREEDOM Bone (2017)	PBO	DEN	-	36	3691	264	3702	86	-	-	1	0
FREEDOM Bone (2017)	PBO	DEN	-	36	3906	92	3902	29	-	-	0	0
FREEDOM Bone (2017)	PBO	DEN	-	12	3691	82	3702	32	-	-	0	1
FRAME Cosman (2016)	PBO	ROMO	-	12	3322	59	3321	16	-	-	1	1

ADAMO Orwoll (2012)	PBO	DEN	-	12	120	1	120	0	-	-	1	1
DIRECT Nakamura (2014)	PBO	DEN	-	24	480	41	472	10	-	-	1	0
DIRECT Nakamura (2014)	PBO	DEN	-	12	480	9	472	6	-	-	0	1
Miyauchi (2010)	PBO	TPTD	-	12	67	4	136	5	-	-	1	1
ACTIVE Miller (2016)	PBO	TPTD	-	18	711	30	717	6	-	-	1	0
ACTIVE Miller (2016)	PBO	TPTD	-	18	821	9	818	3	-	-	0	0
Neer (2001)	PBO	TPTD	-	24	448	64	444	22	-	-	1	0
Morii (2003)	PBO	RLX	-	12	87	2	79	0	-	-	1	1
Liu (2004)	PBO	RLX	-	12	102	5	102	0	-	-	1	1
Silverman (2008)	PBO	RLX	-	36	1741	71	1696	40	-	-	1	0
Silverman (2008)	PBO	RLX	-	36	1741	16	1696	15	-	-	0	0
MORE Maricic (2002)	PBO	RLX	-	12	2292	19	2259	6	-	-	0	1
MORE Maricic (2002)	PBO	RLX	-	36	2292	81	2259	47	-	-	0	0
MORE Maricic (2002)	PBO	RLX	-	36	2292	231	2259	148	-	-	1	0
Lufkin (1998)	PBO	RLX	-	12	45	18	43	21	-	-	1	1
Saag (2007)	ALN	TPTD	-	36	169	13	173	3	-	-	1	0
Saag (2007)	ALN	TPTD	-	36	169	4	173	0	-	-	0	0
Walker (2013)	RIS	TPTD	-	18	10	1	9	0	-	-	1	0
VERO Kendler (2018)	RIS	TPTD	-	24	533	64	516	28	-	-	1	0
VERO Kendler (2018)	RIS	TPTD	-	12	533	11	516	4	-	-	0	1
Hadji (2012)	RIS	TPTD	-	18	309	33	317	16	-	-	1	0
MOVE Malouf-Sierra (2017)	RIS	TPTD	-	18	106	1	116	0	-	-	1	0
Cosman (2011)	ZOL	TPTD	-	12	137	5	137	1	-	-	1	1
EVA Recker (2007)	ALN	RLX	-	10.26	255	8	259	5	-	-	1	0
EVA Recker (2007)	ALN	RLX	-	10.26	713	3	699	0	-	-	0	0
Muscoso (2004)	ALN	RLX	RIS	12	1000	2	100	0	100	0	0	1
Muscoso (2004)	ALN	RLX	RIS	24	1000	6	100	0	100	0	1	0
ARCH Saag (2017)	ALN	ROMO	-	12	1703	85	1696	55	-	-	0	1
ARCH Saag (2017)	ALN	ROMO/ALN	-	24	1834	147	1825	74	-	-	1	0
ARCH Saag (2017)	ALN	ROMO/ALN	-	24	2047	18	2046	10	-	-	0	0
Panico (2011)	ALN	TPTD	-	18	39	6	42	1	-	-	1	0
Saag (2018)	RIS	DEN	-	12	342	15	333	10	-	-	1	1
Mok (2011)	PBO	RLX	-	12	56	3	51	0	-	-	1	1
Miller (2004)	PBO	ALN	-	12	41	3	80	6	-	-	1	1
Miller (2004)	PBO	ALN	-	12	58	3	109	5	-	-	0	0

M: main analysis, S1: Sensitivity analysis 1, S2: Sensitivity analysis 2, S3: Sensitivity analysis 3.

Table 28: Data contributing to the NMA of non-vertebral fractures

study	t1	t2	t3	t	n1	r1	n2	r2	n3	r3
FREEDOM Cummings (2009)	PBO	DEN	-	36	3906	293	3902	238	-	-
FRAME Cosman (2016)	PBO	ROMO	-	12	3591	75	3589	56	-	-
Orwoll (2003)	PBO	TPTD	-	12	147	3	151	2	-	-
ADAMO Orwoll (2012)	PBO	DEN	-	12	120	2	120	1	-	-
DIRECT Nakamura (2014)	PBO	DEN	-	24	480	20	472	19	-	-
Koh (2016)	PBO	DEN	-	6	66	1	69	1	-	-
Miyauchi (2010)	PBO	TPTD	-	12	67	1	136	1	-	-
ACTIVE Miller (2016)	PBO	TPTD	-	18	821	33	818	24	-	-
Neer (2001)	PBO	TPTD	-	24	544	30	541	14	-	-
Silverman (2008)	PBO	RLX	-	36	1885	118	1849	109	-	-
Ishibashi (2017)	PBO	RLX	-	12	63	1	63	2	-	-
STRUCTURE Langdahl (2017)	ROMO	TPTD	-	12	218	7	214	8	-	-
STAND Kendler (2010)	ALN	DEN	-	12	249	4	253	8	-	-
DAPS Freemantle (2012)	ALN	DEN	-	12	118	1	125	1	-	-
Saag (2009)	ALN	TPTD	-	36	214	15	214	16	-	-
EuroGIOPs Gluer (2013)	RIS	TPTD	-	18	47	5	45	0	-	-
VERO Kendler (2018)	RIS	TPTD	-	24	680	38	680	25	-	-
Hadji (2012)	RIS	TPTD	-	18	350	29	360	28	-	-
Malouf-Sierra (2017)	RIS	TPTD	-	18	110	10	106	5	-	-
Cosman (2011)	ZOL	TPTD	-	12	137	8	137	7	-	-
Muscoso (2004)	ALN	RLX	RIS	24	1000	4	100	0	100	0
ARCH Saag (2017)	ALN	ROMO/ALN	-	32.4	2047	217	2046	178	-	-
EFFECT (US) Luckey (2004)	ALN	RLX	-	12	199	5	206	8	-	-
ZONE Nakamura (2017)	PBO	ZOL	-	24	331	37	330	20	-	-
Lufkin (1998)	PBO	RLX	-	12	45	3	43	0	-	-
Saag (2018)	RIS	DEN	-	12	397	10	398	17	-	-
Michalska (2006)	PBO	ALN	RLX	24	33	2	33	1	33	1
Fogelman (2000)	PBO	RIS	-	36	125	13	112	7	-	-
VERT-USA Harris (1999)	PBO	RIS	-	36	815	52	812	33	-	-
VERT-EU Reginster (2000)	PBO	RIS	-	24	406	51	406	36	-	-
Hooper (2005)	PBO	RIS	-	12	125	6	129	5	-	-
Ringe (2006)	PBO	RIS	-	48	158	17	158	10	-	-
FIT I Black (1996)	PBO	ALN	-	36	1005	148	1022	122	-	-
FIT II Cumming (1998)	PBO	ALN	-	48	2218	294	2214	261	-	-
Orwoll (2000)	PBO	ALN	-	24	94	5	146	6	-	-
FOSIT Pols (1999)	PBO	ALN	-	12	958	37	950	19	-	-
Bone (2000)	PBO	ALN	-	24	50	4	92	5	-	-
HORIZON-PFT Black (2007)	PBO	ZOL	-	11	3861	388	3875	292	-	-

HORIZON-RFT Lyles (2007)	PBO	ZOL	-	36	1062	107	1065	79	-	-
BONE Chesnut (2004)	PBO	IBNdaily	-	36	975	80	977	89	-	-
MOTION Miller (2008)	ALN	IBNmonthly	-	12	859	12	874	14	-	-
Morii (2003)	PBO	RLX	-	12	97	4	88	1	-	-

Table 29: Data contributing to the NMA hip fractures

study	t1	t2	t3	t	n1	r1	n2	r2	n3	r3
FREEDOM Cummings (2009)	PBO	DEN	-	36	3906	43	3902	26	-	-
FRAME Cosman (2016)	PBO	ROMO	-	12	3591	13	3589	7	-	-
DIRECT Nakamura (2014)	PBO	DEN	-	24	480	2	472	0	-	-
ACTIVE Miller (2016)	PBO	TPTD	-	18	821	2	818	0	-	-
Neer (2001)	PBO	TPTD	-	24	544	4	541	1	-	-
STRUCTURE Langdahl (2017)	ROMO	TPTD	-	12	218	1	218	0	-	-
Miller (2016)	ZOL	DEN	-	12	320	2	320	1	-	-
EuroGIOPs Gluer (2013)	RIS	TPTD	-	18	47	1	45	0	-	-
VERO Kendler (2018)	RIS	TPTD	-	24	680	5	680	2	-	-
Hadji (2012)	RIS	TPTD	-	18	350	2	360	5	-	-
EFFECT Sambrook (2004)	ALN	RLX	-	12	246	0	241	1	-	-
MOVE Malouf (2017)	RIS	TPTD	-	18	110	7	106	2	-	-
Muscoso (2004)	ALN	RLX	RIS	24	1000	3	100	0	100	0
ARCH Saag (2017)	ALN	ROMO/ALN	-	32.4	2047	66	2046	41	-	-
Saag (2018)	RIS	DEN	-	12	397	1	398	1	-	-
Silverman (2008)	PBO	RLX	-	36	1885	6	1849	5	-	-
VERT-USA Harris (1999)	PBO	RIS	-	36	815	15	812	12	-	-
VERT-EU Reginster (2000)	PBO	RIS	-	36	406	11	406	9	-	-
FIT I Black (1996)	PBO	ALN	-	36	1005	22	1022	11	-	-
FIT II Cumming (1998)	PBO	ALN	-	48	2218	24	2214	19	-	-
Greenspan (2002)	PBO	ALN	-	24	164	4	163	2	-	-
HORIZON-PFT Black (2007)	PBO	ZOL	-	36	3861	88	3875	52	-	-
HORIZON-RFT Lyles (2007)	PBO	ZOL	-	36	1062	33	1065	23	-	-

Table 30: Data contributing to the NMA of wrist fractures

study	t1	t2	t3	t	n1	r1	n2	r2	n3	r3
ACTIVE Miller (2016)	PBO	TPTD	-	18	821	15	818	17	-	-
Neer (2001)	PBO	TPTD	-	24	544	7	541	2	-	-
Ishibashi (2017)	PBO	RLX	-	12	63	0	63	1	-	-
STRUCTURE Langdahl (2017)	ROMO	TPTD	-	12	218	1	218	0	-	-
STAND Kendler (2010)	ALN	DEN	-	12	249	2	253	3	-	-
VERO Kendler (2018)	RIS	TPTD	-	24	680	10	680	6	-	-
Hadji (2012)	RIS	TPTD	-	18	350	2	360	4	-	-
Muscoso (2004)	ALN	RLX	RIS	24	1000	1	100	0	100	0
EFFECT US Luckey (2004)	ALN	RLX	-	12	199	0	206	1	-	-
Silverman (2008)	PBO	RLX	-	36	1885	31	1849	46	-	-
VERT-USA Harris (1999)	PBO	RIS	-	36	815	22	812	14	-	-
VERT-EU Reginster (2000)	PBO	RIS	-	36	406	21	406	15	-	-
FIT I Black (1996)	PBO	ALN	-	36	1005	41	1022	22	-	-
FIT II Cumming (1998)	PBO	ALN	-	48	2218	70	2214	83	-	-
McClung (2009)	PBO	IBNmonthly	-	12	83	0	77	1	-	-

Table 31: Data contributing to the NMA of wrist fractures

study	t1	t2	t	n1	r1	n2	r2
ADAMO Orwoll (2012)	PBO	DEN	12	120	1	120	0
ACTIVE (2016)	PBO	TPTD	18	821	3	818	2
Neer (2001)	PBO	TPTD	24	544	2	541	2
STRUCTURE Langdahl (2017)	ROMO	TPTD	12	218	0	218	1
STAND Kendler (2010)	ALN	DEN	12	249	0	253	1
EuroGIOPs Gluer (2013)	RIS	TPTD	18	47	1	45	0
VERO Kendler (2018)	RIS	TPTD	24	680	2	680	4
Hadji (2012)	RIS	TPTD	18	350	5	360	4
MOVE Malouf-Sierra (2017)	RIS	TPTD	18	110	1	106	1
EFFECT (US) Luckey (2004)	ALN	RLX	12	199	0	206	1
Saag (2018)	RIS	DEN	12	391	3	398	3
VERT-MN Harris (1999)	PBO	RIS	36	815	10	812	4
VERT-MN Reginster (2000)	PBO	RIS	36	406	14	406	7

Appendix 9: Network meta-analysis additional results

Appendix 9.2 NMA results from random effects model

Treatment effects vs placebo, from the RE model shown in Figure 13 below and a summary of model fit and heterogeneity is shown in Table 32. For all outcomes the DIC was larger for the RE 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 RE model are generally consistent with primary model.

