NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Theramex:
   a. Company Submission
   b. Company updated NMA
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification stage 1: questions and company responses
   b. Clarification stage 2: questions and company responses (section A)
   c. Clarification stage 2: questions and company responses (section B)

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Royal Osteoporosis Society
   b. British society of rheumatology

4. **Expert personal perspectives** from:
   a. Eugene McCloskey – clinical expert, nominated by Theramex
   b. Alison Smith – patient expert nominated by Royal Osteoporosis Society
   c. Phillipa Russell – patient expert nominated by Royal Osteoporosis Society

5. **External Assessment Report** prepared by ScHARR

6. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture [ID882]

Document B

Company evidence submission

September 2023

File name	Version	Contains confidential information	Date
ID882 abaloparatide_osteoporosis_Document B_[redacted]	1.0	Yes	21/09/2023

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Abbreviations

ACTIVE	Abaloparatide Comparator Trial In Vertebral Endpoints
ACTIVExtend	Abaloparatide Comparator Trial In Vertebral Endpoints Extension study
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
AMP	adenosine monophosphate
ANCOVA	analysis of covariance
ARR	absolute risk reduction
BMD	bone mineral density
BMI	body mass index
BNF	British National Formulary
BP	bisphosphonates
BTM	bone turnover marker
CEAC	cost-effectiveness acceptability curve
CG	clinical guideline
CKS	clinical knowledge summary
CHMP	Committee on Human Medicinal Products
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPI	consumer price index
CrI	credible interval
CSR	clinical study report
DALY	disability-adjusted life years
DIC	deviance information criterion
DSA	deterministic sensitivity analysis
DXA	dual-energy x-ray absorptiometry
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5 Dimensions
ERG	Evidence Review Group
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis
EU	European Union
FEM	fixed-effects model
FRAX	Fracture Risk Assessment Tool
GI	gastrointestinal
GP	general practitioner
GMR	geometric mean ratio
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICUROS	International Costs and Utilities Related to Osteoporotic Fractures Study
ID	identification
IOF	International Osteoporosis Foundation
IQR	interquartile range
ITT	intent-to-treat

IV	intravenous
K–M	Kaplan–Meier
LOCF	last observation carried forward
LY	life year
MACE	major adverse cardiovascular events
MAX	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MOF	major osteoporotic fracture
NA	not applicable
NHB	net health benefit
NHNV	non-hip-nonvertebral
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
NOGG	National Osteoporosis Guideline Group
NR	not reported
OD	once daily
OM	once monthly
OWSA	one-way sensitivity analysis
OY	once yearly
PAR	public assessment report
PAS	patient access scheme
PCS	physical component score
PICOS	population, intervention, comparison, outcomes and study design
PP	per-protocol
PPI	proton pump inhibitor
PSS	Personal Social Services
PRIMA	Preliminary Independent Model Advice
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PSA	probabilistic sensitivity analysis
PSSRU	personal Social Services Research Unit
QALY	quality-adjusted life year
QS	quality standard
QoL	quality of life
RANKL	receptor activator of nuclear factor-kappa-B ligand
RCT	randomised controlled trial
REM	random-effects model
RR	Relative risk
RRFRAX	relative risk estimated by FRAX
RRR	relative risk reduction
RWE	real-world evidence
SAE	serious adverse event
SC	subcutaneous
s-CTX	serum carboxy-terminal cross-linking telopeptide of type I collagen

SD	standard deviation
SE	standard error
SF-36	Short Form 36 Health Survey
SLR	systematic literature review
SmPC	Summary of Product Characteristics
s-P1NP	serum procollagen type I N-terminal pro-peptide
STA	single technology appraisal
TA	technology appraisal
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
UK	United Kingdom
US	United States
VB	Visual Basic
WHO	World Health Organization
WTP	willingness to pay

SUMMARY

- Osteoporosis is a highly prevalent, progressive skeletal disease characterised by low bone mass and deterioration of bone structure, leading to an increase in bone fragility and risk of fracture; it is most common in postmenopausal women
- Other fixed risk factors for osteoporosis include family history, certain medications (e.g., corticosteroids and protein pump inhibitors) and the presence of other diseases (e.g., rheumatoid arthritis and diabetes)
- Using the World Health Organization (WHO) classification, osteoporosis is diagnosed in individuals that have a BMD that is 2.5 SDs or more below the mean BMD of a young adult reference population (T-score of ≤–2.5).11 Individuals with a T-score ≤–2.5 with existing fracture are diagnosed with severe osteoporosis
- Fractures are associated with an increased risk of mortality, particularly hip and vertebral fractures, with mortality risk highest in the first year following fracture
- In the first year after a hip fracture there is a 10–fold increased mortality risk with overall mortality reported as approximately 20%
- In England and Wales, more than two million women have osteoporosis and approximately 180,000 fractures occur each year as a result of the disease
- Vertebral fractures are the most common type of osteoporotic fracture, with more than one in ten women over the age of 50 experiencing a fracture
- Nonvertebral fractures (e.g., hip, wrist and forearm) account for up to 50% of all fractures, with hip fractures causing the most morbidity
- A prior fracture is associated with an increased risk of a future fracture, with the highest risk within 2 years of the first fracture
- The disability, chronic pain, loss of independence, and morbidity of osteoporosis and related fractures negatively impact the daily lives of postmenopausal women with osteoporosis and substantially reduce health-related quality of life (HRQoL)
- Osteoporosis imposes a substantial financial burden on healthcare systems, primarily driven by fractures
- The goal of therapy for postmenopausal women with osteoporosis is to reduce the risk of fracture and improve bone strength
- Pharmacologic treatments include antiresorptive agents (that inhibit bone resorption with secondary effects on bone formation) and anabolic agents (that stimulate bone formation, with variable effects on bone resorption)
- Antiresorptive agents (oral and intravenous [IV] bisphosphonates, and the non-bisphosphonates, denosumab and raloxifene) are recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of osteoporosis in postmenopausal women at high risk of fracture
- There are only two anabolic agents available for the treatment of osteoporosis in postmenopausal women at very high risk of fracture (teriparatide and romosozumab)
- Teriparatide is a recombinant fragment of human parathyroid hormone (PTH) (1-34) (20 µg subcutaneous [SC] injection once daily) and romosozumab a humanised monoclonal antibody (210 mg [administered as two SC injections of 105 mg each] once monthly)
- Anabolic therapy is recommended for a limited time only

- After treatment cessation patients transition to a sequential therapy typically involving an antiresorptive agent (e.g., an oral bisphosphonate) to maintain the bone mineral density (BMD) gains achieved with teriparatide and romosozumab
- The United Kingdom (UK) clinical guideline for the prevention and treatment of osteoporosis published by the National Osteoporosis Guideline Group (NOGG), recommends that teriparatide and romosozumab should be considered as first-line treatment options in postmenopausal women at very high risk of fracture, particularly in those with vertebral fractures
- NICE recommends romosozumab regardless of previous treatment as an option for people at very high risk of fracture (consistent with UK guidelines), however NICE restricts teriparatide use to the treatment of osteoporosis in postmenopausal women at very high risk of fracture who are intolerant/contraindicated to, or who have had an unsatisfactory response to bisphosphonates
- It is estimated that [redacted] of patients with postmenopausal osteoporosis in the UK are treated with anabolic agents; most patients who receive an anabolic are treated with teriparatide ([redacted] of those within the anabolic drug class; [redacted] of all patients with postmenopausal osteoporosis)
- Teriparatide improves BMD in the spine, it can lead to mild hypercalcaemia mainly due to an increase in bone resorption, limiting the BMD gains particularly at cortical sites such as the hip. The clinical effect of teriparatide on spine BMD is more evident in the second year of treatment.
- Although teriparatide can be self-administered it requires storage in a refrigerator (2°C – 8°C). Incorrect storage by patients may destroy the medicine, possibly leading to nonadherence to treatment and wastage incurring financial loss to the National Health Service (NHS)
- Romosozumab improves BMD in both the spine and hip within six months of treatment and does not require storage in a refrigerator after first use, which may improve adherence to treatment and reduce wastage
- Romosozumab is contraindicated in patients with a history of myocardial infarction or stroke. Osteoporosis and cardiovascular disease have similar risk factors; evidence suggests that people with osteoporosis are at an increased risk of coronary artery disease and stroke, which emphasises the need for alternative treatments
- There remains a high unmet need for further anabolic treatment options for postmenopausal women with osteoporosis at very high risk of fracture that:
    - Reduce both vertebral and nonvertebral fractures
    - Are safe and well-tolerated
    - Do not require refrigeration and are easy to administer by the patient
- Abaloparatide, an anabolic agent (80 µg SC injection once daily), is a 34-amino acid peptide that shares 41% homology to parathyroid hormone-related peptide [PTHrP(1-34)], and is a novel selector activator of the PTH1 receptor signalling pathway
- The mechanism of action of abaloparatide differs from teriparatide, there is a much smaller transient increase in bone resorption with abaloparatide compared to teriparatide, suggesting that abaloparatide has a wider anabolic window than teriparatide
- Refrigeration is not required for storage after first use which may increase adherence and reduce wastage

- In clinical practice abaloparatide will provide an alternative anabolic treatment option to teriparatide and romosozumab for the treatment of osteoporosis in postmenopausal women at very high risk of fracture

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Abaloparatide is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Within this licensed indication, the target population considered in this submission is postmenopausal women with osteoporosis at very high risk of fracture, in line with the pivotal Phase 3 abaloparatide study (Abaloparatide Comparator Trial In Vertebral Endpoints [ACTIVE]).[1] In the ACTIVE study postmenopausal women aged 49 to 86 years with osteoporosis were eligible if they had a BMD T-score ≤–2.5 and >–5.0 at the lumbar spine or femoral neck together with radiologic evidence of ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral within the past 5 years. Postmenopausal women >65 years with fracture criteria and a T-score of ≤–2.0 and >–5.0, or without fracture criteria and a T-score ≤–3.0 and >–5.0 were also eligible for study entry.

The target population is narrower than the licensed indication and is focused on the patient population for whom abaloparatide is expected to provide the most clinical benefit. In clinical practice current anabolic treatments (teriparatide and romosozumab) are reserved for patients at very high risk of fracture.

A summary of the decision problem is shown in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	• Postmenopausal women with osteoporosis at increased risk of fracture	• Postmenopausal women with osteoporosis at very high risk of fracture	The submission positions abaloparatide for use in a narrower population of the licensed indication who have the greatest unmet need, and for whom abaloparatide is expected to provide the most clinical benefit. This population is in line with the ACTIVE study and clinical practice, where current anabolic treatments (teriparatide and romosozumab) are reserved for patients at very high risk of fracture.
Intervention	• Abaloparatide	• Abaloparatide for 18 months, followed by alendronate	• Abaloparatide is licensed as an 18-month course of treatment • The SmPC for abaloparatide states that "following cessation of abaloparatide therapy, patients may be continued on other osteoporosis therapies such as bisphosphonates".[2]
Comparator(s)	• Bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium, zoledronic acid) • Non-bisphosphonates (denosumab, romosozumab, strontium ranelate, teriparatide, raloxifene) • No active treatment	• Teriparatide for 24 months followed by alendronate • Romosozumab for 12 months followed by alendronate • No active treatment	Theramex would like to clarify that bisphosphonates and denosumab (antiresorptive agents) are not appropriate comparators to abaloparatide. In practice abaloparatide would be used as part of a sequential therapy for women at very high risk of fracture. This sequential therapy includes an antiresorptive agent (after an anabolic agent) as opposed to displacing them. As such, the relevant comparators are the

			anabolic agents (teriparatide and romosozumab) and no active treatment, with the latter represented by the placebo arm of the ACTIVE study. Strontium ranelate and raloxifene are not considered as comparators. Strontium ranelate is no longer part of routine clinical practice in England and Wales. Raloxifene is indicated for the prevention and treatment of osteoporosis in postmenopausal women but is not specially directed to women at very high risk of fracture. No active treatment was not included in the model as the most relevant comparators for patients at very high risk of fracture in the UK are teriparatide and romosozumab.
Outcomes	• Osteoporotic fragility fracture • Bone mineral density • Mortality • Adverse effects of treatment • Health-related quality of life	• In line with the final scope	NA

Abbreviations: NA, not applicable; SmPC, Summary of Product Characteristics

B.1.2 Description of the technology being appraised

A description of abaloparatide is presented in Table 2. The Summary of Product Characteristics (SmPC) and the UK Public Assessment Report (PAR), are provided in Appendix C.

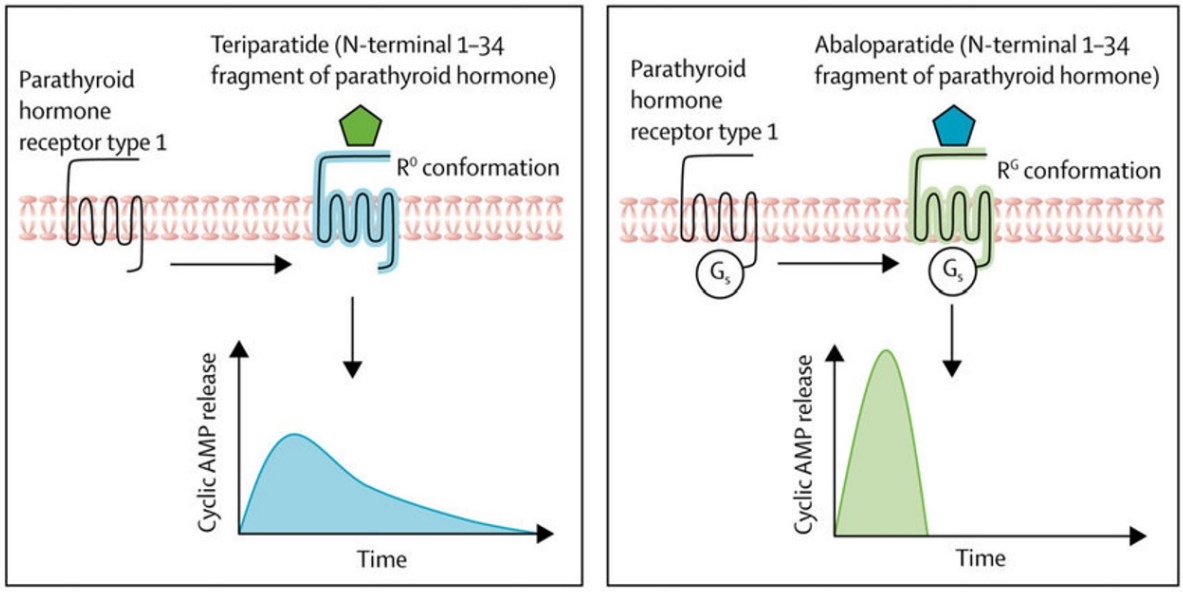
Table 2: Technology being evaluated

UK approved name and brand name	Abaloparatide (ELADYNOS®)
Mechanism of action	Abaloparatide is a 34-amino acid peptide that shares 41% homology to parathyroid hormone-related peptide [PTHrP(1-34)] and is an activator of the PTH1 receptor signalling pathway. As an anabolic agent abaloparatide stimulates new growth formation on trabecular and cortical bone surfaces by stimulation of osteoblastic activity. Abaloparatide causes transient and limited increases in bone resorption and increases bone density.[2] Stimulating bone formation before enhancing bone resorption, is the period when anabolic agents are maximally anabolic (referred to as the 'anabolic window'). The mechanism of action of abaloparatide differs to that of the PTHrP, teriparatide. Both agents act on the PTH1 receptor but in different ways. Abaloparatide is more selective for the R^G conformation of the PTH1 receptor, inducing a faster and more transient signalling response, than teriparatide which is more selective for the R^0 conformation of the PTH1 receptor (Figure 1).[3] The major difference is a much smaller transient increase in bone resorption with abaloparatide compared with teriparatide, suggesting there is a wider anabolic window with abaloparatide that results in a greater amount of bone formation than with teriparatide.[3]
Marketing authorisation/CE mark status	MHRA marketing authorisation for abaloparatide (PLGB56979/0001) was granted on 27th March 2023.
Indications and any restriction(s) as described in the SmPC	Abaloparatide is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.[2] Abaloparatide is contraindicated for patients with:[2] • Hypersensitivity to the active substance or any of the excipients listed in Section 6.1 of the SmPC (phenol, water for injections, sodium acetate trihydrate [for pH adjustment], and acetic acid [for pH adjustment])
Method of administration and dosage	**Dosage:**[2] • The recommended daily dose of abaloparatide is 80 µg once daily • Each prefilled pen contains 3 mg of abaloparatide in 1.5 mL of solution (corresponding to 2 mg per mL) • The maximum total duration of treatment with abaloparatide should be 18 months • Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate • Following cessation of abaloparatide therapy, patients may be continued on other osteoporosis therapies, such as bisphosphonates **Administration**:[2] • Abaloparatide is administered as a once daily subcutaneous injection

	• The first injection(s) administered by the patient or caregiver should be performed under the guidance of an appropriately qualified healthcare professional • Patients and/or caregivers should be trained in the subcutaneous administration of abaloparatide (see Section 6.6 of the SmPC) • A detailed instruction for use is included in each pack to instruct patients on the correct use of the injection pen • Abaloparatide should be injected in the lower abdomen. The site of the injection should be rotated every day • Injections should be administered at approximately the same time every day
Additional tests or investigations	NA
List price and the average cost of a course of treatment	List price of abaloparatide: £294.54 for one-prefilled pen with 30 doses in 1.5 mL solution Cost for a fixed-duration 18-month treatment (based on list price): £5,301.72
Patient access scheme (if applicable)	A PAS has been proposed for abaloparatide. The proposed abaloparatide with PAS price is [redacted] per prefilled pen with 30 doses in 1.5 mL solution, equivalent to a discount of [redacted] off the list price

Abbreviations: MHRA, Medicines and Healthcare Products Regulatory Agency; NA, not applicable; PAS, Patient Access Scheme; NICE, National Institute for Health and Care Excellence; PTHrP, parathyroid hormone-related peptide; SmPC, Summary of Product Characteristics

Figure 1: Mechanism of action of abaloparatide and teriparatide



Abbreviations: AMP, adenosine monophosphate
Source: Adapted from Khosla and Hofbauer 2017[3]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Description

Osteoporosis is a highly prevalent, progressive skeletal disease characterised by low bone mass and deterioration of bone structure, leading to an increase in bone fragility and risk of fracture.[4,5]

The disease results from an imbalance (a reduction in bone formation and an increase in bone resorption) in the naturally occurring bone remodelling cycle.[6] This imbalance increases with advancing age and decreasing levels of sex hormones and is most common in postmenopausal women. Declining oestrogen levels just before and during menopause lead to a rapid phase of bone loss that lasts 4 to 8 years.[7] This rapid phase of bone loss is followed by a slower continuous phase that persists throughout life.

Fragility fractures resulting from low trauma such as a fall from a standing height or less, or no identifiable trauma at all, are the clinical outcome of osteoporosis. Approximately 50% of women experience one or more fragility fractures in their lifetime.[4] While fractures occur most commonly in the vertebrae (spine), hip and wrists, they can also occur in the arm, pelvis, ribs, and other bones.[8] The high prevalence of fractures imposes a major burden on patients causing chronic pain, disability resulting in loss of independence, and an increased risk of morbidity and mortality, negatively impacting HRQoL.[9]

B.1.3.1.2 Risk factors

In addition to female sex, older age and menopause, several other modifiable and fixed risk factors, have been identified that increase the risk of developing osteoporosis (Table 3).[10]

Table 3: Risk factors for osteoporosis

Fixed risk factors	Modifiable risk factors
• Rheumatoid arthritis, endocrine disorders (e.g., diabetes, hyperparathyroidism), COPD and asthma, nutritional/GI problems, immobility, chronic kidney disease, HIV/AIDS, cancers, haematological disorders, psycho-physiological disorders, and mental illness (e.g., dementia, anorexia) • Family history of osteoporosis • Medications, including long-term use of glucocorticoids, certain steroid hormones, proton pump inhibitors, certain medications to treat diabetes, certain antidepressants, certain immunosuppressants, thyroid hormone treatment, aromatase inhibitors, certain chemotherapy agents, certain anticonvulsants, anti-epileptics and anti-coagulants	• Cigarette smoking • Excessive alcohol use (> 2 units of alcohol per day) • Low body mass index (BMI < 19 kg/m^2) • Poor nutrition • Eating disorders • Vitamin D deficiency • Sedentary lifestyle • Low dietary calcium intake

Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HIV, human immunodeficiency virus
Source: International Osteoporosis Foundation[10]

B.1.3.1.3 Diagnosis

Osteoporosis is often referred to as a “silent disease” as bone loss occurs without symptoms and may remain undetected until a fracture occurs.[11]

BMD measurements are used to diagnose osteoporosis commonly determined by dual-energy x-ray absorptiometry (DXA).[12] The WHO criteria for diagnosis of osteoporosis are based on the standard deviation (SD) difference between an individual’s BMD and that of a young adult reference population.[13] This value referred to as the “T-score” is defined as the number of SDs by which an individual’s BMD is above or below the mean BMD of a healthy young reference mean. Using the WHO classification, osteoporosis is diagnosed in individuals that have a BMD that is 2.5 SDs or more below the mean BMD of a young adult reference population (T-score of ≤–2.5).[11] Individuals with a T-score ≤–2.5 with existing fracture are diagnosed with severe osteoporosis.[11]

Assessing fracture risk is important to guide treatment. In England and Wales, the risk of fracture in individuals with osteoporosis is determined using online programmes such as the Fracture Risk Assessment Tool (FRAX®) or Q-Fracture.[8] These online programmes help to predict a person's risk of fracture between the ages of 40 and 90. The algorithms used provide an initial 10-year probability of hip fracture and of a major osteoporotic fracture (spine, hip, forearm or humerus). When BMD is included in a FRAX assessment, the risk of fracture is determined by the higher of the hip and major osteoporotic fracture risk assessments.[4] The assessment can be used to identify patients at low, intermediate, high, or very high risk of fracture.

B.1.3.1.4 Mortality

The increased risk of mortality following fractures, particularly hip and vertebral fractures, is well recognised, although it is unclear if this is due to fracture alone or pre-existing comorbidities.[14,15] Mortality risk is the highest in the first year following fracture and the mortality risk following hip and vertebral fractures is increased for up to 10 years.[14]

The risk of mortality related to a hip fracture is 2.8% for a 50-year-old woman during her remaining lifetime, equivalent to, and four times higher than her risk of death from breast cancer and endometrial cancer, respectively.[16] In the first year after a hip fracture there is a 10–fold increased mortality risk with overall mortality reported as approximately 20%.[5,16] Excess mortality associated with hip fractures is well documented, with older adults having a five- to eight-fold increased risk of mortality (from any cause) during the first 3 months after a hip fracture.[17,18] Patients who sustain a hip fracture are more likely to be elderly, institutionalised and frail, with multiple comorbidities.[18,19] These patients are less likely than younger people to be able to tolerate the stresses on the body associated with a hip fracture and its surgical fixation. Designing a system that caters for frailty, such as early admission to a dedicated geriatric unit, has been shown to reduce morbidity and mortality in elderly patients with hip fracture.[18] However, such facilities also require funding and resources and the use of medications aimed at preventing fractures may help to reduce the burden on these units.

Postoperative complications following a hip fracture can also result in excess mortality. A large study of 2,448 patients with hip fractures found 20% of those patients developed a postoperative complication, with chest infections (9%) and heart failure (5%) being the most common.[20] Developing heart failure following a hip fracture has a very poor prognosis, with most patients (92%) with heart failure dying within a year of surgery and 65% of patients

dying within 30 days of surgery. For chest infections, the 1-year mortality rate was 71% and the 30-day mortality rate was 43%.[20] Preventing the development of these complications should also be a priority in units looking to improve mortality from hip fractures. An eight-fold increased risk of mortality after suffering a vertebral fracture has been reported.[16] In a General Practice Research Database UK study the survival rate was 86.5% 1 year after vertebral fracture, decreasing to 56.5% at 5 years.[21] Only a small proportion of patients with vertebral fractures (5–8%) require admission to hospital in the acute phase.[22] These patients tend to be older (mean 81 years) and frail, with comorbidities. Increasing age and several comorbidities are associated with longer hospital stays and higher mortality, and complications can result from the use of pain relief and being immobilised due to bed rest.[22]

B.1.3.1.5 Epidemiology

Osteoporosis is a major non-communicable disease affecting one in three women over the age of 50 worldwide.[23] As a result of the aging population and lifestyle changes, the prevalence of osteoporosis and associated fractures has increased significantly.[12, 13] In England and Wales, more than two million women have osteoporosis and approximately 180,000 fractures occur each year as a result of the disease.[5] Of these, 70,000 are hip fractures, 25,000 are clinical vertebral fractures, and 41,000 are wrist fractures.[25] A 19.6% increase in fragility fractures is expected by 2030 if current practice remains unchanged.[4]

B.1.3.2 Burden of osteoporosis

Osteoporosis and associated fractures are an important public health concern imposing a significant burden on patients and the NHS.

B.1.3.2.1 Clinical burden

Fractures and their complications are the most important health consequence for patients causing chronic pain, functional decline, disability leading to loss of independence and an increased risk of morbidity and mortality.[4,8,9]

In the UK, fragility fractures are estimated to account for 579,722 disability-adjusted life years (DALYs) lost, most are caused by years living with disability.[4] This is equivalent to 24 DALYs per 1,000 people aged over 50 years, similar to the DALYs lost with dementia.[4]

A prior fracture is associated with an increased risk of a future fracture, with the highest risk within two years of the first fracture.[26–28] As such, patients with a recent osteoporotic fracture are at very high risk or imminent risk of future fracture.

B.1.3.2.1.1 Vertebral fractures

Vertebral fractures are the most common type of osteoporotic fracture, with more than one in 10 women over the age of 50 experiencing a fracture.[22,29] Vertebral fractures frequently occur with very little trauma such as bending or lifting, although they can also occur due to a fall.[29] These fractures cause chronic pain, loss of function, loss of height and kyphosis (curvature of the spine).[30] Most patients with vertebral fractures are managed in the community, but can require significant support including pain management, physiotherapy and frequent visits to a general practitioner.[22] Severe kyphosis may lead to lung function impairment, gastrointestinal (GI) problems such as digestion and difficulty in performing activities of daily living.[5] Subsequent fracture risk is increased with vertebral fractures more than any other type of fracture. Following one vertebral fracture there is a five–fold increased risk for a future vertebral fracture and a two– to three–fold increased risk for a nonvertebral

fracture.[31,32] Moreover, approximately 20% of women sustaining a vertebral fracture will experience a further vertebral fracture within the first year of the initial fracture.[32]

B.1.3.2.1.2 Nonvertebral fractures

Nonvertebral fractures are defined as fractures not occurring in the spine or skull such as the hip, wrist, and forearm.[33] Although hip fractures result in the most morbidity, non-hip nonvertebral fractures accounting for up to 50% of fractures also result in substantial morbidity.[33,34] For example, wrist fractures restrict daily activities and can completely disable certain patients, with 50% of patients reporting only poor or fair functioning six months after fracture.[35]

Hip fractures, often caused by a fall, require hospital admission for surgery in the majority of cases.[5] Approximately 10% to 20% of patients experience a recurrent hip fracture, with almost 25% occurring in the first year and 70% within 5 years of the initial fracture.[16] Hip fractures are associated with chronic pain, a reduction in mobility, and cause permanent disability in 50% of patients.[5,16] After a hip fracture, approximately 40% of patients that survive are unable to walk independently, and around 60% of patients still require assistance 1 year after fracture.[16] Rehabilitation is lengthy with 30% of patients never regaining their pre-fracture function.[5] The loss of independence following hip fracture, results in approximately 10% to 20% of patients moving to residential nursing homes.[16] Interviews with women aged 75 years and older, who were living independently, assessed their views on the limitations associated with hip fractures.[36] Of the surveyed women, 80% reported that they would rather die than be admitted to a nursing home following a hip fracture.[36]

B.1.3.2.2 Patient burden

The disability, chronic pain, loss of independence, and morbidity of osteoporosis and related fractures negatively impact the daily lives of postmenopausal women with osteoporosis. The patient burden of osteoporosis in UK has recently been highlighted in a research study (“Life with Osteoporosis 2021”) completed by, or on behalf of 3,266 people with osteoporosis between 7 June and 7 July 2021.[37]

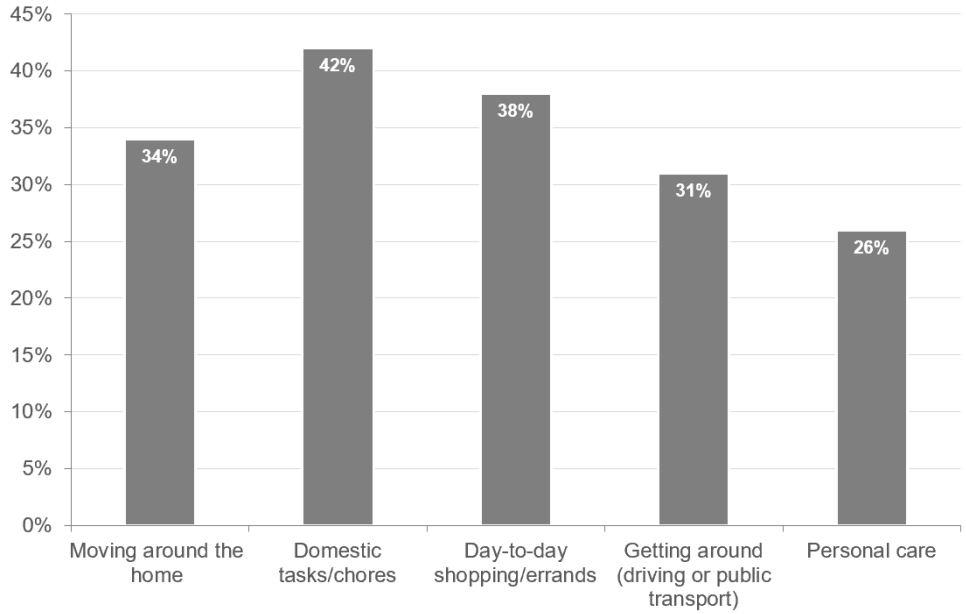
B.1.3.2.2.1 Pain

Almost two in three people from the study reported having osteoporosis-related pain, with over 25% reporting long-term pain. Moreover, 16% of people with long-term pain had experienced pain for over 10 years. Of those with long-term pain over one in three reported their pain as constant and over one in three reported their pain as severe or unbearable. Pain has a large effect on emotional well-being, particularly constant pain, causing anger, low mood, lack of confidence and fear of sustaining another fracture.[37]

B.1.3.2.2.2 Daily activities

Osteoporotic fractures affect daily activities such as walking, eating, dressing, bathing, shopping, housework, and travel. In the “Life with Osteoporosis” study people with osteoporosis reported difficulty with domestic tasks and chores, moving around the house (ability to bend, walk or pick up heavy objects), getting around (driving or public transport), and personal care (Figure 2).[37] Half of people with osteoporosis had reduced or stopped going on holiday and 39% had stopped visiting relatives, travelling or going on holiday due to pain or mobility problems.[37]

Figure 2: The impact of osteoporosis on daily tasks



Source: Adapted from "Life with Osteoporosis 2021"[37]

B.1.3.2.2.3 Emotional well-being

In addition to the physical effects of osteoporosis, people often find it difficult to maintain their emotional well-being. Approximately 50% of people in the "Life with Osteoporosis" study reported the impact of osteoporosis on emotional well-being with concerns about future health, body image and sexual intimacy. The inability to fulfil social roles or loss of independence also leads to feelings of loneliness, depression, and anxiety. In the study, people reported being fearful for the future, with most people worried about losing their independence (83%) and concerned about future falls and fractures (92%).[37] Over half of people that had experienced a fracture had lost height or experienced a change in their body shape, with many worrying that the change in body shape made them look like they were overweight or pregnant. Nearly half of people with osteoporosis had reduced or stopped their social activities and a third felt socially isolated.[37]

B.1.3.2.2.4 Work and finances

Osteoporosis impacts the ability to work causing financial pressures. In the "Life with Osteoporosis" study three in 10 people reported impacts on their working lives and 25% of those who were impacted had to leave their employment due to their osteoporosis. Approximately, 75% of people whose working lives had been affected felt financially burdened by the cost of managing their osteoporosis (e.g., paying for cleaners or gardeners or items to help with mobility).[37]

B.1.3.2.2.5 Patient quotes

Example quotes from people with osteoporosis from the "Life with Osteoporosis" study further highlight the negative impact of osteoporosis on daily living and emotional well-being. (Table 4).

Table 4: Example quotes on patient burden reported by 3,266 people with osteoporosis in the "Life with Osteoporosis" study

Impact	Example patient quotes
Activities of daily living	"I have limited ability to do housework, decorating, hedge-cutting etc. I now have to pay to get these done."
Physical	"Walking is a problem for me, I can't walk for great distances. If I ever need to leave the house, I take a taxi as I am unable to walk far without the aid of a trolley and walking stick which I have recently bought." "There's a lot I can't do now, but in my head I'm still quite young and fit - all of my friends are really fit and it's difficult to see them doing things which I can't." "I have had to adapt my levels and type of physical activity, to keep my spine as safe as I can."
Pain	"I have a jabbing pain in my back which I feel with every movement." "I take paracetamol and morphine to help me to get in and out of bed - that is when the pain is at its worst." "I did wonder at times "why am I bothering to live? Wouldn't I be better off out of all of this?" because there is no pause in my pain."
Independence	"I'm a very independent person, so the thought of losing my independence would take my world away. I do not have family to call on, I do everything myself."
Sleep	"I have a raised bed and have bought an electric recliner to help me to feel more comfortable when I sleep. I feel lucky if I'm able to get three hours of sleep at a time."
Relationships	"I am now afraid of sexual intimacy because I am afraid that I could break as my pelvis is too weak. This makes me lonely."
Social	"I have lost contact with the groups of friends I had through sporting activities. I get a bit down that I am not able to do as much physically for my family as I used to do."
Emotional	"I feel absolutely terrible. Very depressed. I can't get clothes to fit. I am embarrassed going out. It doesn't help that my husband calls me a hunchback. I feel worthless." "I am scared stiff of getting a hump and I desperately want someone to help me with preventing this. My osteoporosis has got a lot worse, I've always just coped with it and got on with it, but it's frightening me now." "I've always been kind of tall and fairly slim. I am the same weight but now I have a pot belly. It looks like I have a weight problem, but it isn't a weight problem and I really hate it."

	"When the doctor told me how bad it was, I felt lonely and frightened, there was no need to instil that fear. I felt that I had been delivered a death sentence."
Finances	"It's a depressing life and we are only 64 and 68. I'm constantly stressed and depressed about our lack of quality of life because we haven't enough money."

Source: "Life with Osteoporosis" study[37]

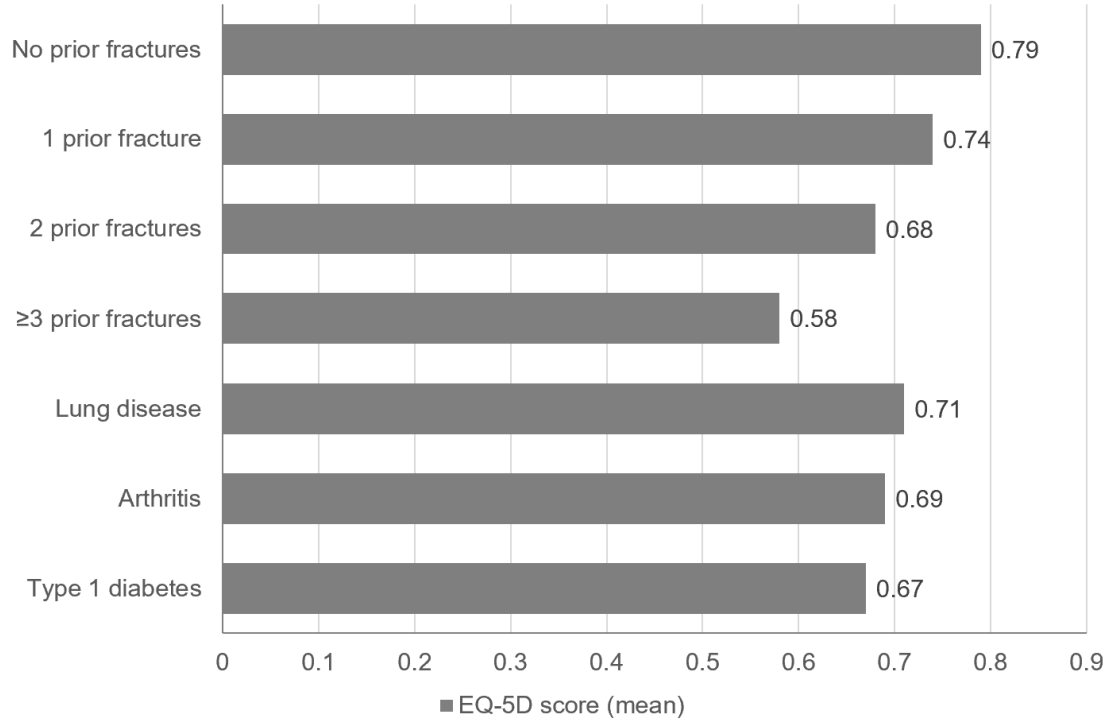
B.1.3.2.3 Health-related quality of life burden

Osteoporosis and fractures impose a substantial negative impact on the HRQoL of postmenopausal women with osteoporosis.[38,39]

The effects of postmenopausal osteoporosis and fracture on HRQoL were assessed in a recent (2022) meta-analysis (n=12 studies) involving postmenopausal women with and without osteoporosis (n=2,897).[38] Postmenopausal women with osteoporosis had significantly lower HRQoL than women without osteoporosis ($p<0.0001$).[38] After analysis of Short Form 36 Health Survey (SF-36) domains, postmenopausal women with osteoporosis had lower HRQoL than postmenopausal women without osteoporosis in the domains of general health ($p=0.0005$), pain ($p<0.0001$), physical functioning ($p=0.004$), emotional well-being ($p=0.04$), social functioning ($p=0.0006$), and mental health ($p<0.0001$).[38] In addition, postmenopausal women with osteoporotic fractures had significantly lower HRQoL than postmenopausal women without fractures ($p<0.0001$). After analysis of the SF-36 domains, postmenopausal women with osteoporotic fractures had lower HRQoL in all domains, in particular, role limitation due to physical health ($p=0.02$) and the physical component summary (PCS) score ($p=0.001$) compared with postmenopausal women without fractures.[38]

A large international observational study (n=57,141) also found that postmenopausal women with a history of fracture had lower mean EuroQoL-5 Dimensions (EQ-5D) scores compared with postmenopausal women without a fracture (Figure 3).[39] The greatest reductions in HRQoL were seen with spine, hip and upper leg fractures (EQ-5D scores, 0.62, 0.64 and 0.61, respectively).[39] Women experiencing osteoporotic fractures had a similar or worse HRQoL than women with chronic diseases such as arthritis (osteoarthritis or rheumatoid arthritis), type 1 diabetes or lung disease (asthma or emphysema) (Figure 3).[39]

Figure 3: Mean EQ-5D scores by the presence of fractures and other medical conditions (n=57,141)



Higher EQ-5D scores indicate better HRQoL
Abbreviations: EQ-5D, EuroQoL-5 Dimensions; HRQoL, health-related quality of life
Source: Adapted from Adachi et al, 2010[39]

B.1.3.2.4 Economic burden

Osteoporosis imposes a substantial financial burden on healthcare systems, primarily driven by fractures. In 2019 the cost of fragility fractures to the NHS was €5.5 billion including the cost of long-term disability (cost from fractures that occurred in previous years).[40] Pharmacologic costs (assessment and treatment) were €111 million.[40] Overall in the UK osteoporotic fracture costs accounted for approximately 2.4% of all healthcare spending in 2019.[40] Institutional care costs after fracture are estimated at more than £1.7 billion (2017).[4] A recent study (2023) also highlights the significant healthcare burden of hip fractures alone. Patients with a hip fracture were identified from 172 hospitals in England and Wales; across hospitals, patients spent a median of 21 days in hospital (in the first 365 days after fracture). The average inpatient cost was £14,642, and most of the inpatient cost was incurred in the first 120 days.[41] Further healthcare cost and resource use data are presented in Section B.3.5.2.

B.1.3.3 Current treatment pathway

The goal of therapy for postmenopausal women with osteoporosis is to reduce the risk of fracture and improve bone strength.[42] The choice of treatment is dependent on fracture risk, the presence of previous fractures, and response to or tolerance of other treatments.

Pharmacologic treatments for postmenopausal women with osteoporosis can be broadly classified into two classes, antiresorptive or anabolic, depending on their mechanism of action.[43] Antiresorptive agents (e.g. oral bisphosphonates and denosumab) primarily inhibit osteoclastic bone resorption with later secondary effects on bone formation. Anabolic agents

(e.g. teriparatide and abaloparatide) primarily stimulate osteoblastic bone formation with variable effects on bone resorption.[4] Romosozumab, a monoclonal antibody, has a dual action stimulating bone formation and reducing bone resorption (hereafter referred to as an anabolic agent).

B.1.3.3.1 Antiresorptive agents

Based on the National Institute for Health and Care Excellence (NICE) guidance oral bisphosphonates (antiresorptive agents) are current first-line pharmacologic treatment options for postmenopausal women at high risk of fracture in England and Wales (NICE technology appraisal [TA] 464 [updated in 2019]):[44]

- Alendronate (70 mg tablet once weekly [OW]), 70 mg/100 ml oral solution OW)
- Risedronate (5 mg tablet once daily [OD] or 35 mg tablet OW)
- Ibandronate (150 mg tablet once monthly [OM])

Alendronate and risedronate are used first-line in most patients. However, oral bisphosphonates are either not tolerated or contraindicated in some patients with osteoporosis, or patients experience an unsatisfactory response. In this situation, another antiresorptive treatment can be offered. These include intravenous [IV] bisphosphonates (zoledronate IV 5 mg/100 ml once yearly [OY] and IV ibandronate 3 mg/3 ml once every 3 months) or non-bisphosphonates (denosumab, a receptor activator of nuclear factor-kappa-B ligand [RANKL] inhibitor [60 mg subcutaneous [SC] injection once every 6 months] and raloxifene, a selective oestrogen modulator [60 mg tablet OD]); (NICE TA464; NICE TA204 [published in 2010]; NICE TA161 [updated in 2018]).[25,44,45]

B.1.3.3.2 Anabolic agents

Evidence suggests that anabolic agents for the treatment of osteoporosis are superior in terms of clinical efficacy and speed of action to antiresorptive agents.[46] Although these agents are restricted in terms of duration of treatment, the increased BMD achieved with anabolics can be maintained with sequential treatment with an antiresorptive, reducing fracture risk over the long-term.[46]

Currently, there are only two anabolic agents available for postmenopausal women at very high risk of fractures in England and Wales, romosozumab and teriparatide.[25,47–49] Teriparatide is a recombinant fragment of human parathyroid hormone (PTH) (1-34) (20 µg SC injection OD) and romosozumab is a humanised monoclonal antibody (210 mg [administered as two SC injections of 105 mg each] OM). Teriparatide and romosozumab treatments are limited to 24 months and 12 months duration, respectively. After treatment cessation patients transition to a sequential therapy typically involving an antiresorptive agent (e.g., an oral bisphosphonate).

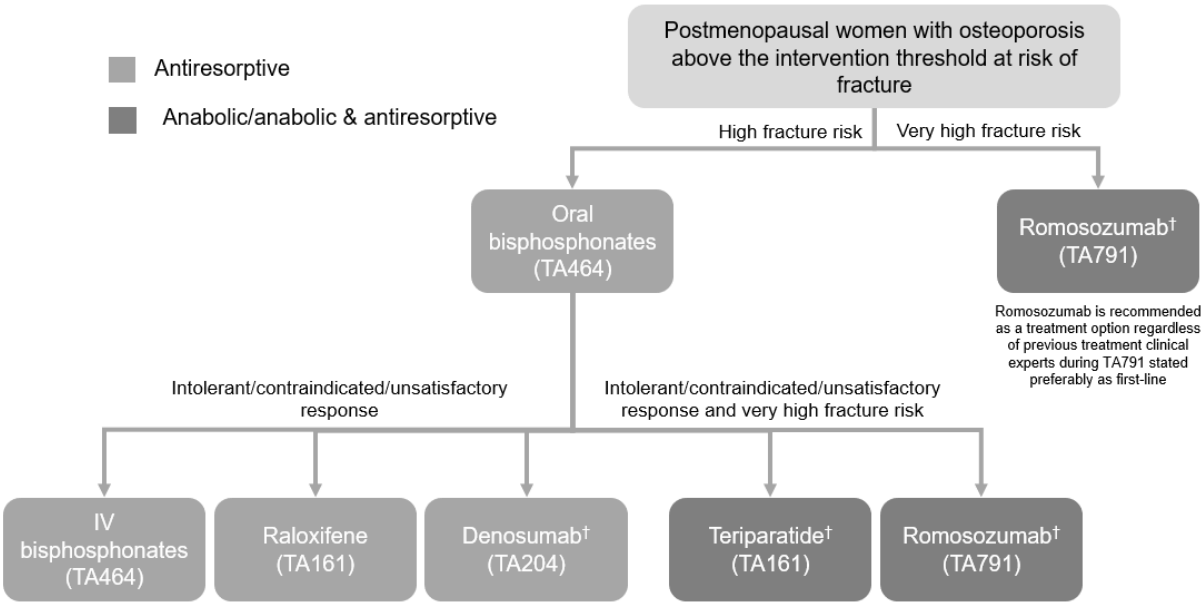
The UK clinical guideline for the prevention and treatment of osteoporosis published by the NOGG, recommends that teriparatide and romosozumab should be considered as first-line treatment options in postmenopausal women at very high risk of fracture, particularly in those with vertebral fractures.[1]

NICE recommends romosozumab regardless of previous treatment as a treatment option for people at very high risk of fracture (defined as experiencing a major osteoporotic (spine, hip, forearm, or upper arm) fracture within the last 24 months) who as such are at imminent risk

of another fracture (NICE TA791).[49] However, the NICE recommendation for teriparatide differs to the UK clinical guideline (NOGG) and recommends its use for secondary prevention of osteoporotic fragility fractures in postmenopausal women at very high risk of fracture who are intolerant/contraindicated to, or who have had an unsatisfactory response to bisphosphonates (NICE TA161, updated in 2018).[25] In the more recent single technology appraisal (STA) for romosozumab (published in 2022) clinical experts stated that giving teriparatide first-line before oral bisphosphonates may be more effective.[49]

The treatment pathway for postmenopausal women with osteoporosis based on current NICE guidance is outlined in Figure 4.

Figure 4: Current treatment pathway in England and Wales based on NICE guidance



† Patients stopping denosumab, teriparatide or romosozumab require a sequential therapy strategy typically involving an antiresorptive drug
Abbreviations: IV, intravenous; TA, technology appraisal

B.1.3.3.3 Market share of current therapies for the treatment of osteoporosis

Overall, the antiresorptive drug class holds the majority market share of osteoporosis treatments [redacted], with most patients treated with oral bisphosphonates [redacted] (Table 5).[50] It is estimated that [redacted] of patients with osteoporosis are treated with anabolic agents (Table 5).[50] Teriparatide holds the majority market share of osteoporosis treatments [redacted] within the anabolic drug class and as such is considered the most relevant comparator for abaloparatide.

Table 5: Market share of current osteoporosis treatments (2022)

Dimension	Antiresorptive drug class				Anabolic drug class		Overall total
	BP (Oral)	BP (IV)	Denosumab	Raloxifene	Teriparatide	Romosozumab	
No. of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
List price of current	-	-	-	-	£271.88 (once daily	£427.75 (two injections once	

anabolic treatment					for 24 months)	monthly for 12 months)	

[a]The number of osteoporosis patients taking raloxifene may be significantly lower than presented due to a proportion of the population taking it to reduce the risk of breast cancer (NICE clinical guideline [CG164])
Abbreviations: BP, bisphosphonates; IV, intravenous
Source: MIDAS data, 2022[50] and BNF 2023[51]

B.1.3.3.4 Current treatment guidelines

B.1.3.3.4.1 NICE

The most relevant NICE technology appraisals for the treatment of postmenopausal women with osteoporosis in England and Wales are provided in Table 6. Other relevant NICE guidelines, quality standards and clinical knowledge summaries for the treatment of postmenopausal women with osteoporosis are provided in Table 7.

Table 6: Relevant NICE technology appraisals

Appraisal ID (date)	Title	Recommendation
TA791 (Published: May 2022)[49]	Romosozumab for treating severe osteoporosis	Romosozumab is recommended as an option for treating severe osteoporosis in people after menopause who are at high risk of fracture, only if: • They have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture) and • The company provides romosozumab according to the commercial arrangement
TA464 (Published August 2017; Last updated July 2019)[44]	Bisphosphonates for treating osteoporosis	Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) and intravenous bisphosphonates (ibandronic acid and zoledronic acid) are recommended, within their marketing authorisations, as options for treating osteoporosis in adults: • Who are eligible for risk assessment as defined in NICE's guideline on osteoporosis and NICE's quality standard on osteoporosis **and** • Who have been assessed as being at higher risk of osteoporotic fragility fracture using the methods recommended in NICE's guideline on osteoporosis and NICE's quality standard on osteoporosis **and** • When bisphosphonate treatment is appropriate, taking into account their risk of fracture, their risk of adverse effects from bisphosphonates, and their clinical circumstances and preferences The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient, or their carers, about the advantages and disadvantages of the treatments available. If generic products are available, start treatment with the least expensive formulation, taking into account administration costs, the dose needed and the cost per dose. These recommendations are not intended to affect treatment with alendronic acid, ibandronic acid, risedronate sodium and zoledronic acid that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding

<table>
<tr><td></td><td></td><td>arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.</td></tr>
<tr><td>TA161 (Published: October 2008; Last updated February 2018)[25]</td><td>Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women</td><td>Raloxifene is recommended as an alternative treatment option for the secondary prevention of osteoporotic fractures in postmenopausal women who:
Are unable to comply with the administration of alendronate and risedronate, or are intolerant/contraindicated to alendronate and risedronate and
Have a combination of T-score, age and number of independent clinical risk fractures as indicated in the table below:
<table>
<tr><th rowspan="2">Age (years)</th><th colspan="3">Number of independent clinical risk factors for fracture</th></tr>
<tr><th>0</th><th>1</th><th>2</th></tr>
<tr><td>50–54</td><td>-[a]</td><td>−3.5</td><td>−3.5</td></tr>
<tr><td>55–59</td><td>−4.0</td><td>−3.5</td><td>−3.5</td></tr>
<tr><td>60–64</td><td>−4.0</td><td>−3.5</td><td>−3.5</td></tr>
<tr><td>65–69</td><td>−4.0</td><td>−3.5</td><td>−3.0</td></tr>
<tr><td>70–74</td><td>−3.0</td><td>−3.0</td><td>−2.5</td></tr>
<tr><td>75 or older</td><td>−3.0</td><td>−2.5</td><td>−2.5</td></tr>
</table>
[a]Treatment with raloxifene is not recommended
Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who:
Are unable to take alendronate and risedronate, or are intolerant/contraindicated to alendronate and risedronate or have had an unsatisfactory response to alendronate or risedronate and
Are 65 years or older and have a T-score of ≤–4.0, or a T-score of ≤–3.5 plus more than two fractures, or are aged 55–64 years and have a T-score of ≤–4 plus more than two fractures</td></tr>
<tr><td>TA160 (Published: October 2008; Last updated February 2018)[52]</td><td>Raloxifene for the primary prevention of osteoporotic fragility fractures in postmenopausal women</td><td>This guidance relates only to treatments for the primary prevention of fragility fractures in postmenopausal women who have osteoporosis. Osteoporosis is defined by a T-score of −2.5 SD or below on DXA scanning. However, the diagnosis may be assumed in women aged 75 years or older if the responsible clinician considers a DXA scan to be clinically inappropriate or unfeasible.
This guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment meet these criteria, calcium and/or vitamin D supplementation should be considered.
This guidance does not cover the following:
The treatment of women who have sustained a clinically apparent osteoporotic fragility fracture (for recommendations for the treatment of women with a prior osteoporotic fragility fracture, see the accompanying NICE technology appraisal, 'Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women').</td></tr>
</table>

<table>
<tr><td></td><td></td><td>

The use of raloxifene for the primary prevention of osteoporotic fragility fractures in women with normal BMD or osteopenia (that is, women with a T-score between −1 and −2.5 SD below peak BMD).
The use of this drug for the primary prevention of osteoporotic fragility fractures in women who are on long-term systemic corticosteroid treatment.

1.1 This recommendation has been replaced by the recommendations in the NICE technology appraisal guidance on bisphosphonates for treating osteoporosis.
1.2 This recommendation has been replaced by the recommendations in the NICE technology appraisal guidance on bisphosphonates for treating osteoporosis.
1.3 The recommendation for strontium ranelate has been withdrawn because strontium ranelate is no longer marketed in the UK.
1.4 Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.
1.5 For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of four or more units per day, and rheumatoid arthritis.
1.6 This recommendation has been replaced by the recommendations in the NICE technology appraisal guidance on bisphosphonates for treating osteoporosis.
1.7 For the purposes of this guidance, intolerance of alendronate or risedronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.
1.8 For the purposes of this guidance, primary prevention refers to opportunistic identification, during visits to a healthcare professional for any reason, of postmenopausal women who are at risk of osteoporotic fragility fractures and who could benefit from drug treatment. It does not imply a dedicated screening programme.
1.9 Women who are currently receiving treatment, but for whom treatment would not have been recommended according to sections 1.1 to 1.4, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
</td></tr>
<tr><td>TA204 (Published October 2010)[45]</td><td>Denosumab for the prevention of osteoporotic fractures in postmenopausal women</td><td>
Denosumab is recommended for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fracture who:

Are unable to comply with the special instructions for administering alendronate and risedronate, or are intolerant/contraindicated to alendronate and risedronate and
Have a combination of T-score, age, and number of independent clinical risk fractures as indicated in the table below:

<table>
<tr><th rowspan="2">Age (years)</th><th colspan="3">Number of independent clinical risk factors for fracture</th></tr>
<tr><th>0</th><th>1</th><th>2</th></tr>
<tr><td>65-69</td><td>-[a]</td><td>−4.5</td><td>−4.0</td></tr>
<tr><td>70-74</td><td>−4.5</td><td>−4.0</td><td>−3.5</td></tr>
<tr><td>75 or older</td><td>−4.0</td><td>−4.0</td><td>−3.0</td></tr>
</table>
</td></tr>
</table>

		[a]Treatment with denosumab is not recommended Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women with increased risk of fracture who: • Cannot comply with the administration of alendronate or risedronate, or are intolerant/contraindicated to these treatments

Abbreviations: BMD, bone mineral density; DXA, dual X-ray absorptiometry; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SD, standard deviation; TA, technology appraisal

Table 7: Other relevant NICE guidelines, quality standards and clinical knowledge summaries

NICE ID (date)	Title
CG146 (Published August 2012; Last updated February 2017)[8]	Osteoporosis: assessing the risk of fragility fracture
QS149 (Published: April 2017)[53]	Osteoporosis
CKS (Published: April 2023)[5]	Osteoporosis – prevention of fragility fractures

Abbreviations: CG, clinical guideline; CKS, clinical knowledge summary; ID, identification; NICE, National Institute for Health and Care Excellence; QS, quality standard

B.1.3.3.4.2 UK guideline (NOGG)

The UK clinical guideline for the prevention and treatment of osteoporosis published by the NOGG recommends the following:[4]

- Fracture risk assessment, patient suitability and preference, and cost-effectiveness should inform the choice of drug treatment
- In most people at risk of fragility fracture, antiresorptive therapy is the first-line option, oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate should be offered first as the most cost-effective interventions
- Alternative options include denosumab, ibandronate, hormone replacement therapy (HRT), raloxifene and strontium ranelate (although strontium is no longer on the market in the UK)
- Teriparatide or romosozumab should be considered as first-line treatment options in postmenopausal women at very high fracture risk, particularly in those with vertebral fractures
- Second-line treatment options include teriparatide in postmenopausal women and romosozumab in postmenopausal women, who are intolerant of bisphosphonate treatment, particularly in those with vertebral fractures
- Treatment with alendronate, zoledronate or denosumab should be initiated without delay following the approved duration of treatment with teriparatide or romosozumab (24 or 12 months respectively)

B.1.3.3.5 Unmet need

Despite the NICE recommendations for teriparatide and romosozumab, UK prescription data suggests that only [redacted] of patients are treated with an anabolic agent, with teriparatide holding the largest market share ([redacted] compared with romosozumab [redacted]).[50]

Teriparatide improves BMD in the spine, it can lead to mild hypercalcaemia mainly due to an increase in bone resorption, limiting the BMD gains particularly at cortical sites such as the hip.[55] The clinical effect of teriparatide on spine BMD is more evident in the second year of treatment.[55] Although teriparatide can be self-administered, it requires storage in a refrigerator (2°C – 8°C).[48] Incorrect storage by patients may destroy the medicine, likely leading to nonadherence to treatment (e.g. if patients are waiting for a replacement prescription) and wastage incurring financial loss to the NHS.

Romosozumab improves BMD in both the spine and hip within six months of treatment.[46] It does not require storage in a refrigerator after first use, which may improve adherence to treatment and reduce wastage. However, romosozumab is contraindicated in patients with a history of myocardial infarction or stroke.[47] Osteoporosis and cardiovascular disease have similar risk factors (including aging, smoking, excess alcohol consumption, sedentary lifestyle, diabetes and dyslipidaemia); evidence suggests that people with osteoporosis are at an increased risk of coronary artery disease and stroke, which emphasises the need for alternative treatments.[56]

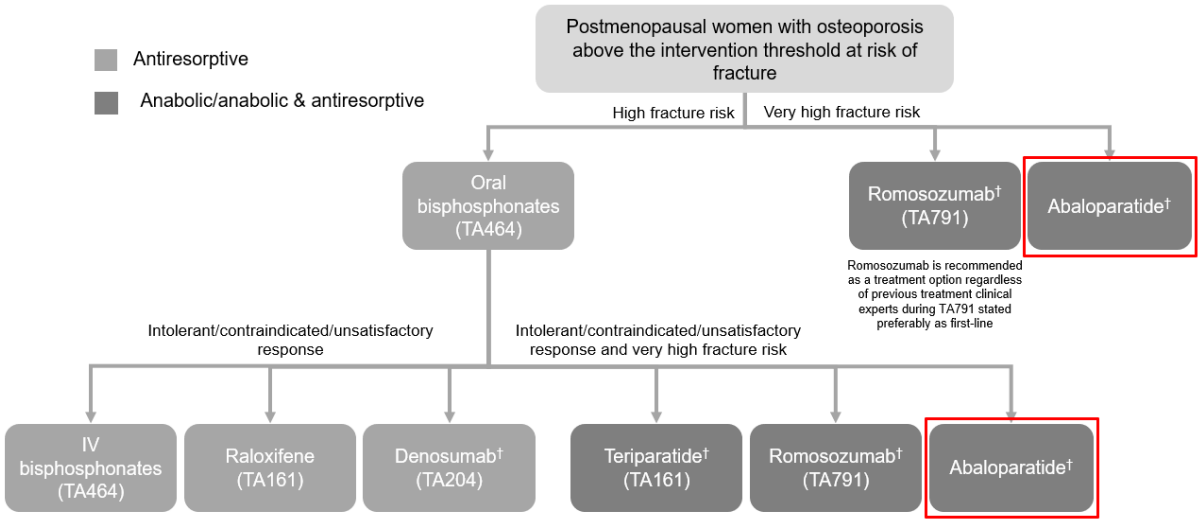
There remains a high unmet need for further anabolic treatment options for postmenopausal women with osteoporosis at very high risk of fracture that:

- Reduce both vertebral and nonvertebral fractures
- Has an acceptable safety and tolerability profile
- Do not require refrigeration minimising drug wastage
- Are easy to administer by the patient

B.1.3.3.6 The proposed place of abaloparatide in the current treatment pathway

Abaloparatide (80 µg SC injection OD) is a 34-amino acid peptide that shares 41% homology to parathyroid hormone-related peptide [PTHrP(1-34)], and is a novel selector activator of the PTH1 receptor signalling pathway.[55] Differing from the molecular mechanism of teriparatide, there is a much smaller transient increase in bone resorption with abaloparatide compared with teriparatide, suggesting that abaloparatide has a wider anabolic window than teriparatide.[2] Refrigeration is not required for the storage of abaloparatide after first use. In clinical practice abaloparatide will provide an alternative anabolic treatment option to teriparatide and romosozumab for the treatment of osteoporosis in postmenopausal women at very high risk of fracture. The proposed place of abaloparatide in the current treatment pathway is outlined in Figure 5.

Figure 5: Proposed place of abaloparatide in the current treatment pathway



† Patients stopping denosumab, teriparatide, romosozumab and abaloparatide require a sequential therapy strategy typically involving an antiresorptive drug
Abbreviations: IV, intravenous; TA, technology appraisal

B.1.4 Equality considerations

Although abaloparatide has a marketing authorisation for postmenopausal women, this should not prevent using abaloparatide for some people who have been through menopause but do not identify as a woman. In NICE TA791 for romosozumab, the committee concluded that romosozumab would be considered within its marketing authorisation, but the recommendation need not specify sex.[49]

B.2 Clinical effectiveness

SUMMARY

- Results from the large (N=2,070) Phase 3 randomised, placebo- and active-controlled trial (ACTIVE) and its long-term extension study (Abaloparatide Comparator Trial In Vertebral Endpoints Extension study [ACTIVExtend]; N=963) demonstrated consistent efficacy of abaloparatide (18 months of abaloparatide treatment followed by 24 months of alendronate) in reducing new vertebral and nonvertebral fractures vs placebo
- ACTIVE met its primary endpoint: abaloparatide treatment significantly reduced the risk of new vertebral fractures vs placebo ($p<0.001$) at 18 months
- Kaplan–Meier (K–M) estimated event rates for nonvertebral fractures were also numerically lower with abaloparatide treatment vs placebo in ACTIVE at 19 months (18 months of the observational period plus 1 month follow-up)
- Abaloparatide treatment resulted in a significant reduction in major osteoporotic fractures vs placebo in ACTIVE at 19 months ($p=0.004$)
- K–M event rates for clinical fractures were also numerically lower with abaloparatide treatment vs placebo in ACTIVE at 19 months, with a clear separation at any time-point during the overall 19 months
- The K–M curves suggested early reduction of nonvertebral, major osteoporotic and clinical fractures with abaloparatide treatment
- Reductions in new vertebral fractures, nonvertebral fractures, major osteoporotic fractures, and clinical fractures with abaloparatide treatment were maintained at Month 43 of ACTIVExtend (abaloparatide/alendronate vs placebo/alendronate)
- Abaloparatide treatment resulted in early and sustained increases in BMD at the total hip, femoral neck and lumbar spine in ACTIVE
    - Improvements in BMD were significantly greater with abaloparatide treatment vs placebo at the total hip, femoral neck and lumbar spine at 18 months (all $p<0.001$; [redacted]
    - BMD increases with abaloparatide treatment were maintained at Month 43 of ACTIVExtend (abaloparatide/alendronate vs placebo/alendronate) and were statistically significant at all time points (all $p<0.001$)
- The primary endpoint was not assessed for abaloparatide vs teriparatide (the active comparator in the ACTIVE trial) as a much larger sample size would be required to provide sufficient power (~22,000 per treatment group to provide 90% power)
    - Abaloparatide and teriparatide showed similar reductions in new vertebral fractures vs placebo
    - K–M event rates for major osteoporotic fractures were numerically lower for abaloparatide vs teriparatide with an early, consistent and stable separation at any time-point during the overall 19 months of the ACTIVE observational period
    - [redacted]
- ACTIVE data also suggested a faster onset of action for abaloparatide vs teriparatide

- [redacted]
- BMD increases for abaloparatide vs teriparatide were also greater at [redacted] and at the total hip and femoral neck at 18 months, with increases in lumbar spine BMD similar between abaloparatide and teriparatide at 18 months

- Increases in cortical BMD with abaloparatide vs teriparatide were consistent with changes in bone turnover markers in ACTIVE and reflect the differing mechanisms of action and enhanced net anabolic effect for abaloparatide (Figure 1)
- Real-world evidence (RWE) validates data generated from randomised control trials and gives valuable insight for physicians and regulators into heterogenous real-world populations
- In the large (N=23,232) RWE study powered to compare the effectiveness and cardiovascular (CV) safety of abaloparatide vs teriparatide, noninferiority was observed for nonvertebral fractures for abaloparatide vs teriparatide (p=0.13; primary endpoint) along with a significant reduction in the risk of hip fractures (22%, p=0.04; exploratory endpoint) with abaloparatide; increases in cortical BMD with abaloparatide may account for the differences in hip fracture reduction
- Abaloparatide demonstrated an acceptable safety profile in ACTIVE and there was no evidence that 18 months of prior treatment with abaloparatide altered the safety profile of sequential treatment with alendronate in ACTIVExtend
- There were no meaningful differences between ACTIVE treatment groups in the proportions of participants with treatment-emergent adverse events (TEAEs), serious AEs or AEs leading to death; no treatment-related deaths were reported
- The most frequently observed TEAEs in the ACTIVE abaloparatide group were hypercalciuria (13.4%) and dizziness (11.1%)
- RWE data showed similar cardiovascular (CV) safety for abaloparatide and teriparatide
- The risk of new events of the composite endpoints of major adverse CV events (MACE) nonfatal myocardial infarction, nonfatal stroke or CV death and MACE with heart failure were similar for both treatment cohorts
- The findings from the network meta-analysis (NMA) suggest that abaloparatide [redacted]

B.2.1 Identification and selection of relevant trials

A systematic literature review (SLR) was conducted to identify clinical evidence regarding the safety and efficacy of abaloparatide and other therapies (alendronic acid, ibandronic acid, risedronate sodium, zoledronic acid, denosumab, romosozumab, teriparatide, raloxifene, no active treatment, placebo, vitamin D and calcium supplementation) for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

Searches for the clinical SLR were conducted on 22 and 25 April 2023. A total of 2,723 records were retrieved in the pre-planned searches. Of these, 1,743 unique records were subjected to title–abstract screening after de-duplication. At full-text review, a total of 270 records were assessed for eligibility using the population, intervention, comparison,

outcomes and study design (PICOS) criteria. After exclusion of 210 records, a total of 60 clinical records were identified. Full details of the SLR methodology, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram and included and excluded studies of the SLR are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified one Phase 3 international, randomised, placebo- and active-controlled trial (ACTIVE)[1] and the long-term extension study of the ACTIVE study (ACTIVExtend)[58,59] (see Table 8 for details) that provide evidence of the efficacy and safety of abaloparatide for the treatment of osteoporosis in postmenopausal women at very high risk of fracture.