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: 0-4.23) and probability 0.39 of being the best treatment. Under the class effects model the HR for ALN is less extreme (0.46, 95% CrI: 0.15-1.27) since 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 [78] with zero events in the ALN arm and 1 event in the RLX arm and so is highly uncertain.

Table 32: Model fit and heterogeneity for RE sensitivity analysis, all outcomes

outcome	absolute model fit		DIC	SD (95%CI)
	D_{res}	DP		
vertebral fractures	93.42	93	156.43	0.15 (0.01,0.37)
non-vertebral fractures	73.93	86	129.50	0.08 (0.01,0.24)
hip*	39.58	47	72.37	0.13 (0.01,0.45)
wrist*	30.21	31	55.89	0.30 (0.04,0.66)
proximal humerus*	22.87	26	44.02	0.17 (0.01,0.58)
femoral neck BMD				

D_{res}: Total residual deviance, DP: data points, DIC: deviance information criterion, SD: between study standard deviation

* For hip, wrist and humerus fractures weakly informative priors were used for the between study and between treatment SD

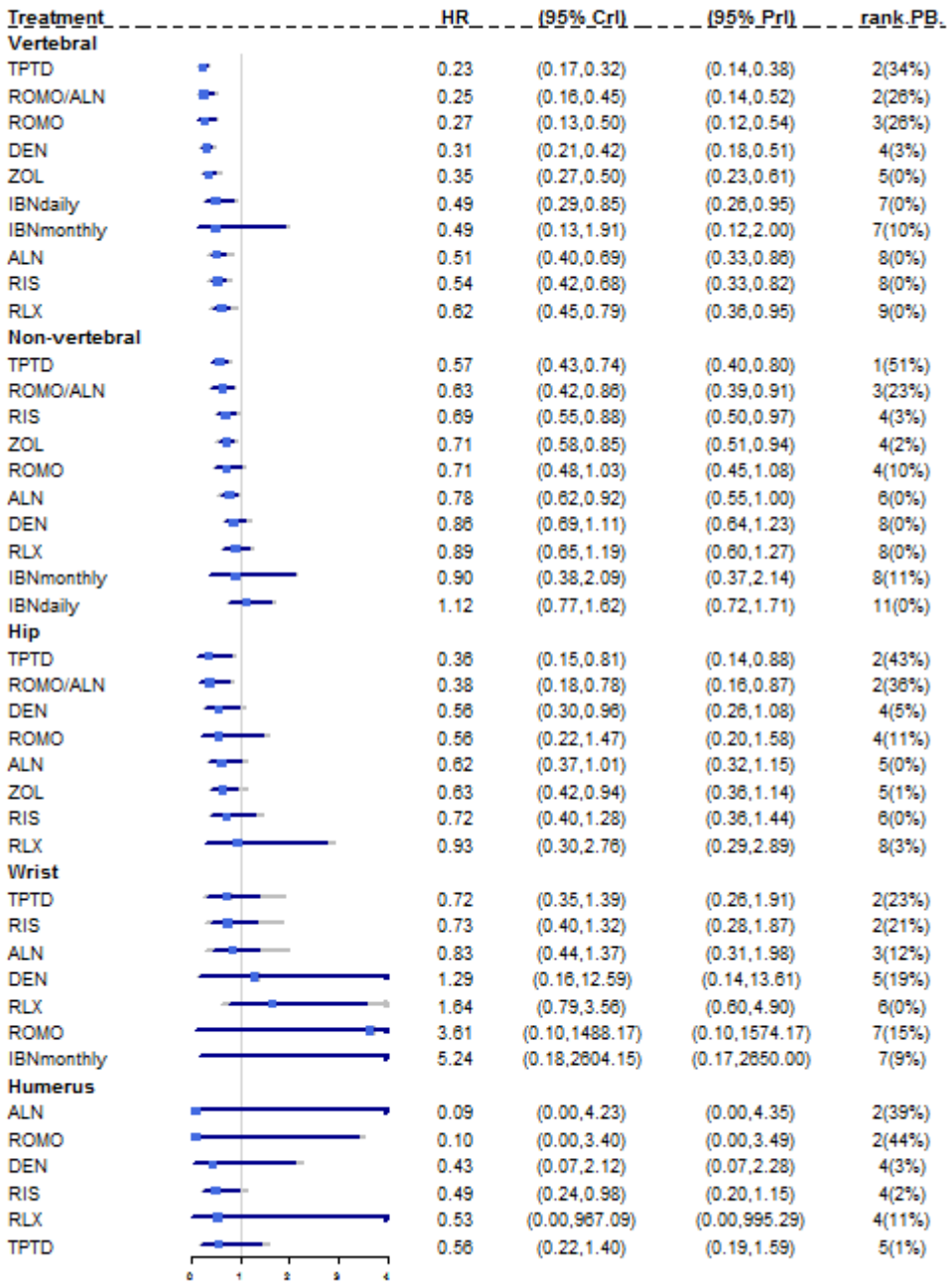

Figure 13: Forest plot of HR for all fracture outcomes using a random effects model

Appendix 9.3 Vertebral fracture sensitivity analyses

4 sensitivity analyses were conducted for the vertebral fracture network:

- S1: 12 month data only
- S2: Clinically assessed fractures only
- S3: Exclusion of studies with quality issues
- S4: Exclusion of studies where prior bisphosphonate treatment had been received

Treatment effects vs placebo, are summarised in Figure 14 below and a summary of model fit and heterogeneity is shown in Table 33.

Table 33: Summary of model fit and heterogeneity between studies and between treatments for vertebral fracture network sensitivity analyses

outcome	**absolute model fit**		**DIC**	**Heterogeneity**	
	D_{res}	**data points**		**between study SD (95%CI)**	**between treatment SD (95%CI)**
vertebral fractures	91.21	93	153.31	0.17 (0.02,0.37)	0.21 (0.01,0.90)
S1: 12 months	56.17	59	95.94	0.17(0.01,0.51)	0.15(0.01,0.86)
S2: Clinical fractures	38.16	38	68.36	0.31(0.02,0.88)	0.286(0.013,1.33)
S3: Excluding qualtity issues	58.27	61	99.4	0.13(0.01,0.38)	0.149(0.01,1.04)
S4: Excluding prior treatment	69.83	72	117.47	0.11(0.01,0.34)	0.117(0.01,0.69)

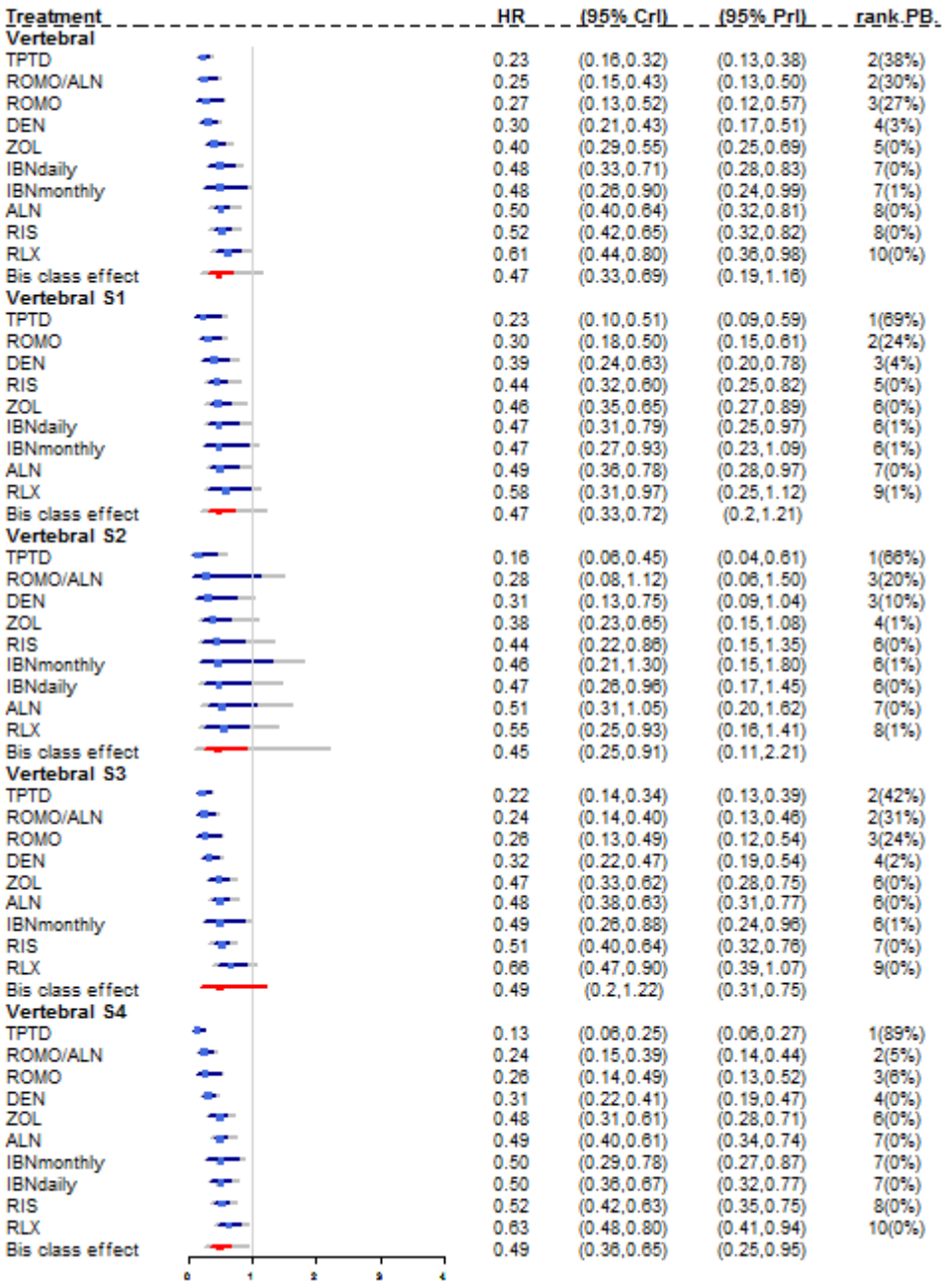

Figure 14: Forest plot of vertebral fracture network sensitivity analyses

Appendix 9.4 Pairwise summary tables

Pairwise summary tables for all outcomes are shown below. Median HR and 95% CrI are presented below the diagonal, median HR and 95% PrI are shown above the diagonal.

Table 34: Pairwise comparisons, vertebral fractures main analysis

	PBO	**ALN**	**RIS**	**ZOL**	**IBNdaily**	**IBNmonthly**	**DEN**	**ROMO**	**TPTD**
PBO		0.50(0.32,0.81)	0.52(0.32,0.82)	0.39(0.25,0.69)	0.48(0.28,0.83)	0.48(0.24,0.99)	0.31(0.17,0.51)	0.27(0.12,0.57)	0.23(0.13,0.38)
ALN	**0.50(0.40,0.64)**		1.06(0.53,1.90)	0.78(0.42,1.61)	0.98(0.47,1.87)	0.96(0.42,2.16)	0.61(0.29,1.20)	0.53(0.21,1.28)	0.47(0.23,0.88)
RIS	**0.52(0.42,0.65)**	1.03(0.77,1.39)		0.74(0.42,1.63)	0.93(0.47,1.86)	0.92(0.41,2.17)	0.58(0.29,1.19)	0.51(0.20,1.25)	0.44(0.23,0.85)
ZOL	**0.40(0.29,0.55)**	0.81(0.54,1.08)	0.77(0.52,1.08)		1.23(0.57,2.43)	1.19(0.53,2.91)	0.79(0.34,1.50)	0.68(0.24,1.60)	0.60(0.26,1.11)
IBNdaily	**0.48(0.33,0.71)**	0.98(0.63,1.43)	0.95(0.61,1.37)	1.18(0.82,1.99)		0.99(0.42,2.40)	0.63(0.29,1.32)	0.55(0.21,1.40)	0.48(0.23,0.99)
IBNmonthly	**0.48(0.26,0.90)**	0.98(0.51,1.75)	0.95(0.47,1.71)	1.14(0.68,2.50)	1.00(0.49,1.98)		0.64(0.25,1.52)	0.55(0.19,1.56)	0.48(0.19,1.13)
DEN	**0.30(0.21,0.43)**	**0.61(0.39,0.91)**	**0.58(0.40,0.88)**	0.77(0.46,1.19)	0.63(0.38,1.03)	0.64(0.31,1.26)		0.87(0.33,2.23)	0.76(0.36,1.57)
ROMO	**0.27(0.13,0.52)**	0.53(0.25,1.06)	0.51(0.25,1.03)	0.67(0.30,1.35)	0.55(0.25,1.16)	0.55(0.22,1.36)	0.87(0.40,1.86)		0.87(0.34,2.22)
TPTD	**0.23(0.16,0.32)**	**0.46(0.31,0.66)**	**0.44(0.32,0.61)**	**0.58(0.36,0.90)**	**0.47(0.29,0.77)**	**0.48(0.25,0.95)**	0.76(0.46,1.20)	0.87(0.41,1.87)	
RLX	**0.61(0.44,0.80)**	1.23(0.82,1.71)	1.17(0.82,1.68)	1.54(0.94,2.32)	1.26(0.78,1.97)	1.27(0.65,2.47)	2.01(1.25,3.13)	2.30(1.09,4.83)	2.66(1.72,4.11)
ROMO/ALN	**0.25(0.15,0.43)**	**0.50(0.30,0.80)**	**0.47(0.28,0.86)**	0.62(0.33,1.11)	**0.51(0.28,0.98)**	0.51(0.24,1.12)	0.81(0.44,1.59)	0.93(0.40,2.29)	1.06(0.60,2.06)

Table 35: Pairwise comparisons, non-vertebral fractures main analysis

	PBO	ALN	RIS	ZOL	IBNdaily	IBNmonthly	DEN	ROMO	TPTD
PBO		0.78(0.56,0.99)	0.73(0.53,0.98)	0.73(0.54,0.95)	0.89(0.60,1.38)	0.79(0.50,1.31)	0.86(0.64,1.23)	0.71(0.45,1.09)	0.58(0.4
ALN	**0.77(0.64,0.90)**		0.95(0.65,1.43)	0.94(0.65,1.42)	1.15(0.75,1.91)	1.02(0.63,1.78)	1.10(0.76,1.84)	0.92(0.56,1.56)	0.75(0.5
RIS	**0.73(0.59,0.88)**	0.96(0.73,1.19)		1.00(0.66,1.48)	1.22(0.76,2.11)	1.07(0.65,1.96)	1.18(0.79,1.91)	0.97(0.57,1.65)	0.80(0.5
ZOL	**0.73(0.61,0.85)**	0.96(0.76,1.17)	1.00(0.79,1.28)		1.23(0.77,2.08)	1.07(0.65,1.93)	1.18(0.79,1.90)	0.97(0.58,1.63)	0.80(0.5
IBNdaily	0.88(0.67,1.32)	1.13(0.91,1.76)	1.20(0.93,1.98)	1.20(0.93,1.91)		0.91(0.47,1.49)	0.95(0.57,1.69)	0.79(0.43,1.43)	0.65(0.3
IBNmonthly	0.78(0.54,1.27)	1.01(0.70,1.66)	1.05(0.74,1.84)	1.05(0.74,1.83)	0.93(0.50,1.32)		1.08(0.61,1.98)	0.90(0.47,1.68)	0.74(0.4
DEN	0.86(0.69,1.12)	1.12(0.87,1.57)	1.18(0.90,1.63)	1.18(0.91,1.63)	0.97(0.62,1.46)	1.09(0.65,1.73)		0.83(0.46,1.38)	0.68(0.4
ROMO	0.71(0.48,1.03)	0.92(0.62,1.39)	0.97(0.64,1.49)	0.97(0.64,1.47)	0.79(0.47,1.28)	0.90(0.50,1.53)	0.82(0.51,1.26)		0.82(0.4
TPTD	**0.58(0.45,0.76)**	0.76(0.57,1.02)	0.80(0.61,1.04)	0.80(0.60,1.08)	**0.66(0.40,0.96)**	0.74(0.42,1.14)	**0.68(0.47,0.94)**	0.82(0.53,1.28)	
RLX	0.90(0.65,1.21)	1.17(0.84,1.63)	1.23(0.85,1.77)	1.23(0.87,1.74)	1.01(0.62,1.53)	1.14(0.66,1.83)	1.05(0.68,1.49)	1.27(0.78,2.05)	**1.55(1.0**
ROMO/ALN	**0.63(0.44,0.86)**	0.81(0.61,1.09)	0.86(0.58,1.25)	0.86(0.59,1.23)	0.70(0.42,1.06)	0.79(0.46,1.26)	0.73(0.46,1.06)	0.88(0.53,1.44)	1.08(0.7

Table 36: Pairwise comparisons, hip fractures main analysis

	PBO	ALN	RIS	ZOL	DEN	ROMO	TPTD	RLX	ROMO
PBO		0.64(0.39,1.04)	0.66(0.40,1.12)	0.63(0.39,1.01)	0.56(0.28,1.04)	0.56(0.20,1.50)	0.34(0.14,0.78)	0.93(0.29,2.82)	0.39(0
ALN	**0.64(0.45,0.88)**		1.03(0.56,2.01)	1.00(0.54,1.85)	0.88(0.38,1.94)	0.88(0.29,2.64)	0.54(0.20,1.37)	1.48(0.44,4.81)	0.62(0
RIS	**0.66(0.46,0.99)**	1.02(0.71,1.63)		0.97(0.51,1.79)	0.85(0.36,1.84)	0.85(0.27,2.63)	0.52(0.21,1.23)	1.41(0.42,4.71)	0.59(0
ZOL	**0.64(0.47,0.86)**	1.00(0.70,1.44)	0.99(0.62,1.38)		0.88(0.39,1.91)	0.88(0.29,2.65)	0.54(0.20,1.34)	1.48(0.44,4.82)	0.62(0
DEN	**0.56(0.31,0.94)**	0.88(0.45,1.63)	0.85(0.43,1.57)	0.88(0.46,1.59)		1.00(0.31,3.31)	0.61(0.21,1.77)	1.68(0.47,5.95)	0.70(0
ROMO	0.56(0.22,1.43)	0.88(0.33,2.41)	0.85(0.31,2.33)	0.88(0.33,2.36)	1.01(0.33,3.04)		0.61(0.17,2.19)	1.65(0.37,7.39)	0.70(0
TPTD	**0.35(0.15,0.73)**	0.54(0.23,1.19)	0.52(0.23,1.06)	0.54(0.23,1.18)	0.62(0.24,1.58)	0.61(0.19,1.97)		2.74(0.68,11.24)	1.14(0
RLX	0.94(0.31,2.67)	1.48(0.49,4.20)	1.42(0.45,4.21)	1.47(0.48,4.27)	1.69(0.50,5.45)	1.64(0.41,6.67)	2.73(0.73,10.19)		0.42(0
ROMO/ALN	**0.39(0.21,0.72)**	0.62(0.36,1.03)	0.59(0.31,1.12)	0.61(0.32,1.13)	0.70(0.32,1.62)	0.70(0.22,2.14)	1.14(0.44,3.09)	0.42(0.13,1.39)	

Table 37: Pairwise comparisons, wrist fractures main analysis

	PBO	ALN	RIS	IBNmonthly	DEN	ROMO	TPTD	RLX
PBO		0.83(0.35,1.77)	0.79(0.34,1.77)	0.84(0.31,2.31)	1.29(0.14,13.46)	3.90(0.10,2150.25)	0.76(0.28,1.88)	1.62(0.62
ALN	0.82(0.51,1.23)		0.96(0.33,2.84)	1.01(0.33,3.46)	1.59(0.17,18.17)	4.86(0.12,2746.02)	0.92(0.28,3.10)	1.95(0.59
RIS	0.79(0.49,1.22)	0.98(0.59,1.52)		1.05(0.34,3.59)	1.65(0.17,19.09)	5.04(0.12,2961.30)	0.96(0.28,3.09)	2.04(0.61
IBNmonthly	0.83(0.42,1.89)	1.00(0.54,2.22)	1.02(0.57,2.42)		1.56(0.14,18.93)	4.72(0.11,2771.52)	0.90(0.23,3.26)	1.94(0.49
DEN	1.29(0.15,12.49)	1.58(0.20,15.16)	1.64(0.20,16.21)	1.54(0.17,15.60)		3.26(0.04,2080.02)	0.57(0.05,6.23)	1.25(0.10
ROMO	3.87(0.11,2062.02)	4.80(0.13,2579.12)	5.02(0.14,2672.92)	4.68(0.12,2477.20)	3.27(0.04,2077.15)		0.19(0.00,7.20)	0.42(0.00
TPTD	0.75(0.38,1.41)	0.92(0.44,1.90)	0.96(0.47,1.88)	0.90(0.34,2.11)	0.57(0.05,5.17)	0.19(0.00,6.39)		2.14(0.59
RLX	1.63(0.80,3.51)	1.98(0.92,4.87)	2.07(0.92,5.04)	1.96(0.71,5.39)	1.27(0.12,11.69)	0.42(0.00,16.12)	2.17(0.86,6.12)	

Table 38: Pairwise comparisons, humerus fractures main analysis

	PBO	ALN	RIS	DEN	ROMO	TPTD	RLX
PBO		0.46(0.13,1.43)	0.48(0.20,1.13)	0.55(0.11,2.60)	0.10(0.00,3.80)	0.55(0.19,1.59)	2.48(0.06,1215.07)
ALN	0.46(0.15,1.27)		1.03(0.36,3.52)	1.21(0.24,6.59)	0.23(0.00,10.16)	1.22(0.32,4.89)	5.48(0.16,2806.02)
RIS	**0.49(0.23,0.96)**	1.01(0.47,2.78)		1.13(0.24,5.46)	0.22(0.00,8.19)	1.15(0.38,3.48)	5.27(0.14,2596.20)
DEN	0.55(0.12,2.41)	1.21(0.26,5.68)	1.14(0.28,4.57)		0.19(0.00,9.50)	1.00(0.18,5.72)	4.63(0.09,2621.17)
ROMO	0.10(0.00,3.66)	0.23(0.00,9.49)	0.22(0.00,7.54)	0.19(0.00,8.82)		5.11(0.16,2773.07)	34.06(0.14,132817.46)
TPTD	0.55(0.21,1.41)	1.22(0.39,4.05)	1.15(0.50,2.63)	1.00(0.20,5.02)	5.10(0.17,2692.22)		4.63(0.11,2511.00)
RLX	2.46(0.06,1204.07)	5.43(0.17,2598.02)	5.19(0.15,2496.67)	4.64(0.10,2526.10)	33.91(0.15,126105.00)	4.58(0.12,2345.00)	

Table 39: Pairwise comparisons, femoral neck BMD main analysis

	PBO	ALN	RIS	ZOL	IBNdaily	IBNmonthly	IBNiv	DEN	ROMO	TPTD	RLX	ROMO/A
PBO		2.48(0.71,4.25)	1.80(0.01,3.58)	3.16(1.27,5.04)	1.84(-0.30,3.85)	2.30(0.41,4.24)	2.38(0.06,4.56)	3.35(1.51,5.16)	4.20(2.24,6.17)	2.58(0.77,4.40)	1.52(-0.33,3.42)	6.09(3.5
ALN	**2.49(2.05,2.91)**		-0.70(-3.20,1.78)	0.68(-1.91,3.19)	-0.65(-3.37,1.98)	-0.19(-2.74,2.37)	-0.12(-2.97,2.66)	0.87(-1.69,3.36)	1.71(-0.94,4.34)	0.10(-2.41,2.57)	-0.97(-3.49,1.60)	3.60(0.5
RIS	**1.80(1.22,2.37)**	-0.69(-1.29,-0.09)		1.36(-1.22,3.95)	0.03(-2.66,2.70)	0.51(-2.03,3.10)	0.58(-2.30,3.37)	1.56(-0.95,4.08)	2.40(-0.25,5.10)	0.79(-1.70,3.30)	-0.26(-2.84,2.35)	4.27(1.2
ZOL	**3.17(2.38,3.95)**	0.68(-0.09,1.49)	**1.37(0.41,2.28)**		-1.32(-4.14,1.41)	-0.86(-3.48,1.85)	-0.77(-3.72,2.08)	0.18(-2.39,2.77)	1.04(-1.67,3.76)	-0.58(-3.21,2.06)	-1.63(-4.24,1.02)	2.92(-0.1
IBNdaily	**1.85(0.53,2.93)**	-0.63(-1.97,0.41)	0.05(-1.24,1.15)	-1.31(-2.86,-0.06)		0.48(-2.17,3.17)	0.54(-2.18,3.28)	1.52(-1.20,4.27)	2.39(-0.52,5.22)	0.75(-1.94,3.51)	-0.29(-3.05,2.52)	4.25(1.0
IBNmonthly	**2.32(1.50,3.13)**	-0.16(-0.99,0.63)	0.51(-0.33,1.41)	-0.83(-1.95,0.15)	0.47(-0.56,1.73)		0.07(-2.80,2.88)	1.04(-1.55,3.64)	1.91(-0.87,4.59)	0.29(-2.38,2.87)	-0.78(-3.47,1.87)	3.78(0.6
IBNiv	**2.39(0.83,3.78)**	-0.10(-1.66,1.32)	0.56(-0.92,2.09)	-0.73(-2.53,0.64)	0.52(-0.69,1.92)	0.06(-1.47,1.54)		0.97(-1.90,3.87)	1.82(-1.16,4.85)	0.21(-2.62,3.15)	-0.86(-3.69,2.15)	3.72(0.3
DEN	**3.36(2.74,3.97)**	**0.87(0.24,1.49)**	**1.56(0.83,2.30)**	0.19(-0.70,1.09)	**1.52(0.33,2.91)**	**1.04(0.16,1.95)**	0.97(-0.50,2.60)		0.85(-1.79,3.53)	-0.78(-3.31,1.80)	-1.82(-4.36,0.80)	2.73(-0.3
ROMO	**4.20(3.23,5.16)**	**1.71(0.67,2.75)**	**2.40(1.28,3.51)**	1.03(-0.22,2.28)	**2.36(0.88,3.95)**	**1.88(0.65,3.12)**	**1.82(0.10,3.65)**	0.84(-0.30,1.96)		-1.63(-4.27,1.00)	-2.66(-5.40,0.03)	1.88(-1.3
TPTD	**2.58(2.00,3.17)**	0.09(-0.56,0.75)	**0.78(0.02,1.54)**	-0.59(-1.52,0.35)	0.73(-0.47,2.14)	0.25(-0.68,1.22)	**0.19(-1.30,1.85)**	-0.78(-1.57,0.01)	-1.62(-2.63,-0.60)		-1.04(-3.65,1.56)	3.51(0.4
RLX	**1.53(0.78,2.31)**	-0.95(-1.74,-0.14)	-0.26(-1.19,0.66)	-1.63(-2.70,-0.56)	-0.30(-1.64,1.17)	-0.79(-1.86,0.31)	-0.85(-2.42,0.87)	-1.82(-2.77,-0.86)	-2.66(-3.89,-1.42)	-1.04(-1.98,-0.09)		4.55(1.4
ROMO/ALN	**6.08(4.25,7.91)**	**3.59(1.81,5.37)**	**4.29(2.40,6.14)**	**2.92(0.93,4.86)**	**4.26(2.14,6.42)**	**3.76(1.79,5.73)**	**3.70(1.41,6.03)**	**2.72(0.83,4.61)**	1.89(-0.22,3.98)	**3.50(1.57,5.41)**	**4.55(2.57,6.50)**	

Appendix 9.5 Assessment of inconsistency

Vertebral fractures

12 treatment contrasts have both direct and indirect evidence, however only 10 of these were assessed for consistency. RIS-ALN was not assessed since the direct comparison is contributed by one small study[80] with a zero count in the control arm. ZOL-TPTD was not assessed since the direct comparison is contributed by one small study,[94] with only 1 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 PBO-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 HR's 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.