When the data for ACTIVE and ACTIVExtend were submitted to the European Medicines Agency (EMA) in 2015, concerns were raised regarding two of the study sites (Sites 131 and 132 from the Czech Republic) and the Committee on Human Medicinal Products (CHMP) therefore requested that the data were reanalysed excluding these two sites. The reanalysed datasets were then accepted by the EMA and data from these analyses (rather than the main analyses) are reported in the SmPC for both the EMA and the UK Medicines and Healthcare Products Regulatory Agency (MHRA).[2,60,61] The results for the reanalysed datasets for ACTIVE and ACTIVExtend are therefore presented in the submission, the results for the original datasets are available in the study publications.[1,58,59]

The reanalysed data (excluding Sites 131 and 132) for both ACTIVE and ACTIVExtend continued to meet the primary endpoint demonstrating that abaloparatide significantly reduced the risk of new vertebral fractures versus placebo and were generally consistent with the original analyses. Abaloparatide also reduced the risk of nonvertebral fractures although the effect versus placebo was not statistically significant in the reanalysed datasets. However, the EMA concluded that there appeared to be no scientific reason to presume efficacy only for vertebral but not nonvertebral fractures, regardless of statistical significance being demonstrated for vertebral (but not nonvertebral) fractures.[61]

The manufacturer also identified a large (N=23,232), RWE study (United States [US] administrative claims database study) for abaloparatide effectiveness and safety in postmenopausal women new to anabolic therapy over a 19-month period after treatment initiation (see Table 8 for details).[60] The aim of the study was to evaluate the real-world comparative effectiveness on nonvertebral fractures and to compare the cardiovascular (CV) safety of abaloparatide vs teriparatide in propensity score-matched cohorts (N=11,616 per cohort).[62]

Table 8: Clinical effectiveness evidence

Study	ACTIVE	ACTIVExtend	RWE study
Study design	Phase 3, randomised, placebo- and active-controlled, multicentre international study (NCT01343004)	Open-label extension study to evaluate the effects of 24 months of treatment with alendronate following 18 months of treatment with abaloparatide or placebo in participants who completed the ACTIVE trial (NCT01657162)	United States administrative claims database study (NCT04974723)

Study geography	International (10 countries)	International (10 countries)	United States
Population	Postmenopausal women aged 49–86 years with osteoporosis at risk of fracture	Participants who received abaloparatide or placebo in the ACTIVE trial and successfully completed the study (with no serious treatment-related adverse events)	Women aged ≥50 years with ≥1 prescription for abaloparatide or teriparatide and no prior anabolic therapy
Intervention	Abaloparatide subcutaneous 80 µg once daily	Oral alendronate (70 mg/week) in patients who received abaloparatide in the ACTIVE trial	NA, real-world use of abaloparatide
Comparator(s)	Placebo Active: Teriparatide subcutaneous 20 µg once daily	Oral alendronate (70 mg/week) in patients who received placebo in the ACTIVE trial	Real-world use of teriparatide
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	No	No
Rationale if study not used in model	NA	The pivotal trial (ACTIVE) provides evidence of the efficacy of abaloparatide vs teriparatide in postmenopausal women aged 49–86 years with osteoporosis at risk of fracture	Robust Phase 3 clinical trial data are available
Reported outcomes specified in the decision problem	• Osteoporotic fragility fracture • Bone mineral density • Adverse effects of treatment	• Osteoporotic fragility fracture • Bone mineral density • Adverse effects of treatment	• Osteoporotic fragility fracture
All other reported outcomes	• Change in bone turnover markers (s-P1NP and s-CTX)	• Change in bone turnover markers (s-P1NP and s-CTX)	Cardiovascular safety
Key publications/data sources	Reanalysed dataset: ACTIVE CSR addendum (data on file)[63]; EMA Assessment report: Eladynos[61]; UK SmPC[2] Original dataset: Miller et al., (2016)[1]	Reanalysed dataset: ACTIVExtend CSR addendum (data on file)[64]; EMA Assessment report: Eladynos[61]; UK SmPC[2] Original dataset: Bone et al., (2018)[59]	Cosman et al., (2022)[62]

Abbreviations: CSR, clinical study report; NA, not applicable; s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; RWE, real-world evidence; s-P1NP, serum procollagen type I N-terminal pro-peptide

The ACTIVExtend study was not used to populate the economic model because the pivotal trial (ACTIVE) provides evidence of the efficacy of abaloparatide vs teriparatide in postmenopausal women aged 49–86 years with osteoporosis at risk of fracture.

The RWE study was not used to populate the economic model but is included in sections B.2.3 to B.2.10.4. The results of this RWE study validate data generated from randomised control trials and gives valuable insight for physicians and regulators into heterogenous real-world populations. This study was not included in the economic model due to the availability of a robust Phase 3 trial.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Phase 3 trial design

B.2.3.1.1 ACTIVE

ACTIVE was a Phase 3, international, randomised, placebo- and active-controlled trial (NCT01343004; BA058-05-003; N=2,463 randomised patients) conducted across 28 centres in 10 countries[1] (Figure 6; Table 9). As outlined in Section B.2.2, the data presented in this submission are from the dataset presented in the SmPC, which includes 2,070 randomised patients from 26 centres in 10 countries.[2,63]

The trial investigated the efficacy and safety of abaloparatide in postmenopausal women with osteoporosis at very high risk of fracture.[1] Participants were healthy ambulatory postmenopausal women aged 49–86 years with osteoporosis who were at risk of fracture based on a T-score ≤-2.5 and >-5.0 at the lumbar spine or femoral neck and radiological evidence of ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years. Also eligible for enrolment were women aged >65 years with the above fracture criteria and T-score ≤-2.0 and >-5.0 or without fracture criteria and a T-score ≤-3.0 and >-5.0; and women aged >65 years who did not meet the fracture criteria whose T-score was ≤-3.0 and >-5.0.

Exclusion criteria were four mild or moderate vertebral fractures, any severe vertebral fractures, <2 evaluable lumbar vertebrae, unevaluable hip BMD measurement, evidence of metabolic bone disease or malabsorption or taking medications that would interfere with bone metabolism, use of bisphosphonate for >3 months in the past 5 years or denosumab within the past year, and history of osteosarcoma.[1]

Patients were randomised in a double-blind manner in a ratio of 1:1:1 to one of three treatment groups for 18 months: placebo (to match abaloparatide), abaloparatide (subcutaneous 80 µg once daily) or teriparatide (subcutaneous 20 µg once daily). The 18-month treatment duration is aligned with the maximum total duration of treatment with abaloparatide specified in the licensed indication.[2] Abaloparatide, and matching placebo were administered in a double-blind manner; teriparatide was given open-label as it is

required to be administered via its trademarked injection pen.[1] All patients took daily supplemental calcium and vitamin D.

The primary efficacy endpoint was the percentage of participants with one or more incidents of new morphometric vertebral fracture in the abaloparatide group versus the placebo group at 18 months.[1] Key secondary efficacy endpoints included incident nonvertebral fractures at 18 months and percentage change from baseline in BMD at the total hip, femoral neck and lumbar spine at 6, 12 and 18 months. Other efficacy endpoints included changes in serum markers of bone turnover (procollagen type I N-terminal pro-peptide [s-P1NP] and carboxy-terminal cross-linking telopeptide of type I collagen [s-CTX]); these were evaluated in a subset of patients at 3, 6, and 12 months. Prespecified exploratory endpoints (assessment of clinical fractures, incidence and time to event) included major osteoporotic fractures (fractures of the upper arm, wrist, hip or clinical spine) and clinical fractures (all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine fractures).

Safety endpoints included the incidence of hypercalcaemia (a prespecified safety endpoint), adverse events (AEs) and serious adverse events (SAEs), vital signs, electrocardiograms, incidence of hypercalciuria, clinical laboratory parameters, renal safety and bone histomorphometry.[1]

B.2.3.1.2 ACTIVExtend

ACTIVExtend (NCT01657162; BA058-05-005) was a 24-month extension study of ACTIVE that assessed the efficacy and safety of 18 months of abaloparatide or placebo followed by 6 months (planned interim analysis of ACTIVExtend) and 24 months (planned final analysis of ACTIVExtend; cumulative 43 months [18 months ACTIVE, 1 month treatment gap for rollover to ACTIVExtend, 24 months ACTIVExtend]) of alendronate in postmenopausal women with osteoporosis (N=1139 patients enrolled and treated).[58,59] As outlined in Section B.2.2, the data in this submission are from the dataset presented in the SmPC, which includes 963 randomised patients.[2,64]

A gap in treatment of up to 1 month (from month 18 to 19) was allowed for rollover and reconsenting from ACTIVE to ACTIVExtend.[58,59] Women in the blinded abaloparatide and placebo groups in the ACTIVE study who completed the 18-month end of treatment visit, were >80% compliant with study medication during the ACTIVE study and, in the opinion of the investigators, were appropriate candidates for treatment with alendronate, and were eligible to participate in the ACTIVExtend study.[58,59] Women were excluded if they had experienced a serious treatment-related AE (TRAE), had stopped taking study medication, were non-compliant or had withdrawn from the ACTIVE study for any reason.

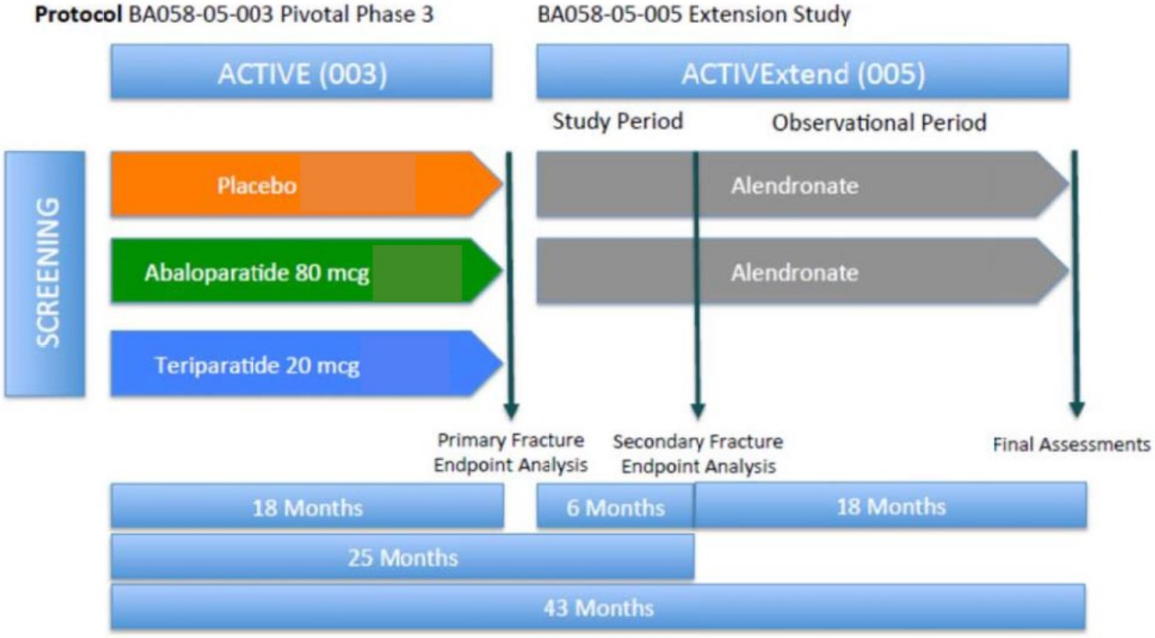
All enrolled patients were treated with alendronate (70 mg/week) for a planned total extension period of 24 months (Figure 1). Investigators and patients remained blinded to the original treatment assignment for 6 months of ACTIVExtend.

The primary efficacy endpoint was the percentage of patients with one or more new morphometric vertebral fractures between the baseline of the ACTIVE study and the end of ACTIVExtend (cumulative 43 months [18 months ACTIVE, 1 month treatment gap for rollover to ACTIVExtend, 24 months ACTIVExtend]) in the abaloparatide/alendronate group vs the placebo/alendronate group. Secondary efficacy endpoints included the incidence and time to first event for nonvertebral, major osteoporotic, and clinical fractures; percentage change in lumbar spine, total hip, and femoral neck BMD from ACTIVE baseline through

cumulative months of ACTIVExtend (25, 31, 37 and 43 months); and changes in serum markers of bone turnover in a subset of patients from ACTIVE baseline through cumulative months of ACTIVExtend (25, 31, 37 and 43 months).

Prespecified exploratory endpoints included the incidence and time to event of nonvertebral, clinical and major osteoporotic fractures from ACTIVExtend baseline to month 6 and 24; and the percentage change from baseline in lumbar spine, total hip and femoral neck BMD from ACTIVExtend baseline to month 6 and 24. Safety endpoints included AE monitoring.

Figure 6: ACTIVE (BA058-05-003) and ACTIVExtend (BA058-05-005) trial design



A 1 month gap in treatment was allowed for reconsenting from ACTIVE to ACTIVExtend
Participants received oral alendronate at a total dose of 70 mg once per week
Abbreviations: ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ACTIVExtend, Abaloparatide Comparator Trial In Vertebral Endpoints Extension Study
Source: Abaloparatide EPAR[61]

A summary of ACTIVE and ACTIVExtend study methodology is provided in Table 9.

Table 9: ACTIVE and ACTIVExtend | Summary of trial methodology

Study	ACTIVE	ACTIVExtend
Study design	Phase 3, randomised, placebo- and active-controlled, multicentre international study (NCT01343004)	Open-label extension study to evaluate the effects of 24 months of treatment with alendronate following 18 months of treatment with abaloparatide or placebo in participants who completed the ACTIVE trial (NCT01657162)
Duration of study	Up to 2 months screening; 1 week pretreatment; observational period 19	1 month period between final ACTIVE visit and initiation of ACTIVExtend (for recruitment

	months (18 months treatment plus 1 month follow-up)	and consenting patients to ACTIVExtend); treatment period 24 months
Settings and locations where data were collected	Main study: 28 sites in 10 countries (Poland [6], Brazil [5], United States [5], Denmark [3], Czech Republic [3], Estonia [2] and one site each in Lithuania, Romania, Hong Kong, and Argentina) Reanalysed dataset excluding Sites 131 and 132: 26 sites in 10 countries (Poland [6], Brazil [5], United States [5], Denmark [3], Czech Republic [1], Estonia [2] and one site each in Lithuania, Romania, Hong Kong, and Argentina)	Main study: 25 sites in 10 countries (Poland [5], Brazil [5], United States [3], Denmark [3], Czech Republic [3], Estonia [2] and one site each in Lithuania, Romania, Hong Kong, and Argentina) Reanalysed dataset excluding Sites 131 and 132: 23 sites in 10 countries (Poland [5], Brazil [5], United States [3], Denmark [3], Czech Republic [1], Estonia [2] and one site each in Lithuania, Romania, Hong Kong, and Argentina)
Participant eligibility criteria	Key inclusion criteria: • Healthy ambulatory postmenopausal women aged 49–86 years with osteoporosis at risk of fracture: • T-score ≤-2.5 and >-5.0 at the lumbar spine or femoral neck and radiological evidence of ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years • Women aged >65 years with the above fracture criteria and T-score ≤-2.0 and >-5.0 • Women aged >65 years who did not meet the fracture criteria whose T-score was ≤ -3.0 and > -5.0	Key inclusion criteria: • Participants who received abaloparatide or placebo in the ACTIVE trial and successfully completed the study (with no serious treatment-related adverse events) • Participants must have been ≤40 days from end of treatment in the ACTIVE trial
	Key exclusion criteria: • 4 mild or moderate vertebral fractures • Any severe vertebral fractures • <2 evaluable lumbar vertebrae • Unevaluable hip BMD measurement • Evidence of metabolic bone disease or malabsorption or taking medications that would interfere with bone metabolism	Key exclusion criteria: • Severe treatment-related adverse event during the ACTIVE trial • Non-compliant or withdrawn from the ACTIVE trial for any reason

	• Use of bisphosphonate for >3 months in the past 5 years or denosumab within the past year • History of osteosarcoma	
Trial drugs	Intervention: Abaloparatide subcutaneous 80 µg once daily Comparators: Placebo Active: Teriparatide subcutaneous 20 µg once daily	Intervention: Oral alendronate (70 mg/week) in patients who received abaloparatide or placebo in the ACTIVE trial
Concomitant medication	Permitted concomitant medication: • Calcium (500–1000 mg/day) and Vitamin D (400–800 IU/day) supplements, or a dose determined by investigator according to patient need, were required to be administered daily from the Pretreatment Period until the end of the Treatment Period and recommended through the Follow-up period • Stable doses of required concomitant medications (e.g., statins, hypertensives). any other required medications must have been discussed with the investigator and recorded on the case report form Prohibited concomitant medication: • Any medications except as specified above within 72 hours prior to dosing on day 1 • Oestrogens as HRT were allowed on entry but could not be initiated during the study except for low dose vaginal oestrogen • Chronic treatment with an anticonvulsant or heparin (patients requiring such treatment were discontinued)	Permitted concomitant medication: • Calcium (500–1000 mg/day) and Vitamin D (400–800 IU/day) supplements continued from the ACTIVE study • Stable doses of required concomitant medications (e.g., statins, hypertensives), any other required medications must have been discussed with the investigator and recorded on the case report form Prohibited concomitant medication: • Oestrogens as HRT were allowed on entry but could not be initiated during the study except for low dose vaginal oestrogen • Treatment with an anticonvulsant or chronic heparin (patients requiring such treatment were discontinued)
Primary outcomes	Incidence of new morphometric vertebral fractures in the	Percentage of patients who sustained one or more new morphometric vertebral fractures between the baseline

	abaloparatide group versus the placebo group	of the ACTIVE study and after 24 months of alendronate in the ACTIVExtend study abaloparatide/alendronate group versus the placebo/alendronate group
Other outcomes used in the model/specified in the scope	• Nonvertebral fractures • Major osteoporotic fracture • Clinical fracture • Bone mineral density • Adverse effects of treatment	• Nonvertebral fractures • Major osteoporotic fracture • Clinical fracture • Bone mineral density • Adverse effects of treatment
Other outcomes of interest	• Change in bone turnover markers (s-P1NP and s-CTX)	• Change in bone turnover markers (s-P1NP and s-CTX)
Pre-planned subgroups	For selected primary and secondary efficacy endpoints: • Age (<65, 65 to <75, ≥75 years) • Years since menopause (<15, 15 to <25, ≥25) • Race (White, Black/African American, Asian, Other) • Region (North America, South America, Europe, Asia) • Any prior fracture (yes, no) • Any prior vertebral fracture (yes, no) • Any prior nonvertebral fracture (yes, no) • Prevalence of vertebral fracture at baseline (0, 1, ≥2) • Severe disease (least BMD T-score ≤–2.5 and prevalent vertebral fracture) at baseline (yes, no) • Lumbar Spine BMD T-score at baseline (≤–2.5, >–2.5) • Lumbar Spine BMD T-score at baseline (≤–3.0, >–3.0) • Total hip BMD T-score at baseline (≤–2.5, >–2.5)	For primary and secondary efficacy endpoints: • Age (<65, 65 to <75, ≥75 years) • Years since menopause (<15, 15 to <25, ≥25) • Race (White, Black/African American, Asian, Other) • Region (North America, South America, Europe, Asia) • Any prior fracture (yes, no) • Any prior vertebral fracture (yes, no) • Any prior nonvertebral fracture (yes, no) • Prevalence of vertebral fracture at baseline (0, 1, ≥2) • Severe disease (least BMD T-score ≤–2.5 and prevalent vertebral fracture) at baseline (yes, no) • Lumbar Spine BMD T-score at baseline (≤–2.5, >–2.5) • Lumbar Spine BMD T-score at baseline (≤–3.0, >–3.0) • Total hip BMD T-score at baseline (≤–2.5, >–2.5)

	• Total hip BMD T-score at baseline (≤–3.0, >–3.0) • Femoral neck BMD T-score at baseline (≤–2.5, >–2.5) • Femoral neck BMD T-score at baseline (≤–3.0, >–3.0)	• Total hip BMD T-score at baseline (≤–3.0, >–3.0) • Femoral neck BMD T-score at baseline (≤–2.5, >–2.5) • Femoral neck BMD T-score at baseline (≤–3.0, >–3.0) • BMI (kg/m^2) at baseline (<25, ≥25)

Abbreviations: BMD, bone mineral density; BMI, body mass index; HRT, hormone replacement therapy
Sources: Miller et al., 2016 (manuscript and supplement)[1]; Cosman et al., 2017[58]; Bone et al., 2018[59]; ACTIVExtend protocol[65]; ACTIVExtend SAP[66]

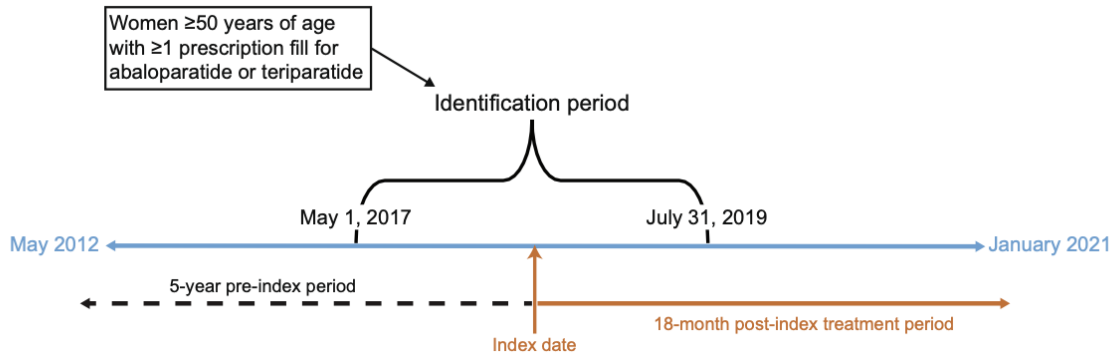
B.2.3.2 Real-world evidence study design

This RWE study was a retrospective observational study (NCT04974723; BA058-05-028) using anonymised US patient claims data from Symphony Health, Integrated Dataverse (IDV)®.[62] The aim of the study was to evaluate the real-world comparative effectiveness on nonvertebral fractures and to compare the CV safety of abaloparatide vs teriparatide in propensity score-matched cohorts (N=11,616 per cohort) during 19 months after treatment initiation.

The index date was defined as the date of initial prescription dispensed for either abaloparatide or teriparatide during the identification period of 1 May 2017 to 31 July 2019, following the 2017 US Food and Drug Administration approval of abaloparatide (Figure 7). Patients were assigned to a cohort based on their index therapy. Data regarding the medical and treatment history for each patient were also included from a 5-year pre-index period.

The post-index treatment period consisted of the 18 months post-index, with a maximum evaluation period of 18 months plus a 30-day follow-up period (total 19 months). Treatment effectiveness was evaluated from immediately after treatment initiation for 18 months plus 30-day follow-up after the index date. CV safety outcomes were evaluated from immediately after treatment initiation and continued while on therapy for up to 18 months plus 30 days follow-up.

Figure 7: Real-world evidence (BA058-05-028) study design



Source: Cosman et al. (2022)[62]; Abaloparatide EPAR[61]

Participants were women aged ≥50 years with ≥1 new prescription fill of abaloparatide or teriparatide during the identification period, ≥1 claim for a medical or hospital visit, and a pharmacy claim in the 12 months before the index date.[62] Exclusion criteria were diagnostic claim at baseline for Paget's disease of the bone or malignancy (except for non-melanoma skin cancers, carcinoma in situ of the cervix or ductal carcinoma in situ of the breast), Charlson Comorbidity Index score >10, prior index anabolic therapy, and anabolic treatment switch after the index date. Propensity score matching was used to create the abaloparatide and teriparatide treatment cohorts.

The primary endpoint was the time to first nonvertebral fracture event. Secondary endpoints included time to the first composite endpoint of major adverse CV events (MACE; nonfatal myocardial infarction [MI], nonfatal stroke or cardiovascular death) with and without heart failure following hospitalisation. Time to first hip fracture was an exploratory effectiveness endpoint. Exploratory safety endpoints included time to first event for MI, stroke, CV death following hospitalisation since anabolic treatment initiation, and heart failure while on therapy.

A summary of the methodology used in the real-world study is provided in Table 10.

Table 10: Real-world evidence study | Summary of study methodology

Study	RWE study
Study design	Retrospective observational study using anonymised patient claims data (NCT04974723)
Duration of study	19 months (18 months plus 30-day follow-up)
Settings and locations where data were collected	United States (patient claims data from Symphony Health, Integrated Dataverse [IDV]®)
Participant eligibility criteria	Key inclusion criteria: Women aged ≥50 years with ≥1 new prescription fill of abaloparatide or teriparatide
	Key exclusion criteria: Diagnostic claim at baseline for Paget's disease of the bone or malignancy (except for non-melanoma skin cancers, carcinoma in situ of the cervix or ductal carcinoma in situ of the breast), Charlson Comorbidity Index score >10, prior index anabolic therapy, anabolic treatment switch after the index date
Trial drugs	No interventions, real-world use of abaloparatide and teriparatide
Concomitant medication	This was a real-world study with no restrictions on concomitant medication. It was expected that participants may have been using concomitant medications, including bisphosphonates, denosumab and HRT
Primary outcomes	Time to first nonvertebral fracture event
Other outcomes used in the model/specified in the scope	NA

Other outcomes of interest	Cardiovascular safety
Pre-planned subgroups	Effectiveness: • Age <75 vs ≥75 years • Race/ethnicity (White, Hispanic, African American, Asian, Other, Unknown [includes 'Missing' race/ethnicity category]) • Prior bisphosphonate use within 5 years prior to index date: with vs without • Prior fracture within 1 year of index date: with vs without Safety: • Age <75 vs ≥75 years • Race/ethnicity (White, Hispanic, African American, Asian, Other, Unknown [includes 'Missing' race/ethnicity category]) • With or without prior cardiovascular risk (including cardiovascular disease, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, diabetes mellitus, obesity, hypertension) • With or without myocardial infarction or stroke within 1 year before the index date

Abbreviations: HRT, hormone replacement therapy; RWE, real-world evidence
Sources: Cosman et al 2022[62], RWE CSR[67]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analyses

Statistical methods used in the ACTIVE and ACTIVExtend trials and the RWE study are summarised in Table 11.

Table 11: Clinical effectiveness studies | Summary of statistical analyses

	ACTIVE	ACTIVExtend	RWE study
Trial name/number	NCT01343004	NCT01657162	NCT04974723
Hypothesis objective	The primary objective was to determine the safety and efficacy of abaloparatide vs placebo for the prevention of vertebral fracture in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis	The primary objective was to determine the percentage of patients with new vertebral fractures from ACTIVE baseline until Month 25 (after 6 months of subsequent abaloparatide treatment in those who received abaloparatide vs placebo in ACTIVE). Final data for this endpoint were then evaluated at the end of the study at Month 43	The primary objective was to determine the time to first nonvertebral fracture event in postmenopausal women receiving real-world abaloparatide vs teriparatide within 18 months plus 30 days follow-up after treatment initiation
Statistical analysis	Statistical analyses were performed using SAS statistical software. A hierarchical testing approach was used for efficacy endpoints using the following sequence: new vertebral fracture (abaloparatide vs placebo); BMD at the total hip, femoral neck, lumbar spine (abaloparatide vs placebo at 18 months); nonvertebral fracture (abaloparatide vs placebo); BMD at the total hip and femoral neck (abaloparatide vs teriparatide at 6 months); nonvertebral fracture (abaloparatide vs teriparatide); BMD at lumbar spine (abaloparatide vs teriparatide at 6 months). If at any step, the two-sided significance level of 5% was not attained, subsequent comparison p values were considered nominal for exploratory purposes. Further statistical analyses (e.g., clinical fractures and major osteoporotic fractures) were reported as prespecified exploratory analyses.	Statistical analyses were performed using SAS statistical software. A hierarchical testing approach was used for efficacy endpoints using the following sequence: vertebral fracture (abaloparatide/alendronate vs placebo/alendronate); BMD at the total hip, femoral neck, lumbar spine (abaloparatide/alendronate vs placebo/alendronate); nonvertebral fracture (abaloparatide/alendronate vs placebo/alendronate); clinical fracture (abaloparatide/alendronate vs placebo/alendronate); major osteoporotic fracture (abaloparatide/alendronate vs placebo/alendronate). If at any step, the two-sided significance level of 5% was not attained, subsequent comparison p values were considered nominal for exploratory purposes. **Primary endpoint (new vertebral fractures from ACTIVE baseline):**	The analysis population consisted of all patients meeting the study inclusion/exclusion criteria and selected after propensity score matching. The same matched population was used for both effectiveness and safety analysis. **Primary endpoint (time to first nonvertebral fracture):** Conducted using an ITT analysis of noninferiority of abaloparatide to teriparatide as measured by the HR. Noninferiority was confirmed if the upper bound of the 2-sided 95% CI of the HR between abaloparatide vs teriparatide was <1.3. Comparisons between the matched treatment cohorts were based on a Cox proportional hazards model, with p values obtained from the log-rank test. **Secondary endpoints (cardiovascular safety outcomes):** Evaluated using an as-treated analysis. The observation period was for up to 18 months while on treatment plus 30-day follow-up, or until the first cardiovascular event or in

	Primary endpoint (prevention of vertebral fractures): Analysis performed on the mITT population. The percentage of patients (95% CI) with one or more new vertebral fractures was provided for each treatment group using the Wilson's score method. Fisher's exact test was used to compare abaloparatide vs placebo. The absolute risk reduction (95% CI) for treatment difference was derived using Newcombe 1998[68] as the primary method. For exploratory purposes, the relative risk reduction (95% CI) was also calculated using the Wald method. The comparison in the primary efficacy endpoint between abaloparatide vs teriparatide groups was descriptive. The primary efficacy analysis was also analysed for patients in the PP population. **Secondary endpoint of nonvertebral fractures:** Analysis performed on the ITT population using the log-rank test for inferential statistics and the Kaplan–Meier method for estimates of event rates. The log-rank test was the primary analysis method to compare the difference in time to first nonvertebral fracture between the abaloparatide vs placebo groups. The Cox proportional hazard model was used to calculate the hazard ratio (95% CI) of incident nonvertebral fractures between these two treatment groups. **Secondary endpoint of BMD:**	Analysis performed on the mITT population. The percentage of patients (95% CI) with one or more new vertebral fractures was provided for each treatment group using the Wilson's score method. Fisher's exact test was used to compare abaloparatide/alendronate vs placebo/alendronate. The absolute risk reduction (95% CI) for treatment difference was derived using Newcombe 1998[68]. The relative risk reduction (95% CI) was also calculated using the Wald method. The primary efficacy analysis was also analysed for patients in the PP population. **Secondary endpoint of nonvertebral fractures:** Analysis performed on the ITT population using the log-rank test for inferential statistics and the Kaplan–Meier method for estimates of event rates. The log-rank test was the primary analysis method to compare the difference in time to first nonvertebral fracture between the abaloparatide/alendronate vs placebo/alendronate groups. The Cox proportional hazard model was used to calculate the hazard ratio (95% CI) of incident nonvertebral fractures between these two treatment groups. **Secondary endpoint of BMD:** Analysis performed on the ITT population. The ANCOVA model with LOCF was the primary analysis method for BMD. To handle missing post-	hospital cardiovascular death, whichever came first.

	Analysis performed on the ITT population. The ANCOVA model with LOCF was the primary analysis method for BMD. To handle missing post-baseline BMD data, the LOCF method was used to impute missing data. The ANCOVA model was used to compare treatment groups for percentage change from baseline in BMD with missing imputation based on LOCF. **Secondary endpoint of bone turnover markers:** Analysed as a log ratio of post-baseline vs baseline using MMRM in a randomly selected subset of ~200 patients per treatment group with paired measurements at baseline and follow-up. GMRs were reported for treatment differences. **Prespecified safety endpoint of hypercalcaemia (albumin-corrected serum calcium ≥10.7 mg/dL [≥2.67 mmol/L]):** Analysed in the Safety population using a chi-squared test.	baseline BMD data, the LOCF method was used to impute missing data. The ANCOVA model was used to compare treatment groups for percentage change from baseline in BMD with missing imputation based on LOCF. **Secondary endpoint of bone turnover markers:** Analysed as a log ratio of post-baseline vs baseline using MMRM in a subset of the bone turnover marker populations from the abaloparatide and placebo groups in the ACTIVE trial. GMRs were reported for treatment differences.	
Sample size, power calculation	A sample size of 622 patients per treatment arm was calculated to provide 90% power at a two-sided alpha of 0.05 to detect a difference of 4% between treatments, assuming a vertebral fracture rate of 7% in placebo group patients and 3% in abaloparatide group patients using large scale approximation of the binomial method. To ensure an analysis size of 622 patients, the protocol aimed to recruit an overall sample size of ~800 patients per treatment arm, anticipating	Initial sample size (aimed at 800 per treatment arm) and power calculations were performed for the ACTIVE study. All patients randomised to the abaloparatide or placebo arms of the ACTIVE study and who completed 18 months of treatment were offered the opportunity to participate in ACTIVExtend. This allowed a potential maximum of 1,600 patients eligible to be enrolled in ACTIVExtend.	The sample size calculation assumed a nonvertebral fracture rate of 3.5% for teriparatide after 18 months. A sample size of 8000 matched samples in each treatment cohort was considered to provide ≥95% power at a 0.05 significance level to estimate the equivalence HR of 1.3 when the actual HR is an equivalence HR of 1.0.

	that ~20% of patients may not have a second evaluable X-ray available for analysis.		
Data management, patient withdrawals	For the primary endpoint, the effect of missing data was evaluated using a sensitivity analysis (excluding patients with no post-baseline X-ray) based on the multiple imputation method. A logistic regression model was used to augment the data set by imputing the missing outcome multiple times to determine the uncertainty of the imputation.	Missing data were imputed as described above.	For this study there were no new primary data collected. The study was conducted using real-world (secondary) data for analysis. Toad Data Point 5.0.3.32 (64 bit) software was used to connect to the Cloudera Hadoop 7.1.4-1 database for data extraction. R software was used for propensity score matching. Datasets and tables, figures, and listings were created on a Citrix Windows platform using SAS V9.4 M6.
Statistical analysis timepoints	All analyses were based on the 18-month end of treatment time-point.	Initial analyses were based on the Month 25 time-point (after 6 months of subsequent abaloparatide treatment in those who received abaloparatide vs placebo in ACTIVE). Final data were then evaluated at the end of the study at Month 43 (after 24 months of abaloparatide treatment).	Analyses were based on 18 months plus 30 days follow-up after treatment initiation.

Abbreviations: ANCOVA, analysis of covariance; BMD, bone mineral density; CI confidence interval; GMR, geometric mean ratio; HR, hazard ratio; ITT, intent-to-treat; LOCF, last observation carried forward; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; PP, per-protocol; RWE, real-world evidence
Source: Miller et al 2016 (manuscript and supplement)[1]; Cosman et al 2017[58]; Bone et al 2018[59]; ACTIVExtend SAP[66]; Cosman et al 2022[62]; RWE protocol[69]; RWE CSR[67]

B.2.4.2 Analysis sets

B.2.4.2.1 Phase 3 trials

Patient data sets analysed in ACTIVE and ACTIVExtend are described in Table 12 and Table 13. Efficacy analyses in the ACTIVE study were performed on three populations: the primary population for vertebral fractures (modified intent-to-treat [mITT] population), the primary population for efficacy endpoints other than vertebral fractures (ITT population) and the per-protocol population (Table 12). The Safety population comprised all patients who received ≥1 dose of study medication.

In ACTIVExtend, efficacy analyses of vertebral fractures were analysed in patients with evaluable spinal radiographs at the ACTIVExtend 6-month (interim analysis) and 24-month (final analysis) visits and at baseline and 18 months in ACTIVE (mITT population [Table 13]). All other efficacy analyses (except for vertebral fractures) were based on an ITT population including all patients in ACTIVE who were enrolled in ACTIVExtend. Safety analyses were based on all ITT patients who received ≥1 dose of alendronate.

Table 12: ACTIVE | Analysis sets

Analysis set	Definition	ACTIVE			
		Number of patients (excluding Sites 131 and 132), n (%)			
		Abaloparatide	Placebo	Teriparatide	Total
mITT	All patients with pretreatment and end of treatment evaluable radiological assessments (spine X-ray)	583	600	600	1,783
ITT	All patients who were randomised into the study by assigning the randomised study medication kit on Day 1	696	688	686	2,070
Per-protocol	Patients in the mITT population who complied with treatment and did not have any protocol violations	531	547	552	1,630
Safety	All patients who received ≥1 dose of study medication	694	687	686	2,067

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat
Sources: Miller et al 2016 (supplement)[1]; ACTIVE CSR addendum[63]

Table 13: ACTIVExtend | Analysis sets

Analysis set	Definition	ACTIVExtend		
		Number of patients (excluding Sites 131 and 132), n (%)		
		Abaloparatide/alendronate	Placebo/alendronate	Total
mITT – 24 months	All patients with pretreatment and ≥1 ACTIVExtend post-baseline evaluable radiological assessments (spine X-ray)	457	489	946
ITT – 24 months	All patients in the ACTIVE study who were enrolled in ACTIVExtend	469	494	963
Per-protocol	Patients in the mITT population who complied with treatment and did not have any protocol violations	436	444	880

Analysis set	Definition	ACTIVExtend		
		Number of patients (excluding Sites 131 and 132), n (%)		
		Abaloparatide/alendronate	Placebo/alendronate	Total
Safety – 24 months	All patients who received ≥1 dose of alendronate	465	493	958

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat
Sources: ACTIVExtend protocol[65]; ACTIVExtend CSR addendum[64]

B.2.4.2.2 Real-world evidence study

Patient data sets analysed in the RWE study are described in Table 14. The analysis population was all patients meeting the study inclusion/exclusion criteria and selected after propensity matching. The same matched population was used for both effectiveness and safety analysis.[62]

Table 14: Real-world evidence study | Analysis sets

Analysis set	Definition	RWE study		
		Number of propensity score-matched patients, N		
		Abaloparatide	Teriparatide	Total
Effectiveness – ITT	Analysis based on the first fracture event during the 18 months plus 30 days follow-up after the index date was analysed regardless of when treatment ended.	11,616	11,616	23,232
Safety – As-treated	Analysis based only on events that occurred any time after treatment initiation and while on therapy (until end of treatment) for up to 18 months plus 30 days follow-up, regardless of the anabolic drug possession gap between any two prescription fills.	11,616	11,616	23,232

Abbreviations: ITT, intent-to-treat; RWE, real-world evidence
Sources: Cosman et al. (2022)[62]; RWE CSR[67], RWE protocol[69]

B.2.4.3 Patient flow

The ACTIVE population reported here excluded 652 patients screened at Sites 131 and 132. Excluding data from Sites 131 and 132, a total of 4,616 patients were screened, of which 2,505 were considered screen failures. A total of 2,070 patients were randomised and comprised the ITT population (excluding the 393 randomised patients from Sites 131 and 132). Patient enrolment by region, country and site, excluding Sites 131 and 132 remained generally well balanced among treatment groups in the ITT population.

For the RWE study, of an initial 79,872 women aged ≥50 years with ≥1 new prescription fills of abaloparatide or teriparatide during the identification period, 24% in each treatment cohort were ineligible due to not having a medical, hospital visit, or pharmacy claim in the 12 months before index date.[62] A larger number of patients were identified in the teriparatide cohort as teriparatide had been on the US market (2002) longer than abaloparatide (2017). A total of 11,617 patients in the abaloparatide cohort and 22,809 for teriparatide met all eligibility criteria. After propensity score matching, 11,616 patients were included in each treatment cohort. Propensity score matching was successful, as indicated by a similar distribution of the propensity score between the two treatment groups.

Further details on patient disposition for each study are presented in Appendix D.

B.2.4.4 Patient baseline characteristics

B.2.4.4.1 Phase 3 trials

Demographic and baseline characteristics were generally well balanced among treatment groups in the ACTIVE study (Table 15). All patients were postmenopausal women aged 50–86 years, inclusive. The median age was 69 years (mean [SD] 69.4 [6.2]); 20.1% of women were aged ≥75 years, including four patients (0.2%) aged 85–86 years. The mean number of years since menopause was 20.9. Three quarters (~75.8%) of patients were white and mean body mass index (BMI) was approximately 24.9 kg/m^2.

The majority of patients (77.2%) had lumbar spine BMD T-scores <-2.5 (indicating significant bone loss) and approximately 18.5% of patients had severe osteoporosis, defined as having at least one BMD T-score of ≤-2.5 at any anatomical sites measured and prevalent vertebral fracture at baseline.

Demographic and baseline characteristics in ACTIVExtend were also generally well balanced between treatment groups (Table 16).

Table 15: ACTIVE | Patient baseline demographic and disease characteristics (excluding Sites 131 and 132; ITT population)

Characteristic	ACTIVE		
	Placebo n=688	Abaloparatide n=696	Teriparatide n=686
Age, mean (SD), years	69.3 (6.1)	69.5 (6.3)	69.4 (6.1)
Time since menopause, mean (SD), years	20.6 (7.9)	21.2 (8.1)	20.9 (8.1)
Weight, mean (SD), (kg)	60.3 (9.8)	60.0 (9.7)	60.2 (10.2)
BMI, mean (SD), (kg/m^2)	24.9 (3.5)	24.8 (3.5)	25.0 (3.5)

Race, n (%)			
White	522 (75.9)	535 (76.9)	513 (74.8)
Asian	131 (19.0)	128 (18.4)	137 (20.0)
Black or African American	23 (3.3)	26 (3.7)	24 (3.5)
Other	12 (1.7)	7 (1.0)	12 (1.7)
Ethnicity, n (%)			
Hispanic or Latino	197 (28.6)	199 (28.6)	192 (28.0)
T-score, mean (SD):			
Femoral neck	–2.2 (0.7)	–2.2 (0.6)	–2.2 (0.7)
Total hip	–1.9 (0.8)	–1.9 (0.7)	–1.9 (0.8)
Lumbar spine	–3.0 (0.8)	–2.9 (0.9)	–2.9 (0.9)
BMD, mean (SD), g/cm^3:			
Femoral neck	0.730 (0.095)	0.730 (0.090)	0.736 (0.094)
Total hip	0.763 (0.099)	0.764 (0.091)	0.770 (0.095)
Lumbar spine	0.817 (0.096)	0.825 (0.106)	0.829 (0.107)
≥1 prevalent vertebral fractures, n (%)	149 (21.7)	145 (20.8)	182 (26.5)
≥1 prior nonvertebral fractures, n (%)[a]	302 (43.9)	308 (44.3)	271 (39.5)
No history of prior fracture, n (%)	297 (43.2)	289 (41.5)	289 (42.1)

[a]Assessed based on fractures that occurred prior to visit 3 (study day 1). Excludes fractures of the spine, sternum, patella, toes, fingers, skull, and facial bones
Abbreviations: BMI, body mass index; BMD, bone mineral density; ITT, intent-to-treat; SD, standard deviation
Sources: ACTIVE CSR addendum[63]; MHRA SmPC[2]; Abaloparatide EPAR[61]

Table 16: ACTIVExtend | Patient baseline demographic and disease characteristics (excluding Sites 131 and 132; ITT population)

Characteristic	ACTIVExtend[a]	
	Placebo/alendronate n=494[b]	Abaloparatide/alendronate n=469[b]
Age, years		
Mean (SD)	69.1 (5.9)	69.3 (6.3)
<65, n (%)	74 (15.0)	67 (14.3)
65 to <75, n (%)	331 (67.0)	310 (66.1)
≥75, n (%)	89 (18.0)	92 (19.6)
Time since menopause, mean (SD), years	20.4 (7.7)	20.9 (8.0)
BMI, mean (SD), (kg/m^2)	24.7 (3.4)	24.7 (3.5)
Race, n (%)		
White	360 (72.9)	344 (73.3)
Asian	106 (21.5)	101 (21.5)
Black or African American	18 (3.6)	19 (4.1)
Other	10 (2.0)	5 (1.1)

Ethnicity, n (%)		
Hispanic or Latino	137 (27.7)	124 (26.4)
Region, n (%)		
North America	7 (1.4)	9 (1.9)
South America	157 (31.8)	145 (30.9)
Europe	225 (45.5)	216 (46.1)
Asia	105 (21.3)	99 (21.1)
T-score, mean (SD)		
Femoral neck	–2.2 (0.7)	–2.2 (0.6)
Total hip	–2.0 (0.8)	–1.9 (0.7)
Lumbar spine	–3.0 (0.8)	–2.9 (0.8)
≥1 prevalent vertebral fractures, n (%)	107 (21.7)	96 (20.5)
≥1 prior nonvertebral fractures, n (%)[c]	209 (42.3)	206 (43.9)
No history of prior fracture, n (%)	225 (45.5)	196 (41.8)

[a]Baseline and demographic characteristics are based on the ACTIVE study baseline time-point
[b]Treatment groups are based on randomisation in the ACTIVE trial
[c]Assessed based on fractures that occurred prior to visit 3 (study day 1). Excludes fractures of the spine, sternum, patella, toes, fingers, skull, and facial bones
Abbreviations: BMI, body mass index; ITT, intent-to-treat; SD, standard deviation
Sources: ACTIVExtend CSR addendum[64]

B.2.4.4.2 Real-world evidence study

Patient baseline demographic characteristics in the RWE study were well balanced between the propensity score-matched groups (Table 17). It is important to note that for both treatment cohorts in the overall propensity score-matched population, race/ethnicity was unknown in approximately 53% of patients and <1% of patients were of known Asian race/ethnicity. There were no major imbalances of osteoporosis disease and treatment history between the propensity score-matched treatment cohorts (Table 17). All prespecified variables were well balanced with a standardised mean difference <0.10.[62]

Table 17: Real-world evidence study | Patient baseline demographic and disease characteristics (all population propensity score-matched)

Characteristic	RWE study		
	Abaloparatide n=11,616	Teriparatide n=11,616	Standardised difference
Age, years[a,b]			
N	11,616	11,616	0.023
Mean (SD)	67.3 (8.4)	67.5 (8.4)	
Age group, years, n (%)[a]			
50–64, n (%)	4,779 (41.1)	4,599 (39.6)	0.032
65–74, n (%)	3,961 (34.1)	4,053 (34.9)	0.017
≥75, n (%)	2,876 (24.8)	2,964 (25.5)	0.017
Race/ethnicity[b], n (%)			

African American	152 (1.3)	151 (1.3)	0.001
Asian	104 (0.9)	98 (0.8)	0.006
White	4,368 (37.6)	4,505 (38.8)	0.024
Hispanic	682 (5.9)	551 (4.7)	0.050
Other	140 (1.2)	122 (1.1)	0.015
Unknown	6,170 (53.1)	6,189 (53.3)	0.003
Osteoporosis disease history			
Diagnosed osteoporosis prior to index date, n (%)	7,508 (64.6)	7,451 (64.1)	0.010
Years since first osteoporosis diagnosis in 5 years pre-index date			
N	7,508	7,451	0.002
Mean (SD)	2.8 (2.2)	2.8 (2.2)	
Fracture at any time pre-index, n (%)	2,968 (25.6)	2,973 (25.6)	0.001
Fracture in the year prior to index date, n (%)	1,876 (16.2)	1,863 (16.0)	0.003
Gastrointestinal disorders, n (%)	4,465 (38.4)	4,467 (38.5)	0.000
Fall risk conditions[c], n (%)	8,413 (72.4)	8,561 (73.7)	0.029
Any cardiovascular risk factor, n (%)[d]	8,910 (76.7)	8,948 (77.0)	0.008
Prior osteoporosis medication, n (%)			
Alendronate	3,131 (27.0)	3,212 (27.7)	0.016
Ibandronate	859 (7.4)	840 (7.2)	0.006
Risedronate	723 (6.2)	725 (6.2)	0.001
Zoledronic acid	418 (3.6)	402 (3.5)	0.007
Denosumab	1,269 (10.9)	1,215 (10.5)	0.015
Hormone replacement therapy	2,837 (24.4)	2,797 (24.1)	0.008
Oral glucocorticoid use, n (%)			
Any prior or current exposure	7,328 (63.1)	7,352 (63.3)	0.004
Current use[e]	754 (6.5)	777 (6.7)	0.008

[a]Due to the Health Insurance Portability and Accountability Act, age >80 years is recorded as 80. Age is matched at the group level (50–64, 65–74, ≥75)
[b]Variables not included in the propensity score matching covariates
[c]Includes stroke, history of falls, mobility issues, visual impairment, hearing impairment, Parkinson's disease, Alzheimer's disease, muscle weakness, atrophy, obesity, rehabilitation, dementia, depression, anxiety and sleep disorders
[d]Includes diagnosis of cardiovascular disease identified by the following terms: cardiac, coronary, pulmonary, cerebrovascular, peripheral arterial, vasculitis, venous, and hypertension; and cardiovascular risk factors of hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, type 2 diabetes, obesity

[e]Current use is 30 days before or after index date
Abbreviations: SD, standard deviation; RWE, real-world evidence
Source: Cosman et al (2022)[62]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of ACTIVE is provided in Table 18.

Table 18: ACTIVE | Quality assessment results using results using Miller et al 2016[1]

Questions	ACTIVE
Was randomisation carried out appropriately?	Yes. Patients were randomised using a permuted-block design with a block size of six in a ratio of 1:1:1 to 1 of the 3 treatment groups.
Was the concealment of treatment allocation adequate?	Yes. Randomised distribution of participants was double-blind.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Randomisation was not stratified by prognostic factors.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes, for abaloparatide and placebo. The teriparatide device was a trademarked pen, it could not be reproduced, and the drug is not approved for dispensing from a different injection device to blind it. After opening the identical assigned study medication kit after randomisation day 1, it became apparent to investigators and patients whether open-label teriparatide or either double-blinded abaloparatide of double-blind placebo had been assigned.
Were there any unexpected imbalances in drop-outs between groups?	No.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Did the analysis include an intention-to-treat analysis?	Yes.
If ITT analysis was included, was this appropriate and were appropriate methods used to account for missing data?	Yes. To evaluate the statistical effect of missing data on incidence of new vertebral fractures, a sensitivity analysis was performed based on the multiple imputation method. This method used a logistic regression model to augment the data set by imputing the missing outcome multiple times to characterise the uncertainty of the imputation.

Abbreviations: ITT, intention-to-treat

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Fracture endpoints | ACTIVE and ACTIVExtend

Fracture outcomes from the ACTIVE study are provided in Table 19.

B.2.6.1.1 New vertebral fractures

The ACTIVE study met its primary endpoint, demonstrating that treatment with abaloparatide significantly reduced the risk of new morphometric vertebral fractures compared with placebo (0.5% vs 4.2% respectively; relative risk reduction [RRR] = 88% [95% confidence interval (CI) 59–96%]; p<0.001) at 18 months[2,61] (Table 19). The results of the sensitivity analysis were similar to those from the primary analysis. In the teriparatide group, the risk of new morphometric vertebral fractures occurred in 0.7% of patients, (RRR compared with placebo 84% [95% CI 54–94%]; p<0.001).

Table 19: ACTIVE | Fracture efficacy endpoints after 18 months of treatment[a] (excluding Sites 131 and 132)

	Study participants with fracture, n (%)[a]			Abaloparatide vs placebo			Abaloparatide vs teriparatide[b]			Teriparatide vs placebo		
	Abaloparatide (n=696)	Placebo (n=688)	Teriparatide (n=686)	Risk reduction (95% CI)[c]	HR (95% CI)[d]	p-value[e]	Risk reduction (95% CI)[c]	HR (95% CI)[d]	p-value[e]	RR (95% CI)[c]	HR (95% CI)[d]	p-value[e]
Primary endpoint (mITT population[a])												
New vertebral fracture[a]	(n=583) 3 (0.5)	(n=600) 25 (4.2)	(n=600) 4 (0.7)	–3.65 (–5.59 to –2.00)	RRR, –0.88 (–0.96 to –0.59)[f]	<0.001				–3.50 (–5.45 to –1.82)	RRR, –0.84 (–0.94 to –0.54)[f]	<0.001
Secondary endpoint (ITT population)												
Nonvertebral fracture	15 (2.7)	21 (3.6)	12 (2.0)	ARR, –0.87 (–2.89 to 1.15)	0.74 (0.38 to 1.43)	0.368	ARR, –0.73 (–1.01 to 2.48)	1.30 (0.61 to 2.79)	0.49	ARR, –1.61 (–3.47 to 0.26)	0.56 (0.28 to 1.15)	0.11
Exploratory endpoints (ITT population)												
Major osteoporotic fracture	7 (1.2)	23 (5.4)	14 (2.2)	ARR, –4.48 (–7.80 to –0.56)	0.31 (0.13 to 0.72)	0.004	ARR, –1.04 (–2.50 to 0.42)	0.51 (0.21 to 1.27)	0.14	ARR, –3.14 (–6.84 to 0.56)	0.60 (0.31 to 1.17)	0.13
Clinical fracture	21 (3.8)	35 (7.4)	21 (3.4)	ARR, –3.64 (–7.63 to 0.35)	0.61 (0.36 to 1.06)	0.08	ARR, 0.33 (–1.82 to 2.47)	1.04 (0.57 to 1.90)	0.90	ARR, –3.97 (–7.91 to –0.03)	0.59 (0.35 to 1.02)	0.06

[a]The percentage of new vertebral fractures was calculated using the modified intent-to-treat population at 18 months (placebo, n=600; abaloparatide, n=583; teriparatide, n=600). The percentage of nonvertebral, major osteoporotic, and clinical fractures was cumulative Kaplan–Meier estimates using the intent-to-treat population at 19 months (the entire observational period including 18 months of treatment plus 1 month of follow-up)

[b]Comparisons vs teriparatide were exploratory. Comparison of abaloparatide vs teriparatide was not performed for the primary endpoint as a sample size of ~22,000 per treatment group would be required to provide 90% power to detect a treatment difference[1]

[c]The 95% CI for risk reduction for new vertebral fractures was calculated using the Newcombe method[68]; 95% CIs for risk reductions for nonvertebral, major osteoporotic, and clinical fractures used standard error by Greenwood's formula with the normal approximation

[d]Values are reported as HR (95% CI) unless otherwise indicated

[e]P values for new vertebral fractures were derived using the Fisher exact test. P values for nonvertebral, major osteoporotic, and clinical fractures were calculated using the log-rank test

[f]Values comparing abaloparatide vs placebo and teriparatide vs placebo are reported as relative risk reductions (95% CIs) for new vertebral fractures

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction

Source: ACTIVE CSR addendum[63], Miller et al 2016 (supplement)[1], MHRA SmPC[2]; Abaloparatide EPAR[61]

At the end of the full 43-month treatment period of the ACTIVE–ACTIVExtend study (18 months treatment in ACTIVE, 1 month for recruitment and consenting to ACTIVExtend, 24 months treatment in ACTIVExtend), the primary endpoint of reduced risk of new vertebral fractures was effectively maintained (Table 20).

Table 20: ACTIVExtend | Fracture efficacy endpoints | Incidence of fractures from active baseline through 24 months of ACTIVExtend (Month 43; excluding Sites 131 and 132)

Endpoint	ACTIVExtend	
	Placebo/alendronate	Abaloparatide/alendronate
Primary end point (mITT population)	**n=489**	**n=457**
≥1 new vertebral fracture, n (%)	26 (5.3)	4 (0.9)
Risk reduction (95% CI)	–4.44 (–6.86, –2.30)	
RRR (95% CI; p value)	–0.84 (–0.94, –0.53; p<0.001)	
Secondary endpoints (ITT population): Kaplan–Meier estimates	**n=494**	**n=469**
≥1 nonvertebral fracture, n (%)	32 (6.7)	19 (4.2)
ARR (95% CI)	–2.53 (–5.42, 0.36)	
HR (95% CI; p value)	0.61 (0.35–1.08; p=0.088)	
≥1 major osteoporotic fracture, n (%)	28 (5.8)	13 (2.8)
ARR (95% CI)	–2.98 (–5.57, –0.38)	
HR (95% CI; p value)	0.48 (0.25–0.92; p=0.024)	
≥1 clinical fracture, n (%)	42 (8.7)	28 (6.1)
ARR (95% CI)	–2.61 (–5.97, 0.74)	
HR (95% CI; p value)	0.68 (0.42–1.10; p=0.119)	

Abbreviations: ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints Extension study; ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mITT, modified intent-to-treat; RRR, relative risk reduction
Source: ACTIVExtend CSR addendum[64]; MHRA SmPC[2]; Abaloparatide EPAR[61]

B.2.6.1.2 Nonvertebral fractures, major osteoporotic fractures and clinical fractures

In ACTIVE, the Kaplan–Meier (K–M) estimated event rate for nonvertebral fractures (fractures excluding those of the spine, sternum, patella, toes, fingers), was numerically lower in the abaloparatide group compared with the placebo group at 19 months (18 months of the observational period plus 1 month follow-up; Table 19). The difference between the abaloparatide and placebo group in the population excluding Sites 131 and 132 was not statistically significant, whereas the original analyses showed a statistically significant difference between abaloparatide and placebo. However, the EMA considered there to be no scientific reason to presume efficacy only for vertebral but not nonvertebral fractures.[61] The K–M time to event curve for nonvertebral fractures was lower in the abaloparatide group vs the placebo group at any time-point during the overall 19 months of the study period (Figure 8).

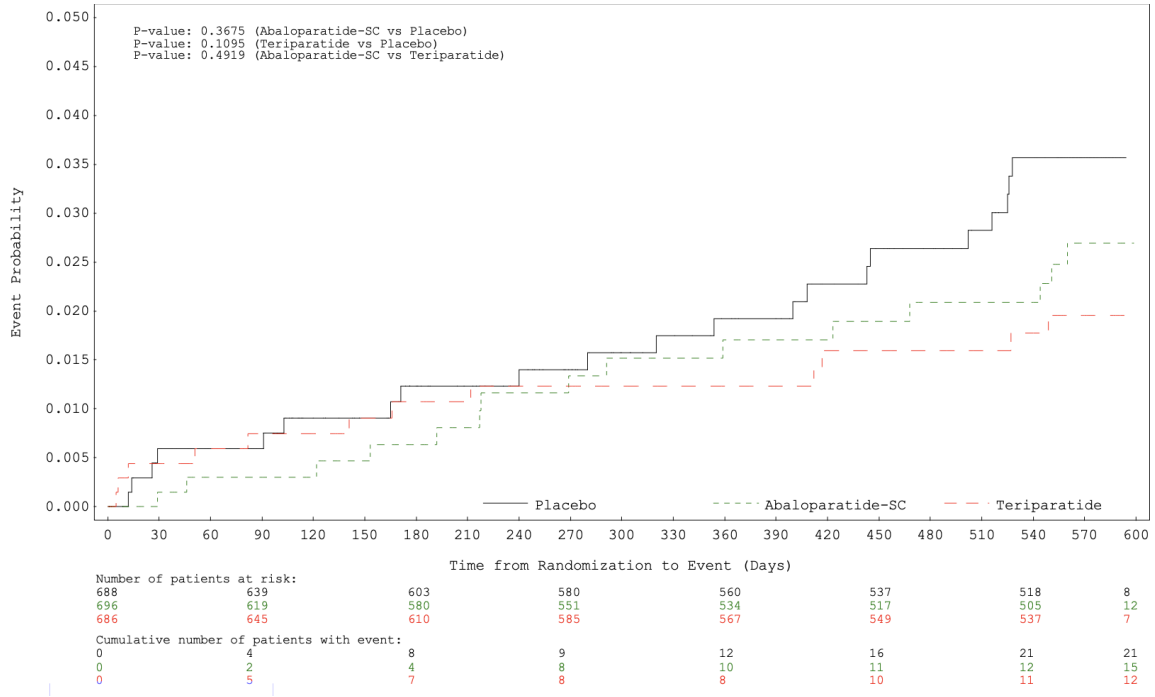
Due to the hierarchical statistical testing approach used for efficacy endpoints (Section B.2.4.1, Table 11), the lack of a significant difference in nonvertebral fractures between the abaloparatide vs placebo meant that the following analyses were exploratory: BMD at the total hip and femoral neck (abaloparatide vs teriparatide at 6 months); nonvertebral fracture

(abaloparatide vs teriparatide); BMD at lumbar spine (abaloparatide vs teriparatide at 6 months). Clinical fractures and major osteoporotic fractures were prespecified exploratory analyses.

The difference in major osteoporotic fracture (fractures of the wrist, upper arm, hip, and clinical spine) event rates was statistically significant for the abaloparatide group vs the placebo group (p=0.004) (Table 19). The K–M event rates were constantly lower in the abaloparatide group vs placebo and vs teriparatide with an early, consistent and stable separation at any time-point during the overall 19 months of the observational period, but the difference between abaloparatide and teriparatide was not statistically significant (Figure 9).

The K–M event rates for clinical fractures (all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including spine pain) were also constantly lower in the abaloparatide group versus placebo with a clear separation at any time-point during the overall 19 months of the observational period (Figure 10), but the difference in clinical fracture event rates was not statistically significant for the abaloparatide group vs the placebo group (Table 19). [redacted] (Figure 10).

Figure 8: ACTIVE | Kaplan–Meier curves of time to event of nonvertebral fractures[a] through 19 months (excluding Sites 131 and 132; ITT population)



[a]All comparisons with teriparatide were exploratory
Abbreviations: ITT, intent-to-treat; SC, subcutaneous
Source: ACTIVE CSR addendum[63]; Abaloparatide EPAR[61]

Figure 9: ACTIVE | Kaplan–Meier curves of time to event of major osteoporotic fractures[a] through 19 months (excluding Sites 131 and 132; ITT population)

[a]All comparisons with teriparatide were exploratory
Abbreviations: ITT, intent-to-treat; SC, subcutaneous
Source: ACTIVE CSR addendum[63]

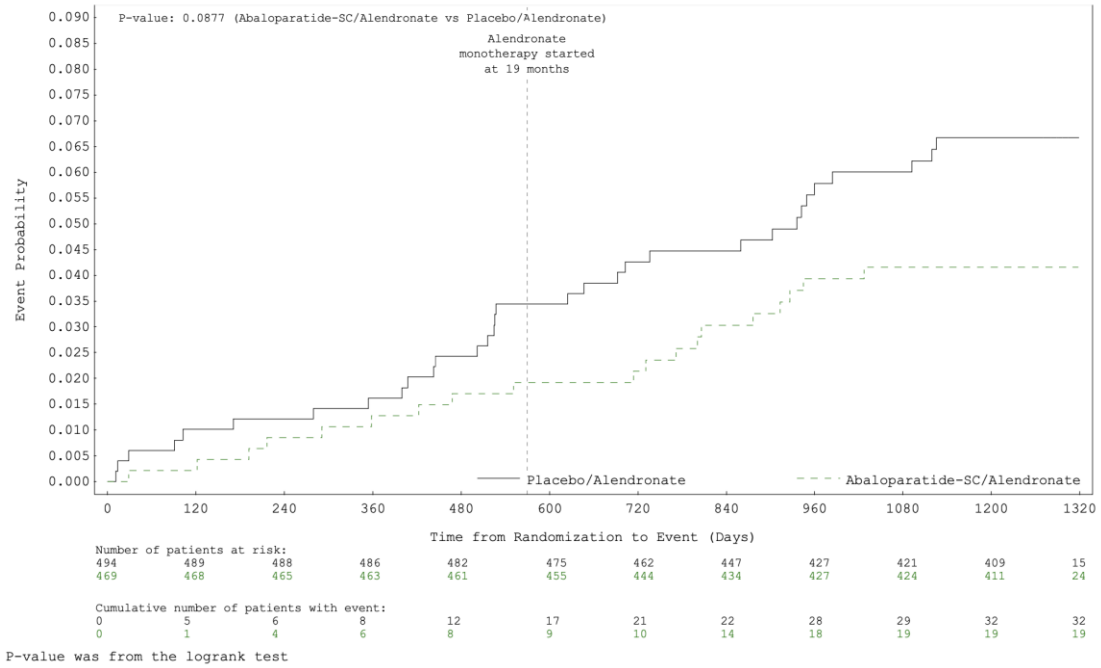
Figure 10: ACTIVE | Kaplan–Meier curves of time to event of clinical fractures[a] through 19 months (excluding Sites 131 and 132; ITT population)

[a]All comparisons with teriparatide were exploratory
Abbreviations: ITT, intent-to-treat; SC, subcutaneous
Source: ACTIVE CSR addendum[63]

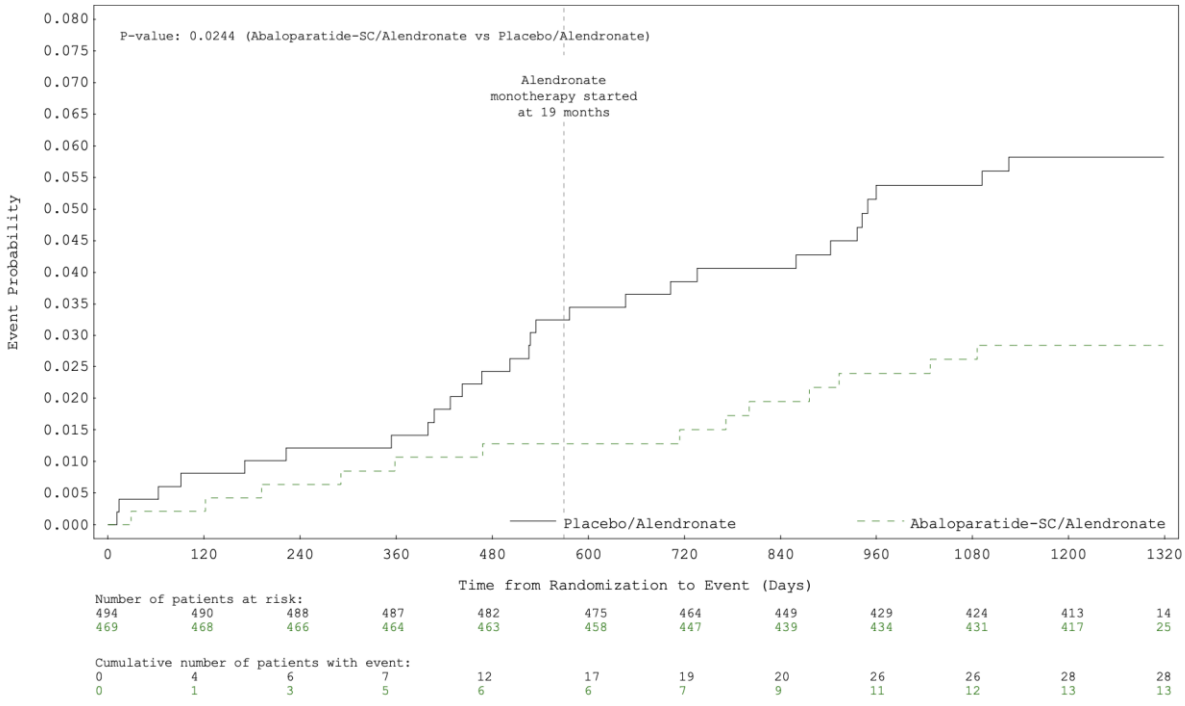
Similar findings were also observed in the final ACTIVExtend analysis at Month 43 (Table 20). As observed for ACTIVE, due to the hierarchical statistical testing approach used for efficacy endpoints (Section B.2.4.1, Table 11), the lack of a significant difference in nonvertebral fractures between the abaloparatide/alendronate vs placebo/alendronate groups in ACTIVExtend meant that the analyses of clinical and major osteoporotic fractures were exploratory. The separation from placebo observed through 19 months of ACTIVE was maintained at cumulative Month 43 through ACTIVExtend for all three fracture types (Figure 11).