Table 40: Node-splitting results, vertebral fractures main analysis

		Heterogeneity		**Model Fit**		**HR's**			**p***
T1	**T2**	**SD**	**SDt**	D_{res}	**DIC**	**All evidence**	**Direct**	**Indirect**	
PBO	ALN	0.14 (0.01,0.34)	0.42 (0.05,1.48)	90.4	152.7	0.50 (0.40,0.64)	0.46 (0.36,0.62)	0.76 (0.43,1.68)	0.18
PBO	RIS	0.16 (0.01,0.37)	0.19 (0.01,0.86)	92.31	155	0.52 (0.41,0.65)	0.57 (0.42,0.74)	0.45 (0.32,0.65)	0.31
PBO	**ZOL**	**0.12 (0.01,0.31)**	**0.13 (0.00,0.92)**	**91.29**	**151.6**	**0.40 (0.29,0.55)**	**0.33 (0.25,0.45)**	**0.56 (0.38,1.25)**	**0.03**
PBO	TPTD	0.17 (0.02,0.37)	0.19 (0.01,0.89)	90.18	153.33	0.23 (0.16,0.32)	0.30 (0.19,0.49)	0.18 (0.11,0.28)	0.12
RIS	ZOL	0.16 (0.01,0.35)	0.23 (0.02,0.97)	92.07	155.02	0.78 (0.52,1.08)	1.78 (0.40,9.98)	0.73 (0.49,1.05)	0.26
RIS	DEN	0.18 (0.01,0.38)	0.21 (0.01,0.91)	91.95	155.44	0.59 (0.39,0.88)	0.67 (0.26,1.65)	0.56 (0.35,0.90)	0.72
RIS	TPTD	0.18 (0.02,0.39)	0.20 (0.01,0.90)	91.82	155.24	0.44 (0.32,0.61)	0.44 (0.27,0.68)	0.45 (0.27,0.72)	0.94
PBO	RLX	0.16 (0.01,0.36)	0.20 (0.01,0.90)	91.58	154.34	0.61 (0.44,0.80)	0.64 (0.47,0.85)	0.30 (0.09,0.90)	0.19
PBO	DEN	0.18 (0.02,0.38)	0.21 (0.01,0.90)	91.97	155.54	0.30 (0.21,0.43)	0.29 (0.19,0.43)	0.35 (0.14,0.90)	0.72

ALN	TPTD	0.15 (0.01,0.35)	0.22 (0.02,0.92)	90.5	153.26	0.46 (0.31,0.66)	0.18 (0.04,0.51)	0.53 (0.35,0.77)	0.06
Consistency model									
		0.17 (0.02,0.37)	0.20 (0.01,0.91)	91.24	152.34				

D_{res}: Total residual deviance, DIC: deviance information criterion, SD: between study standard deviation, SDt: between bisphosphonate treatment standard deviation

* Bayesian p-value

Non-vertebral fractures

14 treatment contrasts have both direct and indirect evidence, however only 13 of these were assessed for consistency. RIS-ALN was not assessed since the direct comparison is contributed by one small study[80] 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 PBO-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 network.

Table 41: Node-splitting results, non-vertebral fractures main analysis

T1	T2	Heterogeneity		Model Fit		HR's			p
		SD	SDt	D_{res}	DIC	All evidence	Direct	Indirect	
PBO	RLX	0.88 (0.62,1.19)	1.14 (0.39,3.23)	74.61	129.85	0.90 (0.65,1.21)	0.88 (0.62,1.19)	1.14 (0.39,3.23)	0.65
PBO	ALN	0.81 (0.65,0.95)	0.66 (0.39,0.91)	73.06	127.94	0.77 (0.64,0.90)	0.81 (0.65,0.95)	0.66 (0.39,0.91)	0.31
PBO	RIS	0.65 (0.48,0.86)	0.80 (0.59,1.12)	73.8	128.78	0.73 (0.59,0.88)	0.65 (0.48,0.86)	0.80 (0.59,1.12)	0.28
PBO	ZOL	0.71 (0.57,0.86)	0.78 (0.42,1.33)	74.3	129.46	0.73 (0.61,0.85)	0.71 (0.57,0.86)	0.78 (0.42,1.33)	0.65
PBO	DEN	0.82 (0.65,1.05)	1.34 (0.69,2.61)	73.41	128.2	0.86 (0.69,1.12)	0.82 (0.65,1.05)	1.34 (0.69,2.61)	0.19
PBO	ROMO	0.75 (0.49,1.14)	0.50 (0.16,1.46)	74.45	129.95	0.71 (0.48,1.03)	0.75 (0.49,1.14)	0.50 (0.16,1.46)	0.49
PBO	TPTD	0.60 (0.39,0.89)	0.57 (0.40,0.80)	74.6	129.91	0.58 (0.45,0.76)	0.60 (0.39,0.89)	0.57 (0.40,0.80)	0.88
ALN	TPTD	1.06 (0.52,2.23)	0.71 (0.52,0.96)	73.84	128.86	0.76 (0.57,1.02)	1.06 (0.52,2.23)	0.71 (0.52,0.96)	0.3
RIS	DEN	1.75 (0.78,4.16)	1.12 (0.85,1.57)	74.15	129.18	1.18 (0.90,1.63)	1.75 (0.78,4.16)	1.12 (0.85,1.57)	0.33
RIS	TPTD	0.69 (0.47,0.99)	0.97 (0.66,1.46)	72.89	128.22	0.80 (0.61,1.04)	0.69 (0.47,0.99)	0.97 (0.66,1.46)	0.22
ZOL	TPTD	0.85 (0.29,2.51)	0.79 (0.58,1.07)	74.84	130.26	0.80 (0.60,1.08)	0.85 (0.29,2.51)	0.79 (0.58,1.07)	0.89
ROMO	TPTD	1.15 (0.37,3.53)	0.77 (0.46,1.24)	74.43	129.92	0.82 (0.53,1.28)	1.15 (0.37,3.53)	0.77 (0.46,1.24)	0.49
ALN	DEN	0.07 (0.00,0.23)	0.16 (0.01,0.74)	74.49	129.77	1.12 (0.87,1.57)	1.83 (0.58,6.33)	1.09 (0.84,1.52)	0.39
Consistency model									
		0.08 (0,0.24)	0.15 (0.01,0.73)	74.047	128.4				

D_{res}: Total residual deviance, DIC: deviance information criterion, SD: between study standard deviation, SDt: between bisphosphonate treatment standard deviation

* Bayesian p-value

Hip fractures

14 treatment contrasts have both direct and indirect evidence, however only 9 of these were assessed for consistency. For 5 of these (RIS-ALN, RIS-DEN, RIS-RLX, ZOL-DEN, ROMO-TPTD) the direct comparison is contributed by small studies[80], [344], Miller 2016.[68] 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 network.

Table 42: Node-splitting results, hip fractures main analysis

T1	T2	Heterogeneity		Model Fit		HR's			
		SD	SDt	D_{res}	DIC	All evidence	Direct	Indirect	
PBO	ALN	0.16 (0.01,0.63)	0.38 (0.02,1.77)	39.72	73.1	0.64 (0.41,0.94)	0.62 (0.35,1.07)	0.62 (0.16,1.92)	
PBO	RIS	0.15 (0.00,0.61)	0.32 (0.01,1.70)	39.32	72.68	0.67 (0.43,1.10)	0.80 (0.40,1.58)	0.57 (0.19,1.22)	
PBO	ZOL	0.16 (0.01,0.63)	0.43 (0.02,1.81)	39.58	72.92	0.64 (0.44,0.92)	0.62 (0.39,1.02)	0.72 (0.20,4.39)	
PBO	DEN	0.15 (0.01,0.59)	0.24 (0.01,1.59)	39.76	73.08	0.56 (0.29,0.99)	0.57 (0.28,1.05)	0.41 (0.04,2.75)	
PBO	ROMO	0.14 (0.01,0.58)	0.23 (0.01,1.60)	40.01	73.68	0.56 (0.20,1.48)	0.52 (0.17,1.48)	1.97 (0.05, 642.60)	
PBO	TPTD	0.15 (0.01,0.59)	0.25 (0.01,1.60)	39.75	73.33	0.34 (0.15,0.77)	0.19 (0.02,1.03)	0.39 (0.14,0.98)	
PBO	RLX	0.14 (0.01,0.58)	0.23 (0.01,1.57)	39.91	73.18	0.94 (0.31,2.85)	0.83 (0.22,3.08)	1.10 (0.10,7.81)	
ALN	RLX	0.15 (0.01,0.58)	0.23 (0.01,1.57)	40.03	73.46	1.49 (0.47,4.66)	1.73 (0.16,11.56)	1.31 (0.31,5.34)	
RIS	TPTD	0.15 (0.01,0.58)	0.25 (0.01,1.58)	39.42	72.97	0.51 (0.23,1.07)	0.59 (0.24,1.41)	0.27 (0.04,1.33)	
Consistency model									
		0.14 (0.01,0.56)	0.23 (0.01,1.54)	39.0876	71.572				

D_{res} : Total residual deviance, DIC: deviance information criterion, SD: between study standard deviation, SDt: between bisphosphonate treatment standard deviation

* Bayesian p-value

Wrist

8 treatment contrasts have both direct and indirect evidence, however only 5 of these were assessed for consistency. For 3 of these (RIS-ALN, ALN-RLX, RIS-RLX) the direct comparison is contributed by small studies.[80,78] 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 network.

Table 43: Node-splitting results, wrist fractures main analysis

T1	T2	Heterogeneity		Model Fit		HR's			p*
		SD	SDt	D_{res}	DIC	All evidence	Direct	Indirect	
PBO	ALN	0.30 (0.03,0.65)	0.21 (0.01,0.68)	29.93	54.51	0.82 (0.51,1.23)	0.86 (0.45,1.48)	0.73 (0.28,1.77)	0.74
PBO	RIS	0.29 (0.04,0.64)	0.19 (0.01,0.64)	29.87	54.47	0.79 (0.48,1.22)	0.67 (0.34,1.32)	0.91 (0.45,1.90)	0.49
PBO	TPTD	0.30 (0.04,0.65)	0.17 (0.01,0.63)	30.3	55.32	0.75 (0.38,1.41)	0.80 (0.33,1.79)	0.66 (0.21,2.10)	0.78
PBO	RLX	0.28 (0.03,0.63)	0.17 (0.01,0.62)	30.61	55.58	1.63 (0.80,3.51)	1.58 (0.75,3.56)	2.18 (0.18,23.47)	0.81
RIS	TPTD	0.30 (0.04,0.66)	0.17 (0.01,0.63)	30.25	55.13	0.96 (0.47,1.88)	0.86 (0.31,2.40)	1.04 (0.37,2.69)	0.78
Consistency model									
		0.28 (0.04,0.62)	0.16 (0.01,0.61)	29.9199	54.203				

D_{res}: Total residual deviance, DIC: deviance information criterion, SD: between study standard deviation, SDt: between bisphosphonate treatment standard deviation

* Bayesian p-value

Humerus

5 treatment contrasts have both direct and indirect evidence, however only 4 of these were assessed for consistency. For the PBO-DEN comparison the direct comparison is contributed by one small study[43] 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 network.

Table 44: Node-splitting results, proximal humerus fractures main analysis

T1	T2	Heterogeneity		Model Fit		HR's			p*
		SD	SD.d	D_{res}	DIC	All evidence	Direct	Indirect	
PBO	RIS	0.18 (0.01,0.59)	0.21 (0.01,0.71)	22.98	43.98	0.48 (0.24,0.96)	0.45 (0.19,0.98)	0.63 (0.12,3.00)	0.71
PBO	TPTD	0.17 (0.01,0.60)	0.21 (0.01,0.72)	22.86	43.99	0.55 (0.21,1.41)	0.77 (0.17,3.30)	0.42 (0.11,1.47)	0.53
RIS	DEN	0.17 (0.01,0.58)	0.22 (0.01,0.72)	23.05	43.93	1.14 (0.28,4.57)	0.97 (0.15,5.91)	1.40 (0.13,14.31)	0.8
RIS	TPTD	0.17 (0.01,0.59)	0.21 (0.01,0.72)	22.61	43.46	1.15 (0.50,2.63)	1.00 (0.38,2.65)	1.80 (0.33,9.58)	0.54
Consistency model									
		0.17 (0.01,0.57)	0.21 (0.01,0.7)	21.9908	41.832				

D_{res}: Total residual deviance, DIC: deviance information criterion, SD: between study standard deviation, SDt: between bisphosphonate treatment standard deviation

* Bayesian p-value

Appendix 9.6 NMA 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 gender, a common meta-regression coefficient is assumed for all treatments (see [345] 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 gender), and the baselines of each study were assumed to follow a normal distribution with common mean and between treatment variance (see Achana [123]for further details). Alternative models were also considered but did not improve model fit. Results are provided Table 45 below.

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 provides 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 since this provided the lowest DIC. Results using this model provided in

Table **45** for all outcomes.

Table 45: Results of meta-analysis on gender, age and baseline response for all outcomes

Outcome/Model	absolute model fit		DIC	heterogeneity		covariate	baseline parameters	
	D_{res}	DP		SD (95%CI)	SDt (95%CI)	estimate (95% CI)	Covariate	SD
Vertebral								
age	92.15	93	155.19	0.176(0.018,0.378)	0.191(0.011,0.882)	-0.028(-0.227,0.192)	NA	NA
gender	91.31	93	154.81	0.185(0.03,0.379)	0.2(0.01,0.939)	0.06(-0.117,0.263)	NA	NA
baseline response	88.57	93	147.16	0.18(0.02,0.37)	0.17(0.01,0.8)	0.13(-0.04,0.3)	-3.1(-3.41,-2.8)	0.96(0.76,1.23)
Non-vertebral								
age	74.62	86	130.01	0.08(0.003,0.244)	0.166(0.009,0.768)	0.014(-0.16,0.207)		
gender	74.75	86	129.92	0.077(0.004,0.236)	0.14(0.006,0.694)	0.062(-0.132,0.256)		
baseline response M2	73.44	86	119.99	0.1(0.01,0.28)	0.15(0.01,0.76)	0.05(-0.16,0.32)	-3.41(-3.61,-3.22)	0.53(0.39,0.73)
Hip								
age	39.83	47	72.83	0.12(0.007,0.434)	0.266(0.011,1.594)	-0.103(-0.782,0.538)	NA	NA
gender	39.55	47	72.39	0.135(0.006,0.47)	0.248(0.01,1.6)	-0.118(-1.048,0.845)	NA	NA
baseline response M2	39.14	47	67.24	0.13(0.01,0.47)	0.29(0.01,1.66)	0.08(-0.37,0.74)	-5.21(-5.62,-4.77)	0.77(0.48,1.29)
Wrist								
age	30	31	54.79	0.216(0.015,0.592)	0.446(0.012,1.885)	-0.638(-1.56,0.261)	NA	NA
baseline response M2	28.42	31	48.6	0.34(0.05,0.7)	0.45(0.02,1.82)	0.37(-1.56,2.58)		
Humerus								
age	23.92	26	46.12	0.179(0.008,0.619)	0.998(0.049,1.953)	0.273(-2.788,3.6)	NA	NA
gender	24.01	26	46.38	0.171(0.008,0.582)	0.988(0.052,1.951)	0.412(-1.351,3.199)	NA	NA
baseline response	22.17	26	38.53	0.18(0.01,0.59)	1(0.05,1.95)	-0.26(-1.36,3.04)	-5.15(-6.03,-3.73)	0.72(0.13,3.09)
Femoral neck BMD								

age	144.5	137	259.24	0.86(0.65,1.14)	0.76(0.25,2.28)	-0.01(-0.07,0.05)	NA	NA
gender	145.7	137	258.73	0.80(0.59,1.08)	0.77(0.28,2.34)	0.01(0,0.02)	NA	NA
baseline response	NA	137	NA	0.81(0.61,1.08)	0.67(0.24,1.65)	0.16(-0.32,0.81)	-0.31(-0.57,-0.04)	1.92(0.91,4.18)

D_{res}: Total residual deviance, DP: data points, DIC: deviance information criterion, SD: between study standard deviation, SDt: between bisphosphonate treatment standard deviation

Table 46: Meta-regression on baseline risk, comparison of alternative models, vertebral fractures

Model	absolute model fit			heterogeneity		covariate		baseline parameters	
	D_{res}	DP	DIC	SD (95%CI)	SDt (95%CI)	estimate (95% CI)	SD (95% CI)	covariate	SD covariate
A1	89.91	93	171.57	1.06(0.06,1.4)	0.31(0.01,1.47)	-1(-1.01,0.09)	NA	NA	NA
A2	**88.57**	**93**	**147.16**	**0.18(0.02,0.37)**	**0.17(0.01,0.8)**	**0.13(-0.04,0.3)**	**NA**	**-3.1(-3.41,-2.8)**	**0.96(0.76,1.23)**
B1	92.85	93	157.38	0.16(0.02,0.39)	0.2(0.01,1.11)	0.03(-0.16,0.22)	0.13(0.01,0.6)	NA	NA
B2	89.48	93	148.39	0.17(0.02,0.37)	0.18(0.01,0.94)	0.14(-0.03,0.33)	0.09(0.01,0.47)	-3.11(-3.41,-2.81)	0.96(0.77,1.24)

D_{res}: Total residual deviance, DP: data points, DIC: deviance information criterion, SD: between study standard deviation, SDt: between bisphosphonate treatment standard deviation

Appendix 10: Studies excluded at full text 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 and 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 in Health 2011;14 (7):A310. https://doi.org/http://dx.doi.org/10.1016/j.jval.2011.08.430	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 in Health 2015;18:A648. https://doi.org/https://dx.doi.org/10.1016/j.jval.2015.09.2329	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 Women's 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 modeling. Health Serv Res 2013;48:1508-25. https://doi.org/https://dx.doi.org/10.1111/1475-6773.12044	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. https://doi.org/https://dx.doi.org/10.1016/j.clinthera.2017.05.348	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. https://doi.org/https://dx.doi.org/10.1002/jbmr.3381	Not a relevant comparison - compares screening to 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. https://doi.org/http://dx.doi.org/10.1007/s00198-006-0257-0	Non UK

Appendix 11: 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 the 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 in 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 in individuals who have fractured with matched controls or population norms, in which case the estimates may be confounded by differences in other factors between cases and controls.

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 to 2018
- EMBASE: Ovid, 1974 to 2018

In line with the NICE reference case, the searches focussed specifically on studies which reported HRQoL estimates for health states which 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 Section 6.1.1) to give a total of 3,853 unique references and a combined sfit 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, 3

non-English papers and 2 commentaries). Leaving 81 studies reporting health utility in patients with an incident osteoporotic fracture. However, values measured during RCT's were excluded due to 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 HUI or SF-6D were excluded. A further study[346] which fulfilled these inclusion criteria was excluded as resulting EQ-5D utilities at specific time points following fracture were only presented graphically, rather than numerically, which mean accurate estimates of the utility values was impossible leaving four remaining studies. A QUORUM diagram representing this process is presented in Figure 15.

These four remaining studies[206-209] are (summarised in Table 47). All four provided HRQoL for hip fracture, three for wrist (distal forearm) fracture,[206, 208, 209] three for vertebral fracture,[206, 208, 209] and one for fracture of the proximal humerus (shoulder).[206] One study also reported HRQoL for fracture of the ankle and other fracture.[206] All four studies all were based on the ICUROS (the International Costs and Utilities Related to Osteoporotic fractures Study) two of the papers presented values for individual countries in the ICUROS cohort (Australia[206] and Estonia[207]) and two presented values for groups of ICUROS counties.[208, 209] One of these papers presents HRQoL utility values for patients in ten ICUROS countries (Austria, Australia, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain and the United Kingdom) who sustained a hip, vertebral and wrist fracture.[209] Utility was measured pre-fracture (recall), post-fracture (within two weeks of the fracture being sustained), four moths post fracture, twelve months post-fracture and eighteen months post-fracture. However, only data from patients who completed all instruments (not just the EQ-5D) at all time points is included. The second paper presents HRQoL utility values for patients in eleven ICUROS countries (Austria, Australia, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain and the United Kingdom) who sustained a hip, vertebral and wrist fracture.[208] Utility was measured pre-fracture (recall), post-fracture (within two weeks of the fracture being sustained), four moths post fracture, twelve months post-fracture and eighteen months post-fracture. However, in this analysis data was 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 was based on significantly more data (1,415 patients for hip fracture, 559 patients or vertebral fracture and 1,047 for wrist (wrist) fracture compared with 505 patients for hip fracture, 316 patients for vertebral fracture and 589 for distal forearm (wrist) fracture. Hence the latter of these two studies was chosen to provide HRQoL values for hip, vertebral and wrist fracture to the model.

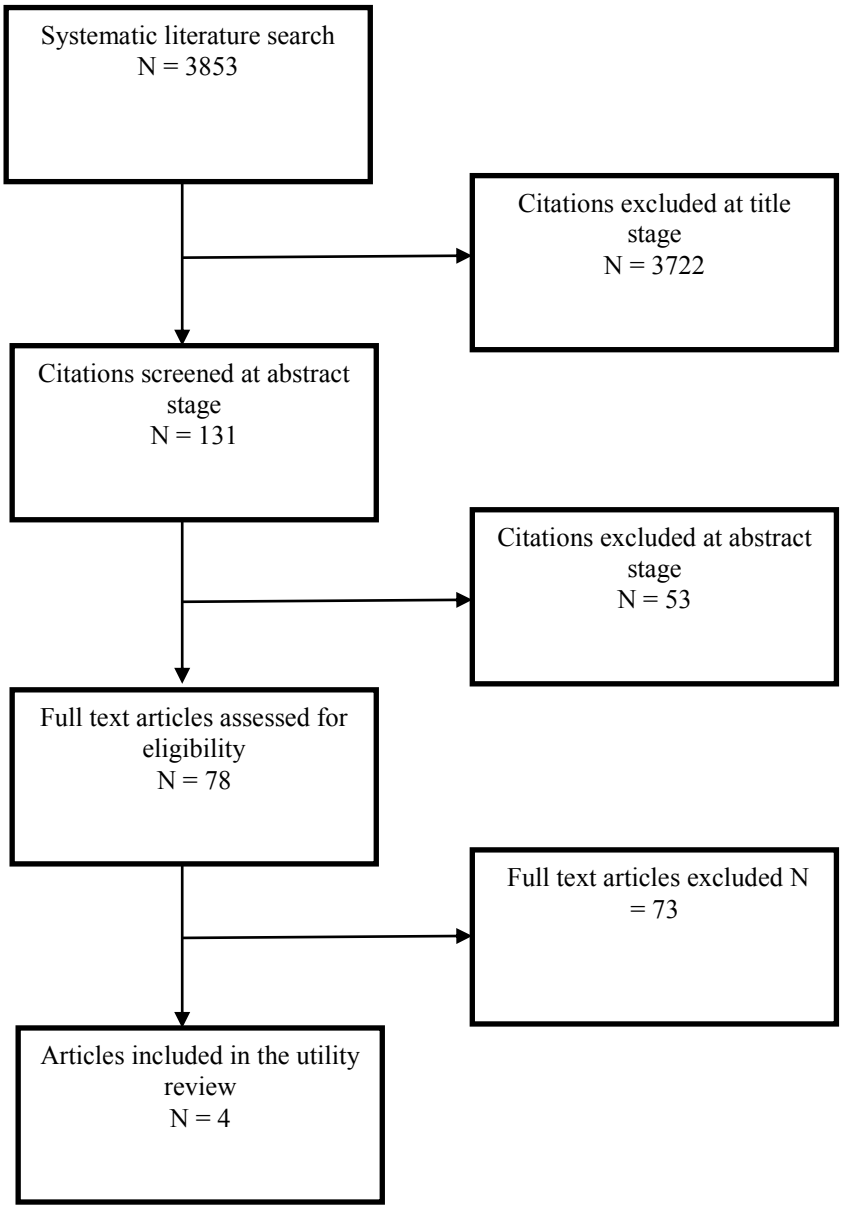

Figure 15: QUORUM representation of the literature review for HRQoL

Table 47: Summary of included papers reporting EQ-5D quality-of-life measures associated with osteoporotic fracture

Author & year of study publication	Country	Study Design	Cohort Description	Sample size at baseline and % of missing data	Valuation set used for EQ-5D	Reason for excluding
Svedbom *et al* 2018.[209]	Multi-centre (10 countries)	Prospective observational cohort study	ICUROS study including 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 health related quality of life 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)	Considered relevant
Svedbom *et al* 2018.[208]	Multi-centre (11 countries)	Prospective observational cohort study		Hip fracture N = 1,415 Vertebral fracture N = 559 Distal forearm fracture N = 1,047 (Patients lost to follow-up were excluded from analyses)	UK (TTO)	Considered relevant
Abimanyi-Ochom *et al* 2015.[206]	Australia	Prospective observational cohort study		All fractures N = 915 (41%)* Hip fracture N = 224 (49%)* Distal forearm fracture N = 308 (24%)* Vertebral fracture N = 92 (45%)* Humerus fracture N = 65 (48%)* Ankle fracture N = 89 (48%)* Other fracture N = 137 (53%)*	UK (TTO)	Considered relevant
Jurisson *et al* 2016.[207]	Estonia	Prospective observational		Hip fracture N = 205 (XX%)	UK (TTO)	Considered relevant

		cohort study				

Notes

* Percentage of baseline cohort lost by eighteen months

HRQoL 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[206] in which the UK value set was used to convert the dimension scores into a utility value. In this study sixty-five patients provided HRQoL vales at baseline (pre-fracture and immediately post-fracture) fifty-seven patients at four months, fifty-four patients at twelve months and thirty-four patients at eighteen months. Only 52% of baseline patients survived to eighteen months and only 63% of the patients who survived to twelve months survived to eighteen months.