Figure 11: ACTIVExtend | Kaplan–Meier curves of time to first incident A) nonvertebral, B) major osteoporotic and C) clinical fractures from ACTIVE baseline through 24 months of ACTIVExtend (Month 43; excluding Sites 131 and 132; ITT population)

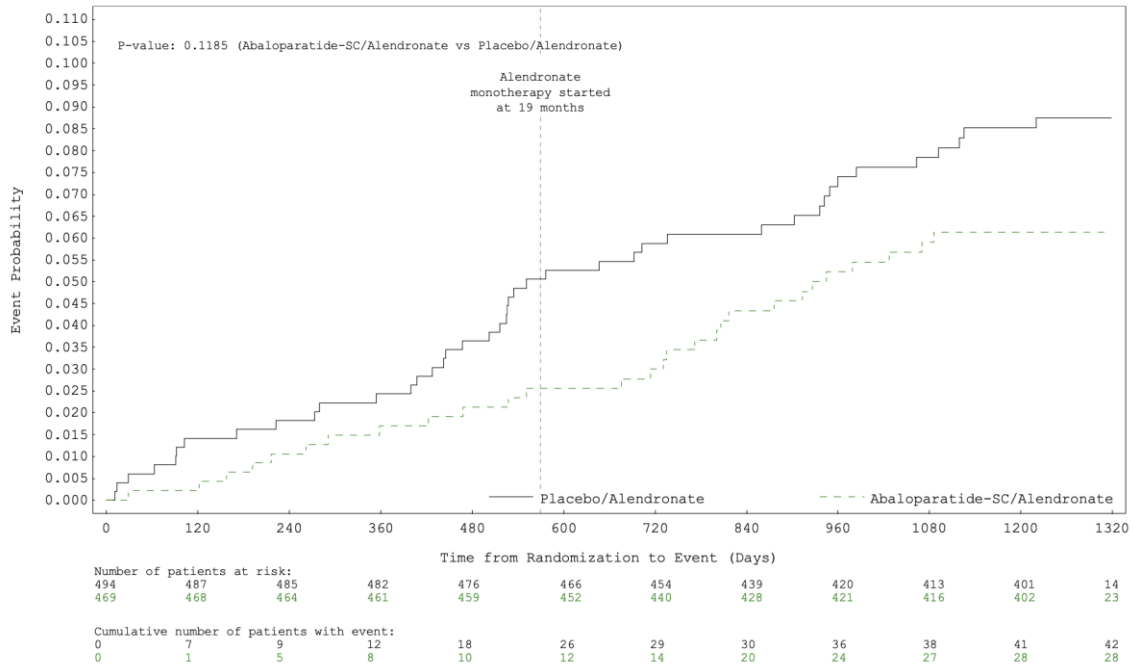
A)



B)



C)



Abbreviations: ITT, intent-to-treat; SC, subcutaneous
Source: ACTIVExtend CSR addendum[64]; Abaloparatide EPAR[61]

B.2.6.2 BMD endpoints | ACTIVE and ACTIVExtend

BMD outcomes from the ACTIVE study are summarised in Table 21.

Improvements in BMD in ACTIVE were significantly greater with abaloparatide vs placebo at the total hip, femoral neck and lumbar spine at 18 months (p<0.001 for all three sites Table 21; Figure 12). [redacted]. BMD increases were sustained throughout ACTIVExtend and were statistically significant at all time points (all p<0.001).

Abaloparatide increased BMD from baseline (nominal p values) [redacted]; at the total hip ([redacted] and p=0.021; exploratory endpoints) and femoral neck ([redacted] and p=0.039) at 12 and 18 months, respectively, vs teriparatide; [redacted]. Increases in lumbar spine BMD were similar between abaloparatide and teriparatide at 18 months (p=0.786). ACTIVE BMD data also suggested a faster onset of action for abaloparatide vs teriparatide.

Sensitivity analyses employing a mixed model for repeated measures (MMRM) approach demonstrated consistent outcomes to those for the primary analysis based on the last observation carried forward (LOCF) method.

Table 21: ACTIVE | BMD endpoints for abaloparatide versus placebo and teriparatide after 6, 12, and 18 months of treatment using LOCF (excluding Sites 131 and 132; ITT population)

ACTIVE					
Time-point	% change from baseline in BMD, mean (SD)		Abaloparatide vs placebo	% change from baseline in BMD, mean (SD)	Abaloparatide vs teriparatide
	Abaloparatide (n=696)	Placebo (n=688)	p value	Teriparatide (n=686)	p-value[a]
6 months					
Total hip	2.04 (2.48) (n=694)	0.29 (2.09) (n=687)	<0.001[a]	[redacted]	[redacted]
Femoral neck	1.42 (2.93) (n=694)	–0.11 (2.77) (n=687)	<0.001[a]	[redacted]	[redacted]
Lumbar spine	5.88 (5.25) (n=695)	0.50 (3.35) (n=688)	<0.001[a]	[redacted]	[redacted]
12 months					
Total hip	2.79 (2.97) (n=694)	0.11 (2.48) (n=687)	<0.001[a]	[redacted]	[redacted]
Femoral neck	2.04 (3.38) (n=694)	–0.42 (3.08) (n=687)	<0.001[a]	[redacted]	[redacted]
Lumbar spine	8.06 (6.72) (n=695)	0.38 (3.52) (n=688)	<0.001[a]	[redacted]	[redacted]
18 months					
Total hip	3.33 (3.41) (n=694)	–0.03 (2.81) (n=687)	<0.001	2.96 (3.33) (n=686)	0.021[a]
Femoral neck	2.68 (3.97) (n=694)	–0.42 (3.55) (n=687)	<0.001	2.30 (3.46) (n=686)	0.039[a]
Lumbar spine	9.09 (7.59) (n=695)	0.47 (3.85) (n=688)	<0.001	9.20 (6.28) (n=686)	0.79[a]

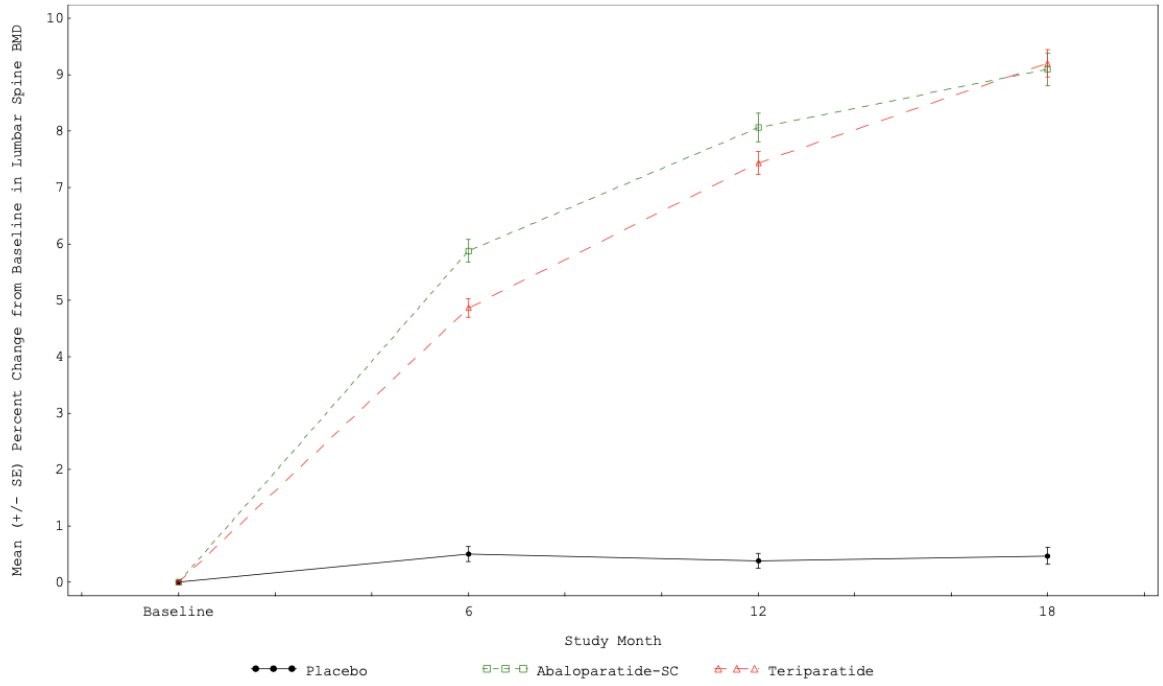
[a]Nominal p values presented for exploratory analyses
BMD, bone mineral density; ITT, intent-to-treat; LOCF, last observation carried forward; SD, standard deviation
Source: ACTIVE CSR addendum[63], MHRA SmPC[2]; Abaloparatide EPAR[61]

Figure 12: ACTIVE | Change from baseline in BMD using LOCF through Month 18 (excluding Sites 131 and 132; ITT population)

A) Total hip

B) Femoral neck

C) Lumbar spine

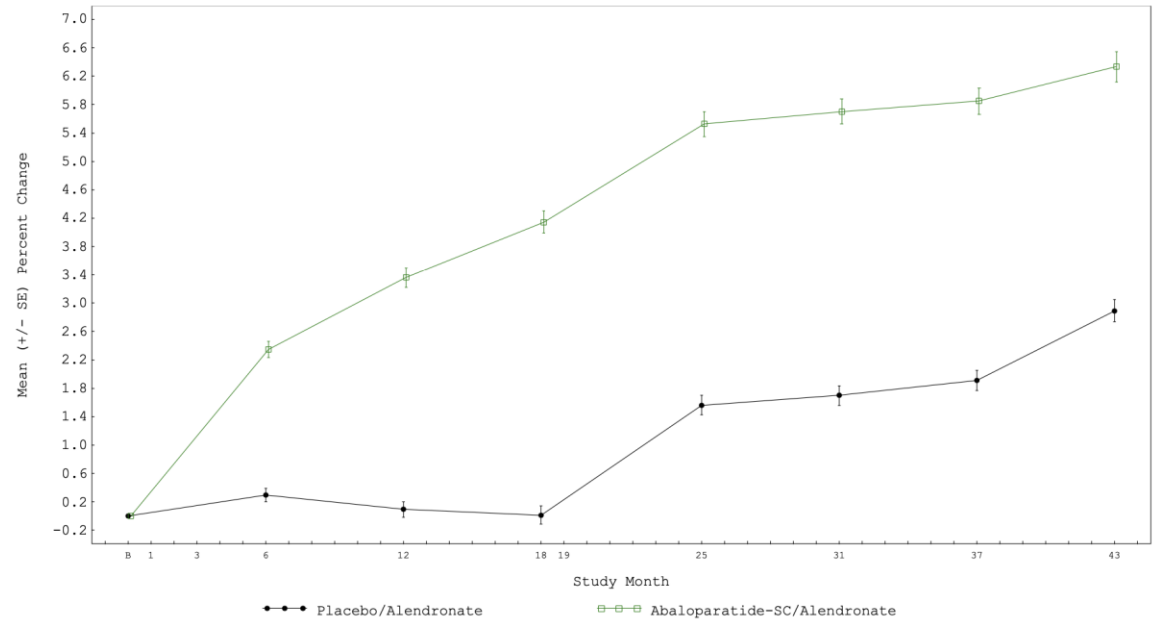


Abbreviations: BMD, bone mineral density; ITT, intent-to-treat; LOCF, last observation carried forward; SC, subcutaneous
Source: ACTIVE CSR addendum[63]; Abaloparatide EPAR[61]

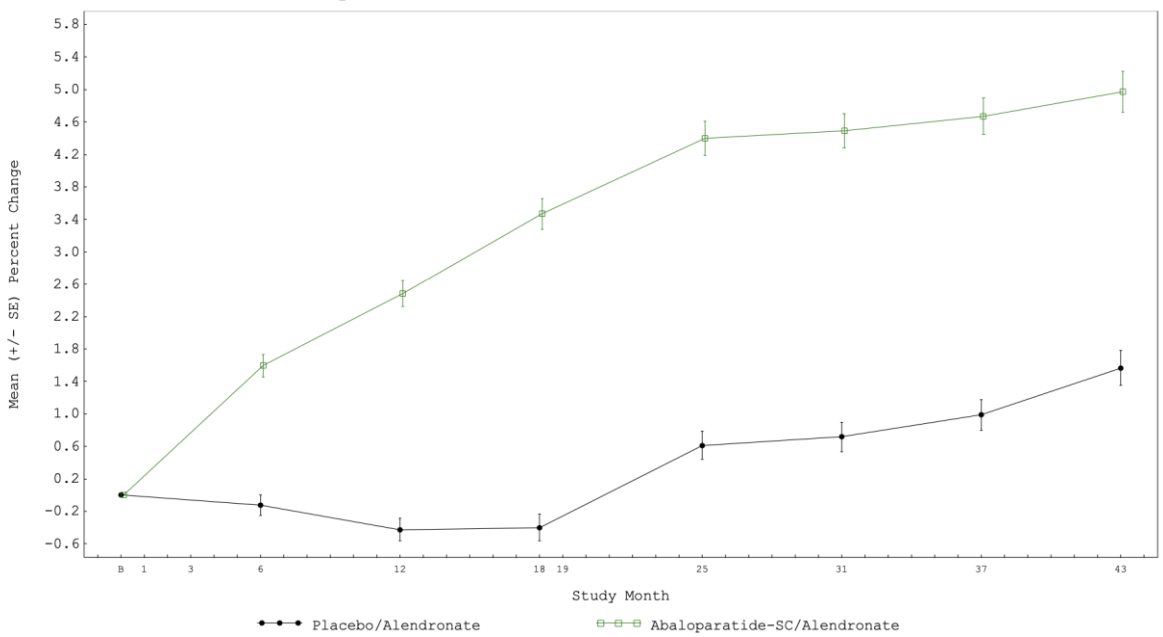
In ACTIVExtend, all gains in BMD realised during ACTIVE with abaloparatide were maintained at Month 43 (Figure 13). The increase in percentage change in BMD at the total hip, femoral neck and lumbar spine in the abaloparatide/alendronate vs placebo/alendronate groups was statistically significant at all time points (all $p<0.001$). Sensitivity analyses using MMRM remained consistent with those from the primary LOCF method.

Figure 13: ACTIVExtend | Percentage changes in BMD from ACTIVE baseline to end of ACTIVExtend (Month 43) using LOCF (excluding Sites 131 and 132; ITT population)

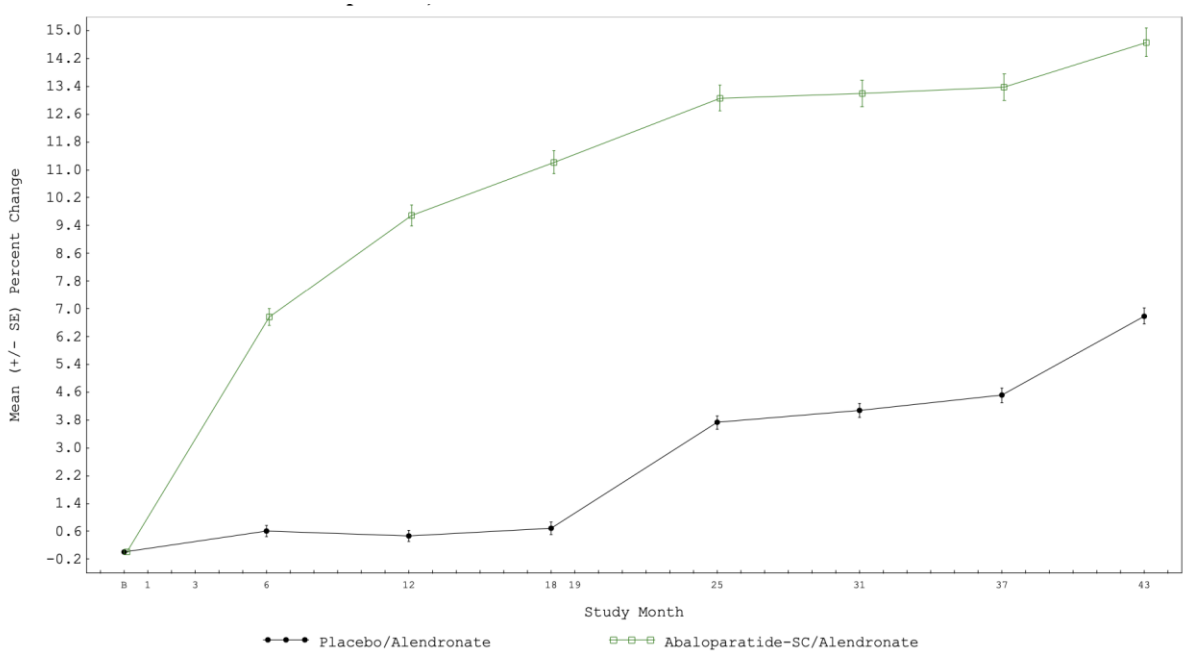
A) Total hip



B) Femoral neck



C) Lumbar spine



ITT, intent-to-treat; LOCF, last observation carried forward; SC, subcutaneous
Sources: ACTIVExtend CSR addendum[64]; Abaloparatide EPAR[61]

B.2.6.3 Bone turnover marker endpoints | ACTIVE and ACTIVExtend

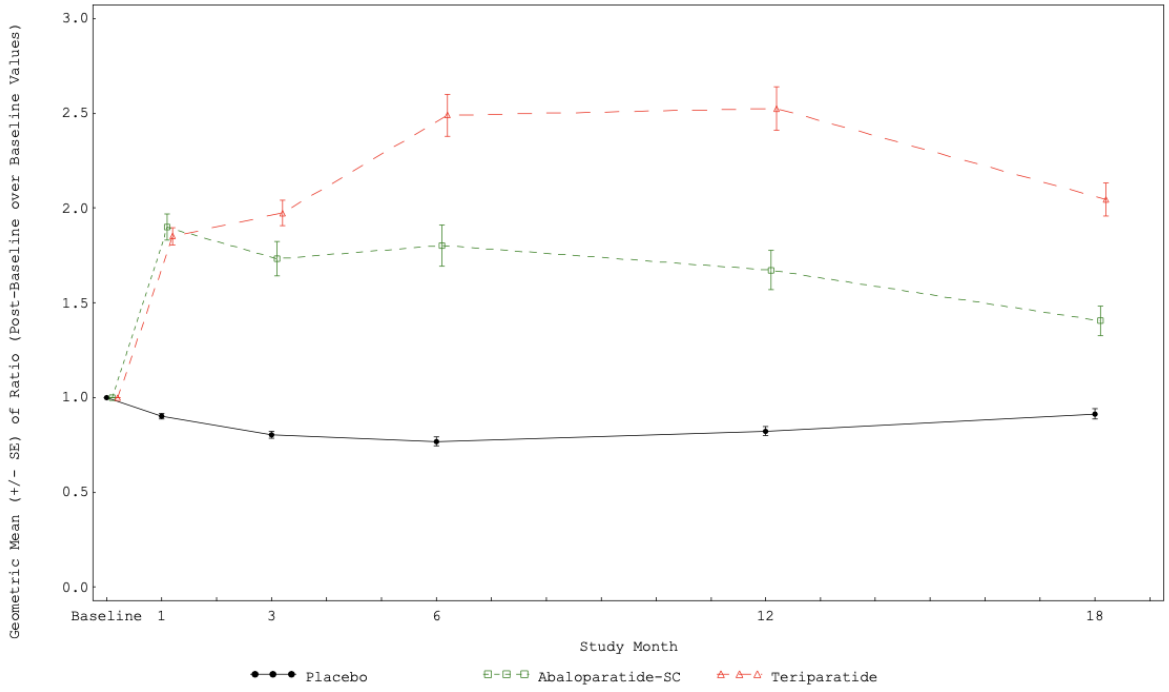
Changes in the bone turnover markers s-P1NP (a bone formation marker) and s-CTX (a bone resorption marker) correlated with BMD data (Section B.2.6.2). Differences between abaloparatide and teriparatide in the ACTIVE trial were consistent with their differing mechanisms of action and the wider anabolic window for abaloparatide (Figure 1). Abaloparatide sustained anabolic build for 18 months with greater anabolic selectivity vs placebo throughout the ACTIVE treatment period. While anabolic activity remained elevated throughout the treatment period vs placebo, there was only a transient rise in bone resorption, consistent with greater net bone gains in the skeleton.

The ACTIVE bone turnover marker population comprised 156 patients in the placebo group, 164 patients in the abaloparatide group and 180 patients in the teriparatide group. In ACTIVE, the bone formation marker s-P1NP showed significant increases among abaloparatide-treated participants compared with placebo at all time points ($p<0.001$) (Figure 14). The increase in s-P1NP was similar for abaloparatide versus teriparatide at 1 month but the trend became higher for teriparatide at 3, 6, 12 and 18 months ($p<0.001$).

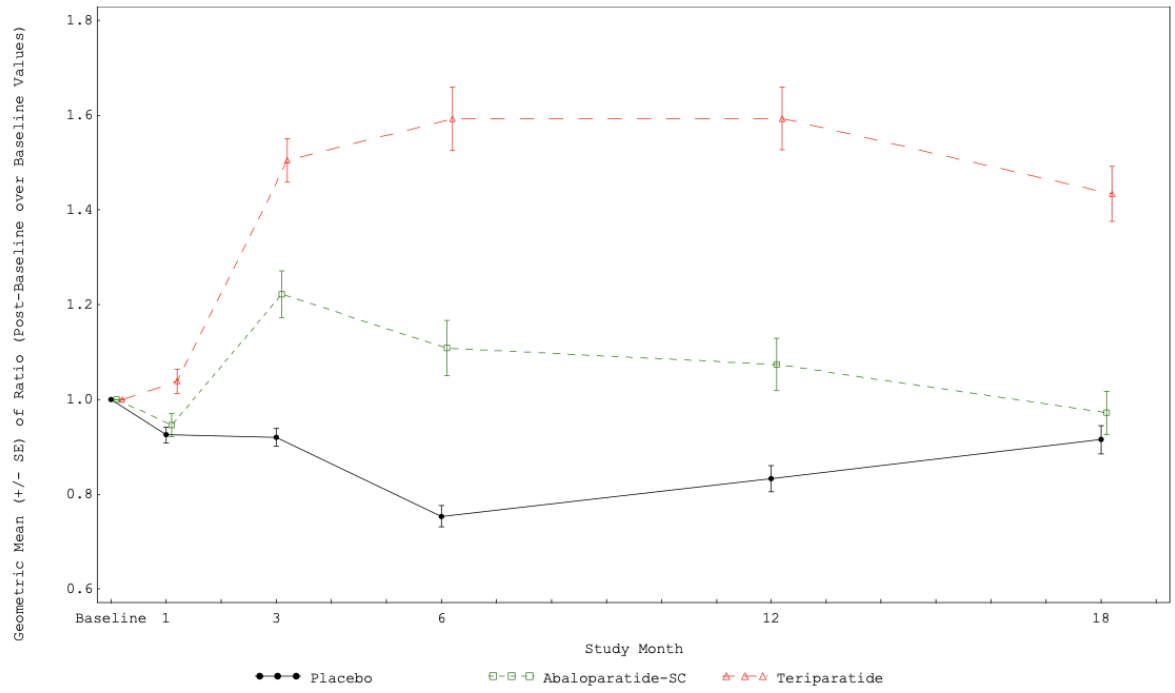
Abaloparatide treatment resulted in a transient increase in the resorption marker s-CTX vs placebo ($p<0.001$) at 3, 6 and 12 months but not at 1 month or 18 months (Figure 14). Increases in s-CTX were greatest with teriparatide and remained elevated throughout the 18-month treatment period.

Figure 14: ACTIVE | Geometric mean (+/- SE) of ratio (post-baseline over baseline values) in serum bone metabolism markers through Month 18 (excluding Sites 131 and 132; BTM population)

A) s-P1NP



B) s-CTX



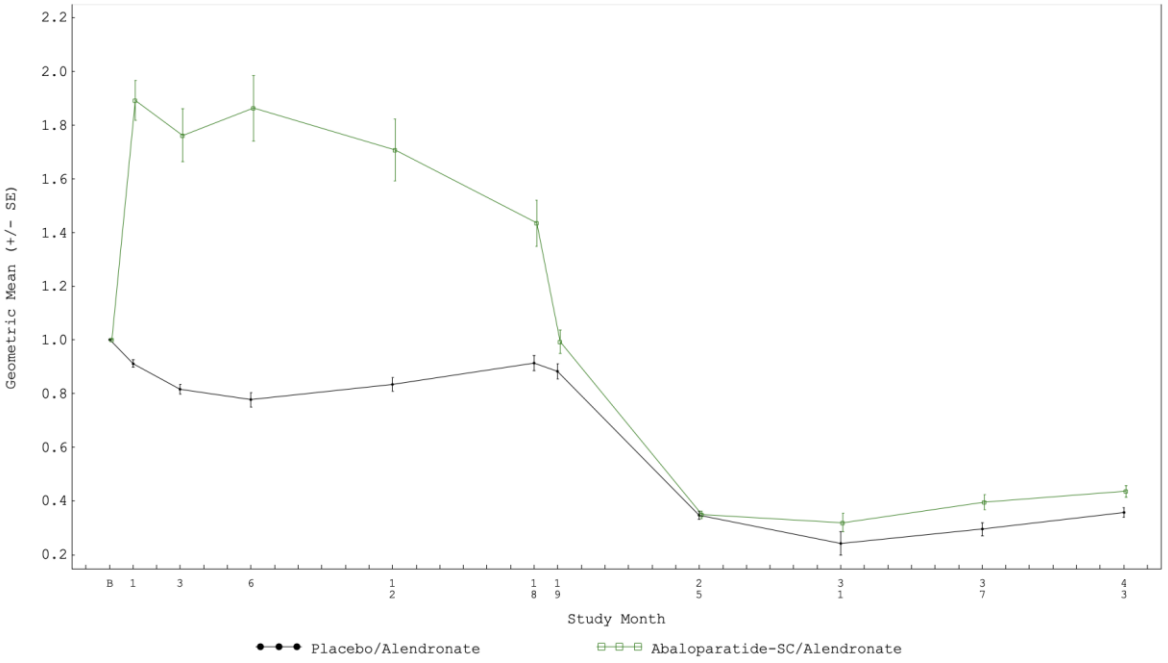
Levels indicate geometric mean (+/- SE) of ratio (post-baseline over baseline values change from baseline for a bone turnover marker population subset (n=156 placebo, n=164 abaloparatide, and n =180 teriparatide for change from baseline at Months 6, 12 and 18 for both s-P1NP and s-CTX)
Abbreviations: BTM, bone turnover marker; s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; SC, subcutaneous; SE, standard error; s-P1NP, serum procollagen type I N-terminal pro-peptide
Source: ACTIVExtend CSR addendum[64]

The ACTIVExtend bone turnover marker population comprised 140 patients in the placebo/alendronate group and 148 patients in the abaloparatide/alendronate group. As expected with antiresorptive therapy, levels of both s-P1NP and s-CTX decreased well below ACTIVE baseline levels during treatment with alendronate (Months 19 to 43) and remained suppressed through Month 43 in both treatment groups (Figure 15).

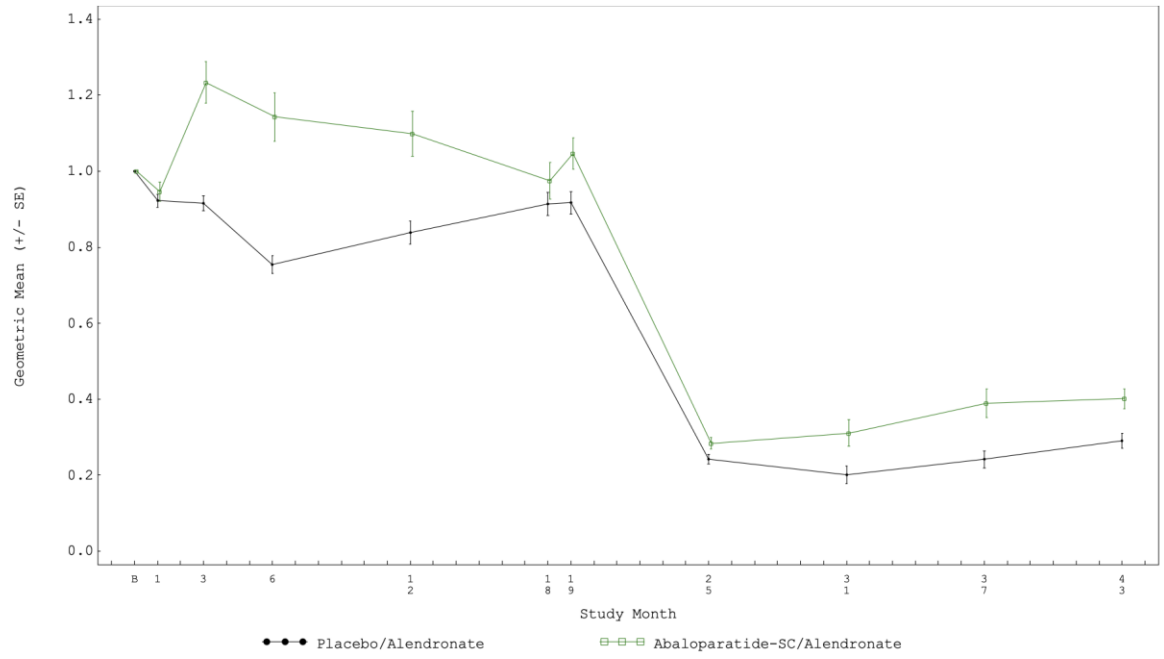
At Month 43, the geometric least square mean of ratio change from ACTIVE baseline in s-P1NP was 0.361 in the placebo/alendronate group vs 0.414 in the abaloparatide/alendronate group (p=0.016). Although geometric least square mean ratios for s-CTX were statistically significantly different between groups at Month 43 (0.304 for placebo/alendronate vs 0.390 for abaloparatide/alendronate; p=0.004), the difference between the groups was not clinically meaningful because the changes for both groups indicated a decrease for s-CTX.

Figure 15: ACTIVExtend | Secondary endpoints | Changes in bone turnover markers from ACTIVE baseline to end of ACTIVExtend (through Month 43) (excluding Sites 131 and 132; BTM population)

A) s-P1NP



B) s-CTX



Alendronate monotherapy started at 19 months
Levels indicate geometric mean (+/- SE) of ratio (post-baseline over baseline values change from ACTIVE baseline for a bone turnover marker population subset (n=140 placebo/alendronate, n=148 abaloparatide/alendronate for change from baseline at Months 6, 12, 18, 19, 25; n=87 placebo/alendronate, n=96 abaloparatide/alendronate for change from baseline at Month 43 for both s-P1NP and s-CTX)
Abbreviations: BTM, bone turnover marker; SC, subcutaneous; s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; SE, standard error; s-P1NP, serum procollagen type I N-terminal pro-peptide
Source: ACTIVExtend CSR addendum[64]

B.2.6.4 Real-world evidence study | Effectiveness outcomes

B.2.6.4.1 Nonvertebral fractures

The primary endpoint in the RWE study was time to first nonvertebral fracture and showed noninferiority of abaloparatide vs teriparatide.[62] The estimated new nonvertebral fracture rate was similar for abaloparatide (2.9%) vs teriparatide (3.2%; hazard ratio [HR] 0.89, p=0.13) (Table 22; Figure 16). Noninferiority was established since the upper bound of the two-sided 95% CI of the HR between abaloparatide and teriparatide was 1.03 (<1.3). Outcomes were consistent among all sub-populations in the sensitivity analyses.

The risk of hip fractures (an exploratory endpoint) was reduced by 22% (0–33%) for abaloparatide vs teriparatide (new event rate, 1.0% vs 1.3%; HR [95% CI] 0.78 [0.62–1.00], p=0.04) (Table 22; Figure 16). When limiting the hip fracture sensitivity analyses to patients with >12 months of consecutive exposure to treatment, the HR (95% CI) still favoured abaloparatide (0.57 [0.35–0.94]).[62] Fracture rates at other sites were generally comparable with the rates observed for nonvertebral and hip fractures.[67] Together with the differences between cortical BMD and bone turnover markers for abaloparatide and teriparatide in the ACTIVE study (Sections B.2.6.2 and B.2.6.3) this finding further supports that abaloparatide may be more efficacious than teriparatide at increasing cortical BMD.

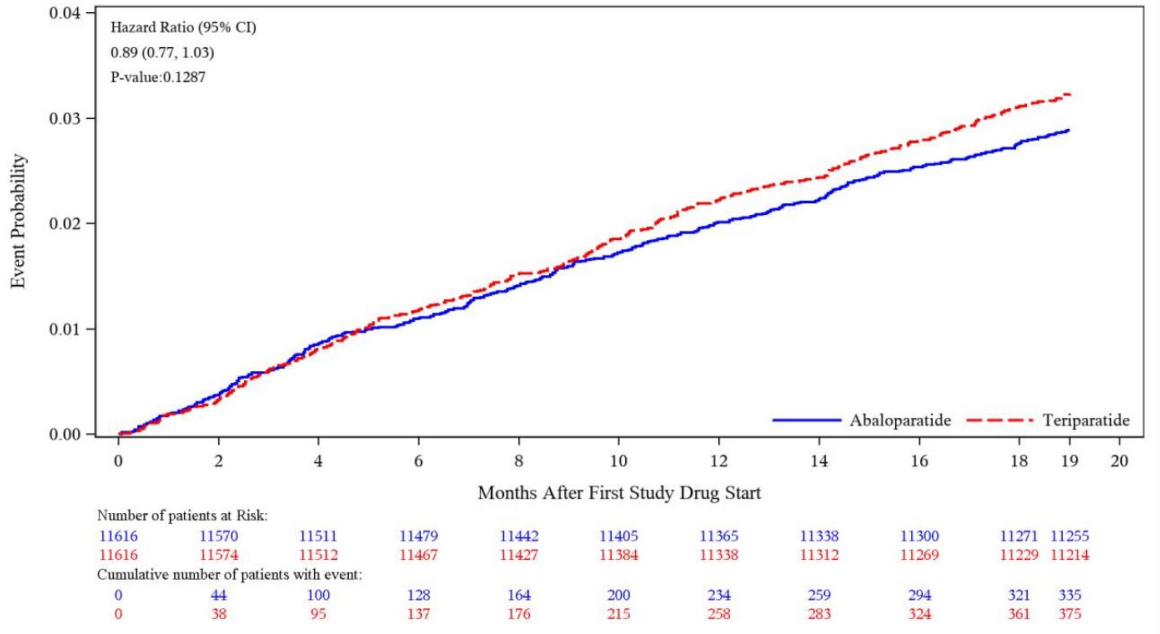
Table 22: Real-world evidence study | Time to first fracture event during 18 months after treatment initiation (overall propensity score-matched population)

Time to event variable	Parameter	RWE study	
		Abaloparatide (n=11,616)	Teriparatide (n=11,616)
Primary endpoint			
Nonvertebral fracture	Number of patients with event, n (%[a])	335 (2.9)	375 (3.2)
	HR (95% CI) vs teriparatide[b]	0.89 (0.77–1.03)	–
	p value vs teriparatide[c]	0.13	–
Exploratory endpoint			
Hip fracture	Number of patients with event, n (%[a])	121 (1.0)	154 (1.3)
	HR (95% CI) vs teriparatide[b]	0.78 (0.62–1.00)	–
	p value vs teriparatide[c]	0.04	–

[a]Percentage reported is Kaplan–Meier estimate at 19 months (observation period of 18 months [540 days] plus 30-day follow-up after the index date)
[b]Cox proportional hazard model was used to calculate the HR with teriparatide as the reference
[c]P values from the log-rank test
Abbreviations: CI, confidence interval; HR, hazard ratio; RWE, real-world evidence
Source: RWE study CSR[67]; Cosman et al (2022)[62]

Figure 16: Real-world evidence study | Time to first incidence of A) nonvertebral fracture and B) hip fracture (overall propensity score-matched population)

A)



B)

Abbreviations: CI, confidence interval
The intent-to-treat analysis observation period was from the index date to the 18 months plus 30 days follow-up
Patients at risk include all patients regardless of when treatment was discontinued, except those who had a fracture event or died
Source: RWE study CSR[67], Cosman et al (2022)[62]

B.2.6.5 Efficacy conclusions

The efficacy and safety of 18 months of abaloparatide treatment followed by 24 months of alendronate were confirmed in a large Phase 3 randomised, placebo- and active-controlled trial (ACTIVE) and its long-term extension study (ACTIVExtend).

The ACTIVE study met its primary endpoint, demonstrating that treatment with abaloparatide significantly reduced the risk of new morphometric vertebral fractures compared with placebo (0.5% vs 4.2% respectively; RRR = 88%; $p<0.001$) at 18 months. At the end of the full 43-month treatment period of the ACTIVE–ACTIVExtend study, the primary endpoint of reduced risk of new vertebral fractures was effectively sustained.

Event rates for nonvertebral fractures in ACTIVE were also numerically lower in the abaloparatide vs placebo groups. Although between-group differences were not statistically significant, the EMA considered there to be no scientific reason to presume efficacy only for vertebral but not nonvertebral fractures. Nonvertebral fracture incidence was also numerically lower in the abaloparatide/alendronate vs placebo/alendronate groups in ACTIVExtend, but this difference was not statistically significant.

Major osteoporotic fracture incidence (exploratory endpoint) was statistically significantly lower in the abaloparatide vs placebo group in ACTIVE was sustained though Month 43 of the ACTIVE–ACTIVExtend study. K–M event rates for major osteoporotic fractures were constantly lower for abaloparatide vs placebo and vs teriparatide with an early, consistent and stable separation at any time-point during the overall 19 months of the ACTIVE

observational period, but the difference between abaloparatide and teriparatide was not statistically significant.

Clinical fracture incidence (exploratory endpoint) was numerically lower in the abaloparatide vs placebo group in ACTIVE and in the abaloparatide/alendronate vs placebo/alendronate in ACTIVExtend, but between-group differences were not statistically significant. [redacted].

In ACTIVE, BMD improvements in the abaloparatide group were significantly greater than the placebo group at the total hip, femoral neck and lumbar spine at 18 months. BMD improvements were also significantly greater in the abaloparatide/alendronate vs placebo/alendronate at Month 43 of ACTIVExtend.

ACTIVE data also suggested a faster onset of action for abaloparatide vs teriparatide (nominal p values), showing increased BMD from baseline at the total hip ($p<0.001$), femoral neck ($p=0.004$), and lumbar spine ($p=0.001$) at 6 months vs teriparatide. BMD increases for abaloparatide vs teriparatide were also greater at 12 months and at the total hip and femoral neck at 18 months, with increases in lumbar spine BMD similar between abaloparatide and teriparatide at 18 months ($p=0.787$). Differences in cortical BMD between abaloparatide and teriparatide were consistent with changes in bone turnover markers, reflect the differing mechanisms of action of abaloparatide and teriparatide and the suggested wider anabolic window for abaloparatide.

Real-world data supported the findings of the ACTIVE and ACTIVExtend trials. In the RWE study, powered to compare abaloparatide vs teriparatide, estimated new nonvertebral fracture rates were similar for patients who received abaloparatide vs teriparatide. The risk of hip fractures (an exploratory endpoint) was significantly reduced with abaloparatide vs teriparatide, further supporting that abaloparatide may be more efficacious at increasing cortical BMD vs teriparatide.

B.2.7 Subgroup analyses

Pre-planned subgroups are listed in Section B.2.3 (Table 9 and Table 10). Forest plots are presented in Appendix E.

ACTIVE

Subgroup analyses for vertebral and other fracture endpoints from baseline were generally consistent with the primary analyses for the effects of abaloparatide vs placebo.

Real-world evidence study

Effectiveness outcomes in propensity score-matched subgroup analyses were generally consistent with the overall cohort for nonvertebral and hip fractures, although fracture events were higher in prespecified subgroups considered to be at high risk for fracture (Table 10) with comparable effectiveness for both the abaloparatide and teriparatide cohorts.[62]

Safety outcomes for the incidence of composite CV events with abaloparatide vs teriparatide were also generally consistent among all subgroups when compared with the overall CV data.

B.2.8 Meta-analysis

B.2.9 Indirect and mixed treatment comparisons

In the absence of head-to-head data, a NMA was conducted to compare the efficacy of abaloparatide with the comparators of relevance to the decision problem in this evaluation, using published evidence identified from the clinical SLR (see Section B.2.1 and Appendix D). The efficacy outcomes considered in the NMA were based on the outcomes specified in the final scope issued by NICE, as well as the availability of data reported in the literature. The outcomes included in the NMA are presented in Table 23.

Table 23: Outcomes for the NMA

Outcome	Type of data or distribution	Output statistics of NMA
Efficacy outcomes: • New vertebral fracture (at 18 months) • New or worsening vertebral fracture (at 18 months) • Nonvertebral fracture (at 12 and 18 months) • Clinical fracture (at 12 and 18 months) • Hip fracture (at 18 months) • Major osteoporotic fracture (at 12 months) • Fractures in other bones/ regions (at 18 months)	Binomial	Relative risk, 95% CrI of the estimate

Abbreviations: CrI, credible interval; NMA, network meta-analyses

B.2.9.1 Identification and selection of relevant studies from the clinical SLR

As described in Section B.2.1 and Appendix D, an SLR was conducted in April 2023. From an initial pool of 1,743 deduplicated studies, a total of 33 studies were found to be eligible for the NMA. Table 24 presents the PICOS criteria used in the feasibility analysis of the NMA. The comparators included in the NMA are based on feasibility assessment.

Table 24: Eligibility (PICOS) criteria used in the NMA

Criteria	Parameter
Population	Postmenopausal women with osteoporosis at increased risk of fracture
Intervention	All relevant comparators
Comparators	• Abaloparatide • Abaloparatide followed by alendronate • Bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid) • Non-bisphosphonates (romosozumab, teriparatide, raloxifene and denosumab) • Placebo
Outcomes	• Efficacy outcomes: • New vertebral fracture • Worsening vertebral fracture • New or worsening vertebral fracture • Nonvertebral fracture • Clinical fracture, hip fracture • Major osteoporotic fracture • Fractures in other bones/regions
Study design	RCT - parallel group (triple/double-blind). Cross-over and open-label extensions of studies were considered if the core studies were parallel group RCTs
Time-point	12, 18, 24 and 36 months
Language	Studies published in the English language only

Abbreviations: NMA, network meta-analysis; PICOS, population, intervention, comparators, outcomes, study design; RCT, randomised controlled trial

B.2.9.2 Risk of bias

A risk of bias assessment was performed on all clinical trials included in the NMA. The studies included for the NMA were critically appraised for methodological quality under these parameters: randomisation and allocation concealment, baseline characteristics, blinding status, outcomes selection and reporting, and statistical analysis (Appendix D).

Overall, the included study for abaloparatide (ACTIVE, excluding Sites 131 and 132) was adjudged to pose a low risk of bias concerning randomisation, baseline characteristics, and statistical methodology. As there were differences in ethnicity and prevalent vertebral fracture rates in the studies included in the NMA, there is a moderate risk of bias from effect modification in the comparison between abaloparatide and other comparators. For more details see Appendix D.

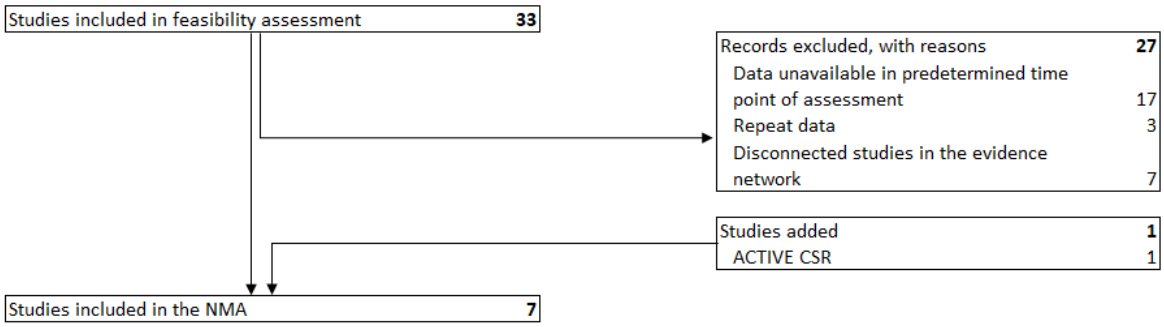
B.2.9.3 Overview of the selected studies

Of the 33 studies included in the feasibility assessment, only seven studies were included in the NMA, including the data taken from the ACTIVE population (excluding Sites 131 and 132). Graphical data were also considered (Figure 17). Twenty-seven studies were excluded due to the following reasons:

1) Data unavailable in predetermined time-point of assessment, N=17
2) Repeat data, N=3
3) Disconnected studies in the evidence network, N=7

Studies without fracture outcomes data at 12, 18, 24, and 36 months were excluded under 'data unavailable in predetermined time-point of assessment'. Since data from the ACTIVE study population excluding Sites 131 and 132[63] were used in the NMA, the published ACTIVE data identified in the SLR were excluded under 'repeat data'. Further, studies that did not contribute to the network by having either a single arm, or not having sequential treatment arms, were excluded under 'disconnected studies.'

Figure 17: Studies included in the NMA (Included/excluded)



Trials included in the NMA are presented in Table 25, with full details shown in Appendix D.3.3. A global evidence network was generated based on the identified evidence (see Figure 18). Networks for all fracture outcomes at 12 and 18 months used ACTIVE (excluding Sites 131 and 132) data for the direct comparison between abaloparatide and placebo and abaloparatide and teriparatide. Therefore, for fracture outcomes, only indirect evidence is available for comparisons of abaloparatide with comparator treatments other than teriparatide and placebo.

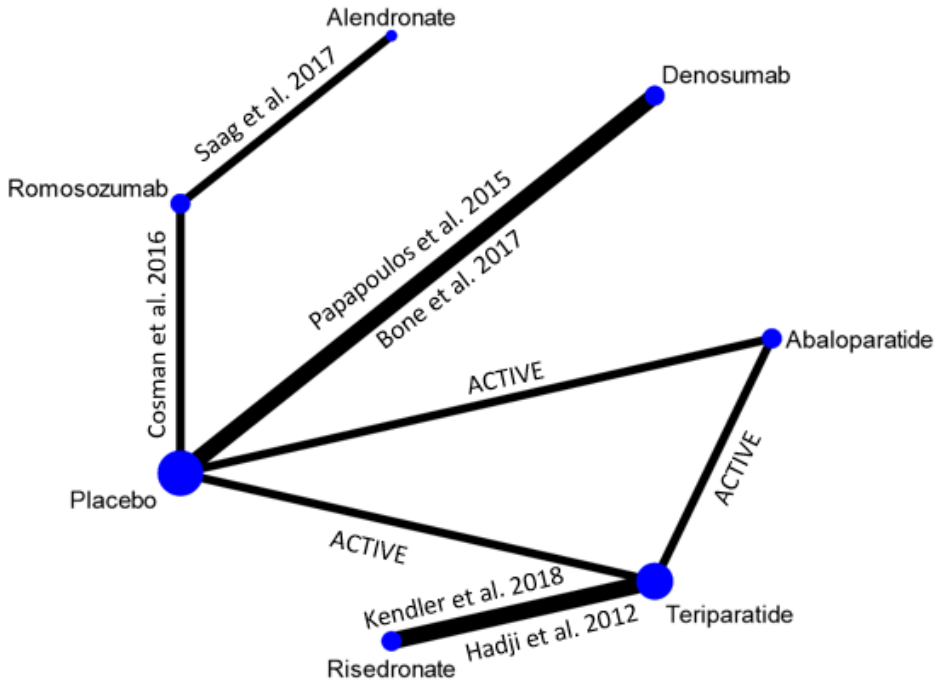
Table 25: Trials included in the NMA

Trial name	Treatment
ACTIVE (excluding Sites 131 and 132)[63]	Placebo Abaloparatide Teriparatide
FRAME(Cosman et al. 2016)[70]	Placebo Romosozumab
NR (Hadji et al. 2012)[71]	Teriparatide Risedronate
ARCH (Saag et al. 2017)[72]	Alendronate

	Romosozumab
FREEDOM (Bone at al. 2017)[73a]	Placebo Denosumab
FREEDOM and FREEDOM extension (Papapoulous 2015)[74b]	Long-term treatment with denosumab
VERO (Kendler et al. 2018)[75]	Teriparatide Risedronate

Abbreviations: NMA, network meta-analysis; NR, not reported.
[a]10 year follow-up data
[b]5 and 8 year follow-up data

Figure 18: Global evidence network for the NMA



Abbreviations: CSR, clinical study report; NMA, network meta-analysisNote: ACTIVE refers to the CSR addendum population (excluding Sites 131 and 132)[63]

B.2.9.4 Heterogeneity assessment of trials included

The included clinical studies differed in treatment duration, sample size, age, and race, suggesting considerable clinical heterogeneity. Across the included studies in NMA, mean baseline age ranged from 69.3 years to 74.9 years. Five studies were double-blind, and two were double-blind and open-label. The sample size of the included studies varied from 350 patients to 3,906 patients. Differences in treatment duration were observed across the included studies ranging from a minimum of 18 months to 120 months. The studies varied in assessment time due to differences in treatment trial durations and timing of study visits. Additional results are presented in Appendix D.

Heterogeneity assessment was not feasible for all outcomes except for nonvertebral fracture at 12 and 18 months.

B.2.9.5 NMA methodology

The NMA was conducted in a Bayesian framework. Binary Bayesian models were used for fracture outcomes. Non-informative priors were used for all analyses. Both fixed and random-effects models (FEM and REM) were presented for fracture outcomes. All analyses were run with 80,000 iterations after a burn-in of 20,000 iterations. All presented results converged. Convergence was assessed by running three chains and convergence was assumed if the Gelman–Rubin statistic was equal to 1. It can be expected that there is always some variation in patient characteristics, study sites, and settings across studies; if these characteristics are effect modifiers of the relative treatment effects of interest, then variability in these effect modifiers can confound the results of an NMA. To allow for heterogeneity between studies, random-effects models were evaluated. Random-effects models assume that treatment effects may vary between studies but come from a common distribution of treatment effects, with a mean for each treatment effect and a common between-study covariance matrix.

The better fitting model was selected based on the deviance information criterion (DIC) value. A difference of more than three points in the DIC was considered as a relevant difference. The model with the lower DIC was considered a better-fitted model. For some outcomes, only a small number of studies were included; the heterogeneity parameter is, therefore, difficult to estimate, necessitating the use of the fixed-effects model.

Homogeneity was assessed using the I^2 statistic, using threshold values to indicate little (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), and considerable (75% to 100%) heterogeneity. Consistency was assessed using the Bucher method, taking a P value of <0.05 as significant inconsistency. Baseline characteristics were compared to assess the similarity of included studies, including mean age and the proportion of patients with relevant fracture. Publication bias was not assessed.

Heterogeneity was assessed using I^2 statistics for comparisons for which more than one study included. No heterogeneity was found. Inconsistency was not feasible as only one study is included in the loop.

For the fracture outcomes, relative risks (RRs) were used to estimate the relative effectiveness of all treatments based on the number of participants in each treatment group in each study and the number of participants developing fractures at each time-point. The methods followed the recommended best practice of the NICE Decision Support Unit for evidence synthesis.[76,77] Results were presented as forest plots showing the effectiveness of abaloparatide vs other comparators.

B.2.9.6 NMA results

The feasibility analysis identified several outcomes that could not be evaluated at 12 or 18 months (Table 26). Therefore, the results are presented only for those outcomes which were deemed feasible. This section presents results that were used in the economic model scenario analysis. Additional results are presented in Appendix D.

Table 26: Feasibility assessment table

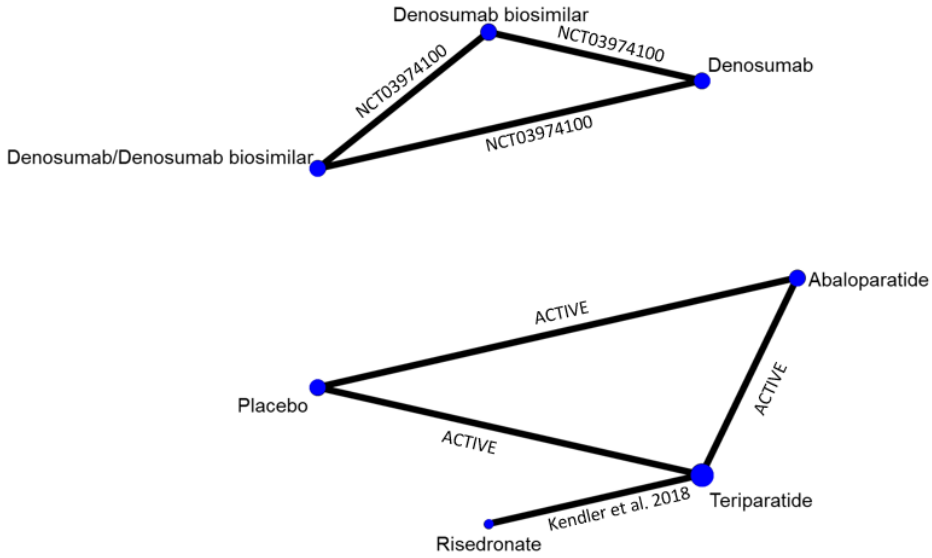
Fracture endpoints	At 12 months	At 18 months
New vertebral fracture	No	Yes
Worsening vertebral fracture	No	No
New or worsening vertebral fracture	No	Yes

Nonvertebral fracture	Yes	Yes
Clinical fracture	Yes	Yes
Hip fracture	No	Yes
Major osteoporotic fracture	Yes	No
Fractures in other bones/ regions	No	Yes

B.2.9.6.1 New vertebral fracture at 18 months

The network of studies reporting data for new vertebral fractures is illustrated in Figure 19. Three studies assessing seven treatments reported new vertebral fracture data at 18 months. As one study was disconnected, only two studies assessing four treatments contributed to this outcome.

Figure 19: Network for analysis – new vertebral fracture at 18 months



Abbreviations: CSR, clinical study report
Note: ACTIVE refers to the CSR addendum population (excluding Sites 131 and 132)[63]

Figure 20: Summary forest plot of new vertebral fracture at 18 months (FEM and REM) abaloparatide versus comparators

Abbreviations: CrI, credible interval; FEM, fixed-effects model; REM, random-effects model; RR, relative risk

The FEM demonstrated that abaloparatide [redacted] the risk of new vertebral fracture compared with placebo [redacted] (Figure 20).

The REM also demonstrated [redacted] for abaloparatide vs other comparators. [redacted] (Figure 20).

Table 27 presents the model fit statistics. DIC and residual deviance were comparable for the FEM and REM, hence, both models were used to draw conclusions.

Table 27: DIC and residual deviance values for new vertebral fracture at 18 months using fixed effect and random effect models

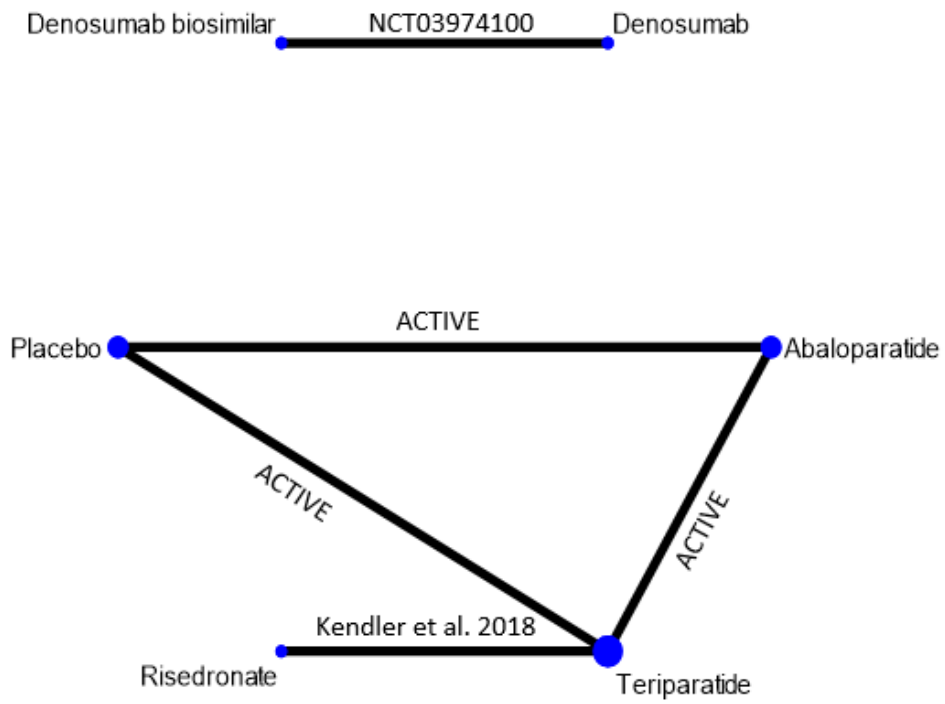
	FEM	REM
DIC	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; FEM, fixed-effects model; REM, random-effects model

B.2.9.6.2 Hip fracture at 18 months

The network of studies reporting data for hip fracture is illustrated in Figure 21. Three studies assessing six treatments reported hip fracture data at 18 months. As one study was disconnected, only two studies assessing four treatments contributed to the NMA.

Figure 21: Network for analysis – hip fracture at 18 months



Abbreviations: CSR, clinical study report
Note: ACTIVE refers to the CSR addendum population (excluding Sites 131 and 132)[63]

Figure 22: Summary forest plot of hip fracture at 18 months (FEM and REM) for abaloparatide vs comparators

Abbreviations: CrI, credible interval; FEM, fixed-effects model; REM, random-effects model; RR, relative risk

The FEM and REM demonstrated [redacted] (Figure 22).

Table 28 presents the model fit statistics. DIC and residual deviance were comparable for the fixed and random-effects model. Hence, both models were used to draw conclusions.

Table 28: DIC and residual deviance values for hip fracture at 18 months using fixed effect and random effect models

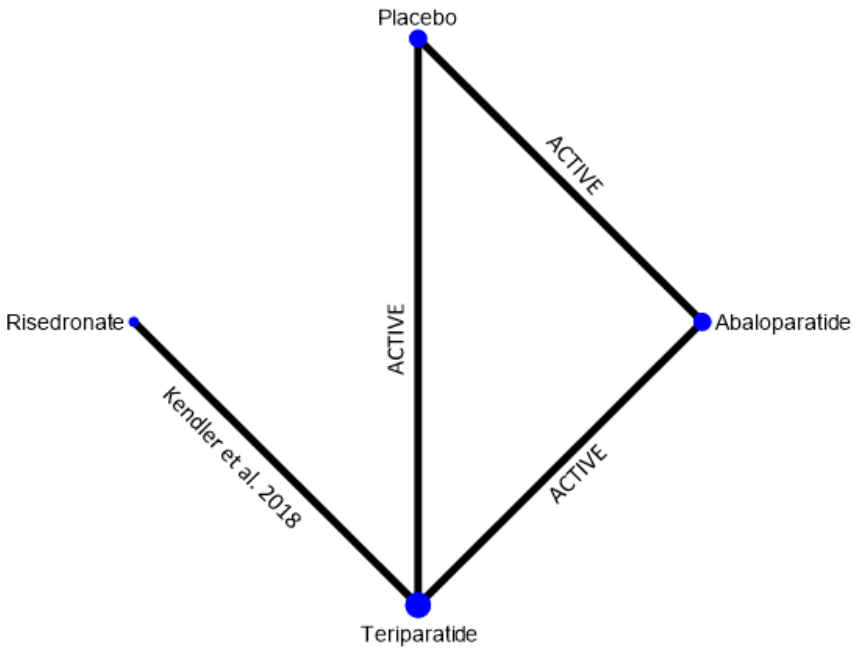
	FEM	REM
DIC	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; FEM, fixed-effects model; REM, random-effects model

B.2.9.6.3 Fractures in other bones / regions at 18 months

The network of studies reporting data for fractures in other bones/regions is illustrated in Figure 23. Two studies assessing four treatments reported fractures in other bones/regions data at 18 months.

Figure 23: Network for analysis – fractures in other bones/regions at 18 months



Abbreviations: CSR, clinical study report
Note: ACTIVE refers to the CSR addendum population (excluding Sites 131 and 132)[63]

Figure 24: Summary forest plot of fractures in other bones/regions at 18 months (FEM and REM) for abaloparatide vs comparators

[redacted]

Abbreviations: CrI, credible interval; FEM, fixed-effects model; REM, random-effects model; RR, relative risk

The FEM demonstrated [redacted] (Figure 24).

The REM also demonstrated [redacted] [Figure 24]).

Table 29 presents the model fit statistics. DIC and residual deviance were comparable for the fixed and random-effects model. Hence, both models were used to draw conclusions.

Table 29: DIC and residual deviance values for fractures in other bones/ regions at 18 months using fixed effect and random effect models

	FEM	REM
DIC	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; FEM, fixed-effects model; REM, random-effects model

B.2.9.7 Uncertainties in the indirect and mixed treatment comparisons

Several limitations of the NMA methodology should be acknowledged:

- There was little direct evidence for comparisons for abaloparatide included in any of the NMAs.
- There were differences in study design and patient populations across studies, including treatment trial durations and timing of study visits. Most studies had differences in mean age, ethnicity, or rate of prevalent vertebral fractures, indicating at least a moderate risk of bias from effect modification.
- There were also differences in the rates of fractures in the placebo arms of different studies, indicating differences in the level of fracture risk in the trial populations that likely extend to unknown and unmeasured effect modifiers, increasing the risk of bias. As such, only the comparisons between abaloparatide, teriparatide and placebo can be considered to have a low risk of bias; all other comparisons are indirect and are considered to have a high risk of bias.
- More trials in the network would be required to explore heterogeneity using a network meta-regression. Due to limited subgroup data available across the studies, a separate analysis was not performed. Data gaps were filled using available graphical data. Due to the restriction on time-point and dosage (NICE-approved dosages), most identified studies were excluded in the NMA.
- Finally, the network in the analysis contained few studies which leads to relatively large uncertainty intervals, as can be seen in the analysis results. Also, as there were no head-to-head data available comparing teriparatide, romosozumab and abaloparatide directly in randomised controlled trials (RCT), the analysis relies solely upon indirect evidence, and as a result the innate limitations accompanying indirect comparison are present.

Despite the above limitations, the analysis used the available data to produce an indirect treatment comparison in line with NICE guidance and was based on data from high-quality randomised trials, to estimate the relative efficacy of abaloparatide versus the relevant treatments for the treatment of osteoporosis in postmenopausal women at increased risk of fracture and so is appropriate to support decision making.

B.2.9.8 Conclusions of the NMA

The findings from the NMA suggest that abaloparatide [redacted] This NMA's findings align with the findings of previously published meta-

analysis results of bisphosphonates and non-bisphosphonates in postmenopausal women with osteoporosis who are at an increased risk of fracture.[78]

B.2.10 Adverse reactions

Key safety evidence from ACTIVE and ACTIVExtend and the RWE study is presented in this section. Abaloparatide demonstrated an acceptable safety profile and there was no evidence that 18 months of prior treatment with abaloparatide altered the safety profile of subsequent alendronate treatment from ACTIVE baseline through the end of the full 43-month treatment period of the ACTIVE–ACTIVExtend study (18 months treatment in ACTIVE, 1 month for recruitment and consenting to ACTIVExtend, 24 months treatment in ACTIVExtend).

B.2.10.1 ACTIVE | Safety outcomes

B.2.10.1.1 ACTIVE | Exposure

The extent of exposure was similar among the Safety population treatment groups. Median duration of treatment exposure was 17.9 months for abaloparatide, 17.9 months for placebo and 17.8 months for teriparatide. Median compliance rates were >99% in all treatment groups through Month 18. There were no relevant differences among treatment groups in the duration of vitamin D or calcium supplementation or in the amount received.

B.2.10.1.2 ACTIVE | Summary of treatment-emergent adverse events

Safety data from ACTIVE are summarised in Table 30. There were no meaningful differences between treatment groups in the proportions of participants with treatment-emergent adverse events (TEAEs), serious AEs or AEs leading to death; none of the deaths were considered by the investigators to be related to study medication.