Values from four papers [206-209] 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 health related quality of life taking 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[208, 209] ensure that data relating to patients excluded at some later point in the study are removed from summary HRQoL utility data at all time points the remaining two papers [206, 207] do not and use all available data at each time point.

The two multicentre papers reported broadly similar values at all time points except for those recorded at two weeks following fracture in which those reported in the paper with the larger dataset[208] were lower than those reported in the paper that excluded more patients for incomplete data[209] (hip fracture: -0.11, vertebral fracture: 0.17, wrist fracture: 0.41 compared with hip fracture: -0.02, vertebral fracture: 0.27, wrist fracture: 0.47) respectively. The study using Australian data but with a UK tariff[206] reported values that were again higher at two weeks following fracture (hip fracture: 0.11, vertebral fracture: 0.32, wrist fracture: 0.53) these higher values were also reflected at four months and twelve months though by a lessening degree until the increase had become negligible by eighteen months. The Estonian study, which again used the UK tariff,[207] also reported higher values at two weeks following fracture (0.07). This may raise concerns about the values used in the model, even though they are based on a significant larger sample size. However, the excluded paper[346] which presented utility values in a graphical rather than a numerical format suggests similar values to the international ICUROS dataset[208] for a UK population with the HRQoL utility value at two weeks post-fracture being approximately -0.15.

For hip, vertebral and wrist fractures the utility multipliers for zero to twelve months, twelve to twenty-four months and beyond twenty-four months are presented by Svedbom *et al*.[208] together with 95% confidence intervals enabling standard deviation to be calculated. However, we assume that improvements in utility in the period between twelve months post-fracture to twenty-four months post-fracture are subject to significant uncertainty and thus we apply the utility values presented for the period beyond twenty-four months post-fracture in the paper for any period beyond twelve 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 two weeks post fracture and remains at this value for the first two weeks by a gradual linear improvement to four months, twelve months and finally eighteen months. We assume that utility at eighteen months is maintained indefinitely. The utility multiplier for the first year post fracture was calculated by dividing the total utility accrued by twelve 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 thirteen and month twenty-four again by the pre-fracture utility value. These data are presented in Table 48.

Table 48: Utility values after hip fracture used in the HTA and in the new review

Description	Hip fracture		Vertebral fracture		Humerus fracture		Distal forearm fracture	
	TA464[140]	ICUROS[208]	TA464[140]	ICUROS[208]	TA464[140]	ICUROS[206]	TA464[140]	ICUROS[208]
Baseline no of patients	282	1,415	76	559	38	65	325	1,047
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
Four months	0.64	0.49	0.49	0.60	0.58	0.70	0.83	0.77
Twelve months	0.69	0.59	0.49	0.70	0.65	0.77	0.88	0.85
Eighteen 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
St. Deviation	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]
St. Deviation	Not reported	0.01	Not reported	0.01	Not reported	0.04	Not reported	0.01

[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

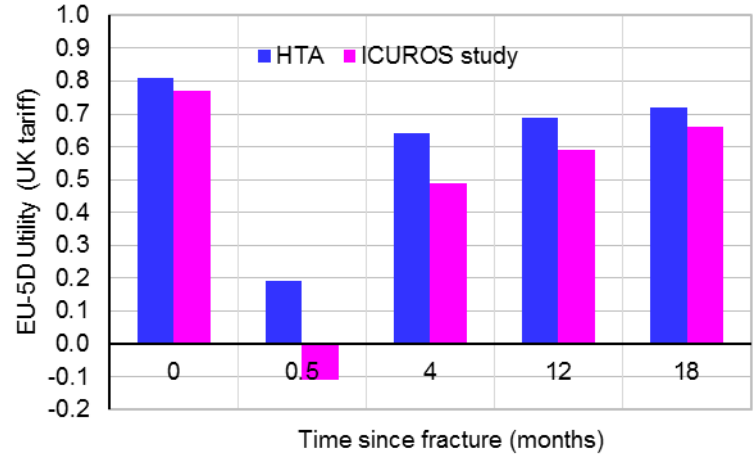

Figure 16: **Utility associated with vertebral fracture used in the HTA report and that chosen from the ICUROS study**

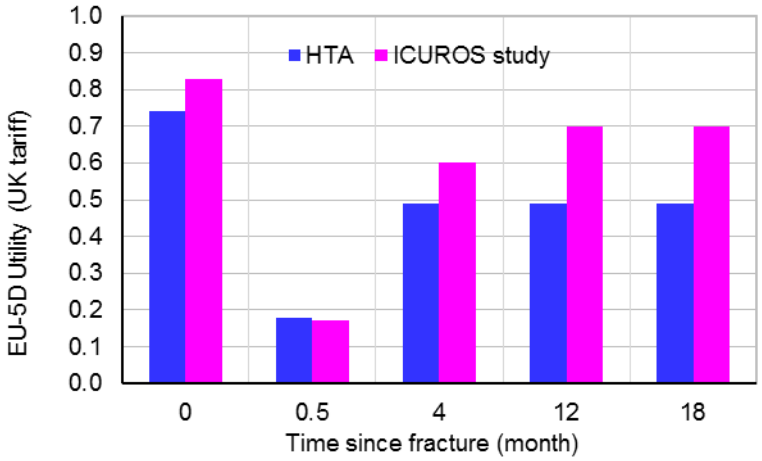

Figure 17: **Utility associated with hip fracture used in the HTA report and that chosen from the ICUROS study**

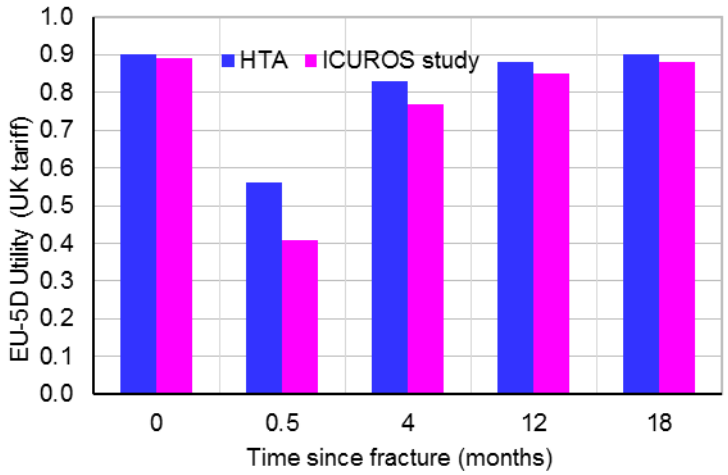

Figure 18: **Utility associated with distal forearm (wrist) fracture used in the HTA report and that chosen from the ICUROS study**

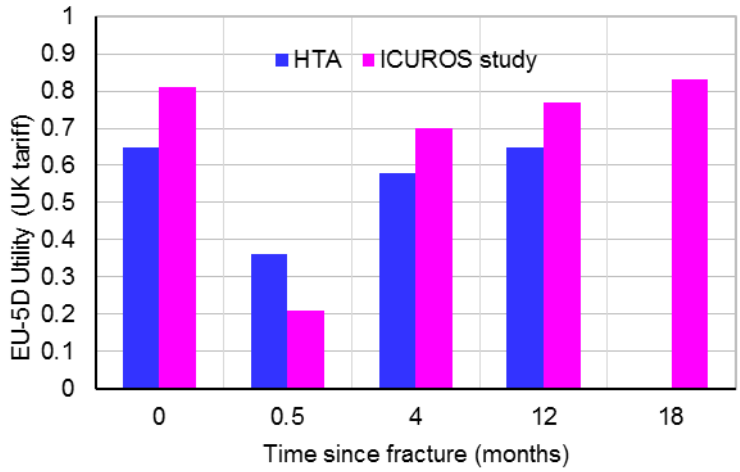

Figure 19: **Utility associated with humerus (shoulder) fracture used in the HTA report and that chosen from the ICUROS study**

Appendix 12: Model validation methods

The model is designed to operate in several different modes which facilitate 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 it behaves as intended. The locals window, within the VBA development environment, which allows the values of any object (i.e. 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 developed 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 range 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 against 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.

The box below 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 within the final analysis (no treatment, 9 interventions with 2 needed to capture the ROMO/ALEND 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 against the TA464 version of the model. New outputs were only incoporated once the model was verified to be equivalent for the additional intervention lines. Model inputs for interventions 6 to 10 and 11 to 15 were set equal to inputs for interventions 1 to 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 are 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 which says whether a treatment switch should occur and one which 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 adverse events 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 determins the offset period). Costs for intervention 6 and intervention 11 were set equal to 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 only included 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 step 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 adverse events (VTE, ONJ and cellulitis) and post-fracture costs and utilities.	Cells which had inputs updated from TA464 were highlighted in orange and were double checked against the values described in final report. Cells which were not marked as changed were double checked against the model used in TA464.

Appendix 13: 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

	Adverse clinical outcomes avoided per 100,000 patients treated when compared to no treatment							Total LYS 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 QFracture to estimate risk of fracture								
ALN	988	201	245	138	405	33	30	0.0026
RIS	1,047	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	1,787	333	467	254	733	53	54	0.0048
RLX	336	-11	164	95	88	20	-35	-0.0029
DEN	1,611	407	587	212	404	89	29	0.0023
TPTD	1,857	390	414	269	784	64	59	0.0052
ROMO/ALN	2,589	553	549	400	1,088	106	89	0.0062

Appendix 14: Basecase results from the probabilistic sensitivity analysis for QFracture

Table 51: Basecase results from 200,000 PSA samples for QFracture risk category 1 (average 10 year fracture risk of 0.5%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£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	£1,403	16.6048	£720	- 0.0001	-£9,181,178	-£721	-£722	Dominated
IBN (i.v.)	£1,541	16.6044	£858	- 0.0005	-£1,784,152	-£867	-£872	Dominated
DEN	£2,454	16.6059	£1,770	0.0010	£1,794,421	-£1,750	-£1,741	£986,470
ROMO/ALN	[redacted]	16.6071	[redacted]	0.0022	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£6,502	16.6055	£5,819	0.0007	£8,610,782	-£5,805	-£5,798	Dominated

*ICER versus next least costly non-dominated strategy

Table 52: Basecase results from 200,000 PSA samples for QFracture risk category 2 (average 10 year fracture risk of 0.7%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£1,152**	**15.3523**	**£0**	**-**	**£0**	**£0**	**£0**	
RIS	£1,243	15.3525	£91	0.0003	£319,027	-£85	-£82	Extendedly dominated
ALN	£1,243	15.3526	£91	0.0003	£290,229	-£85	-£82	£290,229
IBN (oral)	£1,246	15.3526	£94	0.0003	£301,165	-£88	-£85	Extendedly dominated
RLX	£1,297	15.3507	£145	- 0.0015	-£96,336	-£175	-£190	Dominated
ZOL	£1,864	15.3525	£713	0.0002	£2,984,339	-£708	-£705	Dominated
IBN (i.v.)	£2,009	15.3518	£857	- 0.0004	-£1,958,289	-£866	-£870	Dominated
DEN	£2,961	15.3539	£1,809	0.0017	£1,092,301	-£1,776	-£1,760	£1,279,494
ROMO/ALN	[redacted]	15.3539	[redacted]	0.0016	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£6,961	15.3532	£5,809	0.0010	£5,871,874	-£5,790	-£5,780	Dominated

*ICER versus next least costly non-dominated strategy

Table 53: Basecase results from 200,000 PSA samples for QFracture risk category 3 (average 10 year fracture risk of 1.0%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£2,260**	**14.0458**	**£0**	**-**	**£0**	**£0**	**£0**	
RIS	£2,349	14.0465	£89	0.0007	£129,889	-£75	-£68	Extendedly dominated
ALN	£2,349	14.0465	£89	0.0007	£125,805	-£75	-£67	Extendedly dominated
IBN (oral)	£2,352	14.0466	£92	0.0008	£119,370	-£77	-£69	£119,370
RLX	£2,378	14.0436	£118	- 0.0023	-£52,066	-£163	-£186	Dominated
ZOL	£2,968	14.0467	£707	0.0009	£808,583	-£690	-£681	£5,875,083
IBN (i.v.)	£3,113	14.0457	£853	- 0.0002	-£5,378,179	-£856	-£858	Dominated
DEN	£4,041	14.0468	£1,781	0.0010	£1,868,896	-£1,762	-£1,752	Extendedly dominated
ROMO/ALN	[redacted]	14.0475	[redacted]	0.0017	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£8,059	14.0474	£5,799	0.0016	£3,731,997	-£5,768	-£5,752	Dominated

*ICER versus next least costly non-dominated strategy

Table 54: Basecase results from 200,000 PSA samples for QFracture risk category 4 (average 10 year fracture risk of 1.4%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£2,722**	**12.6966**	**£0**	**-**	**£0**	**£0**	**£0**	
ALN	£2,804	12.6973	£82	0.0007	£126,025	-£69	-£63	Extendedly dominated
RIS	£2,804	12.6974	£83	0.0008	£100,618	-£66	-£58	£100,618
IBN (oral)	£2,813	12.6973	£91	0.0007	£137,375	-£78	-£71	Dominated
RLX	£2,847	12.6952	£126	- 0.0014	-£91,201	-£153	-£167	Dominated
ZOL	£3,421	12.6976	£699	0.0010	£723,860	-£680	-£670	Extendedly dominated
IBN (i.v.)	£3,572	12.6964	£850	- 0.0002	-£4,066,084	-£854	-£856	Dominated
DEN	£4,487	12.6994	£1,766	0.0028	£632,830	-£1,710	-£1,682	£855,463
ROMO/ALN	[redacted]	12.7002	[redacted]	0.0036	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£8,497	12.6985	£5,776	0.0019	£3,083,847	-£5,738	-£5,720	Dominated

*ICER versus next least costly non-dominated strategy

Table 55: Basecase results from 200,000 PSA samples for QFracture risk category 5 (average 10 year fracture risk of 2.0%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£2,936**	**11.6723**	**£0**	**-**	**£0**	**£0**	**£0**	
ALN	£3,016	11.6734	£80	0.0010	£77,059	-£59	-£49	£77,059
RIS	£3,019	11.6733	£82	0.0010	£81,404	-£62	-£52	Dominated
IBN (oral)	£3,021	11.6732	£84	0.0009	£93,736	-£66	-£57	Dominated
RLX	£3,067	11.6712	£130	- 0.0011	-£118,232	-£153	-£164	Dominated
ZOL	£3,625	11.6739	£688	0.0016	£442,296	-£657	-£642	Extendedly dominated
IBN (i.v.)	£3,784	11.6722	£848	- 0.0001	-£11,357,805	-£849	-£850	Dominated
DEN	£4,695	11.6757	£1,759	0.0034	£523,142	-£1,692	-£1,658	£721,645
ROMO/ALN	[redacted]	11.6763	[redacted]	0.0040	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£8,695	11.6748	£5,759	0.0024	£2,356,350	-£5,710	-£5,686	Dominated

*ICER versus next least costly non-dominated strategy

Table 56: Basecase results from 200,000 PSA samples for QFracture risk category 6 (average 10 year fracture risk of 2.7%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£3,064**	**10.6107**	**£0**	**-**	**£0**	**£0**	**£0**	
ALN	£3,142	10.6119	£78	0.0012	£65,281	-£54	-£42	Dominated
RIS	£3,143	10.6119	£79	0.0012	£64,979	-£55	-£42	£64,979
IBN (oral)	£3,147	10.6119	£83	0.0012	£68,805	-£59	-£47	Dominated
RLX	£3,164	10.6095	£100	- 0.0012	-£83,809	-£124	-£136	Dominated
ZOL	£3,753	10.6126	£689	0.0019	£353,780	-£650	-£631	Extendedly dominated
IBN (i.v.)	£3,908	10.6109	£843	0.0002	£4,373,315	-£840	-£838	Dominated
DEN	£4,774	10.6141	£1,710	0.0034	£502,655	-£1,642	-£1,608	£745,595
ROMO/ALN	[redacted]	10.6150	[redacted]	0.0043	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£8,798	10.6136	£5,733	0.0029	£1,964,475	-£5,675	-£5,646	Dominated

*ICER versus next least costly non-dominated strategy

Table 57: Basecase results from 200,000 PSA samples for QFracture risk category 7 (average 10 year fracture risk of 3.9%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£3,277**	**9.5502**	**£0**	**-**	**£0**	**£0**	**£0**	
ALN	£3,339	9.5522	£62	0.0020	£30,452	-£21	-£1	£30,452
RIS	£3,340	9.5521	£63	0.0020	£32,482	-£24	-£5	Dominated
IBN (oral)	£3,345	9.5521	£68	0.0020	£34,713	-£29	-£9	Dominated
RLX	£3,448	9.5476	£171	- 0.0026	-£65,412	-£223	-£249	Dominated
ZOL	£3,933	9.5533	£656	0.0031	£210,441	-£594	-£562	£552,756
IBN (i.v.)	£4,109	9.5509	£832	0.0007	£1,250,818	-£819	-£812	Dominated
DEN	£5,009	9.5539	£1,733	0.0037	£462,072	-£1,658	-£1,620	Extendedly dominated
ROMO/ALN	[redacted]	9.5562	[redacted]	0.0060	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£8,954	9.5544	£5,677	0.0042	£1,366,400	-£5,594	-£5,553	Dominated

*ICER versus next least costly non-dominated strategy

Table 58: Basecase results from 200,000 PSA samples for QFracture risk category 8 (average 10 year fracture risk of 5.5%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	£3,958	8.4539	£0	-	£0	£0	£0	
ALN	**£4,001**	**8.4568**	**£43**	**0.0029**	**£14,820**	**£15**	**£44**	**£14,820**
RIS	£4,007	8.4568	£48	0.0028	£17,119	£8	£36	Dominated
IBN (oral)	£4,021	8.4568	£63	0.0029	£21,840	-£5	£23	Extendedly dominated
RLX	£4,081	8.4531	£123	- 0.0008	-£146,142	-£139	-£148	Dominated
ZOL	£4,591	8.4589	£633	0.0050	£127,491	-£534	-£484	£273,143
IBN (i.v.)	£4,784	8.4554	£826	0.0015	£564,407	-£796	-£782	Dominated
DEN	£5,613	8.4605	£1,655	0.0066	£250,729	-£1,523	-£1,457	£625,518
ROMO/ALN	[redacted]	8.4637	[redacted]	0.0098	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£9,593	8.4597	£5,635	0.0058	£971,695	-£5,519	-£5,461	Dominated

*ICER versus next least costly non-dominated strategy

Table 59: Basecase results from 200,000 PSA samples for QFracture risk category 9 (average 10 year fracture risk of 8.4%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	£6,197	6.6409	£0	-	£0	£0	£0	
ALN	**£6,221**	**6.6451**	**£24**	**0.0042**	**£5,622**	**£60**	**£102**	**£5,622**
RIS	£6,227	6.6450	£30	0.0041	£7,235	£53	£94	Dominated
IBN (oral)	£6,234	6.6448	£37	0.0039	£9,443	£41	£80	Dominated
RLX	£6,308	6.6391	£110	- 0.0017	-£63,265	-£145	-£163	Dominated
ZOL	£6,794	6.6472	£597	0.0064	£93,903	-£470	-£406	£266,114
IBN (i.v.)	£6,998	6.6429	£801	0.0020	£398,475	-£761	-£741	Dominated
DEN	£7,730	6.6501	£1,533	0.0092	£166,441	-£1,349	-£1,257	£327,719
ROMO/ALN	[redacted]	6.6513	[redacted]	0.0105	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£11,717	6.6491	£5,520	0.0082	£671,001	-£5,355	-£5,273	Dominated

*ICER versus next least costly non-dominated strategy

Table 60: Basecase results from 200,000 PSA samples for QFracture risk category 10 (average 10 year fracture risk of 16.0%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
ALN	**£13,370**	**4.0837**	**-£51**	**0.0058**	**-£8,820**	**£167**	**£225**	
RIS	£13,384	4.0833	-£37	0.0054	-£6,896	£144	£197	Dominated
IBN (oral)	£13,393	4.0831	-£28	0.0051	-£5,417	£130	£181	Dominated
NT	£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	£1,347	0.0107	£126,392	-£1,134	-£1,028	£315,774
ROMO/ALN	[redacted]	4.0919	[redacted]	0.0140	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£18,604	4.0893	£5,183	0.0113	£457,894	-£4,957	-£4,844	Dominated

*ICER versus next least costly non-dominated strategy

Appendix 15: Basecase results from the probabilistic sensitivity analysis for FRAX

Table 61: Basecase results from 200,000 PSA samples for FRAX risk category 1 (average 10 year fracture risk of 3.1%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£4,241**	**13.6665**	**£0**	**-**	**£0**	**£0**	**£0**	
RIS	£4,315	13.6687	£73	0.0023	£32,429	-£28	-£5	Extendedly dominated
ALN	£4,315	13.6690	£73	0.0026	£28,541	-£22	£4	£28,541
IBN (oral)	£4,319	13.6687	£78	0.0023	£34,519	-£33	-£10	Dominated
RLX	£4,350	13.6641	£109	- 0.0023	-£47,105	-£156	-£179	Dominated
ZOL	£4,926	13.6705	£685	0.0040	£170,998	-£605	-£565	£427,431
IBN (i.v.)	£5,088	13.6671	£846	0.0007	£1,214,068	-£832	-£825	Dominated
DEN	£5,981	13.6708	£1,740	0.0044	£398,751	-£1,653	-£1,609	Extendedly dominated
ROMO/ALN	[redacted]	13.6726	[redacted]	0.0061	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£10,011	13.6711	£5,770	0.0046	£1,254,448	-£5,678	-£5,632	Dominated

*ICER versus next least costly non-dominated strategy

Table 62: Basecase results from 200,000 PSA samples for FRAX risk category 2 (average 10 year fracture risk of 4.3%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	**£4,487**	**13.6230**	**£0**	**-**	**£0**	**£0**	**£0**	
RLX	£4,524	13.6228	£37	- 0.0002	-£199,169	-£41	-£43	Dominated
RIS	£4,555	13.6255	£68	0.0025	£27,654	-£19	£6	Extendedly dominated
ALN	£4,556	13.6256	£69	0.0025	£27,325	-£19	£7	£27,325
IBN (oral)	£4,557	13.6256	£70	0.0026	£27,349	-£19	£7	£28,946
ZOL	£5,151	13.6276	£664	0.0046	£145,587	-£572	-£527	£297,575
IBN (i.v.)	£5,331	13.6240	£844	0.0010	£853,480	-£825	-£815	Dominated
DEN	£6,159	13.6297	£1,672	0.0067	£250,782	-£1,539	-£1,472	£478,086
ROMO/ALN	[redacted]	13.6320	[redacted]	0.0090	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£10,236	13.6282	£5,749	0.0052	£1,115,769	-£5,646	-£5,595	Dominated

*ICER versus next least costly non-dominated strategy

Table 63: Basecase results from 200,000 PSA samples for FRAX risk category 3 (average 10 year fracture risk of 5.0%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	£4,976	13.8999	£0	-	£0	£0	£0	
RIS	**£5,033**	**13.9035**	**£57**	**0.0037**	**£15,575**	**£16**	**£53**	**£15,575**
ALN	£5,037	13.9035	£61	0.0037	£16,808	£12	£48	Dominated
IBN (oral)	£5,039	13.9034	£63	0.0035	£17,728	£8	£43	Dominated
RLX	£5,045	13.8992	£69	- 0.0007	-£105,444	-£83	-£89	Dominated
ZOL	£5,635	13.9058	£659	0.0059	£110,846	-£540	-£481	£263,566
IBN (i.v.)	£5,810	13.9017	£834	0.0019	£443,563	-£797	-£778	Dominated
DEN	£6,636	13.9084	£1,660	0.0085	£195,106	-£1,489	-£1,404	£390,788
ROMO/ALN	[redacted]	13.9117	[redacted]	0.0118	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£10,708	13.9067	£5,732	0.0069	£832,835	-£5,594	-£5,526	Dominated