Treatment-related TEAEs and AEs leading to study discontinuation occurred more frequently in the abaloparatide group vs the placebo group.

Table 30: ACTIVE | Summary of adverse events at Month 18 (excluding Sites 131 and 132; Safety population)

Event, n (%)	ACTIVE		
	Abaloparatide n=694	Placebo n=687	Teriparatide n=686
All TEAEs	627 (90.3)	607 (88.4)	614 (89.5)
Treatment-related TEAEs	296 (42.7)	195 (28.4)	280 (40.8)
Severe TEAEs	38 (5.5)	37 (5.4)	36 (5.2)
Severe treatment-related TEAEs	7 (1.0)	2 (0.3)	4 (0.6)
Serious TEAEs	62 (8.9)	66 (9.6)	65 (9.5)
Adverse events leading to deaths[a]	3 (0.4)	3 (0.4)	2 (0.3)
Adverse events leading to discontinuation	68 (9.8)	42 (6.1)	47 (6.9)
Discontinuation due to a >7.0% BMD decrease[b]	1/189 (0.5)	11/157 (7.0)	0/140 (0)

[a]Causes of death in the abaloparatide group: sepsis, bronchiectasis, ischaemic heart disease. Causes of death in the placebo group: bowel cancer, intestinal obstruction, sudden death. Causes of death in the teriparatide group: pancreatic cancer, cardio-respiratory arrest
[b]The denominator indicates the total number of subjects who discontinued study participation
Abbreviations: BMD, bone mineral density; TEAEs, treatment-emergent adverse events
Source: ACTIVE CSR addendum[63]

B.2.10.1.3 ACTIVE | Most common TEAEs

The most frequently reported AEs (≥5% in the abaloparatide group) at Month 18 in the ACTIVE trial are shown in Table 31.

The overall incidence of hypercalcaemia (a prespecified safety endpoint) was significantly lower in the abaloparatide group than in the teriparatide group (3.3% vs 6.0%, RRR –0.45 [95% CI –0.66 to –0.09], p=0.019), although the incidence of hypercalcaemia was lower in the placebo group (0.4%) than both these treatment groups.

The incidence of hypercalcaemia at 4 hours post-dose was also lower in the abaloparatide group vs the teriparatide group (3.3% in the vs 5.7%, p=0.035), with the incidence lowest in the placebo group (0.2%). Pre-dose hypercalcaemia incidence was similar in all three groups (abaloparatide 0.2%, teriparatide 1.0%, placebo 0.2%).

Table 31: ACTIVE | Most frequently observed TEAEs (in ≥5% of patients in the abaloparatide treatment group) and hypercalcaemia at Month 18 (excluding Sites 131 and 132; Safety population)

Event	ACTIVE					
	Abaloparatide n=694		Placebo n=687		Teriparatide n=686	
	Any Grade	Severe	Any Grade	Severe	Any Grade	Severe
Most frequently observed TEAEs (in ≥5% of patients in the abaloparatide treatment group), n (%)						
Hypercalciuria	93 (13.4)	0	73 (10.6)	0	101 (14.7)	0
Dizziness	77 (11.1)	2 (0.3)	49 (7.1)	1 (0.1)	56 (8.2)	0
Upper respiratory tract infection	65 (9.4)	0	61 (8.9)	0	65 (9.5)	0
Back pain	60 (8.6)	1 (0.1)	69 (10.0)	1 (0.1)	52 (7.6)	1 (0.1)
Headache	59 (8.5)	1 (0.1)	40 (5.8)	0	49 (7.1)	0
Nausea	59 (8.5)	1 (0.1)	21 (3.1)	0	37 (5.4)	0
Arthralgia	58 (8.4)	0	61 (8.9)	2 (0.3)	60 (8.7)	0
Hypertension	47 (6.8)	0	37 (5.4)	0	36 (5.2)	0
Influenza	43 (6.2)	0	21 (3.1)	0	23 (3.4)	1 (0.1)
Nasopharyngitis	43 (6.2)	0	56 (8.2)	0	43 (6.3)	0
Palpitations	39 (5.6)	1 (0.1)	3 (0.4)	0	12 (1.7)	0
Urinary tract infection	37 (5.3)	0	36 (5.2)	0	34 (5.0)	0
Hypercalcaemia[a] (prespecified safety endpoint), n/N (%)						
Hypercalcaemia[a]	23/692 (3.3)[b]	–[c]	3/685 (0.4)	–[c]	41/684 (6.0)	–[c]

Coded by MedDRA v17.1
[a]Hypercalcaemia was defined as albumin-corrected serum calcium of at least 10.7 mg/dL (2.67 mmol/L) at any time-point, which was a prespecified safety end point and was analysed using the $\chi 2$ test. Values are reported as n with hypercalcaemia/N with data in study group (%); [b]For abaloparatide and teriparatide vs placebo, p<0.001; for abaloparatide vs teriparatide, p=0.019; [c]The prespecified safety endpoint of hypercalcaemia was assessed based on any grade
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event
Source: ACTIVE CSR addendum[63]; Abaloparatide EPAR[61]

B.2.10.1.4 ACTIVE | Most common TRAEs

The most frequently reported TRAEs (≥5% in the abaloparatide group) in ACTIVE are shown in Table 32.

Table 32: ACTIVE | Most frequently observed TRAEs of any grade (in ≥5% of patients in the abaloparatide group) at Month 18 (excluding Sites 131 and 132; Safety population)

Event	ACTIVE		
	Abaloparatide n=694	Placebo n=687	Teriparatide n=686
Hypercalciuria	81 (11.7)	55 (8.0)	78 (11.4)
Dizziness	51 (7.3)	18 (2.6)	39 (5.7)
Nausea	38 (5.5)	9 (1.3)	25 (3.6)

Coded by MedDRA v17.1
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TRAE, treatment-related adverse event
Source: ACTIVE CSR addendum[63]

B.2.10.1.5 ACTIVE | Treatment discontinuation due to adverse events

There were more TEAEs leading to ACTIVE study discontinuation in the abaloparatide group (n=68 [9.8%]) than in the placebo group (n=41 [6.0%]) or the teriparatide group (n=46 [6.7%]) at Month 18.

The most common TEAEs leading to study discontinuation in the abaloparatide group included nausea (n=11 [1.6%]), dizziness (n=10 [1.4%]), headache (n=8 [1.2%]), and palpitations (n=6 [0.9%]), which were generally mild to moderate in severity. Serious TEAEs leading to study discontinuation occurred in 14 patients (2.0%) in the abaloparatide group, 4 patients (0.6%) in the placebo group and 14 patients (2.0%) in the teriparatide group.

B.2.10.1.6 ACTIVE | Serious adverse events

The overall incidence of serious TEAEs in the ACTIVE trial was similar between treatment groups. Serious AEs were reported in 62 patients (8.9%) in the abaloparatide group, 65 patients (9.5%) in the placebo group, and 64 patients (9.3%) in the teriparatide group.at Month 18.

The only serious TEAEs to occur in ≥2 patients were osteoarthritis (3 [0.4%], 3 [0.4%], 1 [0.1%], in the abaloparatide, teriparatide and placebo groups, respectively) and breast cancer (3 [0.4%], 4 [0.6%], 1 [0.1%]] in the abaloparatide, teriparatide and placebo groups, respectively).

Serious TRAEs were observed in the teriparatide group only (3 patients [0.4%]); these consisted of hypercalcaemia (n=1 [0.1%]), drug eruption (n=1 [0.1%]) and hypertension (n=1 [0.1%]).

B.2.10.1.7 ACTIVE | Adverse events of special interest

Prespecified adverse events of special interest (AESIs) in ACTIVE included hypercalcaemia, hypercalciuria, hypophosphatemia, hypersensitivity, orthostatic hypotension and renal impairment. Palpitations, nausea and dizziness were also assessed as AESIs.

AESI data at Month 18 are presented in Table 33.

Table 33: ACTIVE | Adverse events of special interest at Month 18 (excluding Sites 131 and 132; Safety population)

AESI, n (%)	ACTIVE		
	Abaloparatide n=694	Placebo n=687	Teriparatide n=686
Hypercalcaemia			
≥1 TEAE	15 (2.2)	4 (0.6)	33 (4.8)
≥1 TRAE	13 (1.9)	3 (0.4)	29 (4.2)
≥1 serious TEAE	0	0	1 (0.1)
≥1 serious TRAE	0	0	1 (0.1)
≥1 AE leading to discontinuation	2 (0.3)	0	4 (0.6)
Hypercalciuria			
≥1 TEAE	99 (14.3)	76 (11.1)	121 (17.6)
≥1 TRAE	87 (12.5)	57 (8.3)	96 (14.0)
≥1 serious TEAE	0	0	1 (0.1)
≥1 serious TRAE	0	0	1 (0.1)
≥1 AE leading to discontinuation	1 (0.1)	0	4 (0.6)
Hypophosphataemia			
≥1 TEAE	0	0	0
Hypersensitivity			
≥1 TEAE	88 (12.7)	68 (9.9)	85 (12.4)
≥1 TRAE	22 (3.2)	11 (1.6)	32 (4.7)
≥1 severe TEAE	1 (0.1)	1 (0.1)	2 (0.3)
≥1 serious TEAE	2 (0.3)	1 (0.1)	2 (0.3)
≥1 serious TRAE	0	0	1 (0.1)
≥1 AE leading to death	0	0	1 (0.1)
≥1 AE leading to discontinuation	6 (0.9)	3 (0.4)	4 (0.6)
Orthostatic hypertension			
≥1 TEAE	197 (28.4)	99 (14.4)	136 (19.8)
≥1 TRAE	112 (16.1)	34 (4.9)	71 (10.3)
≥1 severe TEAE	6 (0.9)	4 (0.6)	0
≥1 serious TEAE	2 (0.3)	2 (0.3)	4 (0.6)
≥1 AE leading to discontinuation	25 (3.6)	6 (0.9)	12 (1.7)
Renal impairment			

≥1 TEAE related to renal impairment	46 (6.6)	47 (6.8)	30 (4.4)
≥1 TRAE	4 (0.6)	8 (1.2)	2 (0.3)
Palpitations			
≥1 TEAE	59 (8.5)	16 (2.3)	24 (3.5)
≥1 TRAE	35 (5.0)	4 (0.6)	13 (1.9)
≥1 severe TEAE	0 (0.1)	0	1 (0.1)
≥1 serious TEAE	1 (0.1)	0	2 (0.3)
≥1 AE leading to discontinuation	8 (1.2)	2 (0.3)	0
Nausea			
≥1 TEAE	62 (8.9)	24 (3.5)	44 (6.4)
≥1 TRAE	39 (5.6)	10 (1.5)	27 (3.9)
≥1 severe TEAE	1 (0.1)	0	0
≥1 serious TEAE	1 (0.1)	0	0
≥1 AE leading to discontinuation	11 (1.6)	2 (0.3)	4 (0.6)
Dizziness			
≥1 TEAE	77 (11.1)	49 (7.1)	57 (8.3)
≥1 TRAE	51 (7.3)	18 (2.6)	39 (5.7)
≥1 severe TEAE	2 (0.3)	1 (0.1)	0
≥1 serious TEAE	0	1 (0.1)	2 (0.3)
≥1 AE leading to discontinuation	10 (1.4)	3 (0.4)	8 (1.2)

Coded by MedDRA v17.1
Abbreviations: AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event
Source: ACTIVE CSR Addendum[63]

B.2.10.1.8 ACTIVE | Clinical laboratory evaluations

There were no apparent trends relative to laboratory findings at Month 18 for haematology, coagulation or urinalysis with respect to abaloparatide treatment to suggest any drug-induced safety concerns.

B.2.10.2 ACTIVExtend | Safety outcomes

Safety outcomes showed no meaningful differences for the abaloparatide/alendronate vs placebo/alendronate groups in the ACTIVExtend study through month 43 (further details are provided in Appendix M). There was therefore no evidence that 18 months of prior treatment with abaloparatide altered the safety profile of subsequent alendronate treatment.

B.2.10.3 Real-world evidence study | Safety outcomes

B.2.10.3.1 Real-world evidence study | Exposure

The overall mean duration of exposure in the RWE study was 301.2 days for abaloparatide and 313.4 days for teriparatide, with >45% of patients in both treatment cohorts exposed to treatment >12 months[62] (Table 34). The mean cumulative treatment duration was 257.8 days for abaloparatide and 269.2 days for teriparatide, with over a third of patients in both treatment cohorts exposed to >12 months of cumulative and consecutive treatment.[62]

Table 34: Real-world evidence study | Treatment exposure (overall propensity score-matched population)

Parameter	RWE study	
	Abaloparatide n=11,616	Teriparatide n=11,616
Overall treatment duration (days)[a]		
N	11,616	11,616
Mean (SD)	301.2 (213.5)	313.4 (215.0)
Median (IQR)	304 (83–539)	331 (84–546)
Overall treatment duration (months)[a]		
N	11,616	11,616
Mean (SD)	10.0 (7.1)	10.4 (7.2)
Median (IQR)	10 (3–18)	11 (3–18)
Overall treatment duration, n (%)		
≤1 month	2,101 (18.1)	2,042 (17.6)
>1 to ≤3 months	1,343 (11.6)	1,173 (10.1)
>3 to ≤6 months	1,187 (10.2)	1,098 (9.5)
>6 to ≤9 months	885 (7.6)	922 (7.9)
>9 to ≤12 months	834 (7.2)	899 (7.7)
>12 months	5,266 (45.3)	5,482 (47.2)
Total number of pens over 19 months after index date[b]		
N	11,616	11,616
Mean (SD)	8.6 (6.4)	9.5 (6.8)
Median (IQR)	8 (2–15)	9 (3–17)
Cumulative treatment duration (days)[c]		
N	11,616	11,616
Mean (SD)	257.8 (192.6)	269.2 (196.7)
Median (IQR)	224 (60–450)	22 (84–476)
Cumulative treatment duration, n (%)[c]		
≤1 month	2,110 (18.2)	2,041 (17.6)

>1 to ≤3 months	1,925 (16.6)	1,610 (13.9)
>3 to ≤6 months	1,397 (12.0)	1,371 (11.8)
>6 to ≤9 months	1,095 (9.4)	1,095 (9.4)
>9 to ≤12 months	1,197 (10.3)	1,069 (9.2)
>12 months	3,892 (33.5)	4,430 (38.1)
Consecutive treatment duration, n (%)[d]		
≤1 month	2,536 (21.8)	2,533 (21.8)
>1 to ≤3 months	1,646 (14.2)	1,486 (12.8)
>3 to ≤6 months	1,497 (12.9)	1,407 (12.1)
>6 to ≤9 months	1,056 (9.1)	1,037 (8.9)
>9 to ≤12 months	890 (7.7)	941 (8.1)
>12 months	3,991 (34.4)	4,212 (36.3)

[a]Duration of exposure (days) = date of last anabolic drug prescription fill plus supply days − index date. Duration of Exposure (months) = duration of exposure (days)/30. The maximum treatment duration was set as 570 days (or 19 months, 18 months plus 30-day follow-up) if a patient was treated for longer than 570 days
[b]According to product labels, one abaloparatide pen has a 30-day supply; one teriparatide pen has a 28-day supply. This was counted as two pens if the numbers of days of supply was between 56 and 60; three pens if days of supply was between 84 and 90
[c]Cumulative treatment duration was the sum of all days from index date to the last drug supply date regardless of treatment gap
[d]Consecutive treatment duration was the sum of all days from index date to the last study drug supply without any gap exceeding 60 days
Abbreviations: IQR, interquartile range; RWE, real-world evidence; SD, standard deviation
Sources: Cosman et al (2022)[62], RWE study CSR[67]

B.2.10.3.2 Real-world evidence study | Cardiovascular safety analysis

RWE data showed similar CV safety for abaloparatide and teriparatide. Through 19 months (18 months plus 30 days follow-up) after the index date, the risk of new events of the composite endpoints of MACE was similar between the abaloparatide (K–M 3.0%) and teriparatide (K–M 3.1%) cohorts (HR [95% CI] 1.00 [0.84–1.20], p=0.97)[62] (Table 35; Figure 25). Similar findings were also observed for the composite endpoints of MACE with heart failure (K–M rates: abaloparatide 6.6% vs teriparatide 6.4%; HR [95% CI] 1.05 [0.93–1.19], p=0.41)[62] (Table 35; Figure 25).

Outcomes were generally consistent among sensitivity analyses compared with the overall cardiovascular event data.[62] Other exploratory composite events were generally comparable with the rates observed for secondary endpoint composite events.

Table 35: Real-world evidence study | Time to first incidence of cardiovascular event during treatment (secondary composite endpoints; overall propensity score-matched population)

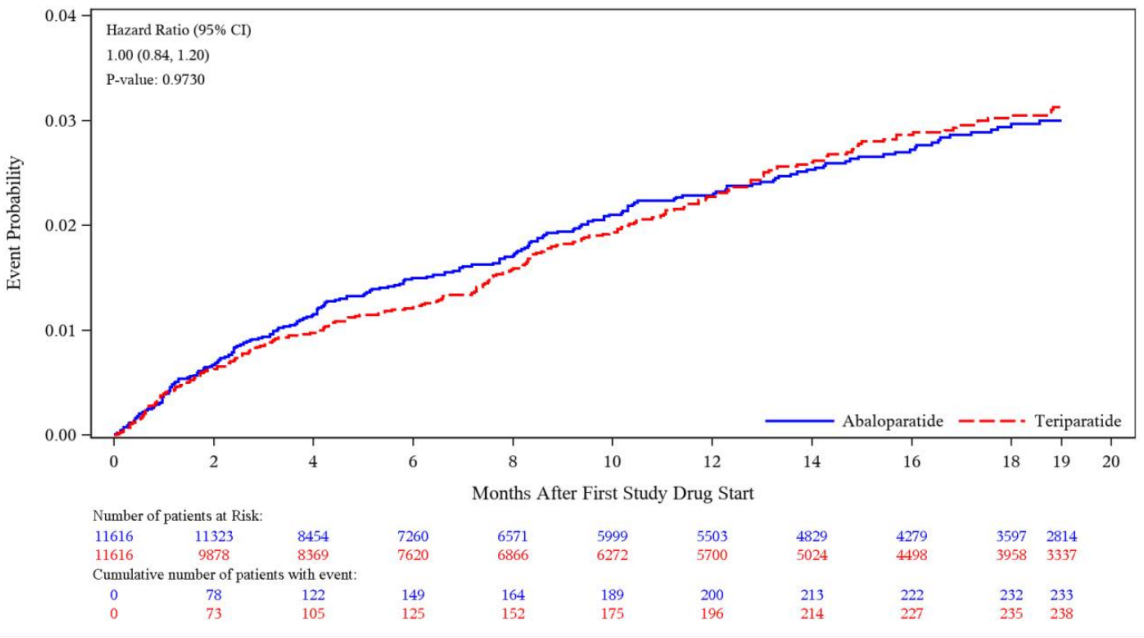
Time to event variable	Parameter	Real-world evidence study	
		Abaloparatide n=11,616	Teriparatide n=11,616

MACE	K–M estimated event rate at 18 months[a], %	3.0	3.1
	Patients with event, n (%)	233 (2.0)	238 (2.0)
	Patients censored, n (%)[b]	11,383 (98.0)	11,378 (98.0)
	HR (95% CI), p value) vs teriparatide[c,d]	1.00 (0.84–1.20), p=0.97	
MACE with heart failure	K–M estimated event rate at 18 months[a], %	6.6	6.4
	Patients with event, n (%)	529 (4.6)	514 (4.4)
	Patients censored, n (%)[b]	11,087 (95.4)	11,102 (95.6)
	HR (p value) vs teriparatide[c,d]	1.05 (0.93–1.19), p=0.41	

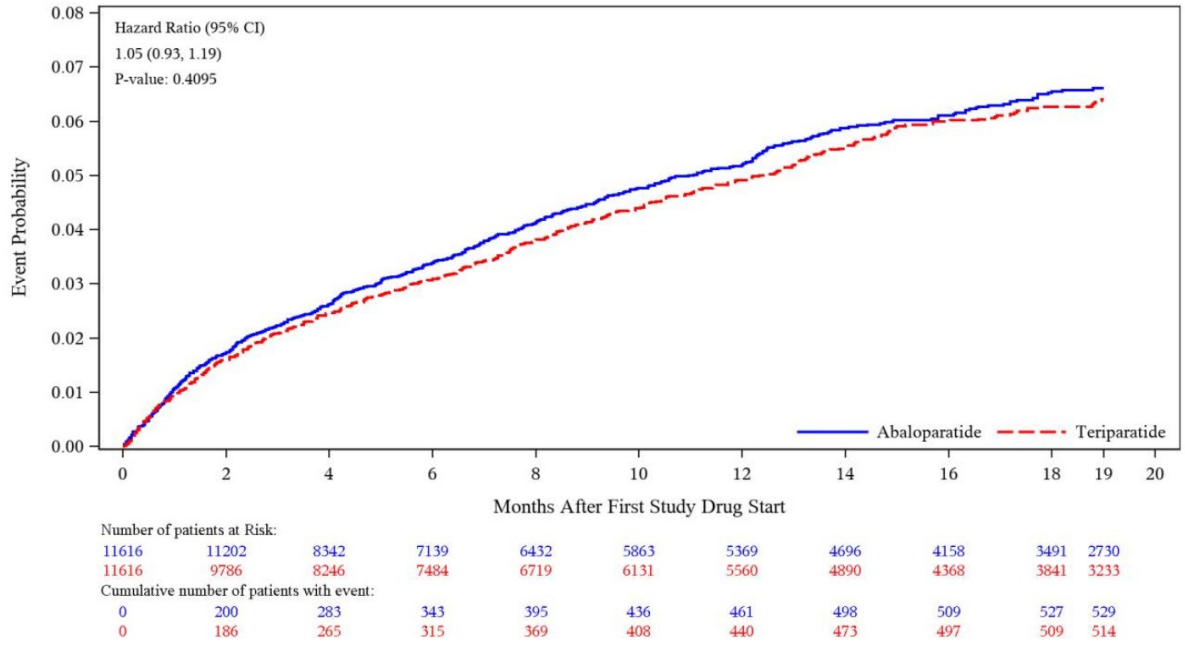
[a]The observation period was 18 months (540 days) plus 30 days follow-up after the index date
[b]Patients were censored at the earlier of 30 days after treatment end, death, or 570 days after index date, if no cardiovascular event before that
[c]Cox proportional hazard model was used to calculate the HR with teriparatide as reference.
[d]p-values were from the log-rank test
Abbreviations: CI, confidence interval; K–M, Kaplan–Meier; MACE, major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death)
Source: RWE study CSR[67]

Figure 25: Real-world evidence study | Time to first incidence of A) MACE and B) MACE with heart failure (overall propensity score-matched population) through Month 19

A)



B)



Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death)
Source: RWE study CSR[62]

B.2.10.4 Safety conclusions

In the ACTIVE trial, abaloparatide demonstrated an acceptable safety profile with a significant reduction in hypercalcaemia vs teriparatide.

The safety profile in the ACTIVExtend Safety population showed no meaningful differences between prior treatment groups (abaloparatide/alendronate vs placebo/alendronate). No safety concerns related to prior abaloparatide therapy were identified in patients subsequently treated with alendronate in the ACTIVExtend Safety population.

RWE data showed similar CV safety for abaloparatide and teriparatide.

B.2.11 Ongoing trials

There are no ongoing studies of relevance to this submission.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence base

B.2.12.1.1 Comparative efficacy and safety vs placebo and teriparatide in the ACTIVE and ACTIVExtend studies

The efficacy of abaloparatide was demonstrated in the large (N=2,070) Phase 3 randomised, placebo- and active-controlled ACTIVE trial and its long-term extension study ACTIVExtend (N=963).[1,59,63,64] The data reported in this submission are from the reanalysed datasets presented in the SmPC, which excluded data from two study sites (Sites 131 and 132) as requested by the EMA.[61,63,64] These studies demonstrated consistent efficacy of abaloparatide (18 months of abaloparatide treatment followed by 24 months of alendronate) in reducing new vertebral and nonvertebral fractures vs placebo.

ACTIVE met its primary endpoint, showing abaloparatide treatment significantly reduced the risk of new vertebral fractures, the most common type of osteoporotic fracture,[22,29] vs placebo ($p<0.001$) at 18 months. K–M estimated event rates for nonvertebral fractures were also numerically lower with abaloparatide treatment vs placebo in ACTIVE at 19 months (18 months of the observational period plus 1 month follow-up); the difference between the abaloparatide and placebo groups in the population excluding Sites 131 and 132 was not statistically significant, whereas the original analyses showed a statistically significant difference between abaloparatide and placebo.[1] However, the EMA considered there to be no scientific reason to presume efficacy only for vertebral but not nonvertebral fractures.[61] The K–M time to event curve for nonvertebral fractures was lower in the abaloparatide group vs the placebo group at any time-point during the overall 19 months of the study period.

Abaloparatide treatment also resulted in a significant reduction in major osteoporotic fractures vs placebo in ACTIVE at 19 months ($p=0.004$). K–M event rates for clinical fractures were numerically lower with abaloparatide treatment vs placebo in ACTIVE at 19 months, with a clear separation between the curves at any time-point during the overall 19 months, but the difference between groups for clinical fracture event rates was not statistically significant. K–M curves also suggested early reduction of nonvertebral, major osteoporotic and clinical fractures with abaloparatide treatment. Fractures and their complications are the most important health consequence for people with osteoporosis, causing chronic pain, functional decline, disability leading to loss of independence and increased risks of morbidity and mortality.[4,8,9] The ability to prevent fractures occurring at the earliest opportunity therefore provides clear clinical benefit for patients and the potential to improve HRQoL.

Patients who completed 18 months of abaloparatide treatment or placebo in ACTIVE were eligible to enter ACTIVExtend, where all patients received alendronate for up to 24 months. The reductions in new vertebral fractures, nonvertebral fractures, major osteoporotic fractures, and clinical fractures with abaloparatide treatment observed in ACTIVE were maintained at Month 43 of ACTIVExtend (abaloparatide/alendronate vs placebo/alendronate).

The early and sustained reductions in fractures with abaloparatide were accompanied by early and sustained increases in BMD at the total hip, femoral neck and lumbar spine in ACTIVE, suggesting early increases in BMD may prevent fractures occurring. Improvements in BMD were significantly greater with abaloparatide treatment vs placebo at the total hip, femoral neck and lumbar spine at 18 months (all p<0.001; [redacted]). BMD increases with abaloparatide treatment were maintained at Month 43 of ACTIVExtend (abaloparatide/alendronate vs placebo/alendronate) and were statistically significant at all time points (all p<0.001)

The primary endpoint in the ACTIVE trial (new vertebral fractures) was not assessed for abaloparatide vs teriparatide (the active comparator) as a much larger sample size would be required to provide sufficient power (~22,000 per treatment group to provide 90% power). However, similar reductions in new vertebral fractures vs placebo were observed for both abaloparatide and teriparatide. K–M event rates for major osteoporotic fractures were numerically lower for abaloparatide vs teriparatide with an early, consistent and stable separation at any time-point during the overall 19 months of the ACTIVE observational period, but the difference between the abaloparatide and teriparatide groups was not statistically significant. [redacted].

ACTIVE data also suggested a faster onset of action for abaloparatide vs teriparatide. [redacted]. BMD increases for abaloparatide vs teriparatide were also greater at [redacted] and at the total hip and femoral neck at 18 months, with increases in lumbar spine BMD similar between abaloparatide and teriparatide at 18 months. Increases in cortical BMD with abaloparatide vs teriparatide were consistent with changes in bone turnover markers in ACTIVE and reflect the differing mechanisms of action and enhanced net anabolic effect for abaloparatide.

Abaloparatide demonstrated an acceptable safety profile in ACTIVE and there was no evidence that 18 months of prior treatment with abaloparatide altered the safety profile of sequential treatment with alendronate in ACTIVExtend. There were no meaningful differences between ACTIVE treatment groups in the proportions of participants with TEAEs, serious AEs or AEs leading to death and no treatment-related deaths were reported. The most frequently observed TEAEs in the ACTIVE abaloparatide group were hypercalciuria (13.4%) and dizziness (11.1%).

B.2.12.1.2 Comparative real-world effectiveness and safety vs teriparatide

Further evidence of the real-world effectiveness and safety of abaloparatide vs teriparatide was provided from a large (N=23,232) RWE study powered to compare the effectiveness and CV safety of abaloparatide vs teriparatide.[62] RWE validates data generated from randomised control trials and gives valuable insight for physicians and regulators into heterogenous real-world populations.

In the RWE study, noninferiority was observed for nonvertebral fractures for abaloparatide vs teriparatide (p=0.13; primary endpoint) along with a significant reduction in the risk of hip fractures (22%, p=0.04; exploratory endpoint) with abaloparatide. Together with the differences between cortical BMD and bone turnover markers for abaloparatide and teriparatide in the ACTIVE study (Section B.2.12.1.1), this finding further supports that abaloparatide may be more efficacious than teriparatide at increasing cortical BMD, with the

associated potential to reduce the risk of hip fracture. Reduction of hip fracture risk is an important clinical outcome as hip fractures are associated with chronic pain and reduced mobility, and cause permanent disability in 50% of patients,[5,16] with around 10% to 20% of patients moving to residential nursing homes.[16]

The RWE study also provided further assurance of the safety of abaloparatide in clinical practice, with similar CV safety observed for abaloparatide and teriparatide. The risk of new events of the composite endpoints of MACE and MACE with heart failure were similar for both treatment cohorts.

B.2.12.1.3 Comparative efficacy of abaloparatide vs other treatments based on a network meta-analysis

In the absence of further head-to-head trials, Theramex conducted an NMA to aid the comparison of abaloparatide with other treatments for reducing fractures (Section B.2.9 and Appendix D.3.4). As expected, given the known challenges in adequately matching patient populations for indirect comparison in this therapy area, the results from these analyses do not consistently favour any single therapy. There is some heterogeneity in the direction of treatment effects, partly due to heterogeneity between published studies that cannot be controlled for, and the available data did not allow for all comparators to be evaluated for all endpoints.

Evidence from this NMA suggested similar efficacy between treatments for the prevention of fractures in postmenopausal women at very high risk of fracture.

B.2.12.2 Strengths and limitations of the clinical evidence base for abaloparatide

B.2.12.2.1 Strengths of the evidence base

The pivotal trials for abaloparatide were a large Phase 3 18-month randomised trial (ACTIVE) with 24-month extension study (ACTIVExtend).

The ACTIVE study was placebo- and active comparator-controlled, allowing comparisons vs both placebo and teriparatide (exploratory for abaloparatide vs teriparatide), although comparison of abaloparatide vs teriparatide was not planned for the primary endpoint as a sample size of ~22,000 per treatment group would be required.[1]

The use of alendronate after abaloparatide in ACTIVExtend provides a formal assessment of a real-world therapeutic setting for women with postmenopausal osteoporosis.[58,59]

The trial data are supported by data from a large RWE study, powered to compare abaloparatide vs teriparatide and providing further assurance of the effectiveness and safety of abaloparatide in clinical practice.[62]

B.2.12.2.2 Potential limitations of the evidence base

More than half of participants in the ACTIVE study had a prior fracture (58% excluding Sites 131 and 132 [63% based on the full study population]); it cannot be determined from these

data whether abaloparatide would have similar preventive and osteoanabolic effects among participants at lower risk for fracture.[1]

As the teriparatide group was open-label, this may have resulted in bias in reporting subjective measures, although key efficacy and safety endpoints were based on abaloparatide vs placebo.

Although ACTIVE and ACTIVExtend cover a total 43-month period, it is not yet known how long the benefits associated with abaloparatide may continue.[1]

The RWE study was subject to the limitations associated with retrospective observational studies and administrative claims data, although propensity score matching was used to limit known confounders and sensitivity analyses confirmed the robustness of the findings.[62]

B.3 Cost-effectiveness

SUMMARY

- The primary objective of this analysis was to evaluate the cost-effectiveness of the sequential treatment abaloparatide/alendronate' compared with two other sequential treatments, namely teriparatide/alendronate and romosozumab/alendronate in postmenopausal women with osteoporosis at very high risk.
- A Markov micro-simulation model was developed to estimate the expected lifetime costs and outcomes of treatment in this patient group.
- The primary comparator in this economic evaluation is teriparatide/alendronate, aligned with the comparator arm in the ACTIVE clinical trial. Also, the model evaluates the outcomes compared with romosozumab/alendronate, as romosozumab is another approved anabolic agent in the UK.
- A previously validated micro-simulation Markov model was adapted to the UK context and was used to estimate the cost-effectiveness of sequential treatment, i.e. abaloparatide/alendronate compared with teriparatide/alendronate and romosozumab/alendronate.
- The health states in the model are "at risk," hip, vertebral, other fracture, and death.
- These results reflect the healthcare payer perspective across a lifetime time horizon and encompass the following costs: disease management, drug acquisition, drug administration and monitoring.
- The primary analysis included the calculation of an incremental cost-effectiveness ratio (ICER) by dividing the incremental costs by the incremental quality-adjusted life year (QALYs) gained.
- Uncertainty was assessed through deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analyses. PSA results are also displayed on the cost-effectiveness plane.
- The results demonstrate that, compared with romosozumab/alendronate, abaloparatide/alendronate is associated with a QALY [redacted] and an incremental cost of [redacted]
- In comparison with teriparatide/alendronate, abaloparatide/alendronate is associated with a QALY [redacted] and an incremental cost of [redacted].
- The cost-effectiveness results for the base case analysis show that using abaloparatide/alendronate vs teriparatide/alendronate resulted in [redacted].
- At a willingness to pay (WTP) threshold of £30,000/QALY, there is a [redacted] probability that the abaloparatide/alendronate would be cost-effective vs teriparatide/alendronate.
- In the DSA, utility multipliers for other fracture, hip fracture states and drug costs had the biggest impact for abaloparatide versus both comparators.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify published economic evaluations of potential relevance to this technology appraisal. Electronic database searches were initially conducted on 26 and

27 April 2023. Full details of the SLR methodology, PRISMA diagram and included and excluded studies of the SLR are provided in Appendix G.

Following searches, exclusion of duplicates, title and abstract screening, and full-text screening, 23 relevant economic evaluations were identified and included for data extraction. Of these studies, 17 were cost-effectiveness studies, five were healthcare resource utilisation (HCRU)/cost studies, and one combined cost-effectiveness and HCRU/cost study. Further details of all 23 studies included in the SLR are provided in Appendix G.

A summary of the published cost-effectiveness studies of pharmacological treatments for osteoporosis which were considered relevant to this submission is presented in Appendix G. Of these studies, the two published cost-effectiveness studies in Sweden (cost-effectiveness of romosozumab for postmenopausal women with severe osteoporosis at high risk of fracture)[79] and the UK (cost-effectiveness of bone forming agents for fracture prevention)[80] were considered the most relevant for informing the abaloparatide economic analysis. In addition to the these published cost-effectiveness studies, the NICE appraisal for romosozumab was also identified (TA791 romosozumab).[49]

Romosozumab is recommended by NICE as an option for treating severe osteoporosis in people after menopause who are at high risk of fracture only if:

- They have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture) and
- The company provides romosozumab according to the commercial arrangement

Insights and learnings were also drawn from TA791 during the development of the economic analysis for abaloparatide.

B.3.2 Economic analysis

The SLR did not identify any published economic evaluations considering abaloparatide for the treatment of postmenopausal women at very high risk of fracture in the UK. Following a comprehensive review, it was deemed appropriate to adapt a previously validated model for the UK context.[49,79,80] Teriparatide and romosozumab were included as comparators in the economic analysis. Teriparatide is aligned with the comparator arm of the ACTIVE study.

B.3.2.1 Patient population

The patient population considered in the analysis is postmenopausal women with osteoporosis at very high risk of fracture, in line with the patient population in the abaloparatide Phase 3 studies (ACTIVE and ACTIVExtend) (Section B.2.4.4). This population is narrower than the licensed indication for abaloparatide and the population in the final NICE scope (postmenopausal women with osteoporosis at increased risk of fracture) and is focused on the patient population for whom abaloparatide is expected to provide the most clinical benefit.

B.3.2.2 Intervention technology and comparators

Evidence suggests that anabolic agents for the treatment of osteoporosis are superior in terms of clinical efficacy and speed of action to antiresorptive agents.[46] Abaloparatide, teriparatide and romosozumab are licensed to be used for 18, 24 and 12 months, respectively.[2,47,48] After treatment cessation patients transition to a sequential therapy, typically involving an antiresorptive agent (e.g., an oral bisphosphonate) for a duration of 60 months as recommended by NOGG guidelines.[4] The increased BMD achieved with anabolic treatments can be maintained with the sequential treatment using an antiresorptive such as an oral bisphosphonate, reducing fracture risk over the long-term.[46]

Table 36 outlines the intervention and comparators used in the model, along with the details about the initial treatment, sequential treatment, and duration of use for each treatment. Although defined in the final scope, 'no active treatment' was not included in the final model. The target population for abaloparatide is postmenopausal women with osteoporosis at very high risk of fracture for whom guidelines recommend treatment with romosozumab or teriparatide, therefore it was considered that in UK clinical practice these are the relevant comparators.[4]

Table 36: Intervention and comparators

Initial treatment	Initial treatment duration	Sequential treatment	Sequential treatment duration	Maximum duration
Abaloparatide (80 µg/daily SC injection)	18 months	Alendronate (70 mg/once weekly tablet)	60 months	78 months
Teriparatide (20 µg/daily SC injection)	24 months	Alendronate (70 mg/once weekly tablet)	60 months	84 months
Romosozumab 210 mg (2 x 105 mg)/monthly SC injection)	12 months	Alendronate (70 mg/once weekly tablet)	60 months	72 months

Abbreviations: SC, subcutaneous

B.3.2.3 Model structure

The model was developed in Microsoft Excel® and programmed using standard Excel® functions where possible. Visual Basic (VB) was used to generate random numbers, aggregate the cost and health outcomes, and run Monte Carlo simulations in the PSA. All model references and assumptions are clearly described within the Excel® file.

A previously validated Markov patient-level micro-simulation model was adapted to the UK context and was used to estimate the cost-effectiveness of sequential treatment, i.e., abaloparatide/alendronate vs teriparatide/alendronate and romosozumab/alendronate. This model structure is aligned with the International Osteoporosis Foundation (IOF)/European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) guidelines for osteoporosis modelling and aligns with the model structure in the romosozumab TA791, previously validated under the NICE Preliminary Independent Model Advice (PRIMA) process.[49,81]

A quality assessment for the published cost-effectiveness studies is provided in Appendix G.

The choice of a Markov micro-simulation model approach in this analysis was due to the following reasons:

- Micro-simulation models have the potential to be more accurate than cohort models, as osteoporosis is a chronic disease characterised by a recurrence of events. A micro-simulation modelling technique is appropriate when the fracture risk is continuous over time.
- Micro-simulation models require no restrictive assumptions regarding patient movement to health states and allow assessing the impact of prior fractures without creating an unmanageable number of health states.
- Health state transition probabilities are dependent on an individual patient's history (such as fracture risk, mortality, and disease progression [fracture re-occurrence]) in the case of osteoporosis. Therefore, need to be tracked individually during the simulation to allow for an accurate depiction of individual fracture risk, multiple fractures, and treatment patterns (e.g., sequencing and treatment persistence).

The model schematic is presented in Figure 26. The model includes five-health states:

1. **At risk:** At risk of fracture
2. **Hip:** Hip fractures
3. **Vertebral:** Vertebral fractures
4. **Other:** Non-hip-nonvertebral fractures (NHNV)
5. **Death**

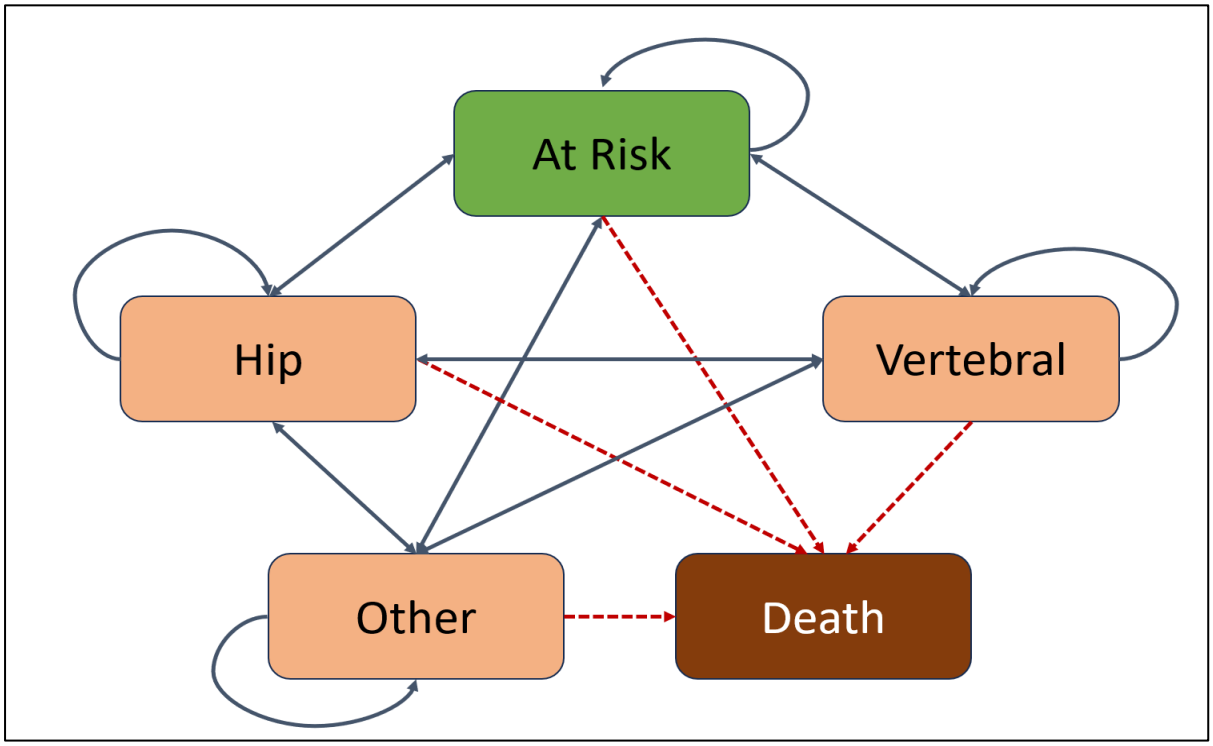
All patients enter the model in the 'at risk of fracture' health state, at the end of each 6-month cycle[a], patients have a probability of transitioning to a fracture health state (hip, vertebral or

[a] Based on the Markov assumption the patient's transition into a health state at the end of the cycle.

other fracture), remaining in the 'at risk of fracture' health state without a new fracture or dying. These probabilities are described in more detail in Section B.3.3.2.4.

Death is an absorbing state, and patients can transition to this state from any of the other four health states. Once patients transition to the 'Death' heath state, they stay there during the remainder of the simulated time horizon. There are no restrictions on the sequence or number of fractures experienced by the patients in the simulation.

Figure 26: Model schematic



Arrows represent possible transitions in the Markov simulation model; the Death health state is the one-off state

The key features of the economic model are summarised in Table 37.

Table 37: Features of the economic analysis

Factor	Chosen values	Justification
Model structure	Markov individual patient-level micro-simulation	An individual patient-level micro-simulation model is considered appropriate for estimating the cost-effectiveness of osteoporosis treatments as patients are assumed to be at changing risk of incurring fractures with long-term consequences. The model structure is aligned with the manufacturer's model structure in TA791[49] (romosozumab) which was considered appropriate by the ERG and was previously validated under the NICE PRIMA process

Factor	Chosen values	Justification
Time horizon	Lifetime	The NICE reference case stipulates that the time horizon should be sufficiently long to capture any differences in costs and outcomes between the technologies been compared. Osteoporosis is a chronic disease that affects postmenopausal women throughout their remaining lifetime. As such, a lifetime time horizon from the patient's age at treatment initiation to the age of 100 years or time of death (whichever comes first) was considered appropriate
Cycle length	6 months	The cycle length of most cost-effectiveness models for osteoporosis treatments is 6 months or 1 year. For anabolic agents (bone forming treatments) which are given for short periods of time (12–24 months), a 6-month cycle length is the most appropriate as it captures short-term treatment effects in patients who are at very high risk of subsequent fracture following a recent fracture. A 1-year cycle is deemed too long and would only allow for one transition in a 12-month treatment course, missing potentially meaningful treatment effects in the short-term
Fracture risk estimation approach	FRAX®-based algorithm to include recent fractures in the estimation of future risk	FRAX® is a Fracture Risk Assessment Tool that estimates a patient's fracture risk and can be used to derive an increased risk of fracture. NICE has used FRAX® for fracture risk estimation in recent HTAs of osteoporosis treatments. The FRAX® algorithm has a drawback that it fails to account for the elevated fracture risk that varies over time following a recent fracture. In this submission, imminent fracture risk is also incorporated alongside the FRAX® based risk estimation. This approach was aligned with IOF/ESCEO guidelines and TA791.[49,81]
Efficacy	Abaloparatide/alendronate and teriparatide/alendronate: ACTIVE trial Romosozumab/alendronate: ARCH trial	Incorporating direct and indirect evidence
Source of utilities	Fracture utility multipliers from the ICUROS study, combined with the	EQ-5D data was not collected in the ACTIVE and ACTIVExtend studies.

Factor	Chosen values	Justification
	UK general population values from Szende et al. (2014).[82,83]	The ICUROS study was designed to assess the QoL impact of fragility fractures over time in adults ≥50 years with osteoporosis across 12 countries including the UK regardless of treatment. This data source was chosen as the study is the largest and most recent prospective study that collected EQ-5D data appropriate for use in an economic analysis. The ICUROS study was also the accepted source of utility values in TA791.[49]
Source of costs	• Abaloparatide: Theramex • Comparators: BNF drug tariff prices (August 2023)[51] • Fracture costs: UK study Gutiérrez et al. (2011 and 2012)[84,85] updated to updated to 2023 costs using the CPI	In accordance with the NICE reference case[86] and fracture costs used in TA791.[49]
Resource use	• Disease management costs: PSSRU 2022[87] • Long-term care: Hernlund et al 2013[88] and updated to 2023 costs using the CPI	In accordance with NICE reference case[86] and used in TA791.[49]
Health effects measures	QALYs	Consistent with NICE reference case[86]
Discount rate for costs and QALYs	3.5%	Consistent with NICE reference case[86]
Perspective on costs	NHS and PSS	Consistent with the NICE reference case[86]

Abbreviations: AE, adverse events; BNF, British National Formulary; CPI, consumer price index; EQ-5D, EuroQoL-5 Dimensions; ERG, Evidence Review Group; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis; FRAX, Fracture Risk Assessment Tool; IOF, International Osteoporosis Foundation; HTA, health technology assessment; ICUROS, International Costs and Utilities Related to Osteoporotic Fractures Study; IOF, International Osteoporosis Foundation; NHS, National Health Services; NICE, National Institute for Health and Care Excellence; PRIMA, Preliminary Independent Model Advice; PSS, Personal Social Services; QALY, quality-adjusted life year; QoL, quality of life; TA, technology appraisal; UK, United Kingdom

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline patient characteristics

The baseline patient characteristics in the model base case are outlined in Table 38.

Table 38: Baseline patient characteristics in the model base case

Model parameter	Value	Source
Gender	Female	ACTIVE data (excluding Sites 131 and 132)[63]
Mean age, years (SD)	69.5 (6.32)	

Model parameter	Value	Source
Mean BMI (SD)	24.80 (3.49)	
Prevalent vertebral fracture, n/N (%)	145/696 (20.8)	
Prior clinical fracture, n/N (%)	334/696 (48.0)	
Prior nonvertebral fracture, n/N (%)	308/696 (44.3)	
Any prior fracture, n/N (%)	407/696 (58.5)	
Mean lumbar spine T-score (SD)	-2.94 (0.88)	
Mean femoral neck T-score (SD)	-2.19 (0.62	
Mean total hip T-score (SD)	-1.93 (0.72)	
Smoked cigarettes/tobacco in the past 5 years, %	12.1	
Prior glucocorticoid use, %	1.3	
Rheumatoid arthritis, %	0.3	
Alcohol ≥ 3 units/day, %	0.1	
Mean 10-year MOF probability, % (SD)	13.10(8.51)	
Mean 10-year hip probability, % (SD)	4.99 (5.24)	

Abbreviations: BMI, body mass index; FRAX®, Fracture Risk Assessment Tool; MOF, major osteoporotic fracture; SD, standard deviation

B.3.3.2 Efficacy

The risk of fracture at any time in the patient population in the model was determined using a combination of:

- The general population's risk of fracture,
- The increased fracture risk associated with osteoporosis, relative to the general population (the RR), and
- The risk reduction due to osteoporosis treatment

B.3.3.2.1 General population risk of fractures

The model inputs for general population risk of hip, vertebral and other fractures are the same as those applied in TA791 (Table 39).[49] They are also the same as those estimated using the method described in the IOF/European Federation of Pharmaceutical Industry Associations (EFPIA)-endorsed study on osteoporosis in the European Union by Hernlund et al. (2013) and reported for women in various age categories from the UK in the accompanying compendium of country-specific reports by Svedbom et al. (2013).[88,89]

The incidence of hip fractures was taken from Singer et al. (1998)[90] and is considered the most comprehensive data on the incidence of hip fracture in the UK. The incidence of vertebral fractures was estimated based on the ratio of vertebral to hip fractures in a

Swedish study due to a lack of UK data.[91] The incidence of other fractures was estimated based on a combination of the incidence of forearm fractures (distal forearm, distal radius and wrist) from Singer et al. (1998) and the ratio of "other fractures" (femur, pelvis, humerus, rib, clavicle, scapula and sternum) to hip fractures in Sweden applied to the incidence of hip fractures as estimated by Singer et al. (1998) for the UK.[90,91]

Table 39: Incidence of fractures per 100,000 person-years in the UK by age

Age, years	Hip	Vertebral	Other
50–54	33	84	633
50–59	51	142	813
60–64	81	143	979
65–69	132	192	1,425
70–74	282	397	1,928
75–79	619	602	2,891
80–84	1,236	777	3,876
85+	2,255	1,061	5,958
Source	Singer et al. (2018)[90]	Kanis et al. (2000)[10]	Singer et al. (2018)[90] and Kanis et al. (2000)[10]

B.3.3.2.2 Increased fracture risk relative to the general population

The use of fracture risk assessment tools, to predict a person's risk of fracture such as the Fracture Risk Assessment Tool (FRAX®) and Q-Fracture, are recommended by NICE clinical guideline CG146.[8]

FRAX® is an online programme that predicts a person's risk of fracture, the algorithms used provide an initial 10-year probability of hip fracture and a major osteoporotic fracture (MOF; spine, hip, forearm or humerus). The fracture risk estimation is based on several clinical risk factors, including age, gender, BMD, history of prior fractures, parental hip fracture history, BMI, ethnicity, smoking habits, alcohol consumption, use of glucocorticoids, presence of rheumatoid arthritis, and secondary osteoporosis. By considering these factors, FRAX® offers a comprehensive evaluation of an individual's fracture risk, which helps healthcare professionals make informed decisions regarding interventions and treatments to prevent future fractures.

The increased fracture risk for the model population, relative to the general population was calculated using the FRAX® algorithm. FRAX® was chosen over Q-Fracture because FRAX® can be used in combination with BMD, is more widely used than Q-Fracture and is included in the NOGG 2022 clinical guideline.[4]

B.3.3.2.3 Imminent risk of fracture

A prior fracture is associated with an increased risk of a future fracture with the imminent risk of fracture highest in the first year following a fracture and then slowly decreasing until there is little excess risk after 5 years. As such patients with a recent osteoporotic fracture are at very high risk (or imminent risk) of future fracture.

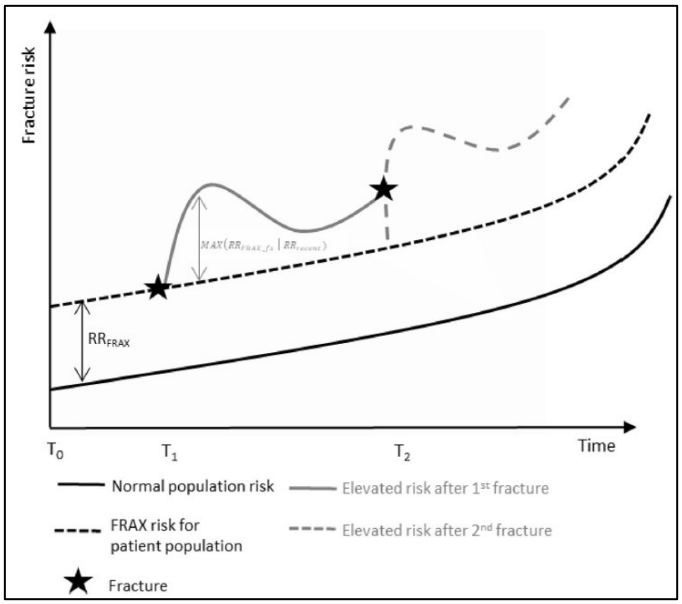
A limitation of the FRAX® algorithm is that is does not capture the imminent risk of fracture, following a prior fracture.

In the model the RR of an imminent risk of fracture is updated every time a patient sustains a fracture. However, the model has the functionality to exclude the imminent risk factor from the analysis if necessary.

The model inputs for the imminent fracture risk, defined as the increased risk of a subsequent fracture after having sustained a first, second or third fracture, were sourced from Söreskog et al. (2020), in line with TA791.[49,92] This study uses a large dataset from a retrospective real-world study in women aged ≥50 years in Sweden with a fragility fracture and estimated HRs for the risk of MOF in women after one, two or three fractures, matched to age- and gender controls.

When subsequent fractures occur within the timeframe of imminent risk following a prior fracture, the increased risk may accumulate over time as “fracture cascades.” Figure 27 illustrates how the trajectory of fracture risk is calculated at various time points for a patient who does not have a fracture at the baseline.

Figure 27: Illustration of fracture risk trajectory accounting for imminent fracture risk after a recent fracture



Abbreviations: MAX, maximum; RR_{FRAX}, relative risk estimated by FRAX® for a given patient profile excluding prior fracture as a clinical risk factor; RR_{FRAX_fx}, relative risk estimated by FRAX® for a given patient profile including prior fracture as a clinical risk factor; RR_{recent}, relative risk of an imminent fracture; T0, time-point 0, at which the patient has no fracture history; T1, time-point 1, at which the patient has sustained the first fracture; T2, time-point 2, at which the patient sustained the second fracture
Source: Söreskog et al. (2021)[80]

B.3.3.2.4 Reduction of fracture risk due to treatment

A relative fracture risk reduction due to treatment is applied to the baseline fracture risks during the treatment period, followed by a period where the treatment effect is declining (the residual effect after treatment discontinuation) (see section B.3.3.4).

The relative risks for abaloparatide, teriparatide and romosozumab, were applied to the baseline fracture risks. The model considers two sets of relative risk sources: one from the Company evidence submission for abaloparatide for osteoporosis in postmenopausal women at increased risk of fracture

ACTIVE trial (excluding Sites 131 and 132), involving abaloparatide and teriparatide, and the other from a NMA (Section B.2.9). The base case efficacy estimates for abaloparatide vs teriparatide were derived from the ACTIVE trial (population excluding Sites 131 and 132 [Table 40]). Due to a lack of evidence in the NMA for romosozumab, the relative fracture risk was derived from the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) study.[70] There were no data reported for romosozumab in any of studies included in the NMA at 18 month time-point.

The scenario analysis efficacy estimates for abaloparatide/alendronate vs teriparatide/ alendronate were derived from the NMA at 18 month time-point (Table 41). Due to a lack of evidence in NMA for romosozumab/alendronate, the relative fracture risk was derived from the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) study.[70] There was no data reported for romosozumab in any of studies included in the NMA at the 18 month time-point.

The RRs for each treatment sequence are presented in Table 40.

Table 40: Base case – Relative risks for each treatment by fracture type

Fracture type	Abaloparatide RR	Teriparatide RR	Romosozumab RR
Base case			
Hip	[redacted]	[redacted]	0.540
Vertebral	[redacted]	[redacted]	0.290
Other	[redacted]	[redacted]	0.670
Source	ACTIVE (excluding Sites 131 and 132)[63]	ACTIVE (excluding Sites 131 and 132)[63]	Cosman et al. (2016)[70]

Abbreviations: RR, relative risk

Table 41: Scenario analysis – Relative risks for each treatment by fracture type

Fracture type	Abaloparatide RR	Teriparatide RR	Romosozumab
Hip	[redacted]	[redacted]	0.540
Vertebral	[redacted]	[redacted]	0.290
Other	[redacted]	[redacted]	0.670
Source	NMA	NMA	Cosman et al. (2016)[70]

Abbreviations: NMA, network meta-analysis; RR, relative risk

B.3.3.2.5 Total fracture risk

At any point in the model's simulation, the fracture risk is computed by considering the risk of fracture in the general population, the excess RR of fracture determined by FRAX® for a specific patient characteristic (excluding the prior fracture), the maximum of the time-dependent RR for an impending fracture, and the FRAX®-estimated RR encompassing the contribution of the prior fracture, multiplied by relative risk reduction due to treatment.

The formula that was used for this calculation is the following:

$$General\ population\ risk * RR_{\text{frax}} * MAX(RR_{\text{frax\_fx}} \mid RR_{\text{recent}}) * Risk\_reduction\_due\_to\_treatment$$

where:

MAX = maximum, RR_{frax} = relative risk estimated by FRAX for a given patient profile excluding prior fracture as a clinical risk factor, RR_{frax_fx} = relative risk estimated by FRAX for a given patient profile, including prior fracture as a clinical risk factor, RR_{recent} = RR of an imminent fracture

B.3.3.3 Persistence

Suboptimal persistence to osteoporosis treatments is observed in clinical practice. In a UK study (n=66,116) of women who had a prescription for an oral bisphosphonate and were ≥50 years of age or had a diagnosis to indicate menopause at an early age, 56% of patients receiving antiresorptive treatments (oral bisphosphonate, oral raloxifene and oral strontium ranelate) discontinued after 6 months and 68% of patients discontinued treatment within 1 year.[93] Anabolic treatments have a better persistence profile compared with antiresorptives.[94,95]

The model captures persistence to treatment in two ways:

- A patient can fully adhere to the initial treatment in a sequence for the maximum duration of the initial treatment or,
- A patient can discontinue the initial treatment and switch to alendronate before the maximum duration of the initial treatment

In the model, it was assumed that a patient initiates a treatment from first cycle and has the potential risk of discontinuing their treatment at any given cycle, and this discontinuation was factored into the assessment of the benefits of treatment.

However, it was assumed that if a patient discontinues the initial treatment in a sequence before the maximum duration of initial treatment, then the patient will not be eligible to switch to alendronate. Sequential treatment was exclusively extended to those patients who fully adhered to the initial treatment protocol.

Persistence rates used in the model for abaloparatide/alendronate, teriparatide/alendronate and romosozumab/alendronate are presented in Table 42.

Discontinuation rates for abaloparatide/alendronate and teriparatide/alendronate were taken from the ACTIVE trial.[63] For abaloparatide/alendronate and teriparatide/alendronate, the discontinuations were available at specific time points. Hence, it was assumed that the discontinuation rate was linearly distributed across the treatment period. The persistence rates for romosozumab were taken from a real-world study.[80]

The model has a functionality to exclude the persistence rates from the analysis; this was explored in the scenario analysis.

Table 42: Proportion of patients on treatments over time

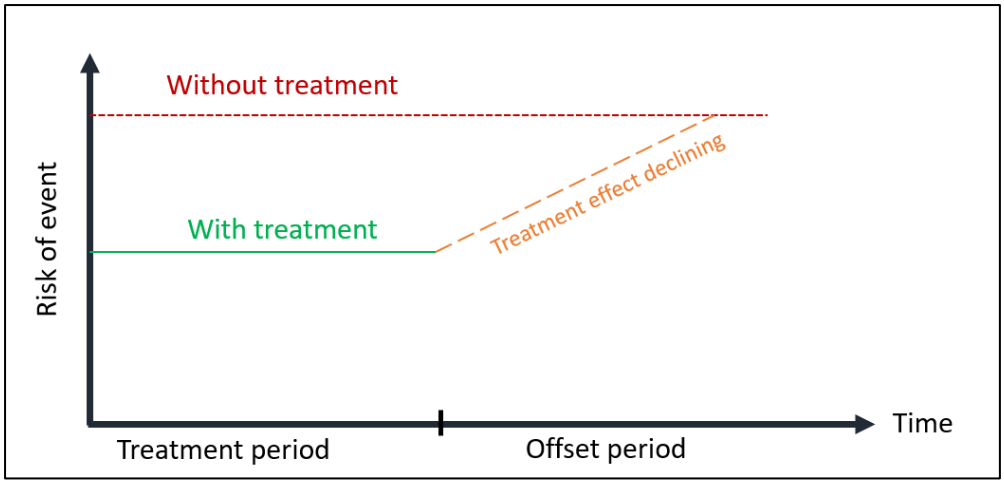
Month since treatment initiation	Abaloparatide	Alendronate after abaloparatide	Teriparatide	Alendronate after teriparatide	Romosozumab	Alendronate after romosozumab
6	[redacted]	[redacted]	[redacted]	[redacted]	80%	–
12	[redacted]	[redacted]	[redacted]	[redacted]	80%	–
18	[redacted]	[redacted]	[redacted]	[redacted]	0%	14%
24	[redacted]	[redacted]	[redacted]	[redacted]	0%	11%
30	[redacted]	[redacted]	[redacted]	[redacted]	0%	9%
36	[redacted]	[redacted]	[redacted]	[redacted]	0%	8%
42	[redacted]	[redacted]	[redacted]	[redacted]	0%	7%
48	[redacted]	[redacted]	[redacted]	[redacted]	0%	6%
54	[redacted]	[redacted]	[redacted]	[redacted]	0%	5%
60	[redacted]	[redacted]	[redacted]	[redacted]	0%	4%
Source	ACTIVE (excluding Sites 131 and 132)[63]	ACTIVE (excluding Sites 131 and 132)[63]	ACTIVE (excluding Sites 131 and 132)[63]	ACTIVE (excluding Sites 131 and 132)[63]	Söreskog et al. 2021	Morley et al. (2020)[79,96]

B.3.3.4 Residual effect

In the model it is assumed that fracture efficacy persists for a period of time (offset time) after treatment is stopped. Two methodologies for incorporating residual effects were explored. These are presented below and are visually represented in Figure 28.

- **Dynamic approach:** In this approach, the offset time is envisioned to match the duration of treatment, leading to shorter offset times for patients who discontinue treatment prematurely. For example, if a patient discontinues in the 2nd cycle, i.e., at 1 year, then the offset time for this patient is the next 1 year. The treatment effect declines linearly in the next year, and the efficacy after 1-year would be the same as no treatment. On the other hand, if the patient adheres to 5 years, then the offset time for that patient would be the next 5 years, and treatment efficacy would decline linearly in 5 years after discontinuation.
- **Fixed approach:** Contrastingly, in this approach, all patients are assigned an identical offset time, regardless of their discontinuation status. If a patient discontinues treatment at the 2nd or 8th cycle, the same preset offset time will be applied to both patients.

Figure 28: Visual depiction of modelling residual effect



The base case maximum treatment duration, offset time, and offset method used in the model are described in Table 43. The maximum treatment duration for abaloparatide/alendronate was taken from the ACTIVExtend study[1] and for romosozumab/alendronate from TA791.[49] The dynamic approach is preferred and aligned with recommendations for economic evaluations in patients with osteoporosis[81] and the approach used in TA791.[49] This choice aligns better with real-world scenarios, as it accounts for instances where a patient stops treatment before the predetermined duration. In such cases, the efficacy estimate is appropriately adjusted using the dynamic discontinuation time.

Table 43: Base case maximum duration, offset time, and offset method used in the model

Treatment	Maximum duration	Offset period	Offset method
Abaloparatide/alendronate	6.5 years	6.5 years	Dynamic

Teriparatide/alendronate	6.0 years	6.0 years	Dynamic
Romosozumab/alendronate	7.0 years	7.0 years	Dynamic

B.3.3.5 Mortality

In the model, mortality is captured in three ways:

- Age-specific mortality of the general population (all-cause mortality)
- RR capturing excess mortality of the disease, and
- Comorbidity adjustment factor

The UK's age and gender-specific all-cause mortality rates were taken from recently published lifetable data, i.e., 2018–2020.[97] At the start of the model, patients only experience the general population mortality.

At any point in the model, when patients experience a fracture, the general population mortality is adjusted by a comorbidity adjustment factor, i.e., 30%: this aligns with TA791 and IOF/ESCEO guidelines.[49,81] This was done because people with fractures are often more fragile and have a higher risk of dying from various reasons, not just the fracture itself.[81,98]

Additionally, the model considered that a patient's risk of death would be higher (compared with people without fractures) based on their history of fractures. For instance, if a patient had a hip fracture in the 4th cycle and other fracture in the 6th cycle, the model would consider the highest risk of dying more than expected (which, in this case, is the excess mortality risk associated with a second year hip fracture).

The excess mortality related to hip was sourced from published literature.[99] In the case of NHNV fractures, the increase in the risk of death was calculated by taking a weighted average of the risk estimates found in a study.[100]The calculation was based on the proportions of various fracture types reported in a published paper.[91]

The relative risks of mortality compared with the average population are presented in Table 44.

Table 44: Relative risk of mortality compared with the general population

Age, years	Hip	Vertebral	Other
50	9.79	12.07	1.23
55	8.64	10.15	1.23
60	7.69	9.04	1.23
65	6.39	7.43	1.23
70	5.54	5.98	1.23
75	4.16	4.39	1.23
80	2.92	2.75	1.23
85	2.15	1.98	1.23

90	1.63	1.36	1.23
Source	Jönsson et al. (2011)[99]	Jönsson et al. (2011)[99]	Kanis et al. (2000)[91]; Barrett et al. (2003)[100]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

The ACTIVE and ACTIVExtend trials did not collect HRQoL data.

B.3.4.2 Health-related quality of life studies

An SLR was conducted to identify relevant HRQoL data. Searches for the clinical SLR were conducted in April 2023. Full details of the SLR methodology, PRISMA diagram and included and excluded studies of the SLR are provided in Appendix H.

A total of 29 studies were included in the SLR, five reported utility values EQ-5D data however, two studies were in Japanese patients[101,102] and one study was in Korean patients.[103] One study was in a mixed population of men and women and data were not presented by fracture site.[104] A study reporting HRQoL in patients taking teriparatide in French centres enrolled in the European Forsteo Observational study in 2014 reported the median EQ-5D health state utility values at 18 months (0.69 [0.52–0.76]) and 36 months (0.69 [0.52–0.80).[105] Although, the latter study was in the appropriate patient population the data were not presented by fracture site, therefore none of the studies identified in the SLR were suitable sources for utility values for the model.

B.3.4.3 Health-related quality of life data used in the cost-effectiveness analyses

Utility multipliers for fractures from the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) were used and merged with general population values from Szende et al. (2014).[82,83] This approach was also used in TA791.[49]

The ICUROS study, encompassing the experience of osteoporosis patients across 12 countries with over 7,000 participants, focused on comprehending the lasting effects of fractures on their quality of life for cost-effectiveness analysis. Notably, this is the most prospective osteoporosis study to date. In the UK alone, 357 fracture instances were examined. Using the EQ-5D tool, ICUROS assessed the HRQoL impact at different time points: immediately following fracture, independent of treatment, and subsequently at 4 months, 12 months, and 18 months post-fracture. This approach provided insights into the immediate and long-term implications of osteoporotic fractures in real-world scenarios. According to the recommendations from IOF/ESCEO guidelines, national ICUROS data is advised for use whenever available.[81] The IOF/ESCEO also recommend using national ICUROS data if available or otherwise the international version.

Utility multipliers for the initial year post-fracture and subsequent years are presented in Table 45. These multipliers were applied to the UK general population utility values estimated by Szende et al. 2014.[82] (Table 46).

Table 45: Utility multipliers by health states

Health state	First year	Subsequent years
Hip	0.545	0.857
Vertebral	0.671	0.841
Other	0.791	0.952

Source: ICUROS study[83]

Table 46: UK general population utilities

Age, years	General population utility
50	0.849
55	0.804
60	0.804
65	0.785
70	0.785
75	0.734
80	0.734

Source: Szende et al. 2014.[82]

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Unit costs used in the cost-effectiveness model are presented in Table 47. Intervention costs were sourced from the list price of abaloparatide including a PAS discount of [redacted]. Comparator costs were sourced from the British National Formulary (BNF), August 2023. The cost of teriparatide in the model base case was for Forsteo® as this is the branded drug. As teriparatide biosimilars are also available these have been included in the scenario analyses (see section B.3.11.1.3).

Table 47: Drug unit costs

Drug	Pack size	Regimen	Units (pens/packs per year)	Unit cost	Annual cost	Source
Abaloparatide	One prefilled pen containing 3 mg abaloparatide in 1.5 mL of solution (30 doses of 80 µg)	OD	12	List price: £294.54 per pen PAS price: [redacted]	List price: £3,534.44 PAS price: [redacted]	List price from manufacturer PAS price from manufacturer
Teriparatide (Forsteo®) Base case	250 µg/ml, net price based on 2.4	OD	13	£271.88 per pen	£3,534.44	BNF August 2023[51]

	ml prefilled pen					
Teriparatide (Movymia®) Scenario analysis	250 µg/ml, net price based on 2.4 ml prefilled pen	OD	13	£235.00 per pen	£3,055.00	
Teriparatide (Sondelbay®) Scenario analysis	250 µg/ml, net price based on 2.4 ml prefilled pen	OD	13	£271.88 per pen	£3,534.44	
Teriparatide (Terrosa®) Scenario analysis	250 µg/ml, net price based on 2.4 ml prefilled pen	OD	13	£239.25 per pen	£3,110.24	
Romosozumab	Injection, 90 mg/ml, consisting of two prefilled disposable injections	Once monthly	12	£427.75 per pen	£5,133.00	
Alendronate	70 mg 4-tablet pack	Once weekly	52.25	£0.96 per pack	£12.54	

Abbreviations: BNF, British National Formulary; OD, once daily; PAS, patient access scheme

B.3.5.1.2 Drug administration cost

Drug administration costs were included in the model for abaloparatide as one nurse visit per year, and they were valued at £9.00 assuming a 15-minute visit and using a unit cost of £36 per hour as provided by the Personal Social Services Research Unit (PSSRU) 2022.[87]

B.3.5.2 Health state unit costs and resource use

B.3.5.2.1 Fracture costs

The costs of hip, vertebral, and other fractures during the first year after a fracture were sourced from the literature[84,85] and updated to 2023 using the consumer price indices (CPIs) as provided by the Office for National Statistics (ONS);[106] and using the calculator.[107]

This resulted in cost estimates of £15,579, £3,412, and £2,384 for the first year after a hip, vertebral, or other fracture, respectively. The costs of fractures in subsequent years were sourced from Davis et al. (2016)[108] and updated to 2023 using the CPI provided by the ONS.[106] These were only applied to hip and vertebral fractures at £136 and £436, respectively.

The costs of long-term care were included as recommended by the IOF/ESCEO guidelines for the conduct of economic evaluations in osteoporosis.[81] The cost of long-term care in a nursing home was sourced from Hernlund et al. 2013[88] and updated to 2023 using the CPIs provided by the ONS[106], resulting in a daily cost of £173. The long-term care cost is multiplied by the proportion of patients admitted to nursing care after an occurrence of hip

fracture. The proportion of patients going for long-term nursing care is sourced from published literature.[109]

The fracture-related and long-term costs used in the model are presented in Table 48.

Table 48: Fracture-related costs and long-term care costs used in the model

Type of fracture	First-year[84,85,106]	Second and subsequent years[106,108]	Long-term care cost[81,88,106,109]
Hip	£15,579	£136	£173
Vertebral	£3,412	£436	£173
Other fractures	£2,384	-	£173

B.3.5.2.2 **Disease management costs**

The per cycle frequencies of resource use by treatment and cost per unit are presented in Table **49**. These reflect treatment-specific resource use such as BMD measurements and general practitioner (GP) visits, which are required to ensure patients are tolerating the treatment well. The unit costs of different resources were derived from PSSRU 2022.[87]

Table 49: Disease management cost and resource use in the model per cycle

Resource	Unit cost	Frequency per 6 months			
		Abaloparatide	Teriparatide	Romosozumab	Alendronate
BMD measurement	£40.00	0.25	0.25	0.25	0.25
GP visit	£41.00	1.0	1.0	1.0	1.0
Nurse visit	£6.45	0.5	0.5	0.5	
Source	PSSRU[87]	Assumption[49]	Assumption[49]	Borgstrom et al. (2004)[110]	Assumption

Abbreviations: BMD, bone mineral density; GP, general practitioner; PSSRU, Personal Social Services Research Unit

B.3.6 Severity

It is not anticipated that the treatment of abaloparatide will be applicable for any form of severity weighting.

B.3.7 Uncertainty

Not applicable.

B.3.8 Managed access proposal

Not applicable.

B.3.9 Summary of base case analysis inputs

A summary of the base case inputs and variables is provided in Appendix N.

B.3.9.1 Assumptions

The key assumptions in the base case are provided in Table **50**.

Table 50: Key model assumptions

Assumptions	Details	Justification/reference
Fracture risk estimation approach	FRAX based algorithm to include recent fractures in the estimation of future risk	FRAX® is a Fracture Risk Assessment Tool that estimates a patient's fracture risk and can be used to derive an increased risk of fracture. NICE has used FRAX® for fracture risk estimation in recent HTAs of osteoporosis treatments. The FRAX® algorithm has a drawback that it fails to account for the elevated fracture risk that varies over time following a recent fracture. In this submission, imminent fracture risk is also incorporated alongside the FRAX® based risk estimation. This approach was aligned with IOF/ESCEO guidelines and TA791.[49,81]
Persistence	Included in the base case	Excluding persistence would result in overestimating treatment duration and consequently inflate the efficacy
Efficacy offset assumption	Dynamic offset in the base case	In the base case, the dynamic approach is chosen to model the residual effect of a treatment's effectiveness. This aligns with real-world scenarios, as it accounts for instances where a patient stops treatment before the predetermined duration. The base case model assumed maximum treatment duration as a preset offset time aligned with the previous NICE submissions[49]
Mortality	Mortality rates were comprised of three rates: age-specific mortality of the general population (all-cause mortality) relative risk capturing excess mortality of the disease comorbidity adjustment factor	As fractures are associated with excess mortality, the excess fracture-related mortality risk was derived from published sources, and the comorbidity adjustment factor was applied to general population mortality

Abbreviations: HTA, health technology assessment; IOF/ESCEO, International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; NICE, National Institute for Health and Care Excellence.

B.3.10 Base case results

B.3.10.1 Base case incremental cost-effectiveness analysis results

Base case results and the net health benefit (NHB) at the £20,000/QALY and £30,000/QALY are presented in Table 51. The results demonstrate that compared with romosozumab, abaloparatide is associated with a QALY [redacted] and an incremental cost of [redacted], resulting in a dominant pairwise ICER. In comparison with teriparatide, abaloparatide is associated with a QALY [redacted] and an incremental cost of [redacted] (Table **51**).

Estimates of clinical outcomes and disaggregated results from the model are presented in Appendix J.

Table 51: Base case results – with PAS

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	Pairwise ICER	NHB at £20,000	NHB at £30,000
Abaloparatide/ alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Romosozumab/ alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]
Teriparatide/ alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year

Results show that at a WTP threshold of £30,000 per QALY gained, the introduction of abaloparatide would increase the overall population health and is a cost-effective use of NHS resources.

B.3.11 Exploring uncertainty

B.3.11.1.1 Probabilistic sensitivity analysis

A PSA was performed using a second-order Monte Carlo simulation with 1,000 iterations. Further details are provided in Appendix N.

The mean PSA results are presented in Table **52** and the cost-effectiveness plane showing the 1,000 iterations is presented in Figure 29. The probabilistic results are consistent with the deterministic analysis with a mean [redacted] at mean incremental cost of [redacted] for the comparison versus romosozumab/alendronate. This results in the ICER being dominant, supporting that abaloparatide is a cost-effective use of NHS resources at the £30,000 per QALY WTP threshold. The results for abaloparatide/alendronate versus teriparatide/alendronate are also consistent with the deterministic analysis (Table 52).

Based on the 1,000 iterations, abaloparatide is projected to be 100% cost-effective at the £30,000 per QALY WTP threshold.

Table 52: PSA results – with PAS

Abaloparatide/alendronate versus	Analysis	Incremental costs, (£)	Incremental QALYs	Incremental cost per QALYs
Teriparatide/alendronate	Deterministic	[redacted]	[redacted]	Dominant
	Probabilistic	[redacted]	[redacted]	Dominant
Romosozumab/alendronate	Deterministic	[redacted]	[redacted]	Dominant
	Probabilistic	[redacted]	[redacted]	Dominant

Abbreviations: PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 29: Cost-effectiveness plane – with PAS

Abbreviations: PAS, patient access scheme; QALY, quality-adjusted life years

B.3.11.1.2 Deterministic sensitivity analysis

One-way sensitivity analysis was undertaken by varying key parameters by their standard error, 95% CI or ±20% of the expected values (base case) based on data availability of the parameter. The following parameters were included as part of the one-way sensitivity analysis. Full details of the parameters which were varied is presented in Appendix N.

- Discount rate: varied from 0% to 6%

- Fracture-related excess mortality: varied by ± 20%
- Treatment-related RRs for fracture reduction: varied by 95% CI
- Costs: included disease management, treatment acquisition, administration, and monitoring; varied by ± 20%
- Utility multiplier for hip, vertebral, and other fractures: varied by ± 20%

Table **53** and Figure 30 present the ICERs and tornado plots of the top 10 parameters which had the largest impact on the ICER for abaloparatide versus romosozumab. Utility multipliers for other fracture, hip fracture states and drug costs had the biggest impact for abaloparatide versus both comparators.

Table **54** and Figure 31 present the ICERs and tornado plots of the top 10 parameters which had the largest impact on the ICER for abaloparatide versus teriparatide.

For all scenarios, abaloparatide remained cost-effective at the £30,000/QALY threshold, demonstrating the robustness of results to individual parameter uncertainty.

Table 53: OWSA results - abaloparatide versus romosozumab – with PAS

Parameter	Base case result	Lower value	Upper value	Lower ICER	Upper ICER	Difference
Health state-based utility other fractures 1st Year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state-based utility hip 1st year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug costs romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug costs abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate in QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate in costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state-based utility vertebral 1st year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily cost of nursing home/long-term care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect of events abaloparatide vertebral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment effect of events abaloparatide other fractures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme; QALY, quality-adjusted life year

Table 54: OWSA results - abaloparatide versus teriparatide- with PAS

Parameter	Base case	Lower value	Upper value	Lower ICER	Upper ICER	Difference
Health state-based utility other fractures 1st Year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state-based utility Hip 1st Year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug costs teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug costs abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate in costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate in QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect of events teriparatide, other fractures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state-based utility Vertebral 1st Year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect of events teriparatide vertebral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily cost of nursing home/long-term care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme; RR, relative risk; QALY, quality-adjusted life year

Figure 30: Tornado plot - abaloparatide versus romosozumab – with PAS

Abbreviations: NMB, met monetary benefit; PAS, patient access scheme; QALY, quality-adjusted life year

Figure 31: Tornado plot - abaloparatide versus teriparatide

Abbreviations: NMB, met monetary benefit; PAS, patient access scheme; QALY, quality-adjusted life year

B.3.11.1.3 Scenario analysis

Scenario analyses were conducted to explore the uncertainties and robustness of the model. Results are presented for abaloparatide versus romosozumab in Table **55** and versus teriparatide in Table 56. The results demonstrate the robustness of the base case for cost-effectiveness. Several scenarios are presented which explore different sources of clinical data and discontinuation rates, and alternative methods for determining offset and the effect of excluding other factors. In most of the scenarios explored in the analysis of abaloparatide versus romosozumab, abaloparatide remains a cost-effective treatment option within the £30,000 per QALY gained threshold (6 out of 8 scenarios). The assumptions which have the highest impact are FRAX based estimation, offset method and persistence.

Table 55: Scenario analysis - abaloparatide versus romosozumab – with PAS

Scenario	Description	Incremental costs	Incremental QALYs	ICER
Base case	-	[redacted]	[redacted]	Dominant
FRAX based estimation	Excluded	[redacted]	[redacted]	[redacted]
Imminent risk of fracture	Excluded	[redacted]	[redacted]	Dominant
Persistence	Excluded	[redacted]	[redacted]	Dominant
Offset method	Fixed	[redacted]	[redacted]	Dominant
Drug administration cost	Excluded	[redacted]	[redacted]	Dominant
CV events	Excluded	[redacted]	[redacted]	Dominant
Source of clinical data	NMA estimates	[redacted]	[redacted]	Dominant

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PAS, patient access scheme; QALY, quality-adjusted life year; TA, technology appraisal

In the scenario analysis for abaloparatide, versus teriparatide, the ICER remains dominant in all scenarios (8 out of 8), the assumptions with the highest impact were FRAX based estimation, persistence and source of discontinuation rates.

Table 56: Scenario analysis - abaloparatide versus teriparatide – with PAS

Scenario	Description	Incremental costs	Incremental QALYs	ICER
Base case	-	[redacted]	[redacted]	Dominant
FRAX based estimation	Excluded	[redacted]	[redacted]	Dominant
Imminent risk of fracture (excluded)	Excluded	[redacted]	[redacted]	Dominant
Persistence	Excluded	[redacted]	[redacted]	Dominant
Offset method	Fixed	[redacted]	[redacted]	Dominant
Drug administration cost	Excluded	[redacted]	[redacted]	Dominant
CV events	Excluded	[redacted]	[redacted]	Dominant
Source of clinical data	NMA estimates	[redacted]	[redacted]	Dominant

Source of discontinuation rates for teriparatide	NICE TA791[49]	[redacted]	[redacted]	Dominant

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PAS, patient access scheme; QALY, quality-adjusted life year; TA, technology assessment

B.3.12 Subgroup analysis

The inclusion/exclusion criteria of ACTIVE study focused on patients who are considered at very high risk of fracture. As such we consider that further subgroup analyses are not considered as relevant. No subgroup analyses were conducted.

B.3.13 Benefits not captured in the QALY calculation

There are likely several additional benefits of abaloparatide which are not captured in the QALY calculation and may impact a patients' HRQoL.

As the treatment is self-administered by the patient, hospital/GP practice visits are minimised which is relevant when considering NHS capacity). In addition, the medication does not require refrigeration after first use.[2] This is helpful for patients, can help to reduce medication wastage and could allow for uninterrupted daily treatment (if the patient does not need to wait for the replacement of a 'spoiled' pen). A real-world study in the US[111] reported that most patients (86%) were satisfied with the abaloparatide regimen, especially with ease of preparation (82%), ease of storage (87%), and storage convenience (89%), an attribute 83% of the patients thought was important. In addition, most patients reported complete satisfaction with the abaloparatide regimen allowing for their ability to conduct daily activities (85%) and convenience to fit into their daily schedule (84%). The authors concluded that the majority of patients were satisfied with abaloparatide and found it convenient/easy to prepare and store. High self-reported adherence may be associated with positive patient experience including ease of use and adequate support from healthcare providers.[111]

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Upon completing the model programming, a rigorous and comprehensive quality check of the model was conducted to ensure the completed model contained no errors and worked as intended. Overall, the model follows the guidelines for osteoporosis modelling as outlined by IOF/ESCEO guidelines.[81]

A series of tests and checks were also conducted on the model engine. Among other reviews, the validator:

- Confirmed that all model inputs were correctly linked to the model engine
- Checked all cells with "IF logic" in detail, confirming that the statements provided the correct value for each condition
- Traced all links between the calculation sheets and results sheet to make sure that the proper outputs were displayed in the correct location
- Thoroughly reviewed and debugged all Visual Basic for Applications code

- Searched for common Microsoft Excel® errors (e.g.,!#REF errors, unused named ranges, broken links, links to external workbooks, copy/paste errors) and resolved them as needed

- Checked all text and formatting to ensure that there were no typographical errors or formatting irregularities

Finally, an extreme value sensitivity analysis was conducted on all applicable model inputs. While conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model, and the refined post-validation model was used to generate the final results.

B.3.15 Interpretation and conclusions of economic evidence

This analysis assessed the incremental cost-effectiveness of abaloparatide/alendronate vs teriparatide/ alendronate and romosozumab/ alendronate from an NHS and PSS perspective in the UK. The model adopted a five-health state micro-simulation Markov structure, with at risk, hip, vertebral, other, and death as health states. The economic evaluation of abaloparatide followed by alendronate was conducted according to UK HTA guidelines.

Treatment with abaloparatide/alendronate is associated with increasing QALYs and preventing fractures.

The cost and outcomes were estimated based on the most relevant sources available in the UK. The results of the base case analysis indicate that abaloparatide/alendronate is associated with an incremental cost of [redacted] and incremental QALY [redacted] compared with teriparatide/alendronate. Therefore, the ICER of abaloparatide/alendronate vs teriparatide/alendronate is dominant. Also, abaloparatide/alendronate is associated with an incremental cost of [redacted] and incremental QALY [redacted] vs romosozumab/alendronate. Therefore, the ICER of abaloparatide/alendronate in comparison to romosozumab/alendronate is also dominant.

The model parameters with the most significant impact on the ICER, as identified from the DSA performed, included the utility multiplier of hip fracture and the drug costs. Scenario analyses showed that the modelling of residual effect method had the most impact on the ICER.

The healthcare resource use and cost parameters used in the model were taken from UK sources. Utility parameters are specific to the value set for the UK. Furthermore, the mortality data were adjusted using UK life table data.

This economic evaluation has several strengths, which include:

- The modelling approach was based on a thorough review of published economic modelling approaches in osteoporosis, considered critiques from HTA submission reports. This provides extensive flexibility in how to estimate the long-term health benefits associated with treatments in osteoporosis

- The model has the functionality to test critical assumptions like imminent fracture risk and persistence effect options
- The modelling approach also accounts for fracture risk based on FRAX® assessment and imminent fracture risk, i.e., risk of new fracture after having a recent fracture
- Healthcare resource use and cost parameters used in the model were derived from recent sources
- Utility multipliers for fractures were derived from the ICUROS and combined with UK general population values to reflect the UK population

This analysis has limitations. The model's outcomes are influenced by the constraints inherent in the NMA. Additional data were needed to mitigate bias within the NMA; this would diminish the uncertainty surrounding the model's findings. In the model, this uncertainty is offset by running one-way and probabilistic sensitivity analyses around clinical parameters.

The cost-effectiveness results for the base case analysis show that the use of abaloparatide/alendronate vs teriparatide/alendronate and vs romosozumab/alendronate resulted in a dominant ICER. At a threshold of £30,000/QALY, there is a 100% probability that the abaloparatide/alendronate would be cost-effective vs teriparatide/alendronate and romosozumab/alendronate.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture [ID882]

Company clarification responses – NMA appendix

4 December 2023

File name	Version	Contains confidential information	Date
ID882 abaloparatide_osteoporosis_Updated NMA [redacted]	**1.0**	**Yes**	**23rd January 2024**

Contents

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Abbreviations

BGR	Brooks Gelman-Rubin
BMD	bone mineral density
CRD	Centre for Reviews and Dissemination
CrI	credible interval
CSR	clinical study report
DARE	Database of Abstracts of Reviews of Effects
DEXA	dual-energy X-ray absorptiometry
DIC	deviance information criterion
EAG	External Assessment Group
FEM	fixed-effects model
FRAX	Fracture Risk Assessment Tool
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICTRP	International Clinical Trials Registry Platform
IQR	interquartile range
ITT	intent-to-treat
IV	intravenous
JAMA	Journal of the American Medical Association
LCrI	Lower confidence interval
LTE	long-term extension
MOF	major osteoporotic fracture
NA	not applicable
NHNV	non-hip-nonvertebral
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
NR	not reported
PD	pharmacodynamic
PICOS	population, intervention, comparison, outcomes and study design
PK	pharmacokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PrI	predictive intervals
QoL	quality of life
RCT	randomised controlled trial
REM	random-effects model
RoB	risk of bias
RR	Relative risk
SC	subcutaneous
SD	standard deviation
SE	standard error
SLR	systematic literature review
SmPC	Summary of Product Characteristics
STA	single technology appraisal
TA	technology appraisal
UCrI	Upper confidence interval
UK	United Kingdom

B.1 Clinical systematic literature review update

B.1.1 Search strategies

The clinical literature review was updated in two ways:

- **Extended timeframe:** The timeframe for the clinical systematic literature review (SLR) was expanded in response to the clarification questions from the external assessment group (EAG). To capture all relevant studies conducted prior to 2012, a pragmatic methodology was employed to update the SLR for use in the updated network meta-analysis (NMA) (see Section B.1.5). This involved leveraging two previously published, technology assessments by Davis et al.2016[1] and Davis et al. 2020).[2] Studies included in the technology assessments were evaluated based on the Population, Intervention, Comparison, Outcomes and Study (PICOS) and the de-prioritisation criteria set in the original SLR. These technology assessments provided detailed information from each study on patients' baseline characteristics and fracture-related data. The included records are presented in Table 4. The excluded records are presented in Table 18.
    - These additional studies were utilised for hip, new vertebral and non-vertebral fracture outcomes only (see Section B.1.5)
- **No requirement for data at pre-defined timepoints:** The 60 records included in the original clinical SLR were re-screened according to new PICOS criteria without the requirement for data at pre-defined timepoints.

B.1.2 Study selection and eligibility criteria for the updated literature review

The records identified in the Davis publications were subject to title and abstract screening against Table 1 and full text screening against Table 2. The change in criteria used for the full text screening was to ensure that the records included which were relevant for the NMA were taken forward to the data extraction stage. Before data extraction, records were de-prioritised according to the criteria in Table 3, to refine the number of records and select those which are relevant to the company submission. At each stage, the screening was conducted by two independent reviewers with any conflicts resolved by a third reviewer.

Table 1 Eligibility criteria for the updated literature review

PICOS	Inclusion criteria	Exclusion criteria
Population	Postmenopausal women with osteoporosis at increased risk of fracture Osteoporosis is defined for this SLR as: BMD T score ≤ -2.5 OR Age of patients ≥ 50 years AND mention of previous fragility fracture For trials that include a mixed population of participants where	• Women with normal or unspecified BMD who have not been selected based on the presence of risk factors • Women with glucocorticoid induced osteoporosis • Women with other indications for osteoporosis treatment e.g., Paget's disease, hypercalcaemia of

PICOS	Inclusion criteria	Exclusion criteria
	not all these inclusion criteria are fulfilled, such studies shall be excluded unless separate data are reported for the population of interest	malignancy, metastatic breast cancer • Men with osteoporosis
Intervention	Abaloparatide (Eladynos)	Not applicable

Comparators	• Bisphosphonates:
	  • Alendronic acid, Ibandronic acid, Risedronate sodium, Zoledronic acid
	• Non-bisphosphonates:
	  • Denosumab, Romosozumab, Teriparatide, Raloxifene
	• No active treatment/placebo
	• Usual care: vitamin D and calcium supplementation
		• Strontium ranelate
		• Odanacatib
		• Combination therapies
		• Exception: usual care
		• Interventions which are not administered in accordance with licensed indications

Outcomes	Studies reporting at least one of the following outcomes shall be included:
	• Osteoporotic fragility fracture:
	  • New or worsening vertebral fracture
	  • Clinical vertebral fracture
	  • Non-vertebral fracture
	  • Clinical fracture
	  • Hip fracture
	• BMD (e.g., % change in BMD)
	• Mortality
	• Adverse effects of treatment
		• Studies not reporting at least one prespecified outcome
		• Studies reporting outcomes relating to fractures associated with major trauma (e.g., road traffic accidents). Studies that reported mixed trauma and/or non-trauma fracture, shall be included only if they have reported separate data for relevant non-trauma fractures

Study design	Studies following parallel RCT design, also including: • Randomised dose finding and formulation trials • Either a placebo or active control arm • No limitation by study phase • Followed-up patients for at least 12 months Extensions studies belonging to a study where all these inclusion criteria are fulfilled should also be included	• Systematic reviews • Pooled analyses of previously published studies • Secondary analysis, subgroup analyses, subpopulation analyses of previously published studies • Studies based on animal models • Pre-clinical and biological studies • Narrative reviews, letters, editorials, opinions, and other forms of non-primary studies • Case series, case reports
Language restrictions	English language records	Non-English language records
Date range	For articles: No time limit For conference abstracts: 01 Jan 2021 onwards	Not applicable

Abbreviations: BMD, bone mineral density; RCT, randomised controlled trial

Table 2 Eligibility criteria for inclusion in the NMA

Domains	Eligibility criteria
Population	Postmenopausal women with osteoporosis at increased risk of fracture
Intervention	• Abaloparatide • Abaloparatide followed by Alendronate
Comparators	• Bisphosphonates: o Alendronic acid, ibandronic acid, risedronate sodium, zoledronic acid • Non-bisphosphonates: o Denosumab, romosozumab, teriparatide, raloxifene • No active treatment/ placebo
Outcomes	Efficacy outcomes:[a] • New vertebral fracture • Worsening vertebral fracture • New or worsening vertebral fracture • Non-vertebral fracture • Clinical fracture • Hip fracture • Major osteoporotic fracture
Language	English language records only

Abbreviations: NMA, Network meta-analysis
[a]Based on feedback from EAG, studies which reported fracture data as safety outcomes were also included in the updated NMA

Table 3 De-prioritisation of records prior to the NMA

Criteria	Description
Sample size	Exclude studies with a sample size less than 200 (n<200)
Geographic location	Exclude studies that at least have not included North America or Western Europe
Language	Only include articles written in English language
Outcomes	Exclude articles with no mention of fracture risk

Abbreviations: n, number; NMA, network meta-analysis

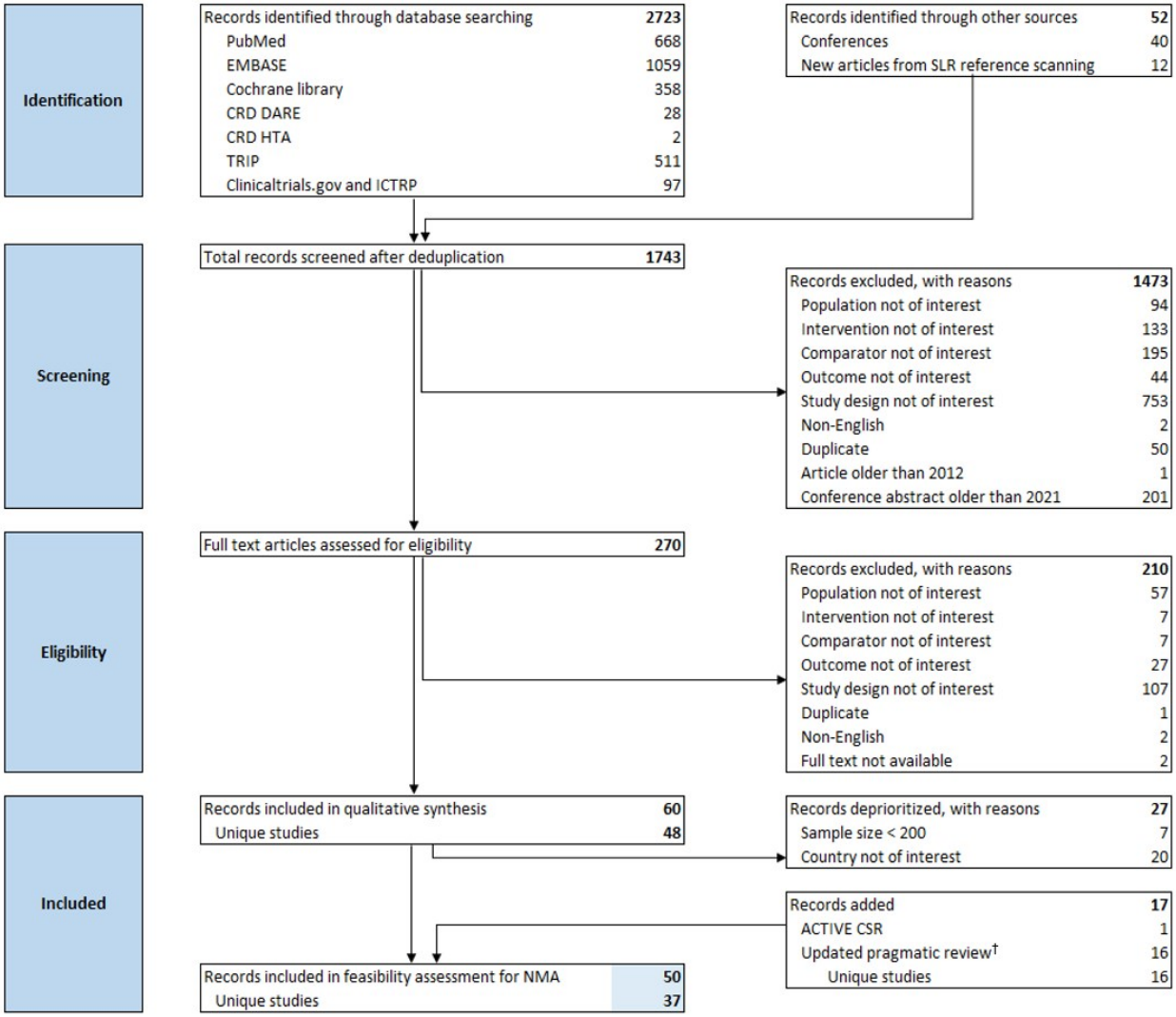
B.1.3 Data extraction for the updated literature review

Data extraction was conducted by a single reviewer and then validated by a separate independent reviewer. In case of any uncertainty, a third reviewer was consulted. For the data extraction, baseline characteristics and fracture data were sourced from the data tables in Davis et al 2016[1] and Davis et al 2020[2]. In addition, the data extraction was focused on the requirements for the NMA, therefore, minimal baseline characteristics, hip, new vertebral and non-vertebral fractures only were extracted.

B.1.4 Results

The PRISMA flow diagram for the clinical SLR (including the updated literature review) is presented in Figure 1. The list of records included for the updated literature review, including those from the original clinical SLR (provided in the company submission dossier) is presented in Table 4. The list of records excluded from the review of the Davis publications is presented in Table 17.

Figure 1 PRISMA flow diagram depicting the flow of records in the clinical SLR including updated literature review



Abbreviations: CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; HRQoL, health-related quality of life; HTA, health technology assessment; ICTRP, International Clinical Trials Registry Platform; SLR, systematic literature review
†The studies added from the pragmatic review contributed only to hip, vertebral and non-vertebral fractures, as other outcomes were not included in the economic model
Note: The full methodology of the original clinical SLR and excel sheet with the reasons for the exclusion of 210 records are presented in the original company submission

B.1.4.1.1 Included records

Table 4 Records included in the feasibility assessment for the NMA

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Source
1	ACTIVE CSR addendum (excluding Sites 131 and 132)	Addendum to the final BA058-05-003 study report analysis of efficacy and safety excluding data from sites 131 and 132	NA	NA

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Source
2	Black, 1996, FIT I; NR	Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group.	Lancet. 1996 Dec 7;348(9041):1535-41	Davis 2016
3	Black, 2007, HORIZON-PFT; NCT00049829	Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis.	N Engl J Med. 2007 May 3;356(18):1809-22	Davis 2016
4	Chesnut, 2004, BONE; NR	Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis.	J Bone Miner Res 2004;19:1241–9	Davis 2016
5	Cosman, 2011, CZOL446H2409; NCT00439244	Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis.	J Bone Miner Res. 2011 Mar;26(3):503-11	Davis 2020
6	Ettinger, 1999, MORE; NR	Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE)	Investigators. JAMA 1999;282:637–45.	Davis 2020
7	Cummings, 2009, FREEDOM; NCT00089791	Denosumab for prevention of fractures in postmenopausal women with osteoporosis.	N Engl J Med 2009;361(8):756–65	Davis 2020
8	Harris, 1999, VERT-NA; NR	Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group.	JAMA. 1999 Oct 13;282(14):1344-52	Davis 2016
9	Liberman, 1995, NR; NR	Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal	N Engl J Med. 1995 Nov 30;333(22):1437-43	Davis 2016

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Source
		osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group.		
10	Miller, 2008, MOTION; MM17385	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 Jan;24(1):207-13	Davis 2016
11	Muscoso, 2004, NR; NR	Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study.	Eur Rev Med Pharmacol Sci. 2004 Mar-Apr;8(2):97-102.	Davis 2016, Davis 2020
12	Neer, 2001, FPT; NCT00670501	Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.	N Engl J Med. 2001 May 10;344(19):1434-41.	Davis 2020
13	Recker, 2007, EVA; NCT00035971	Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass.	Bone. 2007 Apr;40(4):843-51	Davis 2020
14	Reginster, 2000, VERT-MN;	Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group.	Osteoporos Int. 2000;11(1):83-91	Davis 2016
15	Silverman, 2008, NR; NCT00205777	Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial.	J Bone Miner Res. 2008;23(12):1923-34	Davis 2020
16	Pols, 1999, FOSIT; NR	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	Osteoporos Int. 1999;9(5):461-8	Davis 2016

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Source
		FOSIT study. Fosamax International Trial Study Group.		
17	Cummings, 1998, PMO; NR	Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial.	JAMA. 1998 Dec 23-30;280(24):2077-82.	Davis 2016
18	Bilezikian JP, 2019, FREEDOM Extension; NCT00523341	Long-term denosumab treatment restores cortical bone loss and reduces fracture risk at the forearm and humerus: analyses from the FREEDOM Extension cross-over group.	Osteoporos Int. 2019 Sep;30(9):1855-1864	Original SLR
19	Black, 2012, HORIZON-PFT Extension (E1); NCT00145327	The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-pivotal fracture trial (PFT)	J Bone Miner Res. 2012 Feb;27(2):243-54.	Original SLR
20	Bone, 2013, FREEDOM Extension; NCT00523341	The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: Results from the FREEDOM extension	J Clin Endocrinol Metab. 2013 Nov;98(11):4483-92.	Original SLR
21	Bone, 2017, FREEDOM and FREEDOM extension; NCT00089791 and NCT00523341	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 Jul;5(7):513-523.	Original SLR
22	Ferrari, 2015, FREEDOM Extension; NCT00523341	Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years	Osteoporos Int. 2015 Dec;26(12):2763-71	Original SLR
23	McClung, 2013, NR	Treatment of postmenopausal osteoporosis with delayed-release	Osteoporos Int. 2013 Jan;24(1):301-10	Original SLR

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Source
		risedronate 35 mg weekly for 2 years		
24	Roux, 2014, NR, NR	Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: Efficacy and safety results from a randomized open-label study	Bone. 2014 Jan;58:48-54.	Original SLR
25	Ferrari, 2019, FREEDOM Extension; NCT00523341	Further nonvertebral fracture reduction beyond 3 years for up to 10 years of denosumab treatment	J Clin Endocrinol Metab. 2019 Aug 1;104(8):3450-3461	Original SLR
26	Bianchi, 2012, DIVA LTE; NCT00048074	Long-term administration of quarterly IV ibandronate is effective and well tolerated in postmenopausal osteoporosis: 5-year data from the DIVA study long-term extension	Osteoporos Int. 2012 Jun;23(6):1769-78.	Original SLR
27	Bone, 2018, ACTIVExtend; NCT01657162	ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis	J Clin Endocrinol Metab. 2018 Aug 1;103(8):2949-2957.	Original SLR
28	Bolognese, 2013, FREEDOM; NCT00089791	Denosumab significantly increases DEXA BMD at both trabecular and cortical sites: Results from the FREEDOM study	J Clin Densitom. 2013 Apr-Jun;16(2):147-53	Original SLR
29	Cosman, 2016, FRAME; NCT01575834	Romosozumab treatment in postmenopausal women with osteoporosis	N Engl J Med. 2016 Oct 20;375(16):1532-1543.	Original SLR
30	Cosman, 2017, ACTIVExtend; NCT01657162	Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: Results of the ACTIVExtend trial	Mayo Clin Proc. 2017 Feb;92(2):200-210.	Original SLR

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Source
31	Deal, 2019, ACTIVExtend; NCT01657162	Response rates for hip, femoral neck, and lumbar spine bone mineral density in patients treated with abaloparatide followed by alendronate: Results from phase 3 ACTIVExtend	Bone Rep. 2019 Nov 2;11:100230.	Original SLR
32	Geusens, 2018, VERO; NCT01709110	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 May;33(5):783-794	Original SLR
33	McClung, 2013, NR; NCT00358176	A novel monthly dosing regimen of risedronate for the treatment of postmenopausal osteoporosis: 2-year data	Calcif Tissue Int. 2013 Jan;92(1):59-67.	Original SLR
34	Papapoulos, 2012, FREEDOM Extension; NCT00523341	Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension	J Bone Miner Res. 2012 Mar;27(3):694-701	Original SLR
35	McClung, 2012, NR; NCT00541658	Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet	Osteoporos Int. 2012 Jan;23(1):267-76	Original SLR
36	McClung, 2013, NR; NCT00247273	Efficacy and safety of risedronate 150-mg once a month in the treatment of postmenopausal osteoporosis: 2-year data	Osteoporos Int. 2013 Jan;24(1):293-9	Original SLR
37	Hadji, 2012, NR; NR	The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures	Osteoporos Int. 2012 Aug;23(8):2141-50	Original SLR
38	Lewiecki, 2019, FRAME; NCT01575834	One year of romosozumab followed by two years of denosumab maintains fracture risk reductions:	J Bone Miner Res. 2019 Mar;34(3):419-428	Original SLR

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Source
		Results of the FRAME extension study		
39	Miller, 2016, NR; NCT01732770	Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates	J Clin Endocrinol Metab. 2016 Aug;101(8):3163-70	Original SLR
40	Miller, 2019, ACTIVE; NCT01343004	Bone mineral density response rates are greater in patients treated with abaloparatide compared with those treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial	Bone. 2019 Mar;120:137-140	Original SLR
41	Miller, 2012, MOBILE LTE, NR	Efficacy of monthly oral ibandronate is sustained over 5 years: the MOBILE long-term extension study	Osteoporos Int. 2012 Jun;23(6):1747-56	Original SLR
42	Kendler, 2018, VERO; NCT01709110	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	Lancet. 2018 Jan 20;391(10117):230-240	Original SLR
43	Leder, 2019, ACTIVExtend; NCT01657162	Fracture and bone mineral density response by baseline risk in patients treated with abaloparatide followed by alendronate: Results from the Phase 3 ACTIVExtend trial	J Bone Miner Res. 2019 Dec;34(12):2213-2219	Original SLR
44	Leder, 2015, NR; NCT00542425	Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis	J Clin Endocrinol Metab. 2015 Feb;100(2):697-706	Original SLR
45	Papapoulos, 2015, FREEDOM and FREEDOM Extension; NCT00089791	The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the	Osteoporos Int. 2015 Dec;26(12):2773-83	Original SLR

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Source
	and NCT00523341	FREEDOM Extension study		
46	Saag, 2017, ARCH; NCT01631214	Romosozumab or alendronate for fracture prevention in women with osteoporosis	N Engl J Med. 2017 Oct 12;377(15):1417-1427	Original SLR
47	NA, NR; NCT03974100	Study investigating PK, PD, efficacy, safety, and immunogenicity of biosimilar denosumab (GP2411) in patients with postmenopausal osteoporosis	NA	Original SLR
48	NA, wearABLe; NCT04064411	Efficacy & safety of abaloparatide-solid microstructured transdermal system in postmenopausal women with osteoporosis	NA	Original SLR
49	Langdahl, 2017, STRUCTURE; NCT01796301	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 Sep 30;390(10102):1585-1594.	Original SLR
50	Miller, 2016, ACTIVE; NCT01343004	Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis a randomized clinical trial	JAMA. 2016 Aug 16;316(7):722-33	Original SLR

Abbreviations: BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; IV, intravenous; JAMA, Journal of the American Medical Association; LTE, long-term extension; NA, not applicable; NCT, National Clinical Trial; NR, not reported; NMA, network meta-analysis; PD, pharmacodynamic; PK, pharmacokinetic, SLR, systematic literature review

B.1.5 Meta-analysis: Indirect and mixed treatment comparisons

In the absence of head-to-head data, a NMA was conducted to compare the efficacy of abaloparatide with the comparators of relevance to the decision problem in this evaluation, using published evidence identified from the updated clinical SLR (see Section B.1). The efficacy outcomes considered in the NMA were based on the outcomes specified in the final scope issued by NICE, as well as the availability of data reported in the literature. The outcomes included in the NMA are presented in Table 5.

Table 5 Outcomes for the NMA

Outcome	Type of data or distribution	Output statistics of NMA
Efficacy outcomes: • New vertebral fracture • New or worsening vertebral fracture • Nonvertebral fracture • Clinical fracture • Hip fracture • Major osteoporotic fracture	Binomial	Median HR, 95% CrI of the estimate Median HR, 95% PrI of the estimate

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses

B.1.5.1 Identification and selection of relevant studies from the clinical SLR

As described in the original submission, a SLR was conducted in April 2023 and a pragmatic extension of this was performed in November 2023.

Based on feedback from the EAG, this SLR was updated (see section B.1) using a pragmatic approach to ensure relevant studies published before 2012 were captured. The original NMA analysed fracture outcomes at specific timepoints only (12, 18, 24 and 36 months), this requirement for data at pre-determined timepoints was removed and the updated NMA now analyses fractures irrespective of timepoint allowing for a broader inclusion of data.

B.1.5.2 Risk of bias

A risk of bias (RoB) assessment was performed on all records included in the NMA. The studies included in the NMA were critically appraised for methodological quality under these parameters: randomisation and allocation concealment, baseline characteristics, blinding status, outcomes selection and reporting, and statistical analysis (Table 6).

Two approaches were used to assess the risk of bias in the publications used in the NMA:

- The trial publications (1 to 8 in Table 7) were directly assessed according to checklist presented in Table 6.
- For the studies identified in the pragmatic literature review (studies 9 to 25 in Table 7), the RoB assessment was extracted from the publications (Davis 2016 and Davis 2020) and adapted to the checklist presented in Table 6.
    - When questions were split or combined in one checklist versus the other, the higher risk of bias was used to ensure a conservative approach.

Table 6 NICE single technology appraisal (STA) checklist [PMG24] for critical evaluation of randomised trials

No	Question	Responses
1	Was randomisation carried out appropriately?	Yes/ No/ Not clear/ NA
2	Was the concealment of treatment allocation adequate?	Yes/ No/ Not clear/ NA
3	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes/ No/ Not clear/ NA
4	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes/ No/ Not clear/ NA
5	Were there any unexpected imbalances in drop-outs between groups?	Yes/ No/ Not clear/ NA
6	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes/ No/ Not clear/ NA
7	Did the analysis include an intention-to-treat analysis?	Yes/ No/ Not clear/ NA
8	If ITT analysis was included, was this appropriate and were appropriate methods used to account for missing data?	Yes/ No/ Not clear/ NA

Abbreviations: NA, not applicable; NICE, National Institute for Health and Care Excellence

Table 7 Quality assessment of trials included in the NMA

#	Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
1	ACTIVE CSR addendum (excluding Sites 131 and 132)	Yes	Yes†	Yes	Yes†	Yes	No	Yes	Yes
2	Cosman 2016	Yes	Yes	Yes	Yes	No	No	Yes	Yes
3	Saag 2017	Yes	Not clear	Not clear	Yes	No	No	Yes	Yes
4	Kendler 2018	Yes	Yes	Not clear	Yes	No	No	Yes	Yes
5	Langdahl 2017	Yes	No	Not clear	No	No	No	Yes	Yes
6	Miller 2016	Not clear	Not clear	No	Not clear‡	Yes§	No	No	No§
7	NCT03974100	Yes	Not clear	Not clear	Yes	No	No	No	No
8	Bone 2013	Yes	No	Not clear	No	No	No	Yes	Yes
9	Black 1996	Yes	Yes	Yes	Yes	No§	No	Yes	Yes§
10	Black 2007	Yes	Yes	Yes	Yes	Yes§	No	No	No§
11	Chestnut 2004	Not clear	Not clear	Not clear	Not clear‡	Yes§	No	No	No§
12	Cummings 2009	Not clear	Yes	Not clear	Not clear‡	Yes§	No	No	No§
13	Harris 1999	Yes	Yes	Yes	Yes	Yes§	No	No	No§
14	Liberman 1995	Not clear	Not clear	Not clear	Yes	Yes§	No	No	No§
15	Miller 2008	Yes	Yes	Yes	Not clear‡	Yes§	Not clear	No	No§

#	Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
16	Muscoso 2004	Not clear	Not clear	Not clear	No	Not clear§	Not clear	Not clear	Not clear§
17	Neer 2001	Not clear	Not clear	Not clear	Yes	Yes§	Yes	No	No§
18	Pols 1999	Not clear	Not clear	Not clear	Not clear‡	Yes§	No	No	No§
19	Reginster 2000	Not clear	Not clear	Not clear	Not clear‡	Yes§	No	No	No§
20	Silverman 2008	Yes	Yes	Yes	Not clear‡	No§	No	Yes	Yes§
21	Cummings 1998	Yes	Yes	Yes	Yes	No§	No	Yes	Yes§
22	Ettinger 1999	Not clear	Yes	Not clear	Yes	Yes	Yes	Yes	No§
23	Hadji 2012	Yes	No	Not clear	No	No	No	Yes	Yes
24	Cosman 2011	Yes	Yes	Yes	No	No	No	Yes	Yes
25	Recker 2007	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Abbreviations: CSR, clinical study report; HTAs, health technology assessments; Q, question; NICE, national institute for health and care excellence. NMA, network meta- analysis

† All parties were blinded to abaloparatide and placebo in the ACTIVE study, while teriparatide is a marketed treatment and could not be re-packaged and consequently blinded. The ACTIVExtend study was one arm open label.

‡ The risk of bias assessment was adapted from two published HTAs using the Cochrane RoB tool to the NICE checklist. When questions differed, the more conservative, higher risk of bias rating was chosen. Specifically, in NICE's Q4 on blinding, which encompasses both performance and detection bias, was informed by two separate Cochrane questions; if these questions diverged in risk rating, the higher risk was selected to preserve a conservative approach.

§ The risk of bias rating derived from the published HTA's attrition bias question (Cochrane assessment) was applied to both questions 5 and 8 of the NICE assessment, without conducting separate evaluation for each question.

B.1.5.3 Overview of the selected studies

During the feasibility assessment, records were excluded for various reasons.

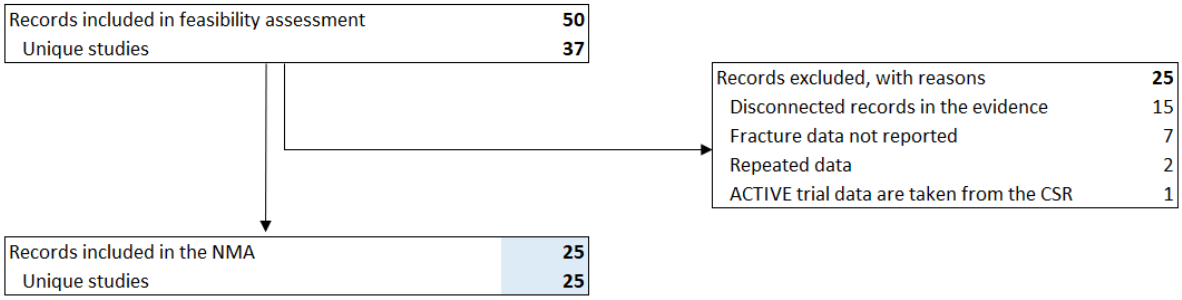
25 records were excluded, for the following reasons:

- Disconnected records in the evidence network, N=15
    - Single treatment arm, N=8
    - Sequential treatment, N=7
- Fracture data not reported, N=7
- Repeat data, N=2
    - VERO study: two publications reported same fracture data, and hence data was selected from one report (Miller et al 2016) ignoring the other report (Geusens, 2018)
    - FREEDOM study: The fracture data from FREEDOM study was reported in two separate publications (Bone et al 2017 and Cummings et al 2009). To avoid redundancy, data was exclusively selected from the report by Cummings et al 2009, while the report by Bone et al 2017 was not considered.

- Active trial data are taken from the CSR (addendum), N=1

The PRISMA flow diagram for the NMA is presented in Figure 2. The full list of records included in the updated NMA is presented in Table 8.

Figure 2 PRISMA flow diagram depicting the flow of studies in the NMA



Abbreviations: CSR, clinical study report; NMA, network meta-analysis

Records included in the NMA are presented in Table 8. Baseline characteristics for all trials are presented in Table 19. A global evidence network was generated based on the identified evidence (see Figure 3).

B.1.5.3.1 Included records

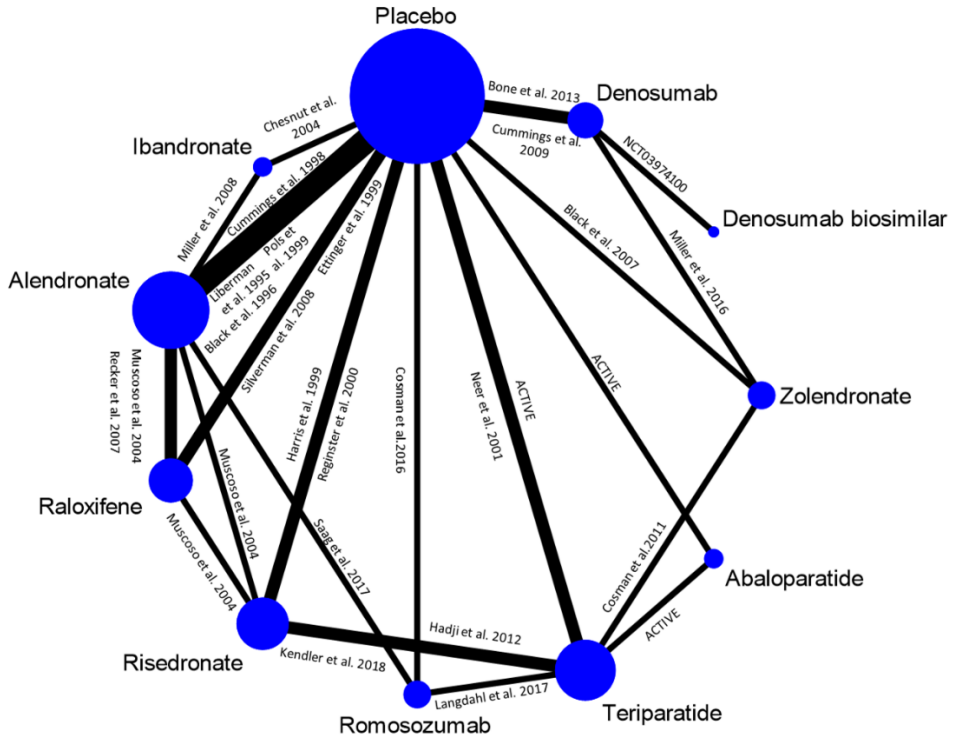
Table 8 Records included in the NMA

	Trial name, reference, NCT number	Treatments
1	ACTIVE (excluding Sites 131 and 132)[3]	Placebo Abaloparatide Teriparatide
2	FRAME (Cosman et al. 2016)[4]	Placebo Romosozumab
3	NR (Hadji et al. 2012)[5]	Teriparatide Risedronate
4	ARCH (Saag et al. 2017)[6]	Alendronate Romosozumab
5	VERO (Kendler et al. 2018)[7]	Teriparatide Risedronate
6	FIT I (Black, 1996)[8]; NR[a]	Placebo Alendronate
7	HORIZON-PFT (Black, 2007)[9]; NCT00049829[a]	Placebo Zolendronate
8	BONE (Chesnut, 2004)[10]; NR[a]	Placebo Ibandronate
9	CZOL446H2409 (Cosman, 2011)[11]; NCT00439244[a]	Teriparatide, Zoledronic acid
10	FREEDOM (Cummings, 2009)[12]; NCT00089791[a]	Placebo Denosumab
11	VERT-NA (Harris, 1999)[13] ; NR[a]	Placebo Risedronate
12	NR (Liberman, 1995)[14]; NR[a]	Placebo Alendronate
13	MOTION (Miller, 2008)[15]; MM17385[a]	Alendronate Ibandronate

	Trial name, reference, NCT number	Treatments
14	NR (Muscoso, 2004)[16]; NR[a]	Raloxifene Risedronate Alendronate
15	FPT (Neer, 2001)[17]; NCT00670501[a]	Placebo Teriparatide
16	EVA (Recker, 2007)[18]; NCT00035971[a]	Alendronate Raloxifene
17	VERT-MN (Reginster, 2000)[19]; NR[a]	Placebo Risedronate
18	NR (Silverman, 2008)[20]; NCT00205777[a]	Placebo Raloxifene
19	STRUCTURE (Langdahl, 2017)[21]; NR[a]	Teriparatide Romosozumab
20	NR (Miller, 2016)[22]; NCT01732770[a]	Zoledronic acid plus placebo Denosumab plus placebo
21	FOSIT (Pols, 1999)[23]; NR[a]	Placebo Alendronate
22	NR, (NR)[24]; NCT03974100[a]	Denosumab biosimilar Denosumab
23	FREEDOM and FREEDOM extension (Bone, 2013)[25]; NR[a]	Placebo Denosumab
24	MORE (Ettinger, 1999); NR	Placebo Raloxifene
25	PMO (Cummings, 1998); NR	Placebo Alendronate

Abbreviations: FPT, fracture prevention trial; i.v., intravenous; NCT, National Clinical Trials; NMA, network meta-analysis; NHNV, non-hip non-vertebral; NR, not reported; s.c. subcutaneous
[a] included for hip, non-vertebral and NHNV networks only
Note: all interventions were included at the licensed dose per SmPCs

Figure 3 Global evidence network for the NMA



Abbreviations: CSR, clinical study report; NMA, network meta-analysis
Note: ACTIVE refers to the CSR addendum population (excluding Sites 131 and 132)[3]

B.1.5.4 Heterogeneity of included trials

The clinical studies included in the network incorporated variations in treatment duration, sample size, age, and race, indicating significant clinical diversity. To accommodate this heterogeneity among studies, we assessed random-effects models. These models presuppose that treatment effects may differ across studies but originate from a shared distribution of treatment effects, characterised by a mean for each treatment effect and a common covariance matrix between studies: see Section B.1.5.5. Baseline characteristics of the included studies are presented in Table 19.

B.1.5.5 NMA methodology

The NMA was conducted in a Bayesian framework- Binomial likelihood and cloglog link models were used for fracture outcomes. Non-informative priors were used for all analyses. Both fixed-effects models (FEM) and REM were presented for fracture outcomes. Regardless of the model, vague prior distributions were used in all analyses for the treatment effects of interest [(d[i]~dnorm(0,0.0001); where d[i] represents the treatment effect for treatment [i] and study effects [mu[s]~dnorm(0,0.0001), where mu[s] represents the study effect for study [s]. Standard random effects NMAs with a vague prior distribution on the between-study SD [sd~dunif(0,2)] parameter were performed.

All analyses were run with 80,000 iterations after a burn-in of 20,000 iterations. All presented results converged. Convergence was assessed by visualising the histories of the chains, of relevant parameters, against the iteration number, overlapping histories, and the Brooks Gelman-Rubin (BGR) statistics. It can be expected that there is always

some variation in patient characteristics, study sites, and settings across studies; if these characteristics are effect modifiers of the relative treatment effects of interest, then variability in these effect modifiers can confound the results of an NMA. To allow for heterogeneity between studies, random-effects models were evaluated.

The better fitting model was selected based on the deviance information criterion (DIC) value. A difference of more than three points in the DIC was considered as a relevant difference. The model with the lower DIC was considered a better-fitted model. In the absence of a formal estimate of heterogeneity a fixed-effects model was deemed appropriate to allow for heterogeneity between studies.

Network meta-analysis (NMA) in its standard form makes an assumption of 'consistency'[26], also called 'coherence' (Lumley, 2002),[27] which means that estimates of treatment effects from direct and indirect evidence are in agreement, subject to the usual variation under the random-effects model for meta-analysis.

Baseline characteristics were compared to assess the similarity of included studies, including mean age and the proportion of patients with prevalent fracture (Table 19). For the fracture outcomes, HRs were used to estimate the relative effectiveness of all treatments based on the number of participants in each treatment group in each study and the number of participants developing fractures at the final timepoint. A HR of < 1 reflects a reduced risk of fracture relative to placebo or the comparator treatment. The methods followed the recommended best practice guidelines of the NICE Decision Support Unit for evidence synthesis.[28,29]

The cost effectiveness model utilises HR for placebo vs abaloparatide, placebo vs romosozumab and placebo vs teriparatide (see Table 12). The data used in the model is presented in Section B.1.5.6.4.1, the forest plots are presented for each outcome in Section B.1.5.6.4.2 through B.1.5.6.4.4.

B.1.5.6 NMA results

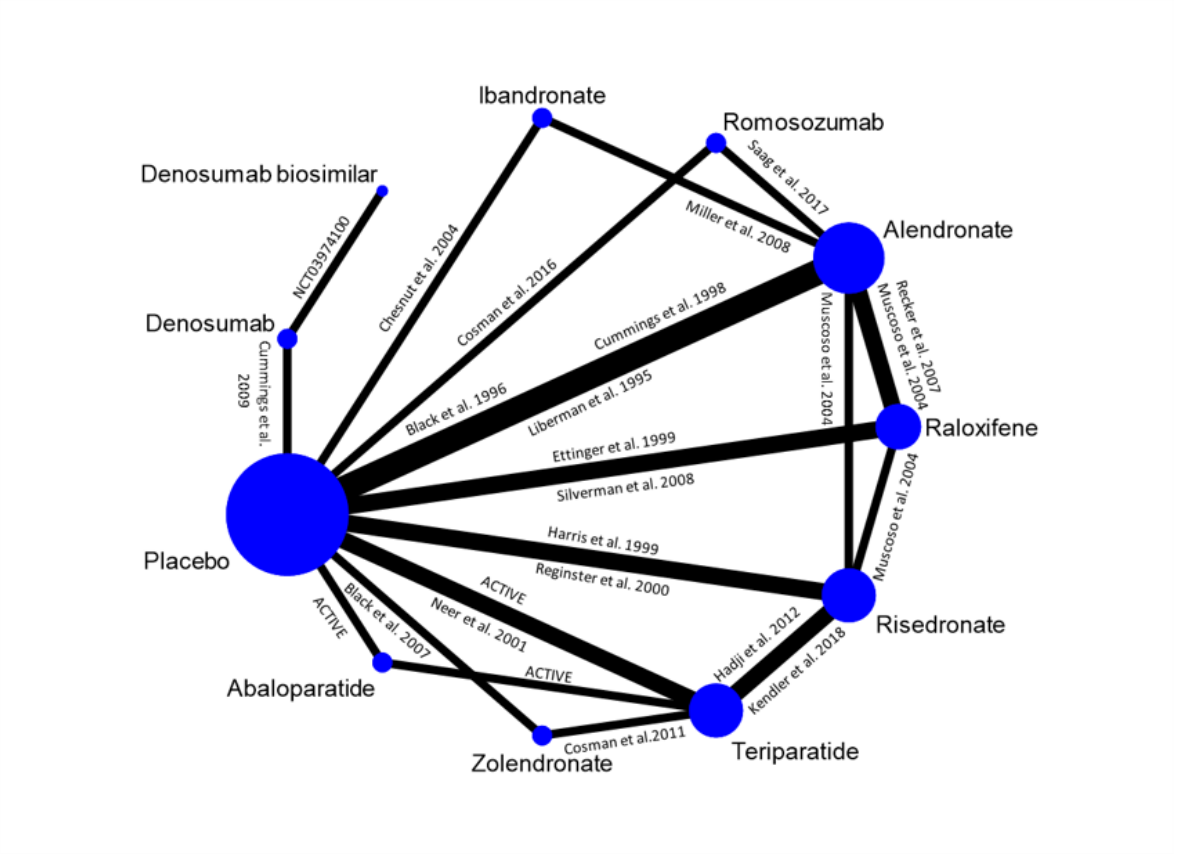
Results are presented to show the effectiveness of abaloparatide vs other comparators. The comparative efficacy of abaloparatide vs comparators for outcomes relevant to the cost-effectiveness model are presented in Section B.1.5.6.1 to Section B.1.5.6.3. Additional outcomes are presented in Section B.3.5. Section B.3.5 presents a comparison of HR (95% PrI) and HR (95% CrI), as well as the between study standard deviation.

The cost effectiveness model utilises HR for placebo vs abaloparatide, placebo vs romosozumab and placebo vs teriparatide (see Table 12). The data used in the model is presented in Section B.1.5.6.4, the forest plots and/or tabulated outcomes are presented for each outcome in Section B.1.5.6.4.2 through Section B.1.5.6.4.4.

B.1.5.6.1 New vertebral fracture

The network of studies reporting data for new vertebral fracture is illustrated in Figure 4. Twenty studies assessing twelve treatments contributed to the analysis. The NMA for non-vertebral fractures is feasible as it estimates the relative treatment effect of abaloparatide across connected or indirectly connected comparators. Table 9 presents a summary of abaloparatide versus all comparators included in this network.

Figure 4 Network for analysis – new vertebral fracture



Abbreviations: CSR, clinical study report
Note: ACTIVE refers to the CSR addendum population (excluding Sites 131 and 132)[3]

Table 9 Risk of new vertebral fracture (FEM and REM) for abaloparatide vs comparators

Abaloparatide vs.	FEM			REM		
	Median HR	LCrI	UCrI	Median HR	LCrI	UCrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibandronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Raloxifene	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risedronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zolendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FEM, fixed-effects model; HR, hazard ratio; LCrI, lower credible interval; REM, random-effects model; UCrI, upper credible interval; vs., versus

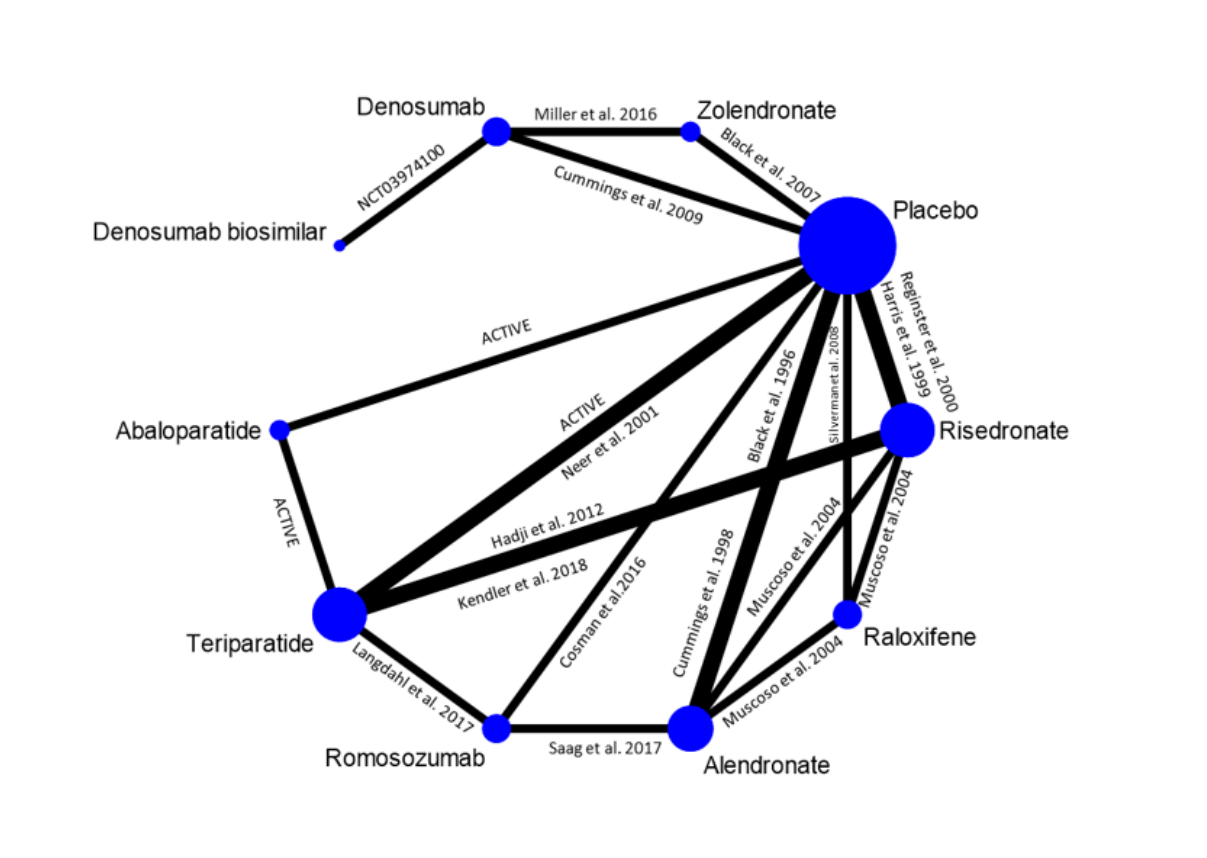
The FEM and REM demonstrated that abaloparatide [redacted] the risk of new vertebral fracture compared with placebo, alendronate, ibandronate, raloxifene and risedronate, and it was [redacted] compared to other comparators explored. The

risk of new vertebral fracture was [redacted] for abaloparatide vs. placebo, alendronate, ibandronate, raloxifene and risedronate in the FEM.[redacted]

B.1.5.6.2 Hip fracture

The network of studies reporting data for hip fractures is illustrated in Figure 5. Seventeen studies assessing ten treatments contributed to the analysis. The NMA for non-vertebral fractures is feasible as it estimates the relative treatment effect of abaloparatide across connected or indirectly connected comparators. Table 10 presents a summary of abaloparatide versus all comparators included in this network.

Figure 5 Network for analysis – hip fracture



Abbreviations: CSR, clinical study report
Note: ACTIVE refers to the CSR addendum population (excluding Sites 131 and 132)[3]

Table 10 Risk of hip fracture (FEM and REM) for abaloparatide vs comparators

Abaloparatide vs.	FEM			REM		
	Median HR	LCrI	UCrI	Median HR	LCrI	UCrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Raloxifene	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abaloparatide vs.	FEM			REM		
	Median HR	LCrI	UCrI	Median HR	LCrI	UCrI
Risedronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zolendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

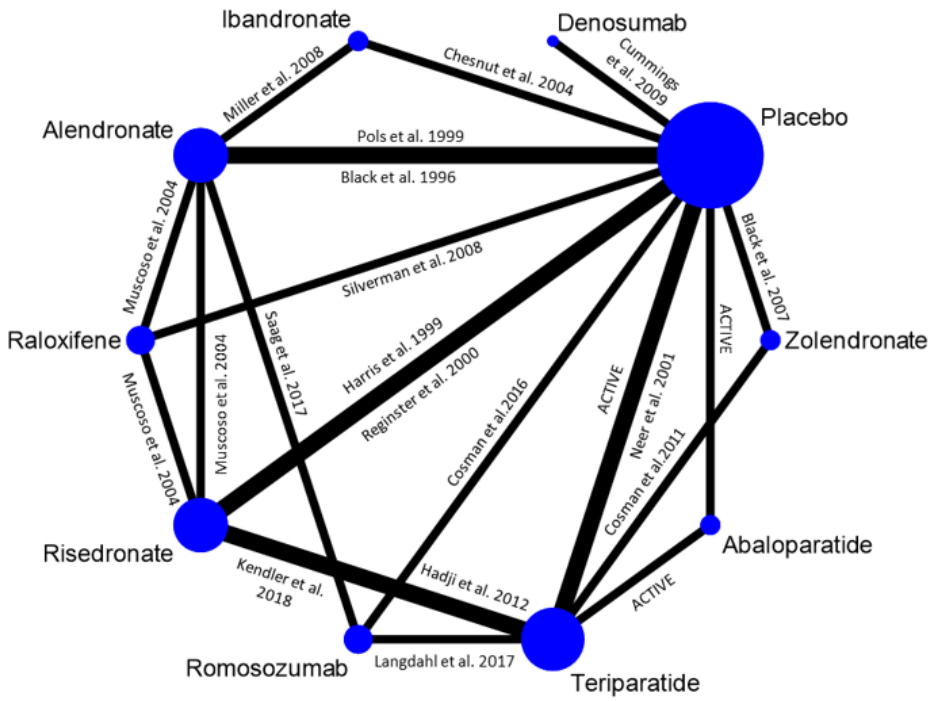
Abbreviations: FEM, fixed-effects model; HR, hazard ratio; LCrI, lower credible interval; REM, random-effects model; UCrI, upper credible interval; vs., versus

The FEM and REM demonstrated that abaloparatide [redacted] reduction in the risk of hip fractures compared to other comparators.

B.1.5.6.3 Non-vertebral fracture

The network of studies reporting data for non-vertebral fractures is illustrated in Figure 6. Nineteen studies assessing ten treatments contributed to the analysis. The NMA for non-vertebral fractures is feasible as it estimates the relative treatment effect of abaloparatide across connected or indirectly connected comparators. Table 11 presents a summary of abaloparatide versus all comparators included in this network.

Figure 6 Network for analysis – non-vertebral fractures



Abbreviations: CSR, clinical study report
Note: ACTIVE refers to the CSR addendum population (excluding Sites 131 and 132)[3]

Table 11 Risk of non-vertebral fracture (FEM and REM) for abaloparatide vs comparators

Abaloparatide vs.	FEM			REM		
	Median HR	LCrI	UCrI	Median HR	LCrI	UCrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibandronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Raloxifene	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risedronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zoledronic acid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FEM, fixed-effects model; HR, hazard ratio; LCrI, lower credible interval; REM, random-effects model; UCrI, upper credible interval; vs., versus

Both the models demonstrated that abaloparatide [redacted] the risk of non-vertebral fracture compared to placebo, alendronate, denosumab, ibandronate, raloxifene, and zoledronic acid. The risk of non-vertebral fracture was [redacted] for abaloparatide vs. placebo, alendronate, denosumab, ibandronate, raloxifene, and zoledronic acid respectively in the FEM. [redacted]

B.1.5.6.4 NMA results for outcomes used in the economic model base case

B.1.5.6.4.1 Overview

The results presented in Section B.1.5.6.1 through B.1.5.6.3 show abaloparatide vs the comparators for each endpoint. The base case of the model uses HR of placebo vs abaloparatide, romosozumab or teriparatide. Table 12 presents the HR from the updated NMA used in the base case of the economic model. Table 13 presents the HR used for the alendronate treatment period in the base case of the economic model.

Table 12 NMA estimates used in the base case for the economic model

Fracture type	Base case NMA estimates		
	vs. placebo	Median HR (95% CrI)	Median HR (95% PrI)
Hip	Abaloparatide	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]
	Teriparatide	[redacted]	[redacted]
Vertebral	Abaloparatide	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]
	Teriparatide	[redacted]	[redacted]
Non-vertebral	Abaloparatide	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]
	Teriparatide	[redacted]	[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; PrI, predictive intervals; NMA, network meta-analysis

Table 13 NMA estimates for alendronate vs placebo in the base case — sequential treatment period (REM)

Fracture type	Base case NMA estimates	
	Median HR (95% CrI)	Median HR (95% PrI)
Hip	[redacted]	[redacted]
Vertebral	[redacted]	[redacted]
Non-vertebral	[redacted]	[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; PrI, predictive intervals; REM, random effects model

B.1.5.6.4.2 New vertebral fracture

Figure 7 presents a summary plot of placebo versus all comparators included in this network. The FEM demonstrated that abaloparatide [redacted] the risk of new vertebral fracture compared with placebo ([redacted] for abaloparatide vs placebo). [redacted] (Figure 7).

[redacted](Figure 7).

Figure 7 Summary forest plot of new vertebral fracture (FEM and REM) for placebo vs comparators

Abbreviations: CrI, credible interval; FEM, fixed-effects model; HR, hazard ratio; REM, random-effects model; vs, versus
Note: Median HR are presented

Table 14 presents the model fit statistics. DIC and residual deviance were comparable for the FEM and REM, hence, both models were used to draw conclusions.

Table 14 DIC and residual deviance values for new vertebral fracture using fixed effect and random effect models

	FEM	REM
DIC	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; FEM, fixed-effects model; REM, random-effects model

B.1.5.6.4.3 Hip fracture

Figure 8 presents a summary plot of placebo versus all comparators included in this network.

The FEM and REM demonstrated a [redacted] risk of hip fracture with abaloparatide vs placebo, and the risk [redacted] for abaloparatide vs other treatments. In the FEM the risk of hip fracture was [redacted] for abaloparatide vs placebo. [redacted]

Figure 8 Summary forest plot of hip fracture (FEM and REM) for placebo vs comparators

Abbreviations: CrI, credible interval; FEM, fixed-effects model; HR, hazard ratio REM, random-effects model; vs, versus
Note: Median HR are presented

Table 15 presents the model fit statistics. DIC and residual deviance were comparable for the FEM and REM, hence, both models were used to draw conclusions.

Table 15 DIC and residual deviance values for hip fracture using fixed effect and random effect models

	FEM	REM
DIC	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; FEM, fixed-effects model; REM, random-effects model

B.1.5.6.4.4 Non-vertebral fractures

Figure 9 presents a summary plot of placebo versus all comparators included in this network.

The FEM analysis indicated a [redacted] in non-vertebral fracture risk with abaloparatide vs placebo. Treatment with abaloparatide was observed to be at [redacted] when compared with the HR for non-vertebral fracture outcomes indicated for the comparators vs placebo. [redacted]

Figure 9 Summary forest plot of non-vertebral fractures (FEM and REM) for placebo vs comparators

Abbreviations: CrI, credible interval; HR, hazard ratio; FEM, fixed-effects model; REM, random-effects model
Note: Median HR are presented

Table 16 presents the model fit statistics. DIC and residual deviance were comparable for the FEM and REM, hence, both models were used to draw conclusions.

Table 16 DIC and residual deviance values for non-vertebral fractures using fixed effect and random effect models

	FEM	REM
DIC	[redacted]	[redacted]
Residual deviance	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; FEM, fixed-effects model; REM, random-effects model

B.1.5.7 Uncertainties in the indirect and mixed treatment comparisons

Several limitations of the NMA methodology should be acknowledged:

- There was little direct evidence for comparisons for abaloparatide included in any of the NMAs.
- As there were no head-to-head data available comparing teriparatide, romosozumab and abaloparatide in an RCT, the analysis relies solely upon indirect evidence, and as a result the innate limitations accompanying indirect comparison are present.

Despite the above limitations, the analysis used the available data to produce an indirect treatment comparison in line with NICE guidance and was based on data from high-quality RCTs, to estimate the relative efficacy of abaloparatide versus therapies used for the treatment of osteoporosis in postmenopausal women at increased risk of fracture and so is appropriate to support decision making.

B.1.5.8 Conclusions of the NMA

The findings from the NMA suggest that abaloparatide has [redacted]. The conclusions of this NMA align with previously published meta-analysis results of bisphosphonates and non-bisphosphonates in postmenopausal women with osteoporosis who are at an increased risk of fracture.[30]

B.2 Cost-effectiveness

Placeholder for economic sections. Company to send clarification response to NICE by 9am on Monday 5th February

B.3 Additional information

B.3.1 Records excluded from the updated literature review

Table 17 presents the studies excluded from the pragmatic literature review of the Davis publications and the deprioritised articles from the original SLR.

Table 17 List of studies excluded from the pragmatic review of the Davis publications and deprioritised articles from the original SLR

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
Davis publications				
Adami, 1995	Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis.	Bone; 17(4):383-90	Outcomes out of scope	Fracture data not reported
Adami, 2008	Effect of raloxifene after recombinant teriparatide [hPTH(1-34)] treatment in postmenopausal women with osteoporosis.	Osteoporos Int.; 19(1):87-94.	Outcomes out of scope	Fracture data not reported
Anastasilakis, 2008	Head-to-head comparison of risedronate vs. teriparatide on bone turnover markers in women with postmenopausal osteoporosis: a randomised trial.	Int J Clin Pract; 62(6):919-24	Outcomes out of scope	Fracture data not reported
Atmaca, 2006	Effects of alendronate and risedronate on bone mineral density and bone turnover markers in late postmenopausal women with osteoporosis.	Adv Ther.; 23(6):842-53	Outcomes out of scope	Fracture data not reported
Bonnick, 2006	Comparison of weekly treatment of postmenopausal osteoporosis with	J Clin Endocrinol Metab.; 91(7):2631-7.	Outcomes out of scope	Fracture data not reported

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	alendronate versus risedronate over two years.			
Brown, 2009	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.; 24(1):153-61	Population outside scope	T score and age outside targeted range, no mention of prior fracture. No subgroup data reported.
Chesnut, 1995	Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling.	Am J Med.; 99(2):144-52.	Population and Outcomes out of scope	Fracture data not reported.
Chesnut, 2005	Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis.	J Bone Miner Res.;19(8):1241-9.	Study design not within specified criteria	Pooled subpopulation analyses of previously published studies
Delmas, 2006	Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study.	Arthritis Rheum.; 54(6):1838-46	Outcomes out of scope	Fracture data not reported
Dursun, 2001	Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis.	Int J Clin Pract.; 55(8):505-9	Population outside targeted range	Small sample size (n<200) and non-US/European population
Fogelman, 2000	Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a	J Clin Endocrinol Metab.; 85(5):1895-900	Population outside targeted range	T score and age outside targeted range. No subgroup data reported.

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	multinational, double-blind, placebo-controlled trial.			
Greenspan, 2003	Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial.	JAMA.; 289(19):2525-33	Population outside targeted range	Insufficient population data.
Greenspan, 2002	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.; 136(10):742-6.	Population not of interest	T score outside targeted range. No subgroup data reported.
Hadji, 2010	Rapid Onset and Sustained Efficacy (ROSE) study of zoledronic acid vs alendronate in postmenopausal women with osteoporosis: quality of life (QOL), compliance and therapy preference.	NA	Date range out of scope	Conference abstract published before 01 Jan 2021
Ho, 2005	Efficacy and tolerability of alendronate once weekly in Asian postmenopausal osteoporotic women.	Ann Pharmacother.; 39(9):1428-33	Outcomes out of scope	Fracture data not reported.
Johnell, 2002	Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis.	Clin Endocrinol Metab.; 87(3):985-92	Population and Outcomes out of scope	BMD outside targeted range. Mixed population; presence of subjects with and without prior fractures. No fractures reported in outcomes.

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
Kendler, 2011	Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate.	Osteoporos Int.; 22(6):1725-35	Population not of interest	BMD T-scores outside targeted range. No subgroup data reported.
Kendler, 2010	Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy.	J Bone Miner Res.; 25(1):72-81	Population not of interest	BMD T-scores outside targeted range. No subgroup data reported.
Leung, 2005	The efficacy and tolerability of risedronate on bone mineral density and bone turnover markers in osteoporotic Chinese women: a randomized placebo-controlled study.	Bone; 36(2):358-64	Outcomes out of scope	BMD and biochemical markers only reported.
Luckey, 2004	Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis.	Menopause; 11(4):405-15	Population not of interest	BMD T-scores outside targeted range. No subgroup data reported.
Lufkin, 1998	Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial.	J Bone Miner Res.; 13(11):1747-54	Population not of interest	Low BMD not osteoporosis (and mean age < 65 years)
Lyles, 2007	Zoledronic acid and clinical fractures and mortality after hip fracture.	N Engl J Med.; 357(18):1799-809.	Population not of interest	Mixed population; male and female patients.
McClung, 2006	Denosumab in postmenopausal women with low bone mineral density	N Engl J Med.; 354(8):821-31	Population not of interest	BMD T-scores outside targeted range. No subgroup data reported.
Michalská, 2006	The effect of raloxifene after discontinuation of long-term	J Clin Endocrinol Metab.; 91(3):870-7	Outcomes out of scope	BMD and biochemical markers only reported.

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	alendronate treatment of postmenopausal osteoporosis			
Miller, 2005	Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study	J Bone Miner Res.; 20(8):1315-22.	Outcomes out of scope	Insufficient fracture data reported.
Miyauchi, 2008	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.; 26(6):624-34	Outcomes out of scope	Insufficient fracture data reported.
Miyauchi, 2010	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.; 47(3):493-502.	Population not of interest	Mixed male and female population.
Reid, 2008	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.; 62(4):575-84	Population not of interest	BMD T-scores and age outside targeted range. No subgroup data reported.
Reid, 2006	Alendronic acid produces greater	Clin Drug Investig; 26(2):63-74.	Population not of interest	BMD T-scores outside targeted

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis : results of FACTS - International.			range. No subgroup data reported.
Reid, 2010	Characterization of and risk factors for the acute-phase response after zoledronic acid.	J Clin Endocrinol Metab.; 95(9):4380-7	Outcomes out of scope	Insufficient fracture data reported
Rosen, 2005	Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study.	J Bone Miner Res.; 20(1):141-51.	Population not of interest	BMD T-scores outside targeted range. No subgroup data reported.
Sambrook, 2004	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.; 255(4):503-11	Population not of interest	BMD T-scores outside targeted range. No subgroup data reported.
Sanad, 2011	Comparison of alendronate and raloxifene in postmenopausal women with osteoporosis.	Climacteric; 14(3):369-77.	Outcomes out of scope	BMD, biochemical markers of bone turnover and serum lipid profile data reported
Sarioglu, 2006	Comparison of the effects of alendronate and risedronate on bone mineral density and bone turnover markers	Rheumatol Int.; 26(3):195-200	Outcomes out of scope	Fracture data not reported

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	in postmenopausal osteoporosis.			
Seeman, 1999	The antifracture efficacy of alendronate.	Int J Clin Pract Suppl.; 101:40-5	Study design and data range not within specified criteria	Conference abstract published before 01 Jan 2021
Sethi, 2008	Efficacy of teriparatide in increasing bone mineral density in postmenopausal women with osteoporosis—an Indian experience.	J Assoc Physicians India.; 56:418-24	Outcomes out of scope	Fracture data not reported
Shilbayeh, 2004	The efficacy and safety of Calidron tablets for management of osteoporosis in Jordanian women: A randomised clinical trial.	Saudi Pharmaceutical Journal; 12(2-3), 86-95.	Outcomes and population out of scope	Fracture data not reported. Non-US/European population (Jordanian).
Adachi, 2011	Zoledronic acid results in better health-related quality of life following hip fracture: the HORIZON-Recurrent Fracture Trial.	Osteoporos Int.; 22(9):2539-49	Outcomes out of scope	HRQoL endpoints reported, not fracture.
Carfora, 1998	Effect of treatment of postmenopausal osteoporosis with continuous daily oral alendronate and the incidence of fractures	Gazzetta Medica Italiana Archivio per le Scienze Mediche; 157(4):105-9	Study design not within specified criteria	Real world evidence data.
McClung, 2009	Efficacy and safety of monthly oral ibandronate in the prevention of postmenopausal bone loss.	Bone; 44(3):418-22	Population not of interest	Age range out of scope and no prior fractures.
Mok, 2011	Raloxifene for prevention of glucocorticoid-induced bone loss: a 12-month randomised double-blinded placebo-controlled trial.	Ann Rheum Dis.; 70(5):778-84	Population not of interest	Patients with glucocorticoid-induced osteoporosis.

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
Orwoll, 2003	The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis.	J Bone Miner Res.; 18(1):9-17	Population not of interest	Male population.
Reid, 2009	Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial.	Lancet; 373(9671):1253-63.	Population not of interest	Patients with glucocorticoid-induced osteoporosis.
Saag, 2009	Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial.	Arthritis Rheum.; 60(11):3346-55	Population not of interest	Patients with glucocorticoid-induced osteoporosis.
Smith, 2004	Randomized controlled trial of alendronate in airways disease and low bone mineral density.	Chron Respir Dis;1(3):131-7	Population not of interest	Patients with airways disease.
Adachi 2001	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.	Population outside scope	Men and women with glucocorticoid-induced osteoporosis
Bone 2000	Alendronate and estrogen effects in postmenopausal women with low	J Clin Endocrinol Metab 2000;85:720–6.	Deprioritised: Sample size <200	NA

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	bone mineral density. Alendronate/ Estrogen Study Group.			
Boonen 2009	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.	Population out of scope	Study conducted in men
Choo 2011	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.	Int J Radiat Oncol Biol Phys 2011;81(Suppl. 2):S42	Population out of scope	Men with androgen deprivation bone loss in non-metastatic prostate cancer
Cohen 1999	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.	Population out of scope	Men and women with glucocorticoid-induced osteoporosis
Eastell, 2009, EUROFORS, NR	Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS).	J Bone Miner Res.; 24(4):726-36	Outcomes out of scope	Fracture data for hip, new vertebral or non-vertebral fractures not reported in the Davis publications
Eisman, 2008, DIVA, NA	Efficacy and tolerability of intravenous ibandronate	J Rheumatol.; 35(3):488-97	Outcomes out of scope	Fracture data for hip, new vertebral or non-vertebral

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	injections in postmenopausal osteoporosis: 2-year results from the DIVA study.			fractures not reported in the Davis publications
Hooper 2005	Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial.	Climacteric 2005;8:251–62.	Deprioritised: did not include population from N America/ W Europe.	NA
Langdahl 2009	Teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status.	Osteoporos Int 2009;20:2095–104.	Population out of scope	Men and women with glucocorticoid-induced osteoporosis
Lester 2008	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.	Population out of scope	Postmenopausal women with breast cancer
Liu 2004	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.	Deprioritised: did not include population from N America/ W Europe.	NA
Maricic 2002	Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis.	Arch Intern Med 2002;162:1140–3.	The data reported in the MORE study is sourced from Ettinger, 1999	NA

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
McClung 2001, NA, NR	Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women.	N Engl J Med.; 344(5):333-40	Outcomes out of scope	Fracture data for hip, new vertebral or non-vertebral fractures not reported in the Davis publications
McClung 2005	Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass.	Arch Intern Med 2005;165:1762–8.	Outcomes out of scope	Fracture data not reported
McClung 2009b	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.	Deprioritised; fracture type not specified	NA
Morii 2003	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.	Deprioritised: did not include population from N America/ W Europe.	NA
Orwoll 2000	Alendronate for the treatment of osteoporosis in men.	N Engl J Med 2000;343:604–10.	Population out of scope	Male population
Panico 2011	Teriparatide vs. alendronate as a treatment for osteoporosis: changes in biochemical markers of bone turnover, BMD and quality of life.	Med Sci Monit 2011;17:CR442–448.	Deprioritised: Sample size <200	NA
Reginster 2006, MOBILE, NA	Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal	Ann Rheum Dis.; 65(5):654-61	Outcomes out of scope	Fracture data for hip, new vertebral or non-vertebral fractures not

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	osteoporosis: 2 year results from the MOBILE study.			reported in the Davis publications
Reid 2000	Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study.	J Bone Miner Res 2000;15:1006–13.	Population out of scope	Men and women with glucocorticoid-induced osteoporosis
Ringe 2006	Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study.	Rheumatol Int 2006;26:427–31.	Population out of scope	Male population
Ringe 2009	Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study.	Rheumatol Int 2009;29:311–15.	Population out of scope	Male population
Saag 1998	Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group.	N Engl J Med 1998;339:292–9.	Population out of scope	Men and women with glucocorticoid-induced osteoporosis
Saag 2007	Teriparatide or alendronate in glucocorticoid-induced osteoporosis.	N Engl J Med 2007;357:2028–39.	Population out of scope	Men and women with glucocorticoid-induced osteoporosis
Sorensen 2003, VERT-MN extension, NA	Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience.	Bone; 32(2):120-6	Outcomes out of scope	Fracture data for hip, new vertebral or non-vertebral fractures not reported in the Davis publications

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
Ste-Marie 2004, VERT-NA extension, NR	Five years of treatment with risedronate and its effects on bone safety in women with postmenopausal osteoporosis.	Calcif Tissue Int.; 75(6):469-76	Outcomes out of scope	Fracture data for hip, new vertebral or non-vertebral fractures not reported in the Davis publications
Taxel 2010, NR; NR	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 Int 2010;106:1473–6.	Population out of scope	Male population with cancer
Original SLR deprioritised publications				
Black 2015, HORIZON-PFT; NCT00718861	The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT).	J Bone Miner Res. 2015 May;30(5):934-44.	Deprioritised: sample size <200	NA
Mochizuki 2023, NR; NR	Comparison of romosozumab versus denosumab treatment on bone mineral density after 1 year in rheumatoid arthritis patients with severe osteoporosis: A randomized clinical pilot study	Mod Rheumatol. 2023 Apr 13;33(3):490-495.	Deprioritised: did not include population from N America/ W Europe	NA
Mochizuki 2023, NR; NR	Comparison of diferent parameters between daily and twice-weekly teriparatide in postmenopausal women with severe osteoporosis	J Bone Miner Metab. 2023 Mar;41(2):220-226.	Deprioritised: did not include population from N America/ W Europe	NA
Bai 2013, NR; NR	Randomized controlled trial of zoledronic acid for	J Int Med Res. 2013 Jun;41(3):697-704.	Deprioritised: did not include population	NA

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	treatment of osteoporosis in women		from N America/ W Europe	
Chiba 2022, TERABIT, NR	Randomized controlled trial of daily teriparatide, weekly high-dose teriparatide, or bisphosphonate in patients with postmenopausal osteoporosis: The TERABIT study	Bone. 2022 Jul;160:116416.	Deprioritised: did not include population from N America/ W Europe	NA
Cosman 2015, NR; NR	Daily or Cyclical Teriparatide Treatment in Women With Osteoporosis on no Prior Therapy and Women on Alendronate.	J Clin Endocrinol Metab. 2015 Jul;100(7):2769-76.	Deprioritised: sample size <200	NA
Das 2022, NR; NR	Effect of Subcutaneous Administration of Denosumab in Postmenopausal Osteoporosis	EJMCM, 2022; 9(3)	Deprioritised: did not include population from N America/ W Europe	NA
Dempster 2016, SHOTZ; NCT00927186	A Longitudinal Study of Skeletal Histomorphometry at 6 and 24 Months Across Four Bone Envelopes in Postmenopausal Women With Osteoporosis Receiving Teriparatide or Zoledronic Acid in the SHOTZ Trial.	J Bone Miner Res. 2016 Jul;31(7):1429-39.	Deprioritised: sample size <200	NA
Gu 2023, NR; NCT05060406	Denosumab biosimilar (LY06006) in Chinese postmenopausal osteoporotic women: A randomized, double-blind, placebo-controlled, multicenter phase III study.	J Orthop Translat. 2022 Oct 29;38:117-125.	Deprioritised: did not include population from N America/ W Europe	NA

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
Ishibashi 2017, NR; NCT01992159	Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study	Bone. 2017 Oct;103:209-215.	Deprioritised: did not include population from N America/ W Europe	NA
Kobayakawa 2022, NR; NR	Verification of efficacy and safety of ibandronate or denosumab for postmenopausal osteoporosis after 12-month treatment with romosozumab as sequential therapy: The prospective VICTOR study.	Bone. 2022 Sep;162:116480.	Deprioritised: did not include population from N America/ W Europe	NA
Koh 2016, NR; NCT01457950	Assessment of Denosumab in Korean Postmenopausal Women with Osteoporosis: Randomized, Double-Blind, Placebo-Controlled Trial with Open-Label Extension.	Yonsei Med J. 2016 Jul;57(4):905-14.	Deprioritised: did not include population from N America/ W Europe	NA
Li 2022, NR; NR	Efficacy of generic teriparatide and alendronate in Chinese postmenopausal women with osteoporosis: a prospective study.	Arch Osteoporos. 2022 Jul 28;17(1):103.	Deprioritised: did not include population from N America/ W Europe	NA
Liang 2017, NR; NR	Intravenous Zoledronic Acid 5 mg on Bone Turnover Markers and Bone Mineral Density in East China Subjects with Newly Diagnosed Osteoporosis: A 24-month Clinical Study	Orthop Surg. 2017 Feb;9(1):103-109.	Deprioritised: did not include population from N America/ W Europe	NA
Matsumoto 2022, ACTIVE-J; NR	Abaloparatide Increases Lumbar Spine and Hip BMD in Japanese Patients With	J Clin Endocrinol Metab. 2022 Sep 28;107(10):e4222-e4231.	Deprioritised: did not include population from N America/ W Europe	NA

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	Osteoporosis: The Phase 3 ACTIVE-J Study			
Nakamura 2012, NR; NR	Dose–response study of denosumab on bone mineral density and bone turnover markers in Japanese postmenopausal women with osteoporosis.	Osteoporos Int. 2012 Mar;23(3):1131-40.	Deprioritised: did not include population from N America/ W Europe	NA
Nakamura 2012, TOWER; NR	Randomized Teriparatide [Human Parathyroid Hormone (PTH) 1–34] Once-Weekly Efficacy Research (TOWER) Trial for Examining the Reduction in New Vertebral Fractures in Subjects with Primary Osteoporosis and High Fracture Risk.	J Clin Endocrinol Metab. 2012 Sep;97(9):3097-106.	Deprioritised: did not include population from N America/ W Europe	NA
Paggiosi 2014, TRIO; NCT00666627	Comparison of the effects of three oral bisphosphonate therapies on the peripheral skeleton in postmenopausal osteoporosis: the TRIO study.	Osteoporos Int. 2014 Dec;25(12):2729-41.	Deprioritised: sample size <200	NA
Popp 2014, HORIZON, NCT00049829	Cortical bone loss at the tibia in postmenopausal women with osteoporosis is associated with incident non-vertebral fractures: Results of a randomized controlled ancillary study of HORIZON	Maturitas. 2014 Mar;77(3):287-93.	Deprioritised: sample size <200	NA
Shi 2017, NR; NR	Effect of Traditional Chinese Medicine Product, QiangGuYin, on	Evid Based Complement Alternat Med. 2017;2017:6062707.	Deprioritised: did not include population from N America/ W Europe	NA

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	Bone Mineral Density and Bone Turnover in Chinese Postmenopausal Osteoporosis			
Tan 2016, NR; NR	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 Oct;41(5):519-23.	Deprioritised: did not include population from N America/ W Europe	NA
Yang 2015, NR; NR	Effect of zoledronic acid on vertebral marrow adiposity in postmenopausal osteoporosis assessed by MR spectroscopy	Skeletal Radiol. 2015 Oct;44(10):1499-505.	Deprioritised: did not include population from N America/ W Europe	NA
Zhang 2023, NR; NCT04128163	A phase III randomized, double-blind, placebo-controlled trial of the denosumab biosimilar QL1206 in postmenopausal Chinese women with osteoporosis and high fracture risk	Acta Pharmacol Sin. 2023 Feb;44(2):446-453.	Deprioritised: did not include population from N America/ W Europe	NA
Zhou 2019, NR; NR	Effects of zoledronic acid on bone mineral density around prostheses and bone metabolism markers after primary total hip arthroplasty in females with postmenopausal osteoporosis	Osteoporos Int. 2019 Aug;30(8):1581-1589.	Deprioritised: did not include population from N America/ W Europe	NA
NA, NR; NCT00718861	A 3-year, Multicenter, Double-blind, Randomized, Placebo-controlled Extension to CZOL446H2301E1	NA	Deprioritised: sample size <200	NA

Author, year	Title	Journal; volume, page number	Reason for exclusion	Details
	to Evaluate the Efficacy and Long Term Safety of 6 and 9 Years Zoledronic Acid Treatment of Postmenopausal Women With Osteoporosis			
NA, NR; NCT02014467	A Twelve-Month Randomized, Double-Blind, Placebo Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Denosumab in Chinese Postmenopausal Women With Osteoporosis at Increased Risk of Fracture	NA	Deprioritised: did not include population from N America/ W Europe	NA
Greenspan 2015, ZEST; NCT02014467	Efficacy and Safety of Single Dose Zoledronic Acid for Osteoporosis in Frail Seniors: A Randomized Clinical Trial	JAMA Intern Med. 2015 Jun;175(6):913-21.	Deprioritised: sample size <200	NA

Abbreviations: BMD, bone mineral density; HRQoL, health-related quality of life; NA, not applicable; SLR, systematic literature review
Note: The full methodology of the original clinical SLR and excel sheet with the reasons for the exclusion of 210 articles are presented in the original company submission.

B.3.2 Records excluded from the updated NMA

Table 18 presents the records excluded from the literature review of the updated NMA.

Table 18 List of records excluded from the updated NMA

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the updated NMA
1.	Black, 2012, HORIZON-PFT Extension (E1); NCT00145327	The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-	J Bone Miner Res. 2012 Feb;27(2):243-54.	The study is disconnected due to sequential treatment.

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the updated NMA
		pivotal fracture trial (PFT)		
2.	McClung, 2013, NR	Treatment of postmenopausal osteoporosis with delayed-release risedronate 35 mg weekly for 2 years	Osteoporos Int. 2013 Jan;24(1):301-10	Fracture data not reported
3.	Roux, 2014, NR, NR	Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: Efficacy and safety results from a randomized open-label study	Bone. 2014 Jan;58:48-54.	Fracture data not reported
4.	Bianchi, 2012, DIVA LTE; NCT00048074	Long-term administration of quarterly IV ibandronate is effective and well tolerated in postmenopausal osteoporosis: 5-year data from the DIVA study long-term extension	Osteoporos Int. 2012 Jun;23(6):1769-78.	The study is disconnected due to single treatment arm
5.	Bone, 2018, ACTIVExtend; NCT01657162	ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis	J Clin Endocrinol Metab. 2018 Aug 1;103(8):2949-2957.	The study is disconnected due to sequential treatment
6.	Bolognese, 2013, FREEDOM; NCT00089791	Denosumab significantly increases DEXA BMD at both trabecular and cortical sites: Results from the FREEDOM study	J Clin Densitom. 2013 Apr-Jun;16(2):147-53	Fracture data not reported
7.	Cosman, 2017, ACTIVExtend; NCT01657162	Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with	Mayo Clin Proc. 2017 Feb;92(2):200-210.	The study is disconnected due to sequential treatment

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the updated NMA
		osteoporosis: Results of the ACTIVExtend trial		
8	Deal, 2019, ACTIVExtend; NCT01657162	Response rates for hip, femoral neck, and lumbar spine bone mineral density in patients treated with abaloparatide followed by alendronate: Results from phase 3 ACTIVExtend	Bone Rep. 2019 Nov 2;11:100230.	The study is disconnected due to sequential treatment
9.	Geusens, 2018, VERO; NCT01709110	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 May;33(5):783-794	Repeat data from VERO trial (Kendler et al, 2018)
10.	McClung, 2013, NR; NCT00358176	A novel monthly dosing regimen of risedronate for the treatment of postmenopausal osteoporosis: 2-Year data	Calcif Tissue Int. 2013 Jan;92(1):59-67.	The study is disconnected due to single treatment arm
11.	Papapoulos, 2012, FREEDOM Extension; NCT00523341	Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension	J Bone Miner Res. 2012 Mar;27(3):694-701	The study is disconnected due to sequential treatment.
12.	McClung, 2012, NR; NCT00541658	Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet	Osteoporos Int. 2012 Jan;23(1):267-76	The study is disconnected due to single treatment arm
13.	McClung, 2013, NR; NCT00247273	Efficacy and safety of risedronate 150-mg once a month in the treatment of postmenopausal osteoporosis: 2-year data	Osteoporos Int. 2013 Jan;24(1):293-9	The study is disconnected due to single treatment arm
14.	Miller, 2019, ACTIVE; NCT01343004	Bone mineral density response rates are greater in patients treated with	Bone. 2019 Mar;120:137-140	Fracture data not reported

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the updated NMA
		abaloparatide compared with those treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial		
15.	Miller, 2012, MOBILE LTE, NR	Efficacy of monthly oral ibandronate is sustained over 5 years: the MOBILE long-term extension study	Osteoporos Int. 2012 Jun;23(6):1747-56	Fracture data not reported
16.	Leder, 2019, ACTIVExtend; NCT01657162	Fracture and bone mineral density response by baseline risk in patients treated with abaloparatide followed by alendronate: Results from the Phase 3 ACTIVExtend trial	J Bone Miner Res. 2019 Dec;34(12):2213-2219	The study is disconnected due to sequential treatment
17	Leder, 2015, NR; NCT00542425	Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis	J Clin Endocrinol Metab. 2015 Feb;100(2):697-706	Fracture data not reported
18	NA, wearABLe; NCT04064411	Efficacy & safety of abaloparatide-solid microstructured transdermal system in postmenopausal women with osteoporosis	NA	Fracture data not reported
19	Miller, 2016, ACTIVE; NCT01343004	Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis a randomized clinical trial	JAMA. 2016 Aug 16;316(7):722-33	Data from the ACTIVE trial are taken from the CSR addendum
20	Bilezikian JP, 2019, FREEDOM Extension; NCT00523341	Long-term denosumab treatment restores cortical bone loss and reduces fracture risk at the forearm and humerus: analyses from the	Osteoporos Int. 2019 Sep;30(9):1855-1864	The study is disconnected due to single treatment arm

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the updated NMA
		FREEDOM Extension cross-over group.		
21	Ferrari, 2015, FREEDOM Extension; NCT00523341	Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years	Osteoporos Int. 2015 Dec;26(12):2763-71	The study is disconnected due to single treatment arm
22	Ferrari, 2019, FREEDOM Extension; NCT00523341	Further nonvertebral fracture reduction beyond 3 years for up to 10 years of denosumab treatment	J Clin Endocrinol Metab. 2019 Aug 1;104(8):3450-3461	The study is disconnected due to single treatment arm
23	Lewiecki, 2019, FRAME Extension Study; NCT01575834	One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: Results of the FRAME extension study	J Bone Miner Res. 2019 Mar;34(3):419-428	The study is disconnected due to sequential treatment
24	Papapoulos, 2015, FREEDOM and FREEDOM Extension; NCT00089791 and NCT00523341	The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study	Osteoporos Int. 2015 Dec;26(12):2773-83	The study is disconnected due to single treatment arm
25	Bone 2017	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.	This is repeat data; the data reported in the FREEDOM study is sourced from Cummings, 2009.

Abbreviations: BMD, bone mineral density; IV, intravenous; NA, not applicable; NR, not reported

B.3.3 Summary of RCTs included in the NMA

Table 19 presents the baseline characteristics of patients from the trials included in the NMA.

Table 19 Summary of baseline characteristics of RCTs included in the NMA

Author - Year	Treatment	Age, Mean (SD) (years)	Ethnicity, White/ Caucasians, N (%)	History of previous fracture, N (%)
NA, ACTIVE CSR Addendum (excluding Sites 131 and 132)	Placebo	69.3 (6.1)	522 (75.9)	Prevalent Vertebral Fracture at Baseline NR (21.7) Prior Clinical Fracture NR (48.5) Prior Nonvertebral Fracture NR (43.9) Prior Fracture NR (56.8) Prior Osteoporotic fracture NR (53.8) Prior Major Osteoporotic Fracture NR (32.8)
	Abaloparatide	69.5 (6.3)	535 (76.9)	Prevalent Vertebral Fracture at Baseline NR (20.8) Prior Clinical Fracture NR (48.0) Prior Nonvertebral Fracture NR (44.3) Prior Fracture NR (58.5) Prior Osteoporotic fracture NR (55.7) Prior Major Osteoporotic Fracture NR (34.2)
	Teriparatide	69.4 (6.1)	513 (74.8)	Prevalent Vertebral Fracture at Baseline NR (26.5) Prior Clinical Fracture NR (44.8) Prior Nonvertebral Fracture NR (39.5) Prior Fracture NR (57.9) Prior Osteoporotic fracture NR (55.1) Prior Major Osteoporotic Fracture NR (30.3)
Cosman 2016	Placebo	70.8 (6.9)	NR	Vertebral fractures, radiographically confirmed, 1, 496 (13.8) ≥2, 149 (4.1) Severity of vertebral fractures, Mild, 378 (10.5) Moderate, 263 (7.3) Severe, 4 (0.1)

	Romosozumab	70.9 (7)	NR	Vertebral fractures, radiographically confirmed, 1, 506 (14.1) ≥2, 166 (4.6) Severity of vertebral fractures, Mild, 378 (10.5) Moderate, 293 (8.2) Severe, 1 (<0.1)
Hadji 2012	Teriparatide	70.5 (8.8)	285 (79.2)	Vertebral fractures, radiographically confirmed, 0, 37 (10.3) 1, 126 (35.0) ≥2, 197 (54.7) Severity of vertebral fractures, Zero or mild, 50 (14.2) Moderate, 160 (45.5) Severe, 142 (40.3)
	Risedronate	71.6 (8.1)	286 (81.7)	Vertebral fractures, radiographically confirmed, 0, 35 (10.0) 1, 104 (29.7) ≥2, 211 (60.3) Severity of vertebral fractures, Zero or mild, 46 (13.4) Moderate, 166 (48.4) Severe, 131 (38.2)
Saag 2017	Alendronate	74.2 (7.5)	NR	Prevalent vertebral fracture: 1964 (95.9) (across total population) Grade of most severe vertebral fractures Mild, 73 (3.6) Moderate, 570 (27.8) Severe, 1321 (64.5)
	Romosozumab	74.4 (7.5)	NR	Prevalent vertebral fracture: 1969 (96.2) (across total population) Grade of most severe vertebral fractures

				Mild, 68 (3.3) Moderate, 532 (26.0) Severe, 1369 (66.9)
Kendler 2018	Teriparatide	72.6 (8.8)	670 (99.0)	Prevalent fractures: Vertebral fractures ≥1, 679 (100%) 1, 231 (34%) 2, 178 (26%) 3, 104 (15%) 4, 60 (9%) ≥5, 106 (16%) Grade of the most severe vertebral fracture SQ (qualitative visual semiquantitative grading) 2, 73 (11%) SQ3, 606 (89%) Non-vertebral fractures: Patients older than 40 years with ≥1 fracture, 298 (44.0) 1, 166 (24%) 2, 80 (12%) 3, 40 (6%) 4, 6 (1%) ≥5, 6 (1%)
	Risedronate	71.6 (8.6)	653 (96.0)	Prevalent fractures: Vertebral fractures ≥1, 679 (100%) 1, 240 (35%) 2, 174 (26%) 3, 101 (15%) 4, 62 (9%) ≥5, 102 (15%) Grade of the most severe vertebral fracture SQ (qualitative visual semiquantitative grading) 2, 67 (10%) SQ3, 612 (90%)

				Non-vertebral fractures: Patients older than 40 years with ≥1 fracture, 284 (42.0) 1, 164 (24%) 2, 81 (12%) 3, 21 (3%) 4, 11 (2%) ≥5, 7 (1%)
NA, NCT03974100	Denosumab biosimilar	64.6 (6.1)	239 (90.9)	NR
	Denosumab	64.7 (5.8)	240 (90.9)	NR
Bone 2013	Placebo	71.8 (5.1)	NR	Prevalent vertebral fractures: 485 (22.0)
	Denosumab	71.9 (5)		Prevalent vertebral fractures: 559 (23.9)
Langdahl 2017	Romosozumab	71.8 (7.4)	191 (88)	Previous fracture: 218 (100.0)
	Teriparatide	71.2 (7.7)	196 (90)	Previous fracture: 217 (<100.0)
Miller 2016	Denosumab	68.5 (7.1)	309 (96.3)	Any previous fracture: 169 (52.6) Osteoporotic fracture: 120 (37.4) Nonvertebral fracture: 109 (34.0) Vertebral fracture: 24 (7.5)
	Zoledronic acid	69.5 (7.7)	314 (97.5)	Any fracture: 159 (49.4) Osteoporotic fracture: 121 (37.6) Nonvertebral fracture: 106 (32.9) Vertebral fracture: 28 (8.7)
Black et al. 1996	Placebo	71.0 (5.6)	97% total trial population	One; NR (68.0) Two; NR (17.0) Three or more; NR (15.0)
	Alendronate	70.1 (5.6)		One; NR (70.0) Two; NR (17.0)

				Three or more; NR (13.0)
Black et al. 2007	Placebo	73.0 (5.4)	NR	None; 1,383 (35.8) One; 1,076 (27.9) Two or more; 1,401 (36.3)
	Zolendronate	73.1 (5.3)	973 (91.4)	None; 1,457 (37.6) One; 1,093 (28.2) Two or more; 1,323 (34.1)
Chesnut et al. 2004	Placebo	68.8 (NR)	NR	One fracture; 906 (NR) Two fractures; 421 (NR)
	Ibandronate	68.7 (NR)	NR	One fracture; 920 (NR) Two fractures; 433 (NR)
Cosman et al. 2011	Teriparatide	63.8 (9.1)	135 (97.8)	76 (55.1)
	Zoledronic acid	66.1 (9.0)	135 (98.5)	90 (65.7)
Cummings et al. 2009	Placebo	72.3 (5.2)	NR	915 (23.4)
	Denosumab	72.3 (5.2)	NR	929 (23.8)
Harris et al. 1999	Placebo	68.0 (7.2)	NR	639 (79.0)
	Risedronate	69.0 (7.7)	NR	645 (80.0)

Liberman et al. 1995	Placebo	64.0 (NR)	NR	Vertebral: 75 (21.2) Non-vertebral: 187 (52.6)
	Alendronate	64.0 (NR)	NR	Vertebral; 106 (20.2) Non-vertebral: 300 (57.0)
Miller et al. 2008	Alendronate	65.6 (NR)	705 (80.8)	45 to present age: NR (38.2) Since age 45 years: NR (31.6)
	Ibandronate	65.6 (NR)	739 (83.3)	45 to present age: NR (39.0) Since age 45 years: (32.5)
Neer et al. 2001	Placebo	69.0 (7.0)	NR (99.0)	448 (100.0)
	Teriparatide	69.0 (7.0)	NR (99.0)	444 (100.0)
Recker et al. 2007	Alendronate	65.7 (7.8)	NR (86.9)	0 (0.0)
	Raloxifene	65.5 (7.7)	NR (86.7)	0 (0.0)
Reginster et al. 2000	Placebo	71.0 (7.0)	NR	Median (range): 3 (0–13)
	Risedronate	71.0 (7.0)	NR	Median (range): 4 (0–13)
Silverman et al. 2008	Placebo	66.5 (6.8)	1,641 (87.1)	981 (56.4)
	Raloxifene	66.4 (6.7)	1,618 (87.5)	954 (56.3)
Pols et al. 1999	Placebo	62.8 (7.4)	901 (94.0)	NR
	Alendronate	62.8 (7.5)	893 (94.0)	NR
Muscoso, 2004	Raloxifene	64 (3.0)	NR	NR
	Risedronate	66 (NR)	NR	NR
	Alendronate	71 (8.0)	NR	NR
Cummings, 1998†	Placebo	67.7 (6.1)	NR (97)	Since age 45 years: NR (35)
	Alendronate	67.6 (6.2)	NR (97)	Since age 45 years: NR (36)
Ettinger, 1999†	Placebo	66.6 (7.1)	NR (95.7)	NR (36.4)
	Raloxifene	66.5 (7.0)	NR (95.7)	NR (38.1)

Note: all interventions included were at the licensed dose as aligned with the Summary of Product Characteristics (SmPC).

†Baseline characteristics for the relevant subgroups were not provided; data that represents the overall population are reported.

Abbreviations: CSR, clinical study report; FRAX, Fracture Risk assessment Tool; NMA, network meta-analysis; IQR, interquartile range; I.V, intravenous; NA, not applicable; NR, not reported; RCT, randomised controlled trial; S.C., subcutaneous

B.3.4 NMA inputs

B.3.4.1 New vertebral fracture

Table 20 presents the NMA inputs for new vertebral fracture.

Table 20 New vertebral fracture

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
Liberman et al. 1995	Placebo	3	355	22
Liberman et al. 1995	Alendronate	3	175	5
Harris et al. 1999	Placebo	3	678	93
Harris et al. 1999	Risedronate	3	696	61
Reginster et al. 2000	Placebo	3	346	89
Reginster et al. 2000	Risedronate	3	344	53
Black et al. 2007	Placebo	3	3861	310
Black et al. 2007	Zolendronate	3	3875	92
Black et al. 1996	Placebo	3	965	192
Black et al. 1996	Alendronate	3	981	83
Chesnut et al. 2004	Placebo	3	975	73
Chesnut et al. 2004	Ibandronate	3	977	37
Miller et al. 2008	Alendronate	1	859	5
Miller et al. 2008	Ibandronate	1	874	5
Neer et al. 2001	Placebo	2	448	64
Neer et al. 2001	Teriparatide	2	444	22
Silverman et al. 2008	Placebo	3	1741	71
Silverman et al. 2008	Raloxifene	3	1696	40
Cosman et al. 2011	Teriparatide	1	137	5
Cosman et al. 2011	Zoledronic acid	1	137	1
Recker et al. 2007	Alendronate	0.90	255	8
Recker et al. 2007	Raloxifene	0.90	259	5
Muscoso et al. 2004	Alendronate	2	1000	6
Muscoso et al. 2004	Raloxifene	2	100	0
Muscoso et al. 2004	Risedronate	2	100	0
Cosman et al.2016	Placebo	1	3322	59

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
Cosman et al.2016	Romosozumab	1	3321	16
Kendler et al. 2018	Teriparatide	2	516	28
Kendler et al. 2018	Risedronate	2	533	64
ACTIVE	Placebo	1.5	600	25
ACTIVE	Abaloparatide	1.5	583	3
ACTIVE	Teriparatide	1.5	600	4
Hadji et al. 2012	Teriparatide	1.5	360	16
Hadji et al. 2012	Risedronate	1.5	350	33
Saag et al. 2017	Alendronate	1	2047	128
Saag et al. 2017	Romosozumab	1	2046	82
NCT03974100	Denosumab biosimilar	1	263	15
NCT03974100	Denosumab	1	264	24
Ettinger et al. 1999	Placebo	3	2292	231
Ettinger et al. 1999	Raloxifene	3	2259	148
Cummings et al. 2009	Placebo	3	3691	264
Cummings et al. 2009	Denosumab	3	3702	86
Cummings et al. 1998	Placebo	4	759	44
Cummings et al. 1998	Alendronate	4	759	22

B.3.4.2 Hip fracture

Table 21 presents the NMA inputs for hip fracture.

Table 21 Hip fracture

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
Cummings et al. 2009	Placebo	3	3906	43
Cummings et al. 2009	Denosumab	3	3902	26
Neer et al. 2001	Placebo	2	544	4
Neer et al. 2001	Teriparatide	2	541	1
Langdahl et al. 2017	Romosozumab	1	218	1
Langdahl et al. 2017	Teriparatide	1	218	0
Miller et al. 2016	Zolendronate	1	320	2
Miller et al. 2016	Denosumab	1	320	1
Muscoso et al. 2004	Alendronate	2	1000	3
Muscoso et al. 2004	Raloxifene	2	100	0
Muscoso et al. 2004	Risedronate	2	100	0
Silverman et al. 2008	Placebo	3	1885	6
Silverman et al. 2008	Raloxifene	3	1849	5
Harris et al. 1999	Placebo	3	815	15
Harris et al. 1999	Risedronate	3	812	12
Reginster et al. 2000	Placebo	3	406	11
Reginster et al. 2000	Risedronate	3	406	9
Black et al. 1996	Placebo	3	1005	22
Black et al. 1996	Alendronate	3	1022	11
Black et al. 2007	Placebo	3	3861	88
Black et al. 2007	Zolendronate	3	3875	52
Cosman et al.2016	Placebo	1	3591	13
Cosman et al.2016	Romosozumab	1	3589	7
Hadji et al. 2012	Teriparatide	1.5	360	5
Hadji et al. 2012	Risedronate	1.5	350	2
Kendler et al. 2018	Teriparatide	2	680	2
Kendler et al. 2018	Risedronate	2	680	5
ACTIVE	Placebo	1.5	688	1
ACTIVE	Abaloparatide	1.5	696	0

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
ACTIVE	Teriparatide	1.5	686	0
Saag et al. 2017	Alendronate	1	2047	22
Saag et al. 2017	Romosozumab	1	2046	14
NCT03974100	Denosumab biosimilar	1	263	2
NCT03974100	Denosumab	1	264	0
Cummings et al. 1998	Placebo	4	818	18
Cummings et al. 1998	Alendronate	4	800	8

Abbreviations: NCT, National Clinical Trial

B.3.4.3 Non-vertebral fracture

Table 22 presents the NMA inputs for non-vertebral fracture.

Table 22 Non-vertebral fracture

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
Black et al.1996	Placebo	3	1005	148
Black et al.1996	Alendronate	3	1022	122
Black et al. 2007	Placebo	0.91	3861	388
Black et al. 2007	Zoledronic acid	0.91	3875	292
Chesnut et al. 2004	Placebo	3	975	80
Chesnut et al. 2004	Ibandronate	3	977	89
Cosman et al. 2011	Zoledronic acid	1	137	8
Cosman et al. 2011	Teriparatide	1	137	7
Cummings et al. 2009	Placebo	3	3906	293
Cummings et al. 2009	Denosumab	3	3902	238
Harris et al. 1999	Placebo	3	815	52
Harris et al. 1999	Risedronate	3	812	33
Miller et al. 2008	Alendronate	1	859	12
Miller et al. 2008	Ibandronate	1	874	14
Muscoso et al. 2004	Alendronate	2	1000	4
Muscoso et al. 2004	Raloxifene	2	100	0
Muscoso et al. 2004	Risedronate	2	100	0
Neer et al. 2001	Placebo	2	544	30
Neer et al. 2001	Teriparatide	2	541	14
Reginster et al. 2000	Placebo	2	406	51
Reginster et al. 2000	Risedronate	2	406	36
Silverman et al. 2008	Placebo	3	1885	118
Silverman et al. 2008	Raloxifene	3	1849	109
Langdahl et al. 2017	Romosozumab	1	218	7
Langdahl et al. 2017	Teriparatide	1	214	8
Pols et al. 1999	Placebo	1	958	37
Pols et al. 1999	Alendronate	1	950	19
Cosman et al.2016	Placebo	1	3591	75
Cosman et al.2016	Romosozumab	1	3589	56

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
Hadji et al. 2012	Risedronate	1.5	350	29
Hadji et al. 2012	Teriparatide	1.5	360	28
Kendler et al. 2018	Teriparatide	2	680	25
Kendler et al. 2018	Risedronate	2	680	38
ACTIVE	Placebo	1.5	688	21
ACTIVE	Abaloparatide	1.5	696	15
ACTIVE	Teriparatide	1.5	686	12
Saag et al. 2017	Alendronate	1	2047	95
Saag et al. 2017	Romosozumab	1	2046	70

B.3.4.4 New or worsening fracture

Table 23 presents the NMA inputs for new or worsening fracture.

Table 23 New or worsening fracture

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
Cosman et al. 2016	Placebo	1	3322	59
Cosman et al. 2016	Romosozumab	1	3321	17
Hadji et al. 2012	Teriparatide	1.5	360	24
Hadji et al. 2012	Risedronate	1.5	350	39
Kendler et al. 2018	Teriparatide	2	516	31
Kendler et al. 2018	Risedronate	2	533	69
Bone et al. 2013	Placebo	3	3206	234
Bone et al. 2013	Denosumab	3	3272	79
ACTIVE	Placebo	1.5	600	26
ACTIVE	Abaloparatide	1.5	583	3
ACTIVE	Teriparatide	1.5	600	5
Saag et al. 2017	Alendronate	1	1703	101
Saag et al. 2017	Romosozumab	1	1696	67

B.3.4.5 Clinical fracture

Table 24 presents the NMA inputs for clinical fracture.

Table 24 Clinical fracture

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
Bone et al. 2013	Placebo	3	3206	327
Bone et al. 2013	Denosumab	3	3272	236
Cosman et al.2016	Placebo	1	3591	90
Cosman et al.2016	Romosozumab	1	3589	58
Kendler et al. 2018	Teriparatide	2	680	30
Kendler et al. 2018	Risedronate	2	680	61
Saag et al. 2017	Alendronate	1	2047	110
Saag et al. 2017	Romosozumab	1	2046	79
ACTIVE	Placebo	1.5	688	35
ACTIVE	Abaloparatide	1.5	696	21
ACTIVE	Teriparatide	1.5	686	21
Cummings et al. 1998	Placebo	4	811	159
Cummings et al. 1998	Alendronate	4	817	107

B.3.4.6 Major osteoporotic fracture

Table 25 presents the NMA inputs for major osteoporotic fracture.

Table 25 Major osteoporotic fracture

Study name	Treatment arm	Timepoint of evaluation (years)	Total number of patients (N)	No of fractures (N)
Cosman et al. 2016	Placebo	1	3591	63
Cosman et al. 2016	Romosozumab	1	3589	38
ACTIVE	Placebo	1.5	688	23
ACTIVE	Abaloparatide	1.5	696	7
ACTIVE	Teriparatide	1.5	686	14
Saag et al. 2017	Alendronate	1	2047	85
Saag et al. 2017	Romosozumab	1	2046	61

B.3.5 Additional NMA results

Hazard ratios with predictive and credible intervals for all fracture outcomes are presented in Table 26.

Table 26 Hazard ratios with predictive and credible intervals for all fracture outcomes

vs. placebo	HR (95% PrI)	HR (95% CrI)
Hip fracture		
Abaloparatide		
Alendronate		
Denosumab		
Denosumab biosimilar		
Raloxifene		
Risedronate		
Romosozumab		
Teriparatide		
Zolendronate		
New vertebral fracture		
Abaloparatide		
Alendronate		
Denosumab		
Denosumab biosimilar		
Ibandronate		
Raloxifene		
Risedronate		
Romosozumab		
Teriparatide		
Zolendronate		
Non-vertebral fracture		
Abaloparatide		
Alendronate		
Denosumab		
Ibandronate		
Raloxifene		
Risedronate		
Romosozumab		
Teriparatide		
Zoledronic acid		
Clinical fracture		
Abaloparatide		
Alendronate		
Denosumab		
Risedronate		
Romosozumab		
Teriparatide		
Major osteoporotic fracture		
Abaloparatide		
Alendronate		
Romosozumab		
Teriparatide		
New or worsening vertebral fracture		
Abaloparatide		
Alendronate		
Denosumab		
Risedronate		

vs. placebo	HR (95% PrI)	HR (95% CrI)
Romosozumab	[redacted]	[redacted]
Teriparatide		

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; PrI, predictive intervals

The estimates of the between study SD with 95% CrI are provided in Table 27.

Table 27 Estimate of between study SD for new vertebral, hip, and non-vertebral fracture NMAs

Outcome	Between-study SD (95% CrI)
Hip fracture	[redacted]
New vertebral fracture	
Non-vertebral fracture	

Abbreviations: CrI, credible interval; NMA, network meta-analysis; SD, standard deviation

B.3.5.1 New or worsening vertebral fracture

The network of studies reporting data for new vertebral fractures is illustrated in Figure 10. Six studies assessing seven treatments reported new or worsening vertebral fracture data. The NMA for new or worsening vertebral fracture is feasible as it estimates the relative treatment effect of abaloparatide across connected or indirectly connected comparators.

Figure 10 Network for analysis – new or worsening vertebral fracture

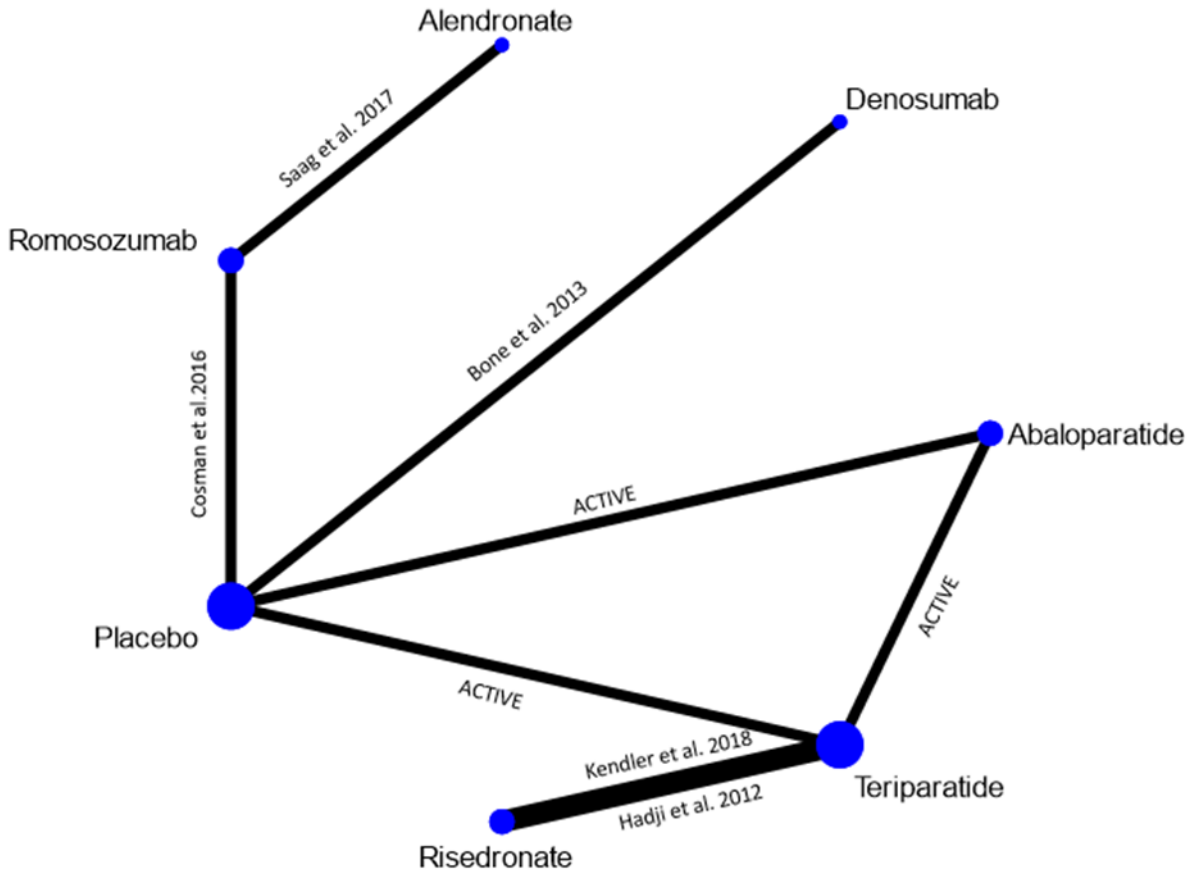


Table 28 presents a summary of abaloparatide versus all comparators included in this network.

Table 28 Risk of new or worsening vertebral fracture (FEM and REM) for abaloparatide vs comparators

Abaloparatide vs.	FEM			REM		
	Median HR	LCrI	UCrI	Median HR	LCrI	UCrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

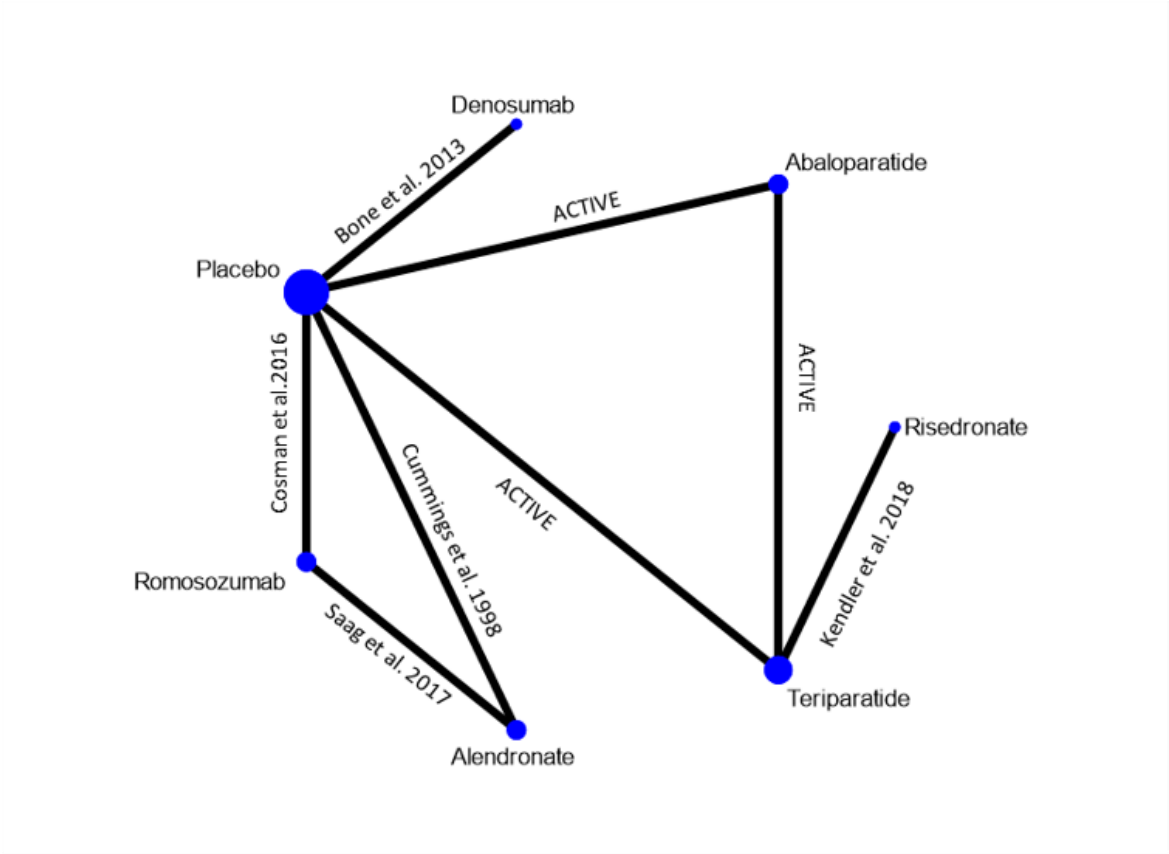
Abbreviations: CrI, credible interval; FEM, fixed-effects model; HR, hazard ratio; LCrI, lower confidence interval; REM, random-effects model; UCrI, upper confidence interval; vs., versus

The FEM demonstrated that abaloparatide [redacted]) of new or worsening vertebral fracture compared to placebo and alendronate, and that it was [redacted] compared to other comparators. [redacted]

B.3.5.2 Clinical fracture

The network of studies reporting data for non-vertebral fractures is illustrated in Figure 11. Five studies assessing seven treatments reported clinical fracture data. The NMA for clinical fracture is feasible as it estimates the relative treatment effect of abaloparatide across connected or indirectly connected comparators.

Figure 11 Network for analysis – clinical fracture



Six studies assessing seven treatments contributed to the analysis. Table 29 presents a summary of abaloparatide versus all comparators included in this network.

Table 29 Risk of clinical fracture (FEM and REM) for abaloparatide vs comparators

Abaloparatide vs.	FEM			REM		
	Median HR	LCrI	UCrI	Median HR	LCrI	UCrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risedronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; FEM, fixed-effects model; HR, hazard ratio; LCrI, lower credible interval; REM, random-effects model; UCrI, upper credible interval; vs., versus

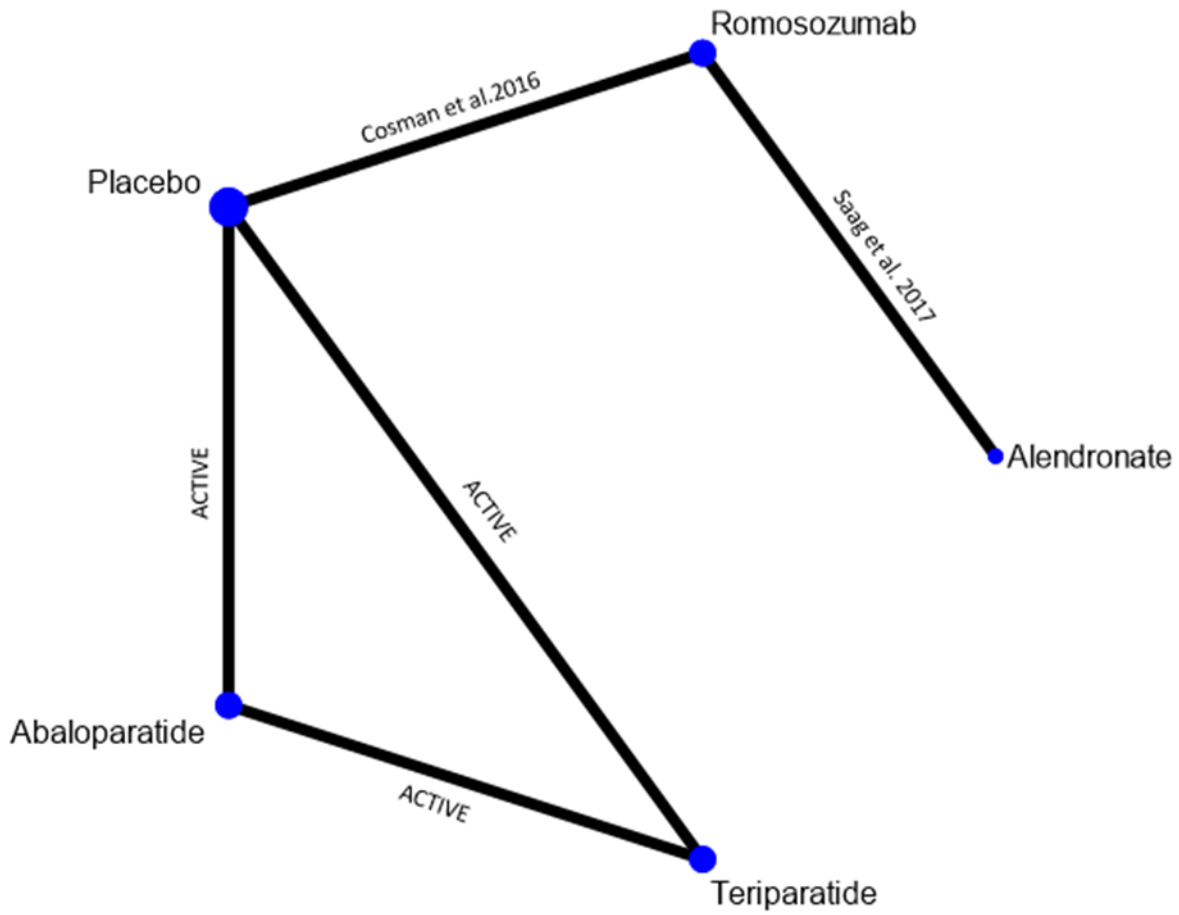
The FEM demonstrated that abaloparatide [redacted] of clinical fracture compared to placebo and risedronate (risk [redacted], and it was [redacted] versus the other comparators. [redacted]

B.3.5.3 Major osteoporotic fracture

The network of studies reporting data for major osteoporotic fractures is illustrated in Figure 12. Three studies assessing five treatments reported major osteoporotic fracture data. The

NMA for MOF is feasible as it estimates the relative treatment effect of abaloparatide across connected or indirectly connected comparators.

Figure 12 Network for analysis – major osteoporotic fracture



Three studies assessing five treatments contributed to the analysis. Table 30 presents a summary plot of abaloparatide versus all comparators.

Table 30 Risk of major osteoporotic fractures (FEM and REM) for abaloparatide vs comparators

Abaloparatide vs.	FEM			REM		
	Median HR	LCrI	UCrI	Median HR	LCrI	UCrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; FEM, fixed-effects model; HR, hazard ratio; LCrI, lower confidence interval; REM, random-effects model UCrI; upper confidence interval; vs., versus

The FEM demonstrated that abaloparatide [redacted] the risk of major osteoporotic fractures compared to placebo and alendronate ([redacted] respectively), and that it was

[redacted] compared to romosozumab and teriparatide. [redacted]

B.3.6 Model inputs

Placeholder for economic sections. Company to send clarification response to NICE by 9am on Monday 5th February

B.3.7 Clinical outcomes and disaggregated results from the model

Placeholder for economic sections. Company to send clarification response to NICE by 9am on Monday 5th February

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture [ID882]

Summary of Information for Patients (SIP)

September 2023

File name	Version	Contains confidential information	Date
ID882 abaloparatide_osteoporosis_SIP	1.0	No	21-Sep-23

Summary of Information for Patients (SIP):

What is the SIP?

The SIP is written by the company who is seeking approval from NICE for their treatment to be sold to the National Health Service (NHS) for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Abaloparatide **Brand name:** Eladynos®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Patient population The patient population in the National Institute for Health and Care Excellence (NICE) final scope is postmenopausal women with osteoporosis who are at increased risk of breaking a bone (fracture), in line with the licensed indication for abaloparatide. The target population considered in the manufacturer's (Theramex) submission to NICE is postmenopausal women with osteoporosis who are at very high risk of fracture, in line with the key Phase 3 abaloparatide study (Abaloparatide Comparator Trial In Vertebral Endpoints [ACTIVE]).[1] This target population is smaller than the population for the licensed indication and the NICE final scope, and is focused on the patients for whom abaloparatide is expected to provide the most clinical benefit. Currently in clinical practice the medicines that are available to stimulate bone formation (teriparatide and romosozumab) are reserved for postmenopausal women with osteoporosis who are at very high risk of fracture.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Abaloparatide is approved for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Abaloparatide received marketing authorisation in the European Union on 12 December 2022 from the European Medicines Agency (EMA). https://www.ema.europa.eu/en/medicines/human/EPAR/eladynos#authorisation-details-section

Abaloparatide received marketing authorisation in the UK on 27 March 2023 from the Medicines and Healthcare Products Regulatory Agency (MHRA). This is the first product launched by Theramex in osteoporosis.

https://mhraproducts4853.blob.core.windows.net/docs/0e669c844f46a30bd91b0ef8178eb5c730034c8c

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Working with patient groups

As a responsible pharmaceutical company, Theramex is in communication with relevant patient organisations in the UK, such as the Royal Osteoporosis Society, to support endeavours to improve the treatment of postmenopausal women affected by osteoporosis. This is common practice, and we adhere closely to industry guidelines and regulations that are in place.

No other collaborations exist that could be considered a potential conflict of interest.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Osteoporosis

Osteoporosis is a very common and progressive disease of the skeleton that weakens bones, making them fragile and more likely to break (fracture).[3,4] The risk of osteoporosis increases with advancing age and decreasing levels of sex hormones (e.g. oestrogen and testosterone) and is most common in postmenopausal women.

Number of patients with osteoporosis

In England and Wales, more than two million women have osteoporosis and approximately 180,000 fractures occur each year as a result of the disease.[2] Of these, 70,000 are hip fractures, 25,000 are clinical vertebral fractures (fractures of the bones in the spine), and 41,000 are wrist fractures.[3]

Clinical burden of osteoporosis

Fractures and their complications have important health consequences for patients and require significant use of healthcare resources. Overall in the UK osteoporotic fracture costs accounted for approximately 2.4% of all healthcare spending in 2019.[4]

Experiencing a fracture imposes a major burden on a patient, causing chronic pain, disability resulting in loss of independence, and an increased risk of illness (morbidity).[8] Osteoporosis and fractures have a substantial negative impact on the health-related quality of life (HRQoL) of postmenopausal women with osteoporosis.[5,6] Drivers of lower quality of life scores include

increased physical pain, limited physical activity, difficulty of movement, decreased ability of self-care, and psychological anxiety.[5]

Approximately half of women experience one or more fractures in their lifetime.[3] Breaking a bone is associated with an increased risk of breaking another one in the future, with the highest risk being within 2 years of the first fracture.[7–9] As such, patients with a recent osteoporotic fracture are at very high risk or imminent risk of another fracture.

Vertebral fractures are the most common type of osteoporotic fracture, with more than one in ten women over the age of 50 experiencing at least one vertebral fracture.[10,11] However, many studies report that only one in three vertebral fractures are diagnosed [12,13] and as such argue that vertebral fractures are largely under diagnosed.[11,14,15] Fractures cause chronic pain, loss of function, loss of height and kyphosis (curvature of the spine). Most patients with vertebral fractures are managed in the community, but can require significant support including pain management, physiotherapy and frequent visits to a general practitioner (GP; family doctor).[1,2] Severe kyphosis may lead to breathing problems, gastrointestinal (GI) problems such as indigestion, and difficulty in performing activities of daily living.[2]

Nonvertebral fractures are defined as fractures not occurring in the spine or skull; these occur in areas such as the hip, wrist, and forearm.[16] Although hip fractures result in the most morbidity, non-hip nonvertebral fractures (which account for up to half of fractures) also result in substantial morbidity.[16,17]

Hip fractures, often caused by a fall, require hospital admission for surgery in the majority of cases.[2] Hip fractures are associated with chronic pain, a reduction in mobility, and cause permanent disability in 50% of patients. A review of 49 clinical trials indicated that patients rarely return to pre-fracture quality of life levels, affecting the lifelong physical and mental functioning of patients.[18]In patients over 65, hip fractures constitute a high risk of losing independent mobility or in the worst cases independent ability to live at home unassisted.[18]

Mortality

The increased risk of death (mortality) following fractures, particularly hip and vertebral fractures, is well recognised, although it is unclear if this is due to fracture alone or to pre-existing illnesses.[19,20] The risk of dying is the highest in the first year following the fracture, and following hip and vertebral fractures the risk of dying is increased for up to 10 years.[19] An eight fold increased risk of mortality after suffering a vertebral fracture has been reported.[21] In a General Practice Research Database UK study the survival rate was 86.5% one year after vertebral fracture, decreasing to 56.5% at five years.[22]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diagnosis

Osteoporosis is often referred to as a "silent disease" as bone loss occurs without symptoms and may remain undetected until a fracture occurs.[23]

Bone mineral density (BMD) measurements are used to diagnose osteoporosis. BMD refers to the amount of minerals within the bone; bones that contain more minerals are denser, so they tend to be stronger and less likely to break.[24] BMD is commonly measured using a type of x-ray called dual-energy x-ray absorptiometry.[25] A "T-score" is defined as the number of standard deviations (SD) by which an individual's BMD is above or below the mean (average) BMD of a healthy young

adult reference population. Using the World Health Organisation classification, osteoporosis is diagnosed in individuals that have a BMD that is 2.5 SD or more below the mean BMD of a young adult reference population (T-score of ≤–2.5).[23] Individuals with a T-score ≤–2.5 with existing fracture are diagnosed with severe osteoporosis.[23]

There are no additional diagnostic tests required with abaloparatide.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Current treatment options

Drug treatments for postmenopausal women with osteoporosis can be broadly classified into two drug classes, antiresorptive or anabolic, depending on their mechanism of action.[26] Antiresorptive treatments (e.g. oral bisphosphonates and denosumab) primarily prevent bone resorption (destruction of bone tissue that promotes bone loss), with later secondary effects on bone formation. Anabolic treatments (e.g. teriparatide and abaloparatide) primarily stimulate bone formation with variable effects on bone resorption.[27] Romosozumab, a monoclonal antibody (an antibody molecule made in the laboratory that has been developed to target a specific molecule to treat a particular disease/condition), has a dual action stimulating bone formation and reducing bone resorption (hereafter referred to as an anabolic agent).

Antiresorptive treatments

Based on NICE guidance oral bisphosphonates e.g. alendronate and risedronate (antiresorptive treatments) are currently used first-line (meaning as the first treatment used) in women at high risk of fracture in England and Wales (NICE technology appraisal [TA] 464):[28] However, oral bisphosphonates are either not tolerated or contraindicated in some patients with osteoporosis, or some patients experience an unsatisfactory response to them. In this situation, another antiresorptive treatment can be offered. These include bisphosphonates (zoledronate and ibandronate) given as an intravenous injection or non-bisphosphonates (denosumab or raloxifene) given as a subcutaneous injection (see NICE TA464 [updated in 2019]; NICE TA204 [published in 2010]; NICE TA161 [updated in 2018] for further information).[3,28,29]

Anabolic treatments

Evidence suggests that anabolic treatments for osteoporosis are more effective and act faster than antiresorptive treatments.[30] These anabolic treatments are restricted in terms of how long they can be taken for, however the beneficial increase in BMD achieved with them can be maintained by giving an antiresorptive treatment after them, reducing fracture risk over the long-term.

Currently, there are only two anabolic agents available for postmenopausal women at very high risk of fractures in England and Wales, romosozumab and teriparatide. Teriparatide is a

recombinant fragment of human parathyroid hormone (PTH) (1-34) administered as a subcutaneous injection once daily. Romosozumab is a humanised monoclonal antibody administered as two subcutaneous injections once monthly. Teriparatide and romosozumab treatments are limited to 24 months and 12 months duration, respectively. After stopping treatment with teriparatide or romosozumab patients move to sequential therapy typically involving an antiresorptive drug (e.g. an oral bisphosphonate, such as alendronate).

NICE recommendations reserve these treatments for postmenopausal women with osteoporosis at very high risk of fracture as follows:

- Romosozumab (regardless of previous treatment) as a treatment option for people at high risk of fracture, defined as experiencing a major osteoporotic (spine, hip, forearm, or upper arm) fracture within the last 24 months, who as such are at imminent risk of another fracture (NICE TA791).[31]
- Teriparatide for secondary prevention of osteoporotic fragility fractures in postmenopausal women who are intolerant/contraindicated to, or who have had an unsatisfactory response to bisphosphonates (NICE TA161, updated in 2018).[3]

In the more recent NICE single technology appraisal (STA) for romosozumab (published in 2022) clinical experts stated that giving teriparatide first-line before oral bisphosphonates may be more effective.[31]

Although teriparatide improves BMD in the spine, it can lead to mild hypercalcaemia (elevated level of calcium in the blood) mainly due to an increase in bone resorption, limiting the BMD gains (e.g. in the hip)[32] The clinical effect of teriparatide on spine BMD is more evident in the second year of treatment.[32] Although teriparatide can be self-administered it requires storage in a refrigerator (2°C – 8°C).

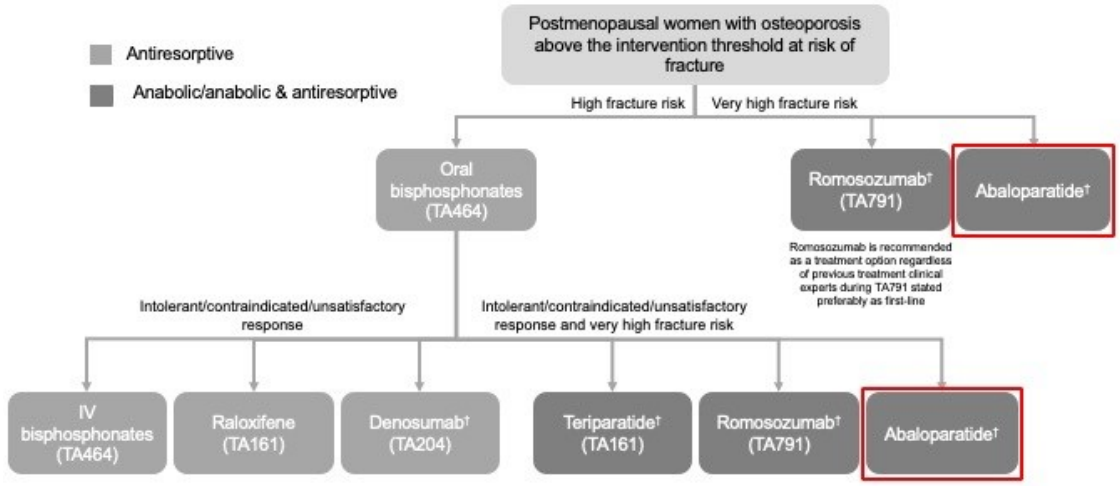
Romosozumab improves BMD in both the spine and hip within 6 months of treatment.[30] It does not require storage in a refrigerator after first use, which may improve adherence to treatment and reduce wastage. However, romosozumab is contraindicated (not recommended) in patients with a history of myocardial infarction (heart attack) or stroke.[33]

There remains a high unmet need for further anabolic treatment options for postmenopausal women with osteoporosis at very high risk of fracture that:

- Reduce both vertebral and nonvertebral fractures
- Has an acceptable safety and tolerability profile
- Do not require refrigeration minimising drug wastage
- Are easy to administer by the patient

In clinical practice abaloparatide will provide an alternative anabolic treatment option to teriparatide and romosozumab for the treatment of osteoporosis in postmenopausal women at very high risk of fracture. The proposed place of abaloparatide in the current treatment pathway is outlined Figure 1.

Figure 1: Proposed place of abaloparatide in the current treatment pathway



† Patients stopping denosumab, teriparatide, romosozumab and abaloparatide require a sequential therapy strategy typically involving an antiresorptive drug
Abbreviations: IV, intravenous; TA, technology appraisal

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Published patient-based evidence

The burden of osteoporosis for patients in the UK has recently been highlighted in a research study ("Life with Osteoporosis 2021") completed by, or on behalf of 3,266 people with osteoporosis between 7 June and 7 July 2021.[34]

Pain

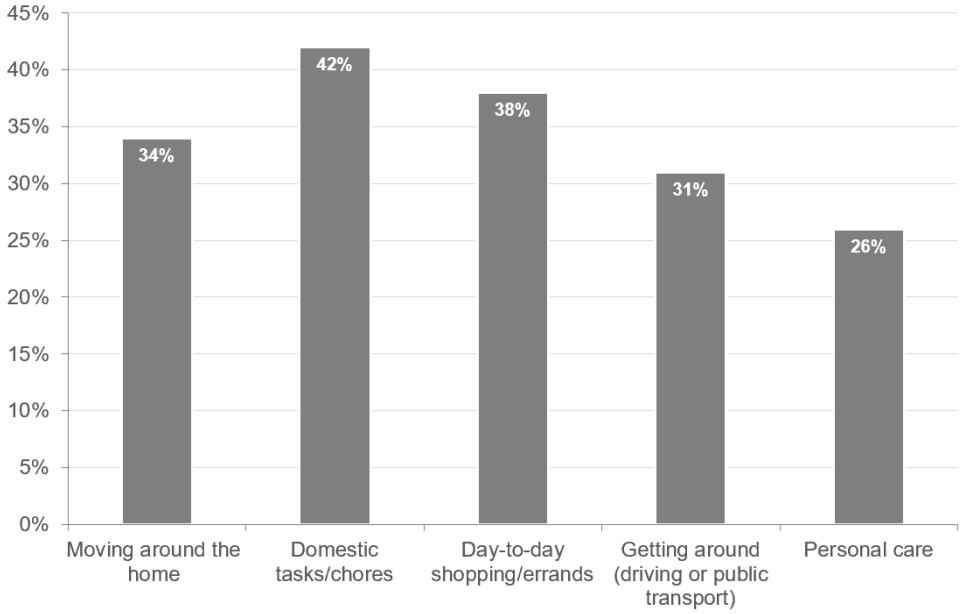
Almost two out of three people from the study reported having osteoporosis-related pain, with over 25% reporting long-term pain. Moreover, 16% of people with long-term pain had experienced pain for over 10 years. Of those with long-term pain, more than one in three reported their pain as constant and more than one in three reported their pain as severe or unbearable. Pain has a large effect on emotional well-being, particularly constant pain, causing anger, low mood, lack of confidence and fear of sustaining another fracture.[34]

Daily activities

Osteoporotic fractures affect daily activities such as walking, eating, dressing, bathing, shopping, housework, and travel. In the "Life with Osteoporosis" study people with osteoporosis reported difficulty with domestic tasks and chores, moving around the house (ability to bend, walk or pick up heavy objects), getting around (driving or public transport), and personal care (Figure 2)[34] Half

of people with osteoporosis had reduced or stopped going on holiday and almost two out of five (39%) had stopped visiting relatives, travelling or going on holiday due to pain or mobility problems.[34]

Figure 2: The impact of osteoporosis on daily tasks



Source: Adapted from "Life with Osteoporosis 2021"[34]

Emotional well-being

Approximately half of people in the "Life with Osteoporosis" study reported the impact of osteoporosis on emotional well-being with concerns about future health, body image and sexual intimacy. The inability to fulfil social roles or loss of independence also leads to feelings of loneliness, depression, and anxiety. In the study, people reported being fearful for the future, with most people worried about losing their independence (83%) and concerned about future falls and fractures (92%).[34] Over half of people that had experienced a fracture had lost height or experienced a change in their body shape, with many worrying that the change in body shape made them look like they were overweight. Nearly half of people with osteoporosis had reduced or stopped their social activities and a third felt socially isolated.[34]

Work and finances

Osteoporosis impacts the ability to work causing financial pressures. In the "Life with Osteoporosis" study three in ten people reported impacts on their working lives and a quarter of those who were impacted had to leave their employment due to their osteoporosis. Approximately three quarters of people whose working lives had been affected felt financially burdened by the cost of managing their osteoporosis (e.g. paying for cleaners or gardeners or items to help with mobility).[34]

Example quotes from women taking part in the "Life with Osteoporosis" study illustrate further the negative impacts of osteoporosis on daily lives and emotional well-being: [34]

- "Walking is a problem for me, I can't walk for great distances. If I ever need to leave the house, I take a taxi as I am unable to walk far without the aid of a trolley and walking stick which I have recently bought."

- "I did wonder at times "why am I bothering to live? Wouldn't I be better off out of all of this?" because there is no pause in my pain."
- "I'm a very independent person, so the thought of losing my independence would take my world away. I do not have family to call on, I do everything myself."
- "I have a raised bed and have bought an electric recliner to help me to feel more comfortable when I sleep. I feel lucky if I'm able to get three hours of sleep at a time."
- "I am now afraid of sexual intimacy because I am afraid that I could break as my pelvis is too weak. This makes me lonely."
- "I have lost contact with the groups of friends I had through sporting activities. I get a bit down that I am not able to do as much physically for my family as I used to do."
- "I feel absolutely terrible. Very depressed. I can't get clothes to fit. I am embarrassed going out. It doesn't help that my husband calls me a hunchback. I feel worthless."
- "When the doctor told me how bad it was, I felt lonely and frightened, there was no need to instil that fear. I felt that I had been delivered a death sentence."
- "It's a depressing life and we are only 64 and 68. I'm constantly stressed and depressed about our lack of quality of life because we haven't enough money."

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body.
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

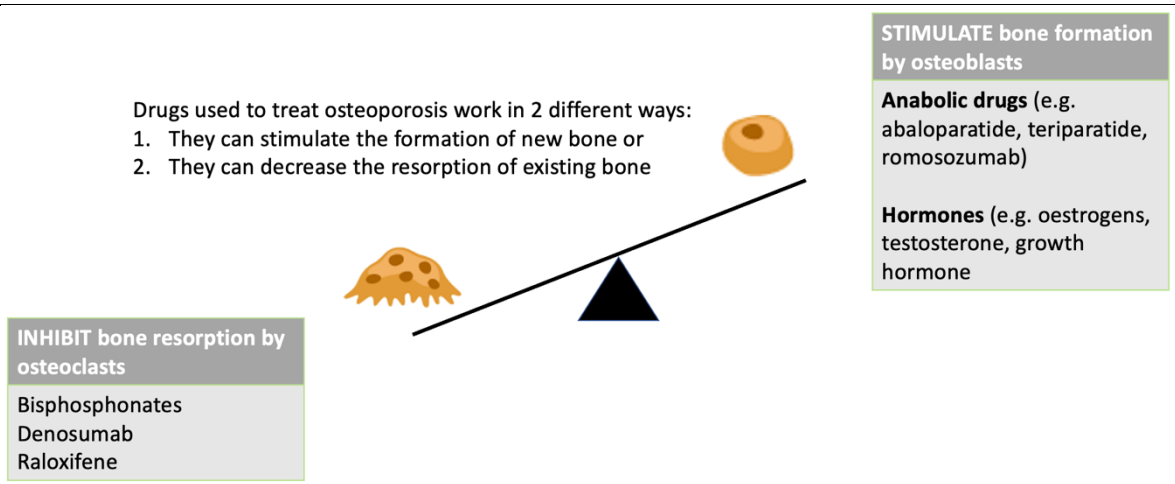
How does abaloparatide work?

The active substance in Eladynos®, abaloparatide, is similar to part of the naturally occurring human parathyroid hormone. It acts like this hormone by activating bone forming cells called osteoblasts to stimulate bone formation, followed by a small increase in bone resorption.

The time during which anabolic treatments stimulate bone formation before increasing bone resorption is the period when anabolic treatments provide the most net benefit (referred to as the 'anabolic window'). The mechanism of action of abaloparatide differs to that of teriparatide (another parathyroid hormone), the major difference being that abaloparatide gives much smaller and short-term increase in bone resorption compared with teriparatide, suggesting there is a wider period of net benefit (anabolic window) with abaloparatide.[35]

Drugs used to treat osteoporosis

Figure 3: antiresorptive and anabolic treatments for osteoporosis



Please refer to the abaloparatide Summary of Product Characteristics, Patient Information Leaflet and Public Assessment Report for more details about the way the treatment works.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Not applicable

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Eladynos is a solution for injection. The recommended dose is one injection (80 micrograms) once daily administered in the lower abdomen (belly). It is recommended that the injection should be administered at the same time each day but in different places on the belly to reduce the risk of injection site reactions. It should not be administered to the areas where the skin is tender, bruised, red, scaly or hard, or in areas with scars or stretch marks.[36] Treatment should not continue for longer than 18 months. If a dose is missed, it should be taken as soon as possible within 12 hours; after 12 hours the missed dose should be skipped. The next dose should not be doubled.[36] Following the end of abaloparatide therapy, patients may be prescribed other osteoporosis therapies such as bisphosphonates.[36]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Completed main clinical trials (Phase 3)

The efficacy (how well a treatment works) and safety of abaloparatide were evaluated in a large Phase 3 clinical trial (ACTIVE) over 18 months that was followed by its extension study ACTIVExtend for a further 24 months.[1,37–40]

ACTIVE

ACTIVE (NCT01343004) was a Phase 3 placebo and active-controlled trial that assessed the efficacy and safety of abaloparatide in postmenopausal women with osteoporosis at very high risk of fracture. A group of patients were given placebo (a substance with no medicinal activity that is given in an identical way to the medicine under investigation) whereas other groups were given abaloparatide or another drug, teriparatide, used as an 'active control'. The abaloparatide and placebo groups of the trial were classed as 'double-blind', meaning that neither the doctors nor the patients knew who was taking abaloparatide or placebo. A double-blind approach is often used in clinical trials so that knowledge of which treatment (or placebo) is being received doesn't affect (bias) the assessment of the drug. Teriparatide could not be administered double-blind as it is given via its own trademarked injection pen.

The primary (main) endpoint (assessment) of the ACTIVE trial was how good abaloparatide was at preventing new vertebral (backbone) fractures over a period of 18 months by comparing the number of fractures in patients who received abaloparatide with those who received placebo. The study also looked at fractures in other bones (nonvertebral, clinical [fractures that would cause a patient to seek medical help] and major osteoporotic fractures) and BMD.

The analysis presented in the NICE submission is based on reanalysed data requested by the European Medicines Agency, which are also provided in the information supplied for abaloparatide for doctors and healthcare workers.[36,38] It includes data from 2,070 patients across 26 study centres in ten countries (Argentina, Brazil, Czech Republic, Denmark, Estonia, Hong Kong, Lithuania, Poland, Romania and the United States of America). The ACTIVE study has completed and ran from March 2011 to October 2014.[1]

To enter the study, patients had to be postmenopausal women aged between 49 and 86 years old with osteoporosis who were at risk of fracture (based on their age, BMD and fracture history). Patients with a history of osteosarcoma (a type of bone cancer), severe vertebral fractures or other diseases that may affect the bone were excluded from the study. Full inclusion and exclusion criteria are published.[1]

ACTIVExtend

The ACTIVE study treatment period lasted for 18 months which is the maximum length of time that abaloparatide can be given for.[36] After 18 months, patients could then then receive another osteoporosis treatment.[36] ACTIVExtend (NCT01657162) was a Phase 3 extension study for patients who had completed the ACTIVE trial and who had taken either placebo or abaloparatide treatment with no serious treatment-related adverse events.[39,40] All patients who enrolled in ACTIVExtend were treated with alendronate (an antiresorptive osteoporosis treatment called a bisphosphonate) for up to 24 months. The investigators and the patients remained blinded to the original treatment (abaloparatide or placebo) for the first 6 months of the extension., but alendronate was given 'open-label', meaning everyone knew they were receiving it.

As per the ACTIVE study, the analysis presented in the NICE submission for ACTIVExtend is based on reanalysed data requested by the European Medicines Agency,[36,38] which included 963 patients.

The ACTIVExtend study is completed and ran from November 2012 to October 2016.

Further data from a study of abaloparatide in real-life clinical practice

Clinical trials study the effects of a drug under controlled trial conditions in a specific patient population. Real-world evidence (RWE) studies provide further information about effectiveness and safety in real-life clinical practice (in people who receive the drug in usual everyday life who are not part of a trial). A RWE study[41] (NCT04974723) of 23,232 patients examined the effectiveness of abaloparatide compared with teriparatide (the other drug used in the ACTIVE trial) for preventing nonvertebral (primary analysis) and hip fractures during 19 months (18 months plus 30-day follow-up) after patients started using one of these treatments.

The study included women aged 50 years and over who were first prescribed abaloparatide or teriparatide by their doctor between May 2017 and July 2019 and excluded women with certain health conditions (full inclusion and exclusion criteria are published[41]).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

As outlined in Section 3d, the efficacy of abaloparatide was evaluated in the ACTIVE trial over 18 months, followed by its extension study ACTIVExtend for a further 24 months.[1,37–40] Further real-world effectiveness data were provided from a large RWE study.[41]

Fracture risk

In ACTIVE, abaloparatide significantly reduced the risk of new vertebral fractures vs (compared with) placebo after 18 months of treatment; 0.5% of patients receiving abaloparatide had a vertebral fracture vs 4.2% of patients in the placebo group, a risk reduction of 88%. This reduced risk was maintained through the full 43-month treatment period of the ACTIVE–ACTIVExtend study (18 months treatment in ACTIVE, 1 month for recruitment and consenting to ACTIVExtend, 24 months treatment in ACTIVExtend [abaloparatide/alendronate vs placebo/alendronate]).

The results also suggested an early reduction of nonvertebral, major osteoporotic and clinical fractures with abaloparatide vs placebo, but the difference between abaloparatide vs placebo was only statistically significant for major osteoporotic fractures (exploratory analysis rather than a main formal analysis [see Section 4b, Glossary of terms for analysis definitions]).

The ACTIVE study was not powered to show statistical differences between abaloparatide vs teriparatide (as around 22,000 patients per treatment group would be needed for this). However, abaloparatide and teriparatide showed similar numerical reductions in new vertebral fractures vs placebo. Rates of major osteoporotic fractures were numerically lower for abaloparatide vs

teriparatide at any time-point and rates for clinical fractures were numerically lower for abaloparatide vs teriparatide for the first 9 months.

In the RWE study, the new nonvertebral fracture rate was similar for abaloparatide (2.9%) vs teriparatide (3.2%) and the risk of hip fractures (an exploratory analysis) was significantly reduced by 22% for abaloparatide vs teriparatide (new hip fracture rates were 1.0% with abaloparatide vs 1.3% with teriparatide).

BMD improvements

In the ACTIVE study, BMD improvements (showing that bone became more dense) were significantly greater with abaloparatide vs placebo at the total hip, femoral neck (part of the hip) and lumbar spine (lower backbone) at 18 months. Increases were also significant for abaloparatide vs placebo in exploratory analyses at the earlier time points of 6 and 12 months. The increased bone density with abaloparatide vs placebo in the ACTIVE study was maintained throughout the ACTIVExtend study.

Exploratory analyses also showed abaloparatide increased BMD vs teriparatide at the total hip, femoral neck and lumbar spine at 6 months; at the total hip and femoral neck at 12 and 18 months, respectively; and at the lumbar spine at 12 months. Increases in lumbar spine BMD were similar between abaloparatide and teriparatide at 18 months. ACTIVE BMD data also suggested a faster onset of action for abaloparatide vs teriparatide.

Bone turnover markers

Levels of bone turnover markers in the blood that provide information on bone formation and resorption were measured in a subgroup of patients from ACTIVE and ACTIVExtend. Changes in these markers aligned with the bone density data and reflected the different ways in which abaloparatide and teriparatide work.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

A real-world study in the United States reported that most patients (86%) were satisfied with the abaloparatide treatment regimen, especially with ease of preparation (82%), ease of storage (87%), and storage convenience (89%), an attribute 83% of the patients thought was important. In addition, most patients reported complete satisfaction with the abaloparatide regimen allowing for their ability to conduct daily activities (85%) and convenience to fit into their daily schedule (84%). Finally, patients reported higher satisfaction with abaloparatide compared with treatments prior to abaloparatide (86% vs 51%). The authors concluded that the majority of patients were satisfied with abaloparatide and found it convenient/easy to prepare and store. High self-reported adherence may be associated with positive patient experience, including ease of use and adequate support from healthcare providers.[42]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Abaloparatide demonstrated acceptable safety results in ACTIVE and there was no evidence that 18 months of prior treatment with abaloparatide affected the safety of subsequent treatment with alendronate in ACTIVExtend.

There were no meaningful differences between ACTIVE treatment groups (abaloparatide, placebo or teriparatide) in the proportions of participants with adverse events (regardless of whether the doctors considered them to be related to treatment), serious adverse events or adverse events leading to death. No treatment-related deaths were reported.

Treatment-related adverse events and adverse events leading to a patient leaving the study (discontinuation) occurred more frequently in the abaloparatide group vs the placebo group. Treatment-related adverse events occurred in 42.7% of patients in the abaloparatide group, 28.4% in the placebo group and 40.8% in the teriparatide group. Adverse events leading to discontinuation were reported for 9.8% of patients in the abaloparatide group, 6.1% in the placebo group and 6.9% in the teriparatide group. Adverse events leading to discontinuation were generally mild to moderate in severity.

The most frequently observed adverse events in the ACTIVE abaloparatide group were hypercalciuria (excess calcium in the urine; 13.4% of patients) and dizziness (11.1% of patients). In most cases these events are not clinically significant (so do not cause too much of a problem for the patient). Supportive care may be required for dizziness and a doctor may want to take blood tests to monitor calcium levels.

The RWE study looked at the effects of abaloparatide on cardiovascular safety (e.g. nonfatal heart attack or stroke, heart failure or cardiovascular death) and showed that abaloparatide and teriparatide have similar cardiovascular safety.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

Key benefits for patients of using abaloparatide include:

- An early reduction of nonvertebral, major osteoporotic and clinical fractures was suggested with abaloparatide vs placebo in the ACTIVE study, with a statistically benefit (reduction) for major osteoporotic fractures.

- Numerically lower rates of major osteoporotic fractures for abaloparatide vs teriparatide (observed at any time-point in the ACTIVE study; rates for clinical fractures were numerically lower for abaloparatide vs teriparatide for the first 9 months).

- A statistically significant benefit (reduction) with abaloparatide vs teriparatide on the risk of hip fractures, based on real-world data.

- The treatment is self-administered by the patient, which avoids the need for repeated visits to the hospital/GP practice.

- Once opened, the treatment does not need to be refrigerated. This offers patients increased flexibility of travelling with their treatment.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Potential disadvantages for patients of using abaloparatide include:

- Daily injections are required, although this is also the case for teriparatide. For both treatments, these injections are done using an injection pen by the patient so do not require hospital/GP visits.

- Adverse events may affect a small proportion of patients. For example, patients may experience dizziness (11.1% of patients receiving abaloparatide in the ACTIVE trial).

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g. whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g. travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness/cost-comparison assessment of new medicines

In assessing whether a medicine represents a cost-effective use of NHS resources, NICE refers to a measure called the incremental cost-effectiveness ratio (ICER).[43] This looks at the cost-effectiveness of the product in question – in this case, abaloparatide– against other treatments currently used to treat the condition.

The ICER is measured in terms of what needs to be spent to gain one quality-adjusted life year (QALY). The QALY is a measure of disease burden and includes both the quality and quantity of life lived. A treatment can increase the number of QALYs a patient experiences by extending life, increasing the quality of life, or both.

How the economic assessment of abaloparatide in postmenopausal women at increased risk of fracture was conducted

There are no existing economic models which assess the costs (or cost-effectiveness) of abaloparatide followed by alendronate for treating postmenopausal women at increased risk of fracture in the UK. Therefore, a previously validated microsimulation Markov model was adapted to the UK context.

The economic model was designed to assess abaloparatide followed by alendronate in postmenopausal women at very high risk of fracture. Teriparatide and romosozumab were included as comparators in the economic analysis.

The model was structured using 'health states', which help to capture both the costs to the NHS and the impact on quantity and quality of life for patients receiving different medicines.

The model health states were 'at risk', 'hip fracture', 'vertebral fracture', 'other fracture' and 'death.[44]'

The costs captured within the analysis include drug costs, administration costs, healthcare resource use costs, fracture-associated costs and the costs associated with managing adverse events (AEs).

The model shows that, compared with both teriparatide followed by alendronate and romosozumab followed by alendronate, abaloparatide followed by alendronate prevents fractures and increases QALYs.

To fulfil our commitment and ensure that patients can have access to abaloparatide, Theramex have put forward a price that will be part of a Patient Access Scheme (PAS).

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Both abaloparatide and teriparatide act on the PTH1 receptor but in different ways. Abaloparatide binds to the R^G conformation of the PTH1 receptor, whereas teriparatide binds to the R^0 conformation.[35] As a result, there is a much smaller and transient increase in bone resorption with abaloparatide compared with teriparatide, suggesting there is a wider anabolic (bone-building) window with abaloparatide that results in a greater amount of bone formation than with teriparatide.[35]

In addition, abaloparatide does not require refrigeration after first use.[36] This is helpful for patients, for example when travelling and to avoid having to remember to return the pen to the refrigerator after each use. It can also help to reduce medication wastage and allow for

uninterrupted daily treatment (if the patient does not need to wait for the replacement of a 'spoiled' pen due to it not being refrigerated).

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Although abaloparatide has a marketing authorisation for postmenopausal women, this should not prevent using abaloparatide for some people who have been through menopause but do not identify as a woman.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: Guidance for patient involvement • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: European Observatory on Health Systems and Policies - Policy Brief • The Royal Osteoporosis Society: https://theros.org.uk

4b) Glossary of terms

Active comparator: Another drug used in a clinical trial to compare results against those from the main drug being investigated (e.g. in the ACTIVE trial, abaloparatide was being investigated with patients in other study groups receiving placebo or the active comparator teriparatide).

Adverse event: An unintended medical event that occurs while you are taking a medicine, although it may not necessarily be caused by that medicine.

Antiresorptive treatments (for osteoporosis): A group of drugs that work primarily by preventing bone resorption (destruction of bone tissue that promotes bone loss), with later secondary effects on bone formation.

Anabolic agents (for osteoporosis): A groups of drugs that includes teriparatide and abaloparatide which work primarily by stimulating bone formation with variable effects on bone resorption.[27]

Bisphosphonates: A group of antiresorptive treatments (defined above) that may be used to treat osteoporosis.

Bone mineral density (BMD): A measure of how dense bones are as bones that are less dense may be weaker and more prone to fractures in future. BMD can be measured using a type of x-ray (called dual-energy x-ray absorptiometry) and you may have heard the result reported as a T-score.

Bone turnover markers: Markers in the blood that provide information on bone formation and resorption and can be assessed from a blood test.

Clinical fractures: Fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine fractures.[1]

Comorbidities: More than one disease or condition. For example, someone with osteoporosis may also have diabetes or heart disease so these would be referred to as comorbidities.

Contraindicated: If a drug is contraindicated it means it should not be used in a particular situation, for example some drugs are contraindicated for people taking other medications or with certain health conditions so they should not be taken by these patients.

Disability-adjusted life years (DALYs): The number of years of healthy life a person is considered to have (or have lost), adjusted to measure of the impact of a disease or injury (so a person with a particular medical condition may be considered to have lost x number of healthy years due to their condition).

Double-blind: a design often used in clinical trials meaning that neither the doctors nor the patients knew which treatment group (e.g. a particular drug or placebo) a patient was assigned to. A double-blind approach is used so that knowledge of which treatment (or placebo) is being received doesn't affect (bias) the assessment of the drug.

Efficacy: How well a treatment works (this term is usually used when reporting clinical trial data).

Effectiveness: How well a treatment works (this term is usually used when reporting data from studies of real-life clinical practice rather than from a clinical trial).

Exploratory analysis: A statistical analysis that is exploratory in nature and is not one of the main assessments of a study. It is sometimes performed where there are not enough data for a formal analysis (such as a primary analysis, defined later). An exploratory analysis can provide useful information but may need further analysis to confirm the results.

European Medicines Agency: The regulatory body that evaluates medicines to see if they should be licensed for use in the European Union.

Femoral neck: Part of the hip.

First-line: The first treatment used for a particular disease/condition.

ICER: incremental cost-effectiveness ratio. Measure of the cost-effectiveness of a medicine against other treatments currently used to treat the condition.

Kyphosis: Curvature of the spine.

Lumbar spine: Lower backbone.

Marketing authorisation: Approval from a regulatory body to market a medicine in a specified country (e.g. Great Britain) or region (e.g. European Union).

Major osteoporotic fractures: Fractures of the upper arm, wrist, hip or clinical spine[1] (clinical spine means a fracture of the spine that would cause a patient to seek medical treatment).

Monoclonal antibody: A type of treatment where an antibody has been developed to target a specific molecule to treat a particular disease/condition.

Nonvertebral fractures: fractures not occurring in the spine or skull, such as the hip, wrist or forearm.

NCT number: The number assigned to a clinical trial when it is registered on https://clinicaltrials.gov, a database that lists clinical trials and provides details of their status (e.g. 'Recruiting', Completed'), methods and results.

Osteoporosis: A disease characterised by low bone mass and deterioration of bone structure, leading to an increase in bone fragility and risk of fracture.

Osteosarcoma: A type of bone cancer

Placebo: A 'dummy drug' given to patients in the placebo control group of a clinical trial. A placebo is designed to look the same as the drug being investigated so that people do not know if they received the actual drug or the placebo. A placebo is given to compare the effects of receiving the drug being investigated versus no drug (over and above any 'placebo effect').

Phase 3 trial: A late-stage clinical trial that usually involves large numbers of patients and is often used as the primary source of data for applications for marketing authorisation of a drug.

Powered (statistical term): Statistical analyses are 'powered' to detect a statistically significant difference, for example between patients on two different treatments. When designing a study, a statistician needs to determine how much 'power' (sensitivity) is needed to show a true difference between treatments. This will determine how many patients need to be in each group to give the required 'power' for the comparison.

Primary analysis: The main statistical analysis performed for a clinical trial based on what the trial investigators think is the most important outcome (endpoint) to measure (e.g. based on the needs of patients). For example, in ACTIVE, the primary analysis was how good abaloparatide was at preventing new vertebral (backbone) fractures in the abaloparatide group vs the placebo group over a period of 18 months.

QALY: quality-adjusted life year. A measure of disease burden, including both the quality and quantity of life lived, used for the economic assessment of medicines.

Randomised: when patients in a clinical study are randomly assigned to a group in the trial (e.g. the group being given the medicine, or the group being given a placebo).

Real-world evidence (RWE): Evidence gained from a 'real-world' study that can be used to evaluate the effectiveness and safety of a drug in real-life clinical practice (e.g. for patients who are not part of a clinical trial but who are prescribed a drug by their doctor to treat their medical condition).

Sequential treatment: A new treatment started after finishing a previous treatment for the same condition.

Single technology appraisal (STA): Technology appraisal guidance from NICE covering a single drug or treatment for a single indication (e.g. a particular disease or a specified group of people with a particular disease).

Standard deviation: A measure of how much a value deviates from the mean (average).

Subcutaneous injection: An injection given just under the skin (into the fatty layer of tissue) using a short needle.

T-score: A way of reporting BMD. A T-score is defined as the number of standard deviations by which an individual's BMD is above or below the mean (average) BMD of a healthy young adult reference population.

Vertebrae: Spine, backbone.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture [ID882]

Clarification questions

December 2023

File name	Version	Contains confidential information	Date
ID882 abaloparatide_osteoporosis_clarification responses_[redacted]	1.0	Yes	4th December 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searching

A1. In Appendix G.1.3. Eligibility Criteria Table 24 on (page 64): The exclusion criteria includes other indications for osteoporosis treatment. In both PubMed (Table 21, page 56) and Embase (Table 22, page 59), please clarify why the application of exclusion terms for the different indications (statements 2-10 in PubMed and Embase) would not risk losing relevant studies that primarily report about the condition of interest i.e. explicitly mentions (as part of their exclusion criteria) that the primary focus of the treatment is for osteoporosis at the exclusion of the other indications in the abstract.

We cannot dismiss the possibility that some papers would be excluded which report on the population of interest in addition to the other indications. However, this would be limited because co-morbidities were excluded based on MeSH terms. MeSH terms also allow you to locate articles which are specifically about a topic, rather than the topic being mentioned in the article for any reason.[1] In addition, given the large number of hits which were screened (N = 7,489), we propose that we have captured a large set of papers which relate to the research question which were then further screened according to the Population, Intervention, Comparison, Outcomes and Study (PICOS) criteria.

In addition to the PubMed and Embase searches, supplementary measures were employed to avoid exclusion of relevant studies through the latter search strategy. This included exploration of sources such as health technology assessment (HTA) body websites, the International HTA (INAHTA) database, and Clinical Research Data (CRD) databases, as shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (original Company submission, Appendix G.2 Figure 20), and appropriate review of reference lists of relevant systematic literature reviews (SLRs.)

A2. Appendix D.1.5, Table 5: Please clarify the rationale for the date limit of 2012 onwards.

The date limit of 2012 was applied based on the understanding that a 10-year time horizon for a literature search is a reasonable restriction to ensure relevance and applicability of results.

To capture all relevant studies conducted prior to 2012, a pragmatic methodology was employed to update the network meta-analysis (NMA). This involved leveraging two previously published, systematic reviews and economic evaluations by Davis et al. 2016[2] and Davis et al 2020[3]. Studies included in these publications were evaluated based on the PICOS and the de-prioritisation criteria set in the original SLR. These publications provided detailed information from each study on patients' baseline characteristics and fracture-related data.

This information, along with data from the initial SLR (further details in the Appendix, Section B.1.1), was used to gather the necessary data inputs for conducting the updated NMA.

Full details of the updated literature review and NMA are provided in the Appendix, B.1.1 and B.1.2. The updated NMA resolves several initial queries raised by the EAG, including questions A21-A25, B20-22, B24, and B27.

ACTIVE and ACTIVExtend

A3. PRIORITY B.1.3.3, Table 6: Please clarify how far the eligible and included patient population in ACTIVE are similar to or different from the very high-risk populations as

defined in NICE guidance for the relevant comparators with specific reference to prior therapies and prior fractures.

In the Company submission, B.1.3.3 Table 6 outlines the NICE guidance for other available treatment options, including the anabolic agents romosozumab (TA791)[4] and teriparatide (TA161)[5] which are the most relevant comparators for abaloparatide. Both of these treatment options are available regardless of previous lines of therapy, although teriparatide is only recommended for patients who are unable to take alendronate and risedronate, or are intolerant/contraindicated to alendronate and risedronate or have had an unsatisfactory response to alendronate or risedronate and who meet the T-score and fracture risk criteria in Table 1.

Table 1 NICE recommendations for romosozumab and teriparatide[4,5]

Treatment	Recommendation	Further information
Romosozumab	Recommended for patients with severe osteoporosis after menopause who have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (and so are at imminent risk of another fracture).	The recommendation for romosozumab for patients at 'imminent risk' is for a narrower population than the high-risk population specified in the corresponding SmPC.[6] There are no further eligibility criteria regarding T-score applied for romosozumab.
Teriparatide	Recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who: • Are unable to take alendronate and risedronate, or are intolerant/contraindicated to alendronate and risedronate or have had an unsatisfactory	No time periods are stated for fracture history and as for romosozumab, the NICE recommendation for teriparatide applies to a narrower patient population than indicated in the SmPC.[7]

Treatment	Recommendation	Further information
	response to alendronate or risedronate and • Are 65 years or older and have a T-score of ≤–4.0, or a T-score of ≤–3.5 plus more than two fractures, or are aged 55–64 years and have a T-score of ≤–4 plus more than two fractures.	

Abbreviations: NICE, National Institute for Health and Care Excellence; SmPC, summary of product characteristics

As per the licensed indications for romosozumab and teriparatide, the application of abaloparatide is not restricted by prior therapy use and the definition of high risk does not include prior lines of therapy.

The inclusion criteria for ACTIVE[8] (below) are generally aligned with the populations eligible for romosozumab or teriparatide in that they specify postmenopausal women with osteoporosis, with fracture risk considering both T-score and fracture history, in association with age, as follows:

- T-score ≤–2.5 and >–5.0 at the lumbar spine or femoral neck and radiological evidence of ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years[8]
- Women aged >65 years with the above fracture criteria and a T-score ≤–2.0 and >–5.0[8]
- Women aged >65 years who did not meet the fracture criteria who had a T-score ≤–3.0 and >–5.0.[8]

Baseline characteristics of the ACTIVE intent-to-treat (ITT) population are reported in Table 15 of Section B.2.4.4.1 of the original Company submission; the data relevant to the inclusion criteria listed above are summarised in Table 2. Further data regarding prevalent vertebral fractures at baseline are presented in response to Question A8.

Table 2 ACTIVE | Patient baseline demographic and disease characteristics relating to fracture risk inclusion criteria (excluding Sites 131 and 132; ITT population)

Characteristic	ACTIVE		
	Placebo n=688	Abaloparatide n=696	Teriparatide n=686
Age, mean (SD), years	69.3 (6.1)	69.5 (6.3)	69.4 (6.1)
Time since menopause, mean (SD), years	20.6 (7.9)	21.2 (8.1)	20.9 (8.1)
T-score, mean (SD):			
Femoral neck	–2.2 (0.7)	–2.2 (0.6)	–2.2 (0.7)
Total hip	–1.9 (0.8)	–1.9 (0.7)	–1.9 (0.8)
Lumbar spine	–3.0 (0.8)	–2.9 (0.9)	–2.9 (0.9)
≥1 prevalent vertebral fractures, n (%)	149 (21.7)	145 (20.8)	182 (26.5)
≥1 prior nonvertebral fractures, n (%)[a]	302 (43.9)	308 (44.3)	271 (39.5)
No history of prior fracture, n (%)	297 (43.2)	289 (41.5)	289 (42.1)

[a]Assessed based on fractures that occurred prior to visit 3 (study day 1). Excludes fractures of the spine, sternum, patella, toes, fingers, skull and facial bones.
Abbreviations: BMD, bone mineral density; ITT, intention-to-treat; SD, standard deviation.
Sources: ACTIVE CSR addendum[9]; MHRA SmPC[10]; Abaloparatide EPAR[11]

A4. PRIORITY B.2.2 and D.5.1, Fig. 14: Please clarify why sites 131 and 132 were excluded from ACTIVE and ACTIVExtend.

When the ACTIVE and ACTIVExtend data were submitted to the European Medicines Agency (EMA) in 2015, Good Clinical Practice (GCP) concerns were raised regarding two of the study sites (Sites 131 and 132 from the Czech Republic) and the Committee on Human Medicinal Products therefore requested that the data were reanalysed excluding these two sites. The reanalysed datasets were then accepted by the EMA and data from these analyses (rather than the main analyses) are reported in the Summary of Product Characteristics for both the EMA and the UK Medicines and Healthcare Products Regulatory Agency (MHRA).[10–12] The results for the reanalysed datasets for ACTIVE and ACTIVExtend are therefore presented in the submission and are used in all analyses conducted; the results for the original datasets inclusive of the two excluded sites are available in the study publications.[8,13,14]

[redacted]

[redacted]

A5. B.2.3.1.1 and Table 9: Please clarify how many, if any participants in ACTIVE were exposed to prior therapy with a bisphosphonate or other non-bisphosphonate, given the eligibility criteria outlined here, as well as the absence of data on this in the reported baseline characteristics (B.2.4.4, Table 15).

In the ACTIVE trial, patients who have been treated with bisphosphonates, fluoride or strontium in the past five years or who had received prior treatment with gallium nitrate, or with as yet unapproved bone-acting investigational agents at any time were excluded from study participation. Patients treated with a short course of bisphosphonates (three months or less) who were intolerant of the treatment may be considered for study participation. The proportions of patients in the safety population who received prior medication are reported in Table 3.

Table 3 Prior medications, safety population (ACTIVE excluding Sites 131 and 132)[15]

ATC Classification Preferred Term	Placebo (N=687)	Abaloparatide-SC (N=694)	Teriparatide (N=686)
Bisphosphonates	11 (1.6)	5 (0.7)	8 (1.2)
Alendronate sodium	4 (0.6)	4 (0.6)	6 (0.9)
Alendronic acid	2 (0.3)	0	1 (0.1)
Ibandronate sodium	2 (0.3)	1 (0.1)	0
Risedronate sodium	2 (0.3)	0	1 (0.1)
Risedronic acid	1 (0.1)	0	0
Bisphosphonates, combinations	0	0	1 (0.1)
Fosavance	0	0	1 (0.1)
Other drugs affecting bone structure and mineralisation	0	0	2 (0.3)
Denosumab	0	0	2 (0.3)

Abbreviations: ATC, Anatomical Therapeutic Chemical; SC, subcutaneous.

A6. B.2.3.1.2: Please clarify why alendronate was chosen as the bisphosphonate for ACTIVExtend?

Alendronate was chosen for ACTIVExtend as it is the most used oral bisphosphonate available in the study geographic areas. This is supported by the market share data

for the UK which shows alendronate to have [redacted]

In addition, as discussed in a recent NICE appraisal of bisphosphonates (TA464)[17], bisphosphonates are considered to be of similar efficacy within the class. Therefore, we have assumed that alendronate is representative of the bisphosphonate class.[17]

A7. B.2.4.2, Table 12: Please clarify the n=24 patients from D.5.1, Table 16 in the abaloparatide arm who had protocol violations and were therefore designated as non-completers (n=531 in mITT, but overall number of non-completers n=507)

Table 16 in Appendix D.5.1 of the Company submission reports the randomised ITT patient population as n=696, the modified ITT (mITT) patient population as n=583 and the per-protocol patient population as n=531 (who, by definition, do not have protocol violations). The number of patients who completed the study is n=507 is based on the ITT population not the per-protocol or mITT population. Therefore, the number of patients who did not complete the study is n=189. There is no patient population of n=24 who were non-completers.

A8. PRIORITY B.2.4.4.1. Table 15; Please provide information on the % of people having 1, 2 or 3 prevalent vertebral fractures at baseline and information on the severity of vertebral fractures at baseline. We note that the number and severity of vertebral fractures were inclusion criteria so these data should be available.

To supplement the information provided in B.2.4.4.1 (Table 15) of the original Company submission, a breakdown of patients with 1, 2 or >3 prevalent vertebral fractures at baseline and information on the severity of the vertebral fractures is presented in Table **4**.

Table 4 Baseline prevalent vertebral fracture (mITT population, excluding sites 131 and 132)[15]

	Placebo n=600	**Abaloparatide-SC n=583**	**Teriparatide n=600**
Prevalent vertebral fracture, n (%)			
No. of prevalent vertebral fractures			
1	90 (15)	93 (16)	112 (18.7)
2	35 (5.8)	20 (3.4)	37 (6.2)
≥3	9 (1.5)	7 (1.2)	13 (2.2)

	Placebo n=600	Abaloparatide-SC n=583	Teriparatide n=600
Grade of most severe vertebral fracture [1]			
Mild	85 (14.2)	74 (12.7)	92 (15.3)
Moderate	42 (7)	38 (6.5)	54 (9)
Severe	7 (1.2)	8 (1.4)	15 (2.5)
Unknown [2]	(0)	(0)	1 (0.2)

[1] The grade of the most severe vertebral fracture was assessed with the use of the Genant grading scale

[2] One subject had prevalent vertebral fracture, but corresponding Genant score is not available.
Abbreviations: mITT, modified intention-to-treat; SC, subcutaneous.

A9. B.2.5 and Appendix D.1.6: Please clarify the process undertaken for risk of bias assessment (justification for choice of tool, number of reviewers, resolution of disagreements etc.).

The risk of bias (RoB) of the included records was assessed using the criteria for assessment of risk of bias and generalisability in parallel group randomised controlled trials (RCTs) provided in the NICE STA Checklist [PMG24].[18] Each record was assessed against the list of questions outlined in Table 5. The risk of bias assessment was performed by two independent reviewers, and any disagreement was resolved by a third, independent reviewer.

Table 5 Quality assessment results for parallel group RCTs

NICE STA checklist	Assessment
Was randomisation carried out appropriately?	Yes/no/not clear/N/A
Was the concealment of treatment allocation adequate?	Yes/no/not clear/N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes/no/not clear/N/A
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes/no/not clear/N/A
Were there any unexpected imbalances in drop-outs between groups?	Yes/no/not clear/N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes/no/not clear/N/A
Did the analysis include an intention-to-treat analysis?	Yes/no/not clear/N/A
If ITT analysis was included, was this appropriate and were appropriate methods used to account for missing data?	Yes/no/not clear/N/A

Abbreviations: ITT, intention-to-treat analysis; N/A, not applicable; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; STA, single technology appraisal.

A10. B.2.5, Table 18: Please clarify the reasoning and data to support the following judgements:

- No unexpected imbalances in drop-outs between groups; No baseline or comparative data are presented on the completers and non-completers in ACTIVE.

- No evidence to suggest that the authors measured more outcomes than they reported.

There was a misunderstanding in answering the checklist question in the original Company submission regarding unexpected imbalances in the drop-outs between the groups. The original answer referred to similar reasons for drop outs, reported in Figure 1 of Miller et al. 2016.[8] However, the numbers of drop-outs between trial arms does differ, with 218, 184 and 160 patients lost to follow up for the abaloparatide, placebo and teriparatide arms, respectively.

The Miller et al. 2016[8] publication presented results on primary, secondary and exploratory outcomes as well as safety endpoints. The protocol and statistical analysis plan (SAP) were also published as supplementary information which corresponded to those outcomes in the primary publication. Therefore, we support the conclusion that the authors did not measure more outcomes than they reported.

The bias checklist has been conducted on the ACTIVE (see Appendix B.1.5.2) and ACTIVExtend addendum clinical study reports (CSRs) which report the restricted dataset (data for sites excluding sites 131 and 132) presented in this submission.

A11. Please clarify the overall assessment of the risk of bias affecting ACTIVE. Currently the statement with regard to this concerns only some domains: B.2.9.2: 'Overall, the included study for abaloparatide (ACTIVE, excluding Sites 131 and 132) was judged to pose a low risk of bias concerning randomisation, baseline characteristics, and statistical methodology'.

The ACTIVE study was judged to contain a low risk of bias based on the assessment of risk of bias using the questions suggested by NICE (NICE STA Checklist), as described in response to question A9 above. It was an oversight that the additional domains were not mentioned in the original Company submission. To clarify this point,

an updated statement is provided statement as follows: 'Overall, the included study for abaloparatide (ACTIVE) was judged to pose a low risk of bias concerning domains pertaining to randomisation, blinding and allocation concealment, baseline characteristics, measurement of outcomes, missing outcome data, and statistical methodology. An ITT analysis was performed, and a logistic regression model was used to augment the data set by imputing the missing outcome multiple times.

A12. Please clarify if the risk of bias assessment concerned only ACTIVE or ACTIVExtend also.

To clarify, Table 18 presented in the original Company submission does pertain only to ACTIVE, using Miller et al. 2016.[8] The risk of bias assessment for studies reporting ACTIVExtend were presented in the embedded excel file in Appendix D.4 of the original submission. The assessment for the publications relating to ACTIVExtend is presented in Table **6** below:

Table 6 Risk of bias assessment for ACTIVExtend publications

NICE STA checklist	Cosman et al 2017[13]	Bone et al 2018[14]
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	No	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Not clear	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis?	Yes	Yes
If ITT analysis was included, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Abbreviations: ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; STA, Single Technology Appraisal

The bias checklist has also been conducted on the ACTIVExtend addendum CSR[19] which reports the restricted dataset (data for sites excluding sites 131 and 132) presented in Table 7.

Table 7 Risk of bias assessment for ACTIVExtend addendum CSR[19]

NICE STA checklist	ACTIVExtend addendum CSR
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	No†
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No‡
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis?	Yes
If ITT analysis was included, was this appropriate and were appropriate methods used to account for missing data?	Yes

Abbreviations: CSR, clinical study report; ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; STA, Single Technology Appraisal
† The ACTIVExtend was an open-label extension study
‡ Patients and investigators remained blinded to prior treatment assignment until all patients completed the first six months of ACTIVExtend

A13. D.5.1: Fig, 14: Please clarify the following numbers and descriptions: 'screened and not randomized, n=41'; and why three patients were randomized but excluded from the safety population.

An additional 41 patients were screened but not randomised due to randomisation being stopped (n=39), and serious adverse event (n=1) and reason missing (n=1).[9] The SAE was a fracture of the left femoral neck which occurred prior to randomisation.[9] The reasons that three patients were excluded from the safety population are: refusal of treatment (n=1) and withdrawal of consent (n=2).[15]

A14. D.5.1: Please provide complete lists of numbers in brackets [] and abbreviations for Fig.14 and Tables 16 and 17.

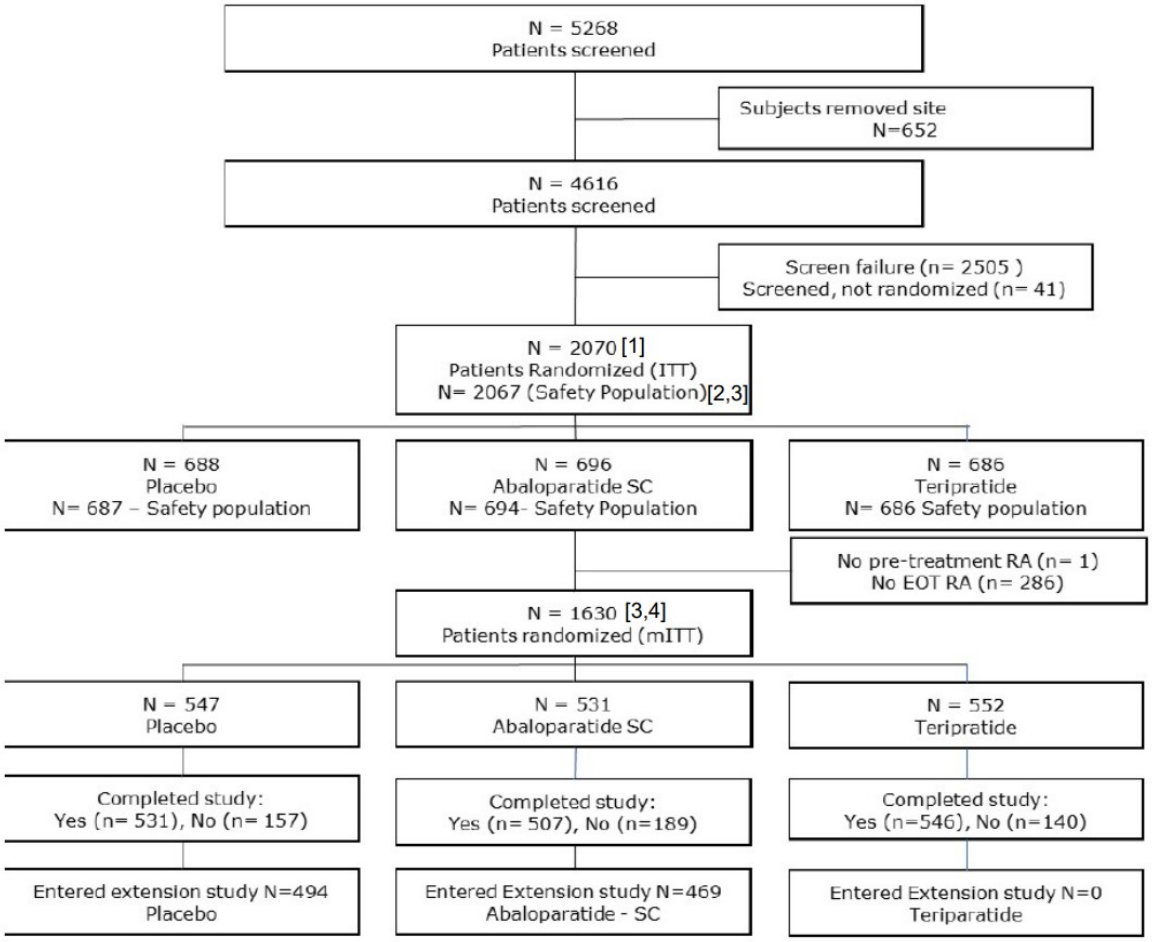
Please find the additional details for the footnotes for Table 16 and 17 and Figure 14 from the Company submission in Table 8.

Table 8 Additional details for footnotes for Tables 16 and 17 and Figure 14

Table/figure in CS	Missing footnotes	Full abbreviations
Figure 14	See annotations on figure below: [1] Includes all patients who were randomized into the study by assigning the randomized study medication kit on Day 1. [2] Includes all randomized patients who received 1 or more doses of study medication. [3] Percentages based on number randomized. [4] Includes all ITT patients who had both the pre-treatment and a post-baseline evaluable radiologic assessment (spine X-ray). [5] Includes all mITT patients who did not have protocol violations as defined in the Statistical Analysis Plan.	EOT, end of treatment; CSR, clinical study report; ITT, intention-to-treat; mITT, modified intention-to-treat; RA, radiological assessment; SC, subcutaneous
Table 16	This table is part of a larger disposition table in the source document (clinical study report), which was presented as a figure and two tables in the CS. There are no footnotes missing, however, [3], [6–8] should have been labelled as 1–4 to avoid confusion.	BMD, bone mineral density; CRF, case report form; CSR, clinical study report; SAE, serious adverse event; SC, subcutaneous
Table 17	[1] Includes all patients who were randomized into the study by assigning the randomized study medication kit on Day 1. [2] Includes all randomized patients who received 1 or more doses of study medication. [3] Percentages based on number randomized. [4] Includes all ITT patients who had both the pre-treatment and a post-baseline evaluable radiologic assessment (spine X-ray). [5] Includes all mITT patients who did not have protocol violations as defined in the Statistical Analysis Plan. [6] Study completion as indicated by the investigator on the End of Study CRF.	CRF, case report form; CSR, clinical study report; ITT, intention-to-treat; mITT, modified intention-to-treat; SC, subcutaneous; SAE, serious adverse event

Abbreviations: CRF, case report form; CS; Company submission ITT, intention-to-treat; mITT, modified intention to-treat

Figure 1 Patient disposition (excluding Sites 131 and 132)



Abbreviations: EOT, end of treatment; CSR, clinical study report; ITT, intention-to-treat; mITT, modified intention-to-treat; RA, radiological assessment; SC, subcutaneous
Source: Abaloparatide EPAR[11]; ACTIVE CSR addendum[9]

A15. D.5.1: Please clarify the number for the mITT population: Table 17 mITT n=583, but in Fig 14 mITT n=531; Table 17 PP analysis n=531.

The mITT population for the abaloparatide arm is n=583. There was an error in the graphical representation of patient disposition shown in the original submission.

A16. Table 19: Please clarify why hazard ratios (HR)'s presented in Table 19 for secondary and exploratory outcomes but relative risk reductions (RRR)s are presented for the primary outcome?

The secondary and exploratory endpoints are cumulative and could be reported at any time during the study. To evaluate the treatment difference in both incidence and the time-to-event perspectives, the Cox proportional hazard model was used to calculate

the hazard ratio (HR). The primary endpoint was evaluated only at Visit 1 and Visit 9; therefore, Cox proportional hazard model could not be used and relative risk reduction (RRR) was the most appropriate way to report differences in treatment arms.

Real world evidence

A17. B.2.2: Please clarify how the RWE study (Cosman 2022, reference #62) was identified (it is not listed in the results of the SLR search, Appendix D.3.1, Table 6).

The clinical SLR focused on RCTs, therefore, the real-world evidence (RWE) study was not identified. The manufacturer/marketing authorisation holder sponsored the study and provided the details to the Company.

A18. The inclusion criteria for the RWE study are described as patients with "≥1 prescription" in some places in the CS (Doc B Table 8 and Appendix D Table 20) and "≥1 new prescription" elsewhere in the CS (Doc B pages 46 and 56). Please clarify if the index date is for the first prescription of either abaloparatide or teriparatide in the identification period. Please clarify if patients were excluded if they had a prescription for either anabolic therapy in the 5 year pre-index period or just prior usage of the anabolic prescribed at the index date. Please also clarify why patients were required to have "≥1 claim for a medical or hospital visit, and a pharmacy claim in the 12 months before the index date" (CS, page 46).

- The inclusion criteria for the RWE study presented in Table 8 is '≥1 prescription and no prior anabolic therapy' which can be read as the same as '≥1 new prescription fill for teriparatide or abaloparatide' (Company submission p46 and p56) as these were the only anabolic therapies available at the time that the study was recruiting.

- We can clarify that the index date is for the first prescription of either abaloparatide or teriparatide in the identification period.

- We clarify that patients were excluded if they had a prescription for either anabolic therapy at any time in the pre-index period. This period could be up to seven years depending on the index date.

- Patients were required to have ≥1 claim for a medical or hospital visit, and a pharmacy claim in the 12 months before the index date to ensure that the patients were covered in the database. In addition, it is an indicator for patients who have been continuously registered in the data source.

Indirect treatment comparison

A19. PRIORITY Section B.2.9.1. It is stated that, “from an initial pool of 1,743 deduplicated studies, a total of 33 studies were found to be eligible for the NMA.” It is later stated in Section B.2.9.3., “of the 33 studies included in the feasibility assessment, only seven studies were included in the NMA”. However, description of the clinical SLR in Appendix D shows 60 studies being included from the 1743 studies screened. 60 studies are then included in D.3.1, Table 6. Please clarify how the 60 records included in the clinical SLR (Appendix D, Figure 1) were reduced to give the 33 studies described as being included in the feasibility assessment in section B.2.9.3. Please also clarify whether the N=60 and N=33 are referring to studies or records.

The process of reducing 60 records to 33 records for the feasibility assessment is described below:

- The reduction from 60 records to 33 involved applying specific PICOS criteria for the NMA (Table 9).

A de-prioritisation stage for final selection for the NMA was then conducted (33 to seven records [Table 10]):

- **Sample size:** Excluded studies with fewer than 200 participants to focus on those with greater statistical power.
- **Geographic location:** Selected studies included North American or Western European populations to ensure relevance and applicability for the UK.
- **Outcomes:** Focused on articles mentioning fracture risk or bone mineral density (BMD), aligning with key research outcomes, and exclude papers which focussed only on safety outcomes.

This stage refined the pool of records to those most relevant and of sufficient quality for the NMA.

- Out of the 33 records considered in the feasibility assessment, only seven records representing six studies were ultimately included in the NMA (Table 11).
- This involved further assessment of the direct applicability and methodological soundness of the studies.

In this process, "N=60" and "N=33" refer to the number of records at each stage of the selection process.

Overall, while NICE methods do not explicitly discuss de-prioritisation criteria, our approach is consistent with the broader principles of ensuring relevance, quality, and applicability in NMAs. It demonstrates a systematic and transparent method for refining the study selection to enhance the validity and reliability of the NMA findings.

Based on the feedback from the EAG in question A25, the NMA has been updated to allow the incorporation of studies with different time durations, pre-2012 publications and where the relative treatment effects are modelled as HRs, rather than RR as in original NMA submitted to NICE. Furthermore, studies which reported fracture data as safety outcomes were also included in the updated NMA, as requested (Appendix B.1.2).

Table 9 Eligibility criteria for inclusion in the NMA

Domains	Eligibility Criteria
Population	Postmenopausal women with osteoporosis at increased risk of fracture
Intervention	Abaloparatide Abaloparatide followed by alendronate
Comparators	Bisphosphonates: Alendronic acid, ibandronic acid, risedronate sodium, zoledronic acid Non-bisphosphonates: Denosumab, romosozumab, teriparatide, raloxifene No active treatment/ placebo
Outcomes	Efficacy outcomes: new vertebral fracture worsening vertebral fracture new or worsening vertebral fracture non-vertebral fracture

Domains	Eligibility Criteria
	clinical fracture hip fracture major osteoporotic fracture fractures in other bones/regions
Study design	Studies following parallel RCT design (triple/double-blind), also including: cross-over and open-label extensions of studies if the core studies were parallel group RCTs.
Language	English language records only
Time points	12, 18, 24 and 36 months

Abbreviations: NMA, Network meta-analysis; RCT, randomised controlled trial

Table 10 De-prioritisation criteria for the NMA

Criteria	Description
Sample size	Exclude studies with a sample size less than 200 (n<200)
Geographic location	Exclude studies that at least have not included North America or Western Europe
Language	Only include articles written in English language
Outcomes	Exclude articles with no mention of fracture risk or bone mineral density (BMD)
Additional criteria: Study setting	In case further restrictions are needed to be applied: Exclude single-centre studies

Abbreviations: BMD, bone mineral density; NMA, network meta-analysis

A20. PRIORITY B. 2.9.3: The PRISMA flow diagrams (Figure 17 in this section and elsewhere such as Appendix D.2, Fig.1) use the terms 'records' and 'studies' interchangeably, but these are not always the same thing. The final number of 'studies' used in the NMA was n=7. How many of the 60 records did this represent?

In the Company submission, the phrase 'the final number of studies included in the NMA was n=7' was inaccurate and should have been phrased as 'the final number of records included in the NMA was n=7', representing 6 studies.' Table 11 presents the seven records/six studies included in the original NMA.

Table 11 Records included in the original NMA

Trial name	Treatment
ACTIVE (excluding Sites 131 and 132)[9]	Placebo Abaloparatide Teriparatide
FRAME (Cosman et al. 2016)[20]	Placebo Romosozumab
NR (Hadji et al. 2012)[21]	Teriparatide Risedronate

ARCH (Saag et al. 2017)[22]	Alendronate Romosozumab
FREEDOM (Bone at al. 2017)[23]	Placebo Denosumab
FREEDOM and FREEDOM extension (Papapoulous 2015)[24]	Long-term treatment with denosumab
VERO (Kendler et al. 2018)[25]	Teriparatide Risedronate

Abbreviations: NMA, network meta-analysis

A21. B.2.9.3: 17 studies were excluded from the NMA because data were not available at the predetermined time point of assessment. CS, Page 82 states, "Studies without fracture outcomes data at 12, 18, 24, and 36 months were excluded under 'data unavailable in predetermined time-point of assessment." However, Table 23 specifying outcomes for the NMA only describes fracture outcomes at 12 and 19 months and NMA are only presented in the CS for these times points. This suggests that studies reporting data only at 24 or 36 months were excluded. In addition, the STRUCTURE study which contributed non-vertebral fracture data at 12 months in the review by Davis et al. (2020) appears to have been excluded. Please clarify if studies had to report data at 18 months to be included in the NMA.

In the original NMA, the outcomes were analysed at two time-points of 12 months and 18 months. Studies did not need to report data at 18 months to be included. However, due to scarcity of data reporting fracture outcomes, studies reporting data at 12±2 months were included in 12 months' time-point and 18±2 months in 18 months' time-point for conducting the analysis. The feasibility was also assessed at 24 and 36 months. Analysis was not feasible at 24 and 36 months due to a disconnected network for all outcomes due to a lack of a common sequential treatment. The NMA has been updated to allow the incorporation of studies with different time durations, pre-2012 publications and where the relative treatment effects are modelled as HR.

The STRUCTURE study[26] was excluded from the original NMA as studies had to report fractures from pre-specified efficacy outcomes. The STRUCTURE study included non-vertebral fracture data at 12 months, however, this was captured as a safety outcome, and was therefore excluded from the original NMA. In response to feedback from the EAG this study is included in the updated SLR/NMA. See Appendix Section B.1.1 and B.1.2.

A22. CS, Figure 18: The network of evidence presented in Figure 18 is much more restrictive than the networks identified by Davis et al (2020) in their review of non-bisphosphonate treatments for osteoporosis. Some studies listed in Table 3 of Davis et al. (2020) would appear to potentially provide additional links and cross-links to the network in CS, Figure 18. For example, the STRUCTURE study (Langdahl 2017) compared romosozumab to teriparatide, and is listed as included study number 15 in Appendix D, Table 6 of the CS, but does not contribute to the non-vertebral fracture network, whereas it did contribute to this network in Davis et al. (2020). In addition, Cosman 2011 comparing teriparatide to zoledronate does not appear in Appendix D, Table 6 of the CS, but it is unclear why this is the case as it contributed to the NMAs in Davis 2020. For each study included in Appendix D, Table 6 of the CS, that did not contribute to the NMA, please provide a reason why they did not contribute. For any additional studies featuring in Table 3 of Davis et al. (2020), that do not feature in Appendix D, Table 6 of the CS, please also provide a reason why they were excluded from the NMA.

Table 12 presents the screening of the 60 records included in the clinical SLR against the PICOS for inclusion in the original NMA (see Table 9 for these criteria). Table 13 presents the screening of studies from Table 3 of Davis et al 2020[3] against the PICOS for inclusion in the original NMA and updated. The NMA has been updated to allow the incorporation of studies with different time durations, pre-2012 publications and where the relative treatment effects are modelled as hazard ratios. Full details of the updated SLR/NMA are presented in Appendix, Section B.1.1 and Section B.1.2. The full list of included studies for the updated NMA is presented in Section B.1.5.3.1 Table 8 in the Appendix.

Table 12 Records included in the original clinical SLR and the reasons for exclusion from the original NMA

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the original NMA submitted to NICE
1.	Bilezikian JP, 2019, FREEDOM Extension; NCT00523341	Long-term denosumab treatment restores cortical bone loss and reduces fracture risk at the forearm and humerus: analyses from the FREEDOM Extension cross-over group.	Osteoporos Int. 2019 Sep;30(9):1855-1864	The study does not report data on the required month.
2.	Black, 2012, HORIZON-PFT Extension (E1); NCT00145327	The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-pivotal fracture trial (PFT)	J Bone Miner Res. 2012 Feb;27(2):243-54.	The study does not report data on the required month.
3.	Bone, 2013, FREEDOM Extension; NCT00523341	The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: Results from the FREEDOM extension	J Clin Endocrinol Metab. 2013 Nov;98(11):4483-92.	The study does not report data on the required month.
4.	Bone, 2017, FREEDOM and FREEDOM extension; NCT00089791 and NCT00523341	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 Jul;5(7):513-523.	Included.
5.	Ferrari, 2015, FREEDOM Extension; NCT00523341	Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years	Osteoporos Int. 2015 Dec;26(12):2763-71	The study does not report data on the required month.
6.	McClung, 2013, NR	Treatment of postmenopausal osteoporosis with delayed-release risedronate 35 mg weekly for 2 years	Osteoporos Int. 2013 Jan;24(1):301-10	The study does not report data on the required month.
7.	Roux, 2014, NR, NR	Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: Efficacy and safety results from a randomized open-label study	Bone. 2014 Jan;58:48-54.	The study does not report data on the required month.
8.	Ferrari, 2019, FREEDOM Extension; NCT00523341	Further nonvertebral fracture reduction beyond 3 years for up to 10 years of denosumab treatment	J Clin Endocrinol Metab. 2019 Aug 1;104(8):3450-3461	The study does not report data on the required month.
9.	Bianchi, 2012, DIVA LTE; NCT00048074	Long-term administration of quarterly IV ibandronate is effective and well tolerated in postmenopausal osteoporosis: 5-year data from the DIVA study long-term extension	Osteoporos Int. 2012 Jun;23(6):1769-78.	The study does not report data on the required month.

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the original NMA submitted to NICE
10.	Bone, 2018, ACTIVExtend; NCT01657162	ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis	J Clin Endocrinol Metab. 2018 Aug 1;103(8):2949-2957.	Data for the ACTIVExtend trials are taken from the CSR addendum.
11.	Bolognese, 2013, FREEDOM; NCT00089791	Denosumab significantly increases DXA BMD at both trabecular and cortical sites: Results from the FREEDOM study	J Clin Densitom. 2013 Apr-Jun;16(2):147-53	The study does not report data on the required month.
12.	Cosman, 2016, FRAME; NCT01575834	Romosozumab treatment in postmenopausal women with osteoporosis	N Engl J Med. 2016 Oct 20;375(16):1532-1543.	Included.
13.	Cosman, 2017, ACTIVExtend; NCT01657162	Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: Results of the ACTIVExtend trial	Mayo Clin Proc. 2017 Feb;92(2):200-210.	The study does not report data on the required month.
14	Deal, 2019, ACTIVExtend; NCT01657162	Response rates for hip, femoral neck, and lumbar spine bone mineral density in patients treated with abaloparatide followed by alendronate: Results from phase 3 ACTIVExtend	Bone Rep. 2019 Nov 2;11:100230.	Data for the ACTIVExtend trial are taken from the CSR addendum.
15.	Langdahl, 2017, STRUCTURE; NCT01796301	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 Sep 30;390(10102):1585-1594.	The study does not report fractures as efficacy outcomes but reports as safety outcomes.
16.	Geusens, 2018, VERO; NCT01709110	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 May;33(5):783-794	The study does not report data on the required month.
17.	McClung, 2013, NR; NCT00358176	A novel monthly dosing regimen of risedronate for the treatment of postmenopausal osteoporosis: 2-Year data	Calcif Tissue Int. 2013 Jan;92(1):59-67.	The study does not report data on the required month.
18.	Papapoulos, 2012, FREEDOM Extension; NCT00523341	Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension	J Bone Miner Res. 2012 Mar;27(3):694-701	The study does not report data on the required month.
19.	McClung, 2012, NR; NCT00541658	Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet	Osteoporos Int. 2012 Jan;23(1):267-76	The study does not report data on the required month.

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the original NMA submitted to NICE
20.	McClung, 2013, NR; NCT00247273	Efficacy and safety of risedronate 150-mg once a month in the treatment of postmenopausal osteoporosis: 2-year data	Osteoporos Int. 2013 Jan;24(1):293-9	The study does not report data on the required month.
21.	Hadji, 2012, NR; NR	The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures	Osteoporos Int. 2012 Aug;23(8):2141-50	Included.
22.	Lewiecki, 2019, FRAME Extension Study; NCT01575834	One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: Results of the FRAME extension study	J Bone Miner Res. 2019 Mar;34(3):419-428	The study involves sequential treatment which makes a disconnected network.
23.	Miller, 2016, NR; NCT01732770	Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates	J Clin Endocrinol Metab. 2016 Aug;101(8):3163-70	The study does not report data on the required month.
24.	Miller, 2019, ACTIVE; NCT01343004	Bone mineral density response rates are greater in patients treated with abaloparatide compared with those treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial	Bone. 2019 Mar;120:137-140	Data from the ACTIVE trial are taken from the CSR addendum.
25.	Miller, 2016, ACTIVE; NCT01343004	Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis a randomized clinical trial	JAMA. 2016 Aug 16;316(7):722-33	Data from the ACTIVE trial are taken from the CSR addendum.
26.	Miller, 2012, MOBILE LTE, NR	Efficacy of monthly oral ibandronate is sustained over 5 years: the MOBILE long-term extension study	Osteoporos Int. 2012 Jun;23(6):1747-56	The study does not report data on the required month.
27.	Kendler, 2018, VERO; NCT01709110	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	Lancet. 2018 Jan 20;391(10117):230-240	Included.
28.	Leder, 2019, ACTIVExtend; NCT01657162	Fracture and bone mineral density response by baseline risk in patients treated with abaloparatide followed by alendronate: Results from the Phase 3 ACTIVExtend trial	J Bone Miner Res. 2019 Dec;34(12):2213-2219	Data for the ACTIVE Extend are taken from the CSR addendum.
29	Leder, 2015, NR; NCT00542425	Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis	J Clin Endocrinol Metab. 2015 Feb;100(2):697-706	The study does not report data on the required month.

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the original NMA submitted to NICE
30.	Papapoulos, 2015, FREEDOM and FREEDOM Extension; NCT00089791 and NCT00523341	The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study	Osteoporos Int. 2015 Dec;26(12):2773-83	Included.
31.	Saag, 2017, ARCH; NCT01631214	Romosozumab or alendronate for fracture prevention in women with osteoporosis	N Engl J Med. 2017 Oct 12;377(15):1417-1427	Included.
32.	NA, NR; NCT03974100	Study investigating PK, PD, efficacy, safety, and immunogenicity of biosimilar denosumab (GP2411) in patients with postmenopausal osteoporosis	NA	The study does not report data on the required month.
33.	NA, wearable; NCT0406441	Efficacy & safety of abaloparatide-solid microstructured transdermal system in postmenopausal women with osteoporosis	NA	The study does not report data on the required month.
34.	Black, 2015, HORIZON-PFT Second Extension (E2); NCT00718861	The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: A randomized second extension to the horizon-pivotal fracture trial (PFT)	J Bone Miner Res. 2015 May;30(5):934-44.	Deprioritized: sample size <200
35.	Mochizuki, 2023, NR; NR	Comparison of romosozumab versus denosumab treatment on bone mineral density after 1 year in rheumatoid arthritis patients with severe osteoporosis: A randomized clinical pilot study	Mod Rheumatol. 2023 Apr 13;33(3):490-495	Deprioritized: did not include population from N America/ W Europe
36.	Bai, 2013, NR; NR	Randomized controlled trial of zoledronic acid for treatment of osteoporosis in women	J Int Med Res. 2013 Jun;41(3):697-704	Deprioritized: did not include population from N America/ W Europe
37.	Chiba, 2022, TERABIT; NR	Randomized controlled trial of daily teriparatide, weekly high-dose teriparatide, or bisphosphonate in patients with postmenopausal osteoporosis: The TERABIT study	Bone. 2022 Jul;160:116416.	Deprioritized: did not include population from N America/ W Europe
38.	Cosman, 2015, NR; NR	Daily or cyclical teriparatide treatment in women with osteoporosis on no prior therapy and women on alendronate	J Clin Endocrinol Metab. 2015 Jul;100(7):2769-76	Deprioritized: sample size <200

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the original NMA submitted to NICE
39.	Das, 2022, NR; NR	Effect of subcutaneous administration of denosumab in postmenopausal osteoporosis	EJMCM; 9(3), 2529-2536	Deprioritized: did not include population from N America/ W Europe
40.	Dempster, 2016, SHOTZ; NCT00927186	A longitudinal study of skeletal histomorphometry at 6 and 24 months across four bone envelopes in postmenopausal women with osteoporosis receiving teriparatide or zoledronic acid in the SHOTZ trial	J Bone Miner Res. 2016 Jul;31(7):1429-39	Deprioritized: sample size <200
41.	Gu, 2023, NR; NCT05060406	Denosumab biosimilar (LY06006) in Chinese postmenopausal osteoporotic women: A randomized, double-blind, placebo-controlled, multicenter phase III study	Orthop Translat. 2022 Oct 29;38:117-125	Deprioritized: did not include population from N America/ W Europe
42.	Ishibashi, 2017, NR; NCT01992159	Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study	Bone. 2017 Oct;103:209-215	Deprioritized: did not include population from N America/ W Europe
43.	Kobayakawa, 2022, VICTOR study; NR	Verification of efficacy and safety of ibandronate or denosumab for postmenopausal osteoporosis after 12-month treatment with romosozumab as sequential therapy: The prospective VICTOR study	Bone. 2022 Sep;162:116480	Deprioritized: did not include population from N America/ W Europe
44.	Koh, 2016, NR; NCT01457950	Assessment of Denosumab in Korean Postmenopausal Women with Osteoporosis: Randomized, Double-Blind, Placebo-Controlled Trial with Open-Label Extension	Yonsei Med J. 2016 Jul;57(4):905-14	Deprioritized: did not include population from N America/ W Europe
45.	Li, 2022, NR; NR	Efficacy of generic teriparatide and alendronate in Chinese postmenopausal women with osteoporosis: a prospective study	Arch Osteoporos. 2022 Jul 28;17(1):103	Deprioritized: did not include population from N America/ W Europe
46.	Liang, 2017, NR; NR	Intravenous Zoledronic Acid 5 mg on Bone Turnover Markers and Bone Mineral Density in East China Subjects with Newly Diagnosed Osteoporosis: A 24-month Clinical Study	Orthop Surg. 2017 Feb;9(1):103-109	Deprioritized: did not include population from N America/ W Europe
47.	Matsumoto, 2022, ACTIVE-J Study; NR	Abaloparatide Increases Lumbar Spine and Hip BMD in Japanese Patients With Osteoporosis: The Phase 3 ACTIVE-J Study	J Clin Endocrinol Metab. 2022 Sep 28;107(10):e4222-e4231	Deprioritized: did not include population from N America/ W Europe

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the original NMA submitted to NICE
48.	Nakamura, 2012, NR; NR	Dose–response study of denosumab on bone mineral density and bone turnover markers in Japanese postmenopausal women with osteoporosis	Osteoporos Int. 2012 Mar;23(3):1131-40	Deprioritized: did not include population from N America/ W Europe
49.	Paggiosi, 2014, TRIO study; NCT00666627	Comparison of the effects of three oral bisphosphonate therapies on the peripheral skeleton in postmenopausal osteoporosis: the TRIO study	Osteoporos Int. 2014 Dec;25(12):2729-41	Deprioritized: sample size <200
50.	Popp, 2014, HORIZON; NCT00049829	Cortical bone loss at the tibia in postmenopausal women with osteoporosis is associated with incident non-vertebral fractures: Results of a randomized controlled ancillary study of HORIZON	Maturitas. 2014 Mar;77(3):287-93	Deprioritized: sample size <200
51.	Shi, 2017, NR; NR	Effect of Traditional Chinese Medicine Product, QiangGuYin, on Bone Mineral Density and Bone Turnover in Chinese Postmenopausal Osteoporosis	Evid Based Complement Alternat Med. 2017;2017:6062707	Deprioritized: did not include population from N America/ W Europe
52.	Tan, 2016, NR; NR	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 Oct;41(5):519-23	Deprioritized: did not include population from N America/ W Europe
53	Yang, 2015, NR; NR	Effect of zoledronic acid on vertebral marrow adiposity in postmenopausal osteoporosis assessed by MR spectroscopy	Skeletal Radiol. 2015 Oct;44(10):1499-505	Deprioritized: did not include population from N America/ W Europe
54.	Zhang, 2023, NR; NCT04128163	A phase III randomized, double-blind, placebo-controlled trial of the denosumab biosimilar QL1206 in postmenopausal Chinese women with osteoporosis and high fracture risk	Acta Pharmacol Sin. 2023 Feb;44(2):446-453	Deprioritized: did not include population from N America/ W Europe
55.	Zhou, 2019, NR; NR	Effects of zoledronic acid on bone mineral density around prostheses and bone metabolism markers after primary total hip arthroplasty in females with postmenopausal osteoporosis	Osteoporos Int. 2019 Aug;30(8):1581-1589	Deprioritized: did not include population from N America/ W Europe
56.	Mochizuki, 2023, NR; NR	Comparison of different parameters between daily and twice-weekly teriparatide in postmenopausal women with severe osteoporosis	J Bone Miner Metab. 2023 Mar;41(2):220-226	Deprioritized: did not include population from N America/ W Europe
57	NA, NR; NCT00718861	A 3-year, multicenter, double-blind, randomized, placebo-controlled extension to CZOL446H2301E1 to evaluate the	NA	Deprioritized: sample size <200

No.	Author, year, trial name, NCT number	Title	Journal; volume, page number	Reason for exclusion from the original NMA submitted to NICE
		efficacy and long term safety of 6 and 9 years zoledronic acid treatment of postmenopausal women with osteoporosis		
58.	NA, NR; NCT02014467	A twelve-month randomized, double-blind, placebo controlled, parallel-group, multicenter study to evaluate the efficacy and safety of denosumab in Chinese postmenopausal women with osteoporosis at increased risk of fracture	NA	Deprioritized: did not include population from N America/ W Europe
59.	Greenspan, 2015, ZEST Study; NCT0055801	Efficacy and safety of single dose zoledronic acid for osteoporosis in frail seniors: a randomized clinical trial	JAMA Intern Med. 2015 Jun;175(6):913-21	Deprioritized: sample size <200
60.	Nakamura, 2012, TOWER; NR	Randomized teriparatide [human parathyroid hormone (PTH) 1–34] once-weekly efficacy research (TOWER) Trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk	J Clin Endocrinol Metab. 2012 Sep;97(9):3097-106	Deprioritized: did not include population from N America/ W Europe

Abbreviations: BMD, bone mineral density; CSR, clinical study report; DXA, dual-energy X-ray absorptiometry; EJMCM, European Journal of Molecular and Clinical Medicine; IV, intravenous; JAMA, Journal of the American Medical Association; LTE, long-term extension; N, north; NA, not applicable; NCT, National Clinical Trials; NMA, network meta-analysis; NR, not reported; PD, pharmacodynamic; PK, pharmacokinetic; W, western

Table 13 Studies from Davis et al 2020 and reasons for exclusion from the original NMA

Reference number in Davis et al 2020	Study Acronym / NCT / identifier	Reason for exclusion from the original NMA submitted to NICE
41	Cummings 2009 (FREEDOM)	Published before 2012
42	Orwoll 2012 (ADAMO)	Men with osteoporosis
43	Nakamura 2014 (Direct)	Mixed population (Japanese subjects with osteoporosis including postmenopausal women and men aged 50 years or older were eligible for the study)
44	Nakamura 2012	Deprioritized: did not include population from N America/ W Europe
45	Koh 2016	Deprioritized: did not include population from N America/ W Europe
46	Adami 2008	Published before 2012
47	Morii 2003	Published before 2012
48	Liu 2004	Published before 2012
49	Gorai 2012	Deprioritized: did not include population from N America/ W Europe
50	Silverman 2008	Published before 2012
51	Ettinger 1999 (MORE)	Published before 2012
52	Lufkin 1998	Published before 2012
53	Mok 2011	Published before 2012
54	Cosman 2016 (FRAME)	Included
55	Ishibashi 2017	Deprioritized: did not include population from N America/ W Europe
56	Lewiecki 2018 (BRIDGE)	Excluded from the updated NMA because no HR data of fracture outcomes
57	Orwoll 2003	Published before 2012
58	Miyauchi 2010	Published before 2012
59	Miyauchi 2008	Published before 2012
60	ACTIVE	Data from the ACTIVE trial are taken from the CSR addendum
61	Leder 2015	Excluded from the updated NMA because no HR data of fracture outcomes
62	Neer 2001 (FPT)	Published before 2012
63	Sethi 2008	Published before 2012
64	DATA (Tsai 2013)	Mixed population. Women at high fracture risk, defined as a BMD T-score ≤−2.5 at the spine, hip, or FN; a T-score ≤−2.0 with at least 1 BMD-independent risk factor (fracture after age 50, parental hip fracture after age 50, prior hyperthyroidism, inability to rise from a chair with arms elevated, or current smoking), or a score ≤−1.0 with a history of a fragility fracture were included. Otherwise, BMD changes have been recorded.
65	Leder, 2015 (DATA-Switch)	Mixed population. Women at high fracture risk, defined as a BMD T-score ≤−2.5 at the

Reference number in Davis et al 2020	Study Acronym / NCT / identifier	Reason for exclusion from the original NMA submitted to NICE
		spine, hip, or FN; a T-score ≤−2.0 with at least 1 BMD-independent risk factor (fracture after age 50, parental hip fracture after age 50, prior hyperthyroidism, inability to rise from a chair with arms elevated, or current smoking), or a score ≤−1.0 with a history of a fragility fracture were included. Otherwise BMD changes have been recorded.
66	Eastell, 2009, EUROFORS (2009)	Published before 2012
67	Langdahl 2017 (STRUCTURE)	Fractures reported as safety outcome, not efficacy outcome
68	McClung 2014	Mixed population (Ambulatory postmenopausal women, 55 to 85 years of age, were eligible if they had low BMD (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 the three sites).
69	DECIDE (2009)	Published before 2012
70	STAND (2010)	Published before 2012
71	DAPS (2011)	Published before 2012
72	AMG 162 Bone Loss (2006)	Published before 2012
73	Recknor 2013	Mixed population (Postmenopausal women aged 55 with a BMD T-score of -2 or less and -4 or greater at the total hip or lumbar spine determined at the local site)
74	Saag 2018	Glucocorticoid-induced osteoporosis
75	Miller 2016	Excluded from the updated NMA because no HR data of fracture outcomes
76	EFFECT (Intl) (2004)	Published before 2012
77	EFFECT (USA) (2004)	Published before 2012
78	Johnell 2002	Published before 2012
79	Muscoso 2004	Published before 2012
80	EVA (2007)	Published before 2012
81	Sanad 2011	Published before 2012
82	Michalska 2006	Published before 2012
83	Saag, 2017 (ARCH)	Included
84	FACT (2005)	Published before 2012
85	Saag 2009	Published before 2012
86	Panico 2011	Published before 2012
87	EuroGIOPs	Osteoporosis in men
88	Anastasilakis 2008	Published before 2012
89	Walker 2013	Osteoporosis in men
90	Kendler, 2018 (VERO)	Included
91	Hadji 2012	Included
92	MOVE	Population not of interest: elderly patients

Reference number in Davis et al 2020	Study Acronym / NCT / identifier	Reason for exclusion from the original NMA submitted to NICE
93	Cosman 2011	Published before 2012

Abbreviations: BMD, bone mineral density; CSR, clinical study report; HR, hazard ratio; N, north; NCT, National Clinical Trial number; NMA, network meta-analysis; W, western

The literature review and NMA have been updated in response to feedback from the EAG, see Appendix, Section B.1.1 and Section B.1.2, respectively.

A23. CS, Figure 18: Alendronate and risedronate feature as nodes in this network diagram. Please clarify why studies comparing these bisphosphonates to placebo were not included in the NMA as these would allow inconsistency within the network to be assessed. If the Cosman 2011 study (teriparatide versus zoledronate) were to be included in the network then studies comparing zoledronate to placebo would also be relevant. Figure 42 of Davis et al. 2016 suggests that for vertebral fracture outcomes, six studies are available comparing alendronate to placebo, 8 studies are available comparing risedronate to placebo and 3 comparing zoledronate to placebo. Please clarify why none of these studies feature in CS, Figure 18.

The reasons for the non-inclusion of the studies presented in Figure 42 of Davis et al 2016[2] are presented in Table 14. The SLR/NMA has been updated and any relevant studies have been included (see Appendix Section B.1.1 and Section B.1.2).

Table 14 Studies included in Figure 42 of Davis et al 2016 and reasons for non-inclusion from the original SLR/NMA

Reference in Davis 2016	Reference details	Reason for non-inclusion in the original SLR/NMA submitted to NICE
45	Chesnut CH III, 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. http://dx.doi.org/10.1359/JBMR.040325	Pre-2012 so not identified in clinical SLR
55	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. Lancet 1996;348:1535–41. http://dx.doi.org/10.1016/S0140-6736(96)07088-2	Pre-2012 so not identified in clinical SLR
56	Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809–22. http://dx.doi.org/10.1056/NEJMoa067312	Pre-2012 so not identified in clinical SLR

Reference in Davis 2016	Reference details	Reason for non-inclusion in the original SLR/NMA submitted to NICE
58	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. http://dx.doi.org/10.1359/jbmr.081214	Pre-2012 so not identified in clinical SLR. Also men
59	Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J, Langdahl B, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med 2012;367:1714–23. http://dx.doi.org/10.1056/NEJMoa1204061	Study conducted in men
60	Carfora E, Sergio F, Bellini P. Effect of treatment of postmenopausal osteoporosis with continuous daily oral alendronate and the incidence of fractures. Gazzetta Med Ital Arch Sci Med 1998;157:105–9.	Pre-2012 so not identified in clinical SLR
63	Cohen S, Levy RM, Keller M, Boling E, 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. http://dx.doi.org/10.1002/1529-0131(199911)42:11<2309::AID-ANR8>3.0.CO;2-K	Pre-2012 so not identified in clinical SLR
64	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. JAMA 1998;280:2077–82. http://dx.doi.org/10.1001/jama.280.24.2077	Pre-2012 so not identified in clinical SLR
65	Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. Int J Clin Pract 2001;55:505–9.	Pre-2012 so not identified in clinical SLR
66	Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster for the BMD-MN Study Group. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2000;85:1895–900.	Pre-2012 so not identified in clinical SLR
70	Harris ST, Watts NB, Genant HK, McKeever C, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA 1999;282:1344–52. http://dx.doi.org/10.1001/jama.282.14.1344	Pre-2012 so not identified in clinical SLR
72	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. http://dx.doi.org/10.1080/13697130500118126	Pre-2012 so not identified in clinical SLR
76	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. N Engl J Med 1995;333:1437–44. http://dx.doi.org/10.1056/NEJM199511303332201	Pre-2012 so not identified in clinical SLR

Reference in Davis 2016	Reference details	Reason for non-inclusion in the original SLR/NMA submitted to NICE
77	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. N Engl J Med 2007;357:1799–809. http://dx.doi.org/10.1056/NEJMoa074941	Pre-2012 so not identified in clinical SLR
81	Miller PD, Epstein S, Sedarati F, Reginster JY. 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. http://dx.doi.org/10.1185/030079908X253889	Pre-2012 so not identified in clinical SLR
82	Muscoso E, Puglisi N, Mamazza C, Lo Giudice M, 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	Pre-2012 so not identified in clinical SLR
83	Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000;343:604–10. http://dx.doi.org/10.1056/NEJM200008313430902	Pre-2012 so not identified in clinical SLR. Also men
85	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. Osteoporos Int 2000;11:83–91. http://dx.doi.org/10.1007/s001980050010	Pre-2012 so not identified in clinical SLR
86	Reid DM, Hughes RA, Laan RF, 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. J Bone Miner Res 2000;15:1006–13. http://dx.doi.org/10.1359/jbmr.2000.15.6.1006	Pre-2012 so not identified in clinical SLR
88	Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2009;373:1253–63. http://dx.doi.org/10.1016/S0140-6736(09)60250-6	Pre-2012 so not identified in clinical SLR
89.	Ringe JD, Faber H, Farahmand P, Dorst A. Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. Rheumatol Int 2006;26:427–31. http://dx.doi.org/10.1007/s00296-005-0004-4	Pre-2012 so not identified in clinical SLR

Abbreviations: JAMA, Journal of the American Medical Association; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; SLR, systematic literature review

A24. CS Section B.2.9. Indirect and mixed treatment comparisons. Please provide further details about the NMA that was conducted:

- Why and where are timepoints 12,18, 24, 36 months predetermined?
- Please justify the use of separate syntheses at each time point, rather than allowing for different study durations (see Question A25 below)
- Page 84 states "Binary Bayesian models" were used. Please provide further details of the statistical model (e.g. what was the link function used). Treatment effects have been reported as relative risks but odds ratios are more common for this data type.
- "Non-informative priors were used for all analyses". For networks with few studies please check and evidence that posterior updating is sufficient for the heterogeneity parameter and consider using informative priors where appropriate.

The timepoints of 12, 18, 24 and 36 months were predetermined in the PICOS eligibility criteria for the NMA (Table 24 of the original Company submission). These timepoints were based on the availability of fracture data in published trials of therapies for the treatment of post-menopausal osteoporosis and the 18-month timepoint of the ACTIVE trial. These timepoints align with the recently published NICE appraisal, TA791.[4]

Separate synthesis of data at each timepoint in the NMA, rather than allowing for different study durations, were used to consider the comparative efficacy more accurately in the short and long term. In addition, this approach aligned with the recently published NICE appraisal, TA791.[4] However, based on feedback from the EAG, the NMA has been updated to remove discrete timepoints (see the Appendix, Section B.1.2 for further details).

Bayesian models were analysed utilising a binomial likelihood and a logit link function. Non-informative priors were used for all analyses in the NMA. The indications from posterior summary statistics and convergence diagnostics suggested that posterior updating was suitable for the heterogeneity parameter.

A25. PRIORITY Please update the NMA using a statistical model that allows incorporation of studies with different time durations, where the relative treatment effects are modelled as hazard ratios. See Nice Technical Support Document 2 example 3 and Davis et al 2020.

Based on the feedback from the EAG, the NMA has been updated to allow the incorporation of studies with different time durations, where the relative treatment effects are modelled as Hazard Ratios (HRs). See the Appendix, Section B.1.2 which presents the updated methodology and results.

The findings from the updated NMA suggest that abaloparatide has [redacted] The conclusions of this NMA align with previously published meta-analysis results of bisphosphonates and non-bisphosphonates in postmenopausal women with osteoporosis who are at an increased risk of fracture.[27]

A26. CS B.2.9.2. Pg 92: "As there were differences in ethnicity and prevalent vertebral fracture rates in the studies included in the NMA, there is a moderate risk of bias from effect modification in the comparison between abaloparatide and other comparators." Are ethnicity and prevalent vertebral fracture rates established treatment effect modifiers? Please summarise the assessment of treatment effect modifiers that was performed to justify the NMA (listing the treatment effect modifiers, and evidence to support this).

Treatment effect modifiers were not formally assessed in the NMA. It can be anticipated that there is always some level of variation in patient characteristics, study sites, and settings across studies; if these characteristics are effect modifiers of the relative treatment effects of interest, then variability in these effect modifiers can confound the results of an NMA. There were also large differences in the rates of fractures in the placebo arms of different studies, indicating large differences in the populations that likely extend to unknown and unmeasured effect modifiers, increasing the level of uncertainty in the NMA results. As there were differences in ethnicity and prevalent vertebral fracture rates in the studies included in the NMA, there is a moderate uncertainty in the comparison between abaloparatide and other comparators. Ethnicity and prevalent vertebral fracture remain an area of investigation

and discussion in relation to treatment effect and are not established treatment effect modifiers in osteoporosis.

Section B: Clarification on cost-effectiveness data

Decision problem

B1. B.1.3.1.5: Please clarify what proportion of postmenopausal women in the UK have osteoporosis and are categorised as being at very high risk of fracture (are eligible for teriparatide and/or romosozumab).

Applying a upper intervention threshold (UIT) of 1.6 for the definition of very high risk fracture in accordance with Kanis et al (2021),[28] it can be estimated that 10% of women aged 50 years or more would be characterised as very high risk (i.e. with a level of risk similar to that of women enrolled in anabolic drug trials). The number of women eligible for treatment represents 40% of postmenopausal women (N=20,451), and the proportion of these women at very high risk, using the UIT of 1.6, was 25.1% (N=5,133). The budget impact model (BIM) utilised sales data for the proportion of patients being treated with anabolic agents, to reflect real-world clinical practice. This resulted in a population of [redacted]

B2. The CS assumes that all anabolic treatments are followed by an antiresorptive and for the purposes of modelling that the antiresorptive used is alendronate. Please clarify, what proportion of patients eligible for teriparatide are unable to receive alendronate as a follow-up treatment due to intolerance/ contraindications? What treatments would be used as an alternative to alendronate in this group and in what proportions?

As per the SmPC,[30] alendronate is contraindicated in patients with hypersensitivity to the active substance or to any of the relevant excipients, abnormalities of the oesophagus (e.g., stricture or achalasia), if there is an inability to stand or sit upright for at least 30 minutes and in those with hypocalcaemia. [30]

Treatment options for patients who are intolerant to or have contraindications to alendronate are IV bisphosphonates, denosumab, raloxifene and hormone replacement therapy (HRT).[31] IOF and EFPIA data show very low uptake of raloxifene

in the UK during 2010, whilst UK osteoporosis market share data shows that [redacted] patients [redacted] were prescribed raloxifene in 2022.[29] In addition, UK market share data of osteoporosis treatments in 2022, shows [redacted]

B3. Clinical experts to the EAG have advised that denosumab and IV bisphosphonates are sometimes used as an alternative antiresorptive, following treatment with an anabolic, in patients unable to receive alendronate due to contraindications/ intolerances. The CS does not assess the cost-effectiveness of any treatment sequences using either denosumab or IV bisphosphonates as the antiresorptive. Please clarify why these are not considered a relevant treatment sequence for either abaloparatide or other anabolic treatments.

The ERG (Evidence Review Group) for the romosozumab appraisal[4] reported uncertainty about the appropriateness and relevance of the comparators used in the economic model they presented. The ERG suggested that the company identify comparators which are representative of UK clinical practice in the imminent risk patient population and limit the comparators in the model to these therapies. The current submission followed this suggested approach. IV bisphosphonates and denosumab were not included in the treatment sequence for the cost-effectiveness model, as their use in the UK is significantly lower than that of oral bisphosphonates. UK Market share data on the usage of osteoporosis treatments from 2022,[29] shows [redacted]

These data reflect the use of these agents in any line therapy, therefore patients receiving this therapy in a sequential regimen post-anabolic treatment, would be lower still.

In addition, the Phase 3 pivotal trial for abaloparatide was conducted with alendronate not IV bisphosphonate or denosumab.[8,9] There are no available data on the efficacy of abaloparatide followed by an IV bisphosphonate or denosumab. Finally, from a clinical perspective, it is expected that the efficacy of an oral and IV bisphosphonate are similar. This was discussed in a recent NICE appraisal of bisphosphonates (NICE TA464)[17], which stated that bisphosphonates are considered to be of similar efficacy

within the class. Therefore, for these reasons, IV bisphosphonates and/or denosumab were not considered to be appropriate therapies to be used as post-anabolic therapy in the cost effectiveness model (CEM) for abaloparatide in the UK.

Modelled population

B4. CS, Section B.3.3.1, Table 38. Please clarify if only the data from the abaloparatide arm in ACTIVE trial (N=696) was used to inform the baseline characteristics in the model (not the placebo or the teriparatide arm).

We can confirm that the abaloparatide arm in the ACTIVE trial was used to inform the baseline characteristics in the model.

B5. CS, Section B.3.3.1, Table 38 and model. In the model, the proportion of patients with 'prior fracture' appears to have been informed by the proportion of patients in the abaloparatide arm in the ACTIVE trial with 'Prevalent vertebral fracture' (20.8%). Why was this used instead of prevalence of any prior fracture (58.5% based on 41.5% having no history of prior fracture in Table 15)? Please clarify if the model allocates patients to starting health states according to their prior fracture history. For example, does it apply chronic utility multipliers or costs to those with a prior history of fracture at baseline?

Prior fracture data contributed to the calculation of fracture risk based on the FRAX algorithm. The data for the 'proportion of patients with prior fracture' was a data error in the model, and the correct value should be 58.5% (based on 100% - 41.5%, i.e. no history of prior fracture). The calculation in the model has been updated accordingly.

The model does not allocate patients to a particular health state based on prior fracture history, neither does it assume a chronic utility multiplier / cost to patients with a prior history of fracture. All patients start the simulation from the "At Risk" health state. This approach is aligned with those used in peer-reviewed, published models as well as in the recent NICE appraisal, TA791.[4,32,33]

B6. CS, Section B.3.3.1, Table 38 and model. Please clarify how the prevalence of the risk factor 'parental history of hip fracture' has been quantified. In the model, the prevalence of prior nonvertebral fracture (44.3%) appears to have been used to estimate the proportion with a parental history of fracture. This should be based on the

history of osteoporotic hip fracture in the parent of the individual not the history of hip fracture in the individual.

The prevalence of the 'parental history of hip fracture' risk factor for the FRAX algorithm was not quantified, as the original model incorrectly utilised the prevalence of prior nonvertebral fracture (44.3%). The FRAX algorithm in the updated model does not include the risk factor of 'parental history of hip fracture' as these data were not collected in the ACTIVE trial.

Modelled structure

B7. Does the model provide any limits on the number of fractures at a single site e.g. maximum of 2 hip fractures?

There were no restrictions on the sequence or number of fractures experienced by the patients in the simulation (CS, page 108). There were also no limits on the number of fractures at a single site. These assumptions reflect the nature of the disease[4] and follows a previously published technology appraisal, TA791.[4]

B8. CS, page 111: The data on incidence of 'other fractures' is described as including femur, pelvis, humerus, rib, clavicle, scapula and sternum. It is noted that previous models (such as the one that informed TA464 described by Davis et al. 2016) grouped femoral shaft fractures with hip fractures based on these being expected to have similar costs and utility implications. Please comment on whether all of these types of non-hip non-vertebral fractures would be expected to be similar in terms of their impact on costs, utilities and risk of mortality following fracture.

For clarity we have updated the 'other' fracture category to 'Non-Hip Non-Vertebral' (NHNV) to align with previous published economic models[4,30] and NICE appraisal[31] and in line with the recommendations for conducting economic evaluations in osteoporosis[34]. NHNV fractures includes forearm (distal forearm, distal radius, and wrist) and "other" fractures (femur, pelvis, humerus, rib, clavicle, scapula, sternum).

B9. The model assumes a full 5 years intended treatment duration for alendronate following completion of an anabolic treatment. This leads to longer treatment durations overall for teriparatide then abaloparatide and for abaloparatide than for romosozumab. The EAG's clinical advisors did not consider that a full 5 years of

antiresorptive treatment would be necessary. Please provide a scenario where the total treatment duration is 5 years including both anabolic and antiresorptive components for all treatment strategies.

Osteoporosis is a chronic and progressive disease that requires lifelong therapy. Indeed, the use of an antiresorptive following anabolic treatment is required to maintain the gains in bone mineral density.[35] As per the alendronate SmPC, the optimal duration of bisphosphonate treatment for osteoporosis has not been established.[30] The need for continued treatment should therefore be re-evaluated periodically based on the benefits and potential risks of alendronate on an individual patient basis, particularly after five or more years of use. The UK guidelines[35] state that oral bisphosphonates should be prescribed for a minimum of five years with up to ten years recommended for the following patients:

- Age ≥ 70 years at the time that the bisphosphonate is started,
- Who have a previous history of a hip or vertebral fracture(s),
- Who experience one or more fragility fractures during the first five years of treatment (if treatment is not changed).

However, it should be noted that this recommendation relates to monotherapy. Guidance on oral bisphosphonate use in a sequential treatment regimen is limited, however, five years is deemed to be an appropriate and potentially conservative approach as the patient population are at high risk for fracture.

The updated model includes a scenario which assumes a total duration of five years for all the treatments as per Table 15 below. The results are presented in Table 16 and also in the Appendix, Section B.2.10.1.3.

Table 15 Treatment duration for the requested scenario analyses

Initial treatment	Initial treatment duration	Sequential treatment	Sequential treatment duration	Maximum duration
Abaloparatide (80 µg/daily SC injection)	18 months	Alendronate (70 mg/once weekly tablet)	42 months	60 months
Teriparatide (20 µg/daily SC injection)	24 months	Alendronate (70 mg/once weekly tablet)	36 months	60 months
Romosozumab 210 mg (2 x 105 mg)/monthly SC injection)	12 months	Alendronate (70 mg/once weekly tablet)	48 months	60 months

Abbreviations: SC, subcutaneous

Table 16 Scenario analysis for treatment duration

Scenario	Description	Incremental costs	Incremental QALYs	ICER
Base case: romosozumab	NA	[redacted]	[redacted]	Dominant
Maximum treatment duration for all treatment sequences	5 years	[redacted]	[redacted]	Dominant
Base case	NA	[redacted]	[redacted]	Dominant
Maximum treatment duration for all treatment sequences	5 years	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life years

Estimation of fracture risk

B10. CS Section B.3.3.2.5, Page 115 says "RR_{frax} = relative risk estimated by FRAX for a given patient profile excluding prior fracture as a clinical risk factor". Has the general population risk, shown in CS Table 39, been adjusted downwards for people without risk factors as it is likely that many fractures occurring in the general population are occurring in those with risk factors.

The general population risk shown in CS Section B.3.3.2.5, Table 39, has not been adjusted downwards for people without risk factors. Any risk factors are likely diluted in the general population to make the unadjusted estimate reasonable. This approach aligns with that used in previous NICE appraisals TA464[17] and TA791.[4]

B11. PRIORITY CS, Section B.3.3.2.1,Table 39 and model sheets 'Model Data' and 'Country specific data': The calculation involved to estimate the 'adjusted events risks' on the 'Model Data' sheet (columns S to U), appears to simply reproduce the absolute risks of fracture predicted by FRAX in the 'FRAX estimates' sheet. This is because, as far as we understand, the ratio of FRAX risk to general population risk is calculated (columns W to Y of 'Model Data' sheet) and then multiplied by the general population risk. If the data from general population fracture risks from Singer et al. (E60 to G67

of ‘Country specific data’) are doubled or halved, it has no impact on the adjusted event rates in ‘model data’ columns S to U. In addition, we would expect the RR associated with FRAX (columns W to Z of the ‘Model Data’ sheet) to be over 1 because the fracture risk for patients should be higher than that for general population (seen in Figure 27). However, the RRs in the submitted model were less than 1 giving lower absolute fracture risks after adjustment for FRAX. If there is an error in the method used to adjust population risks for FRAX, then please correct the model such that it behaves in the manner described in CS Sections B.3.3.2.1 to B.3.3.2.3. Alternatively, if the EAG has misunderstood this aspect of the model, please clarify how the data in Table 39 influence the cost-effectiveness estimates within the model spreadsheets.

The model was updated to correctly reflect the RR values as estimated by FRAX, so that values are greater than 1 for a high-risk population compared to the general population. The specific amendments in the "Model Data" sheet are as follows:

- Calculation of FRAX RR, incorporating T-score and clinical risk factors (Columns V to X).
- Determination of general population incidence rates by age group (Columns Z to AB).
- Adjustment of fracture risk using FRAX RR multiplied by the general population incidence (Columns R to T).

These changes ensure that any modifications in the "Country Specific data" (cells E60 to G67) are accurately depicted in the adjusted event risks (columns R to T) of the "Model Data" sheet. This correction aligns with the methodologies described in Sections B.3.3.2.1 to B.3.3.2.3 of the Company submission, accurately reflecting the influence of Table 39 data on the cost-effectiveness estimates within the model.

B12. PRIORITY CS, Section B.3.3.2.1, Table 39 and model. Please clarify how the data in Table 39 have been used to estimate risk per patient per cycle for the different age categories shown. Table 39 is described as presenting the incidence of each type of fractures per 100,000 person-years by age group. However, in the ‘Country specific data’ sheet (cells E6:G56), the absolute risk of each type of fracture for each age group appears to have been estimated as a proportion of the number of fractures for a

determined age group over the sum of all fractures of that type (i.e. taking the value in each row in Table 39 and dividing them by the sum of the column rather than dividing each row by 100,000 person-years). For example, for patients aged 85+, Table 39 specifies 2255 hip fractures per 100,000 person years (i.e. approximately 2% of absolute risk per year). However, in the model the absolute risk per annum of hip fracture for an 85 year old was calculated as =1-EXP(-(-LN(1-(2255/4689)/5)), where 4689 is the sum of the incidences across the different age categories. This gives a hip fracture risk per cycle of around 12%. The EAG believes that the incidence sums should be replaced by the value 100,000 in 'Country specific data' cells E68:G68. The EAG also believes that the formulae in 'Country specific data' sheet cells E6:G56 are not properly adjusting for time at risk. If the incidence data from Singer et al. are per year, then the EAG believes that the formula should be adjusting from 1 year to 0.5 years (the cycle length), whereas it currently appears to be adjusting from 5 years to 1 year.

The calculation in the model has been updated based on the recommendations from the EAG to per cycle incidence and calculated based on per 100,000. For example, based on 33 events in the general population per 100,000 (age 50–54 years), the fracture risk of 0.02% is calculated using the formula:

=1-EXP(-(-LN(1-(33/100000)))*0.5) = 0.02%.

B13. CS section B.3.3.2.2 and model worksheet 'FRAX estimates'. The FRAX estimates appear to be estimated according to age, BMD and number of clinical risk factors. Different risk factors in FRAX have different RRs associated with them therefore it is necessary to specify the exact risk factors to get an accurate FRAX prediction. Please clarify how the FRAX risks were calculated according to the number of risk factors rather then presence or absence of specific risk factors.

The risk factors used in the model (namely, body mass index [BMI], previous fracture, parental hip fracture history, current smoking, glucocorticoids use, rheumatoid arthritis, alcohol consumption of ≥ 3 units per day, and femoral neck BMD) are simulated according to the binomial distribution based on the proportion of patients having those risk factors. The abaloparatide arm in the ACTIVE trial was used to inform the baseline characteristics in the model. The total risk is calculated in column N of the "Model Data" sheet, based on which the FRAX relative risk is being simulated for each

patient profile. As the relative risk available from the FRAX tool is based on total clinical risk factors rather than the presence or absence of any specific clinical risk factor, the absence or presence of clinical risk factors was simulated in a particular patient based on the proportions of patients having that risk factor. These data were then summed up to calculate the total risk factor. Based on the total number of risk factors present in a patient, given a T-score and an age, the RR was calculated. This methodology aligns with the that proposed in the FRAX risk assessment tool developed by the University of Sheffield.[36]

B14. PRIORITY CS section B.3.3.2.2 and model worksheet 'FRAX estimates': FRAX provides estimates of the 10-year risk of major osteoporotic fracture (MOF) which includes the risk of fractures at the hip, wrist, spine and shoulder. What proportion of the MOF risk predicted by FRAX (tabulated in the 'FRAX estimates' sheet of the model) has been allocated to vertebral fractures, hip and other fractures when calculating the adjustment factors for FRAX risk (Columns W to Y of the 'Model Data' sheet and referred to as RR_{frax} on page 113)? The EAG notes that the risk of vertebral fracture and other fractures (in the absence of treatment) are identical after adjustment for FRAX risk (Adjusted event risk in columns T and U of the 'Model Data' sheet). It appears that 100% of the MOF fracture risk predicted by FRAX is being applied to both vertebral and other fractures. In addition, the absolute values appear to match the one-year risks from column M of the 'FRAX estimates' sheet and not the 6 month risks from Column N. Please reconsider your approach and correct the model accordingly.

The outputs of the FRAX algorithm are 10-year probabilities for MOF and for hip fractures. Therefore, the hip 10-year MOF probability is assigned 100% to hip fractures. The MOF 10-year probability is assigned in full (100%) to both vertebral fractures and non-hip non vertebral fractures (previously designated as 'other fractures' in the original Company submission/model). This approach is aligned with a peer reviewed, published model[33] and the romosozumab NICE appraisal, TA791.[4]

B15. Please clarify whether the RR for a recent fracture, which is pulled in from the 'imminent risk' sheet, uses time since the most recent fracture of that type or time since first fracture of that type. In the model submitted, there is a second vertebral fracture

at 7 years, after a first vertebral fracture at 2.5 years, but the time used to look up the imminent fracture risk appears to be 54 months, which is time since the first fracture.

The model uses time from the index fracture rather than the time from most recent fracture as we have utilised the HR provided in the real-world study conducted by Söreskog et al. (2020). Specifically, columns AU, AX, and BA in the model determine the time elapsed since the index fracture, which is the basis for calculating the RR of an imminent fracture. This is evident when the value in these columns is zero, indicating that the patient has just suffered the index fracture.

Two examples illustrate how the imminent risk is computed within the model:

1. A 50-year-old patient sustains an index hip fracture in cycle 5. The model applies a relative risk of 3.4. Should a subsequent hip fracture occur at 8 months post-index fracture, the RR adjusts to 3.9. If a third hip fracture takes place 20 months after the index fracture, the imminent risk applied shifts to 2.3.

2. For an 80-year-old patient with an index hip fracture in cycle 5, the initial RR is 1.4. A following hip fracture at 2 months post-index leads to an RR of 1.7. If there is a third hip fracture after 5 months from the index fracture, the model applies an imminent risk of 1.1.

Full details are provided in the Appendix, Section B.2.2.2.3.

B16. CS Section B.3.3.2.5. The equation on Page 115 of the submission implies that the maximum of the RR for prior fracture based on Söreskog et al. (2020) (RR_{recent}) and the RR for a prior fracture based on FRAX is taken (RR_{frax_fx}). Please identify where in the model this maximisation occurs. Please also provide the RRs associated with a prior fracture from FRAX (RR_{frax_fx}) used in the maximisation.

This maximisation has been applied in columns BH to BJ for all treatment sequences in the simulation sheets in the model (i.e., Simulation Abaloparatide, Simulation Romosozumab and Simulation Teriparatide). As this was a microsimulation model, the RR used for maximisation was different for each patient and was based on the particular patient profile; in the model this information can be found in “Model Data” sheet columns AD to AF.

An example of the risk of a hip fracture in a 65-year old patient is provided below:

- General fracture risk is 0.0007
- FRAX-based risk is 2.00
- The RR associated with a prior fracture according to FRAX is 1.67
- The RR associated with a recent MOF is 3.42
- The final event risk is calculated based on = 0.0007 x 2.00 x maximum of (1.67, 3.42)

B17. CS Section B.3.3.2.3 and model 'Imminent risk' worksheet. Please justify why the current assumption adopted for the imminent risk of fracture for patients who have 3 vertebral, hip or other fractures is that the same RR is maintained from 24 months onwards (based on values in Soreskog et al (2020)).

In alignment with the findings from Söreskog et al. (2020)[37], the model maintains the same RR for subsequent fractures 24 months post the third fracture. Söreskog et al. employed a rigorous survival regression analysis, matching women with fractures to controls without fractures by gender and birth year. It was observed that risk of subsequent fracture was highest within 0–24 months following an index fracture, then decreased but remained elevated as compared to controls. This aligns with the approach taken in the romosozumab appraisal.[38]

B18. Please provide an analysis showing how the 10-year risk of fracture in the model for untreated patients compares with the 10-year risk predicted by both QFracture and FRAX for the modelled population provided in CS Table 38. This would provide a means to validate the estimates of risk applied in the model. Please do this for both hip and MOF risks.

The fracture risk of a patient with the characteristics presented in Table 17 has been calculated using FRAX and QFracture. The results are presented in Table 18 and are summarised below.

The company economic model's estimates for the 10-year risk of major osteoporotic fractures (MOF) and hip fractures are largely consistent with the FRAX tool's predictions for the specified patient profile, showing 38% for MOF and 16% for hip fractures, compared to 40% and 20% by FRAX, respectively. This slight variance may

be due to model-specific adjustments or assumptions. However, the estimates differ more substantially from QFracture predictions, which are 16.9% for MOF and 7.5% for hip fractures. The discrepancies between the tools can be attributed to different risk factors and population data that each algorithm uses. QFracture may not include certain clinical risk factors that are present in FRAX, such as parental history of hip fracture or glucocorticoid use, which can result in lower risk predictions from QFracture.

Table 17 Characteristics of the simulated patient for comparative fracture risk assessment by FRAX and QFracture

Characteristic	Value
Age	69.5
Sex	Female
BMI	24.8
T-score	-2.19
Any prior fracture	Yes
Parent hip fracture	Yes
Smoking status	Yes
Glucocorticoids	No
Rheumatoid arthritis	No
Alcohol 3 or more units/day	Yes

Abbreviations: BMI, body mass index; FRAX, Fracture Risk Assessment Tool

Table 18 Fracture 'risk calculated by FRAX and QFracture for a simulated patient profile

	MOF 10-year probability	Hip 10-year probability
QFracture	12.6%	8.7%
FRAX assessment tool	26%	10%
Economic model	28%	10%

Abbreviations: BMI, body mass index; FRAX, Fracture Risk Assessment Tool; MOF, major osteoporotic fracture

Efficacy applied in the model

B19. CS Section B.3.3.2.4, Table 40. Please clarify whether the RRs for romosozumab are based on 12-month outcomes from FRAME and whether any adjustment has been made to account for these being based on a 12-month rather than an 18-month timeframe. Please also clarify which fracture outcomes from the FRAME trial have been used for each fracture type and justify your choice. For example, the risk ratio (RR) for new vertebral fracture at 12 months for romosozumab versus placebo in Figure 2 of Cosman et al. (2016) is 0.27 whereas the value of 0.29 cited in Table 40 appears to be the RR for new or worsening vertebral fracture at 12 months (see Cosman et al. 2016, Supplementary Table S2). Please also clarify the choice of outcome used to inform the RR for 'other' fractures in Table 40.

The RRs for romosozumab are based on the 12-month outcomes from FRAME,[20] and no adjustments were made to account for comparison with the different treatment durations for abaloparatide and teriparatide. Further, the overall treatment duration of romosozumab is 12 months, followed by 48 months of alendronate: thus, adjustment to 18 months was not conducted. The following outcomes from the FRAME trial were used in the original base case submitted to NICE[20]:

- Major nonvertebral fracture was used for 'other fractures'
- New or worsening vertebral fracture was used for 'vertebral fracture', and
- Hip fracture was used for 'hip fracture'

The discrepancy between RR for new vertebral fracture at 12 months for romosozumab versus placebo in Figure 2 of Cosman et al. (2016)[20] and the value cited in Table 40 of the Company submission is due to the use of 'new or worsening vertebral fracture' in the Company submission rather than 'new vertebral fracture' which is presented in figure 2 of Cosman et al. (2016)[20].

The model has been updated so that the 'other fractures' category has been updated to 'NHNV'. The trial data (ACTIVE and FRAME) are included in the updated model as a scenario. The base case has been updated to use HRs from the NMA. Full details of this scenario are presented in the Appendix, Section B.2.10.1.3.

B20. PRIORITY CS Section B.3.3.2.4: Please clarify why it was considered reasonable to make an unadjusted indirect comparison between the 12-month data

from FRAME and the 18-month data from ACTIVE in the economic analysis, but it was not considered appropriate to use the NMA results at 12 months for non-vertebral fracture, major osteoporotic fracture or clinical fracture, as provided in Appendix D, in the model.

The base case in the original economic model used the efficacy data available from the ACTIVE and FRAME trials. It was not feasible to use the results from the original NMA due to the lack of data at 18-months for romosozumab and 12-months for abaloparatide. However, in response to the EAG feedback, the NMA methodology was updated to allow the incorporation of studies with different time durations and publications prior to 2012. The unadjusted indirect comparison in the economic model base case was revised to incorporate the HRs from the updated NMA, which is considered to better account for the heterogeneity in the cross-trial populations.

To accommodate the heterogeneity among studies in the NMA, random-effects models were assessed. These models presuppose that treatment effects may differ across studies but originate from a shared distribution of treatment effects, characterised by a mean for each treatment effect and a common covariance matrix between studies.

B21. CS Section B.3.3.2.4 – The model appears make an unadjusted indirect comparison by using the RR for romosozumab versus placebo from FRAME trial without any adjustment). Please clarify the homogeneity/similarity of the populations in the ACTIVE trial