*ICER versus next least costly non-dominated strategy

Table 64: Basecase results from 200,000 PSA samples for FRAX risk category 4 (average 10 year fracture risk of 5.6%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	£5,465	14.2478	£0	-	£0	£0	£0	
ALN	**£5,521**	**14.2515**	**£56**	**0.0036**	**£15,524**	**£16**	**£53**	**£15,524**
IBN (oral)	£5,524	14.2514	£59	0.0036	£16,459	£13	£49	Dominated
RIS	£5,525	14.2513	£60	0.0035	£17,389	£9	£44	Dominated
RLX	£5,558	14.2458	£94	- 0.0020	-£47,071	-£133	-£153	Dominated
ZOL	£6,116	14.2546	£651	0.0068	£96,012	-£516	-£448	£189,147
IBN (i.v.)	£6,295	14.2497	£831	0.0019	£430,771	-£792	-£773	Dominated
DEN	£7,152	14.2555	£1,687	0.0076	£220,601	-£1,534	-£1,458	£1,197,064
ROMO/ALN	[redacted]	14.2569	[redacted]	0.0091	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£11,185	14.2555	£5,720	0.0077	£745,024	-£5,567	-£5,490	Dominated

*ICER versus next least costly non-dominated strategy

Table 65: Basecase results from 200,000 PSA samples for FRAX risk category 5 (average 10 year fracture risk of 6.2%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	£5,792	12.8154	£0	-	£0	£0	£0	
ALN	£5,845	12.8201	£54	0.0047	£11,362	£41	£88	Extendedly dominated
RIS	**£5,846**	**12.8202**	**£54**	**0.0048**	**£11,265**	**£42**	**£90**	**£11,265**
IBN (oral)	£5,849	12.8200	£57	0.0047	£12,209	£36	£83	Dominated
RLX	£5,873	12.8144	£81	- 0.0010	-£82,569	-£101	-£110	Dominated
ZOL	£6,435	12.8232	£644	0.0078	£82,355	-£487	-£409	£194,815
IBN (i.v.)	£6,623	12.8178	£831	0.0024	£342,182	-£783	-£758	Dominated
DEN	£7,435	12.8243	£1,643	0.0089	£184,386	-£1,465	-£1,375	Extendedly dominated
ROMO/ALN	[redacted]	12.8286	[redacted]	0.0132	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£11,479	12.8244	£5,687	0.0090	£632,511	-£5,507	-£5,417	Dominated

*ICER versus next least costly non-dominated strategy

Table 66: Basecase results from 200,000 PSA samples for FRAX risk category 6 (average 10 year fracture risk of 7.3%)

	Mean outcomes (discounted)		Incremental outcomes versus no treatment (discounted)		ICER vs. no treatment	Net benefit at £20K per QALY	Net benefit at £30K per QALY	Incremental analysis*
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	£5,868	11.0066	£0	-	£0	£0	£0	
RIS	£5,906	11.0111	£39	0.0044	£8,736	£50	£95	£8,736
ALN	£5,910	11.0114	£43	0.0048	£8,951	£53	£101	£11,817
IBN (oral)	£5,922	11.0110	£54	0.0044	£12,389	£33	£77	Dominated
RLX	£6,012	11.0049	£145	- 0.0018	-£82,686	-£180	-£197	Dominated
ZOL	£6,491	11.0142	£623	0.0076	£82,446	-£472	-£396	£209,233
IBN (i.v.)	£6,692	11.0089	£825	0.0023	£362,332	-£779	-£756	Dominated
DEN	£7,557	11.0154	£1,690	0.0087	£193,385	-£1,515	-£1,428	Extendedly dominated
ROMO/ALN	[redacted]	11.0208	[redacted]	0.0142	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£11,507	11.0157	£5,640	0.0091	£622,664	-£5,459	-£5,368	Dominated

*ICER versus next least costly non-dominated strategy

Table 67: Basecase results from 200,000 PSA samples for FRAX risk category 7 (average 10 year fracture risk of 8.8%)

	Mean outcomes (discounted)		Incremental outcomes versus no treatment (discounted)		ICER vs. no treatment	Net benefit at £20K per QALY	Net benefit at £30K per QALY	Incremental analysis*
Treatment strategy	Cost	QALYs	Cost	QALYs				
NT	£5,488	9.3617	£0	-	£0	£0	£0	
ALN	**£5,508**	**9.3671**	**£20**	**0.0054**	**£3,791**	**£87**	**£140**	**£3,791**
RIS	£5,511	9.3667	£23	0.0050	£4,572	£77	£128	Dominated
IBN (oral)	£5,518	9.3667	£30	0.0050	£6,035	£70	£120	Dominated
RLX	£5,584	9.3615	£96	- 0.0002	-£455,927	-£100	-£102	Dominated
ZOL	£6,070	9.3709	£582	0.0092	£63,432	-£399	-£307	£147,034
IBN (i.v.)	£6,301	9.3639	£813	0.0022	£367,423	-£769	-£747	Dominated
DEN	£7,082	9.3731	£1,594	0.0113	£140,582	-£1,367	-£1,254	Extendedly dominated
ROMO/ALN	[redacted]	9.3788	[redacted]	0.0170	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£11,069	9.3720	£5,581	0.0103	£542,248	-£5,375	-£5,272	Dominated

*ICER versus next least costly non-dominated strategy

Table 68: Basecase results from 200,000 PSA samples for FRAX risk category 8 (average 10 year fracture risk of 10.7%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
ALN	**£5,754**	**8.1143**	**-£11**	**0.0066**	**-£1,716**	**£142**	**£208**	
RIS	£5,764	8.1143	-£2	0.0065	-£297	£132	£198	Dominated
NT	£5,766	8.1077	£0	-	£0	£0	£0	Dominated
IBN (oral)	£5,770	8.1141	£5	0.0064	£734	£123	£187	Dominated
RLX	£5,820	8.1087	£54	0.0009	£57,050	-£35	-£26	Dominated
ZOL	£6,308	8.1184	£542	0.0106	£51,057	-£330	-£224	£136,054
IBN (i.v.)	£6,556	8.1114	£790	0.0037	£215,680	-£717	-£680	Dominated
DEN	£7,247	8.1233	£1,482	0.0156	£95,158	-£1,170	-£1,014	£189,738
ROMO/ALN	[redacted]	8.1266	[redacted]	0.0189	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£11,275	8.1203	£5,510	0.0125	£439,478	-£5,259	-£5,133	Dominated

*ICER versus next least costly non-dominated strategy

Table 69: Basecase results from 200,000 PSA samples for FRAX risk category 9 (average 10 year fracture risk of 14.9%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
ALN	**£8,078**	**7.0926**	**-£43**	**0.0082**	**-£5,233**	**£208**	**£290**	
RIS	£8,082	7.0923	-£39	0.0080	-£4,904	£200	£280	Dominated
IBN (oral)	£8,085	7.0922	-£36	0.0079	-£4,537	£194	£273	Dominated
NT	£8,121	7.0843	£0	-	£0	£0	£0	Dominated
RLX	£8,251	7.0837	£130	- 0.0006	-£206,484	-£142	-£148	Dominated
ZOL	£8,615	7.0974	£494	0.0131	£37,737	-£232	-£101	£110,826
IBN (i.v.)	£8,881	7.0890	£760	0.0047	£163,225	-£666	-£620	Dominated
DEN	£9,560	7.1004	£1,439	0.0161	£89,300	-£1,116	-£955	£312,269
ROMO/ALN	[redacted]	7.1056	[redacted]	0.0213	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£13,523	7.1000	£5,402	0.0157	£343,693	-£5,088	-£4,930	Dominated

*ICER versus next least costly non-dominated strategy

Table 70: Basecase results from 200,000 PSA samples for FRAX risk category 10 (average 10 year fracture risk of 25.1%)

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
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
NT	£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	£1,210	0.0206	£58,730	-£798	-£592	£197,979
ROMO/ALN	[redacted]	4.7303	[redacted]	0.0273	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£18,252	4.7238	£5,092	0.0208	£244,558	-£4,676	-£4,468	Dominated

*ICER versus next least costly non-dominated strategy

Appendix 16: Sensitivity analyses for economic evaluation

NB: These sensitivity analyses are based on the model using midpoint parameter inputs rather than the average outcomes across the PSA

Table 71: ICERs versus no treatment (NT) by risk deciles for QFracture and FRAX when using the basecase scanrio

Risk decile	**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	£2,190	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	£3,769	£1,096	Dominates	Dominates	Dominates	£1,350
RIS	£25,690	£22,982	£15,820	£17,515	£10,337	£3,911	£1,349	Dominates	Dominates	Dominates	£1,814
IBN (oral)	£25,107	£23,022	£15,393	£16,536	£11,305	£3,733	£1,713	Dominates	Dominates	Dominates	£1,756
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 72: ICERs versus no treatment (NT) by risk deciles for QFracture and FRAX when assuming full persistence with treatment

Risk decile	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	£1,273	Dominates	£25,717
IBN (oral)	£249,462	£167,996	£116,962	£80,518	£62,242	£32,880	£21,962	£10,972	£1,310	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	£8,667	£7,096	£4,570	Dominates	Dominates	Dominates	Dominates	£629
RIS	£21,225	£13,435	£10,374	£9,194	£7,051	£4,739	Dominates	Dominates	Dominates	Dominates	£1,061
IBN (oral)	£21,651	£13,923	£10,577	£9,059	£7,570	£5,066	£26	Dominates	Dominates	Dominates	£1,060
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 73: ICERs versus no treatment (NT) by risk deciles for QFracture and FRAX when using the class-effect estimates for bisphosphonates

Risk decile	**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	£5,185	Dominates	£31,647
RIS	£799,955	£486,510	£172,280	£106,937	£85,656	£59,255	£27,980	£12,480	£5,185	Dominates	£31,647
IBN (oral)	£826,668	£502,375	£178,069	£110,735	£88,733	£61,464	£29,355	£13,378	£5,907	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	£4,553	£1,530	Dominates	Dominates	Dominates	£2,591
RIS	£27,834	£19,286	£16,881	£14,023	£10,907	£4,553	£1,530	Dominates	Dominates	Dominates	£2,591
IBN (oral)	£28,967	£20,169	£17,695	£14,715	£11,600	£5,160	£2,044	Dominates	Dominates	Dominates	£3,131
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 74: Scenario results for high risk patient with FRAX risk of 30% (based on 500,000 PSA samples with fixed patient characteristics)

	Mean outcomes (discounted)		Incremental outcomes versus no treatment (discounted)		ICER vs. no treatment	Net benefit at £20K per QALY	Net benefit at £30K per QALY	Incremental analysis*
Treatment strategy	Cost	QALYs	Cost	QALYs				
ALN	£7,476	6.6254	-£235	0.0199	-£11,804	**£634**	£834	
RIS	£7,479	6.6248	-£232	0.0193	-£12,014	£618	£811	Dominated
IBN (oral)	£7,509	6.6242	-£202	0.0187	-£10,776	£576	£764	Dominated
NT	£7,711	6.6055	£0	-	£0	£0	£0	Dominated
RLX	£7,832	6.6067	£121	0.0012	£105,283	-£98	-£87	Dominated
ZOL	£8,001	6.6308	£290	0.0253	£11,427	£217	£471	Extendedly dominated
IBN (i.v.)	£8,329	6.6193	£618	0.0138	£44,785	-£342	-£204	Dominated
DEN	£8,491	6.6631	£780	0.0576	£13,544	£372	**£948**	£26,977
ROMO/ALN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£12,820	6.6418	£5,109	0.0363	£140,684	-£4,383	-£4,020	Dominated

*ICER versus 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)

	Mean outcomes (discounted)		Incremental outcomes versus no treatment (discounted)		ICER vs. no treatment	Net benefit at £20K per QALY	Net benefit at £30K per QALY	Incremental analysis*
Treatment strategy	Cost	QALYs	Cost	QALYs				
ALN	£2,782	6.8336	-£24	0.0071	-£3,393	£167	£238	
RIS	£2,782	6.8335	-£24	0.0069	-£3,463	£163	£233	Dominated
IBN (oral)	£2,794	6.8331	-£12	0.0065	-£1,819	£143	£208	Dominated
NT	£2,806	6.8265	£0	-	£0	£0	£0	Dominated
RLX	£2,947	6.8256	£141	- 0.0009	-£152,373	-£159	-£169	Dominated
ZOL	£3,387	6.8352	£581	0.0087	£66,928	-£407	-£321	Extendedly dominated
IBN (i.v.)	£3,577	6.8307	£771	0.0042	£183,707	-£687	-£645	Dominated
DEN	£4,205	6.8478	£1,399	0.0212	£65,851	-£974	-£761	£100,788
ROMO/ALN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPTD	£8,315	6.8398	£5,509	0.0133	£414,209	-£5,243	-£5,110	Dominated

*ICER versus next least costly non-dominated strategy

Table 76: ICERs versus no treatment (NT) by risk deciles for QFracture and FRAX when making alternative assumptions for the offset period†

Risk decile	**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	£9,373	Dominating	£37,101
RIS	£833,648	£378,035	£155,152	£176,091	£87,929	£98,283	£33,908	£19,143	£9,239	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	£6,445	£1,671	Dominating	Dominating	£5,789
RIS	£41,868	£30,603	£20,138	£17,014	£15,644	£11,783	£7,082	£2,179	Dominating	Dominating	£6,585
IBN (oral)	£43,872	£29,515	£21,422	£17,188	£15,311	£10,602	£7,219	£2,062	Dominating	Dominating	£6,353
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
† Assuming offset period equal to treatment time for ZOL, RLX, DEN and assuming offset period equal to 1 year for ALN, RIS, IBN (oral), IBN (i.v.), TPTD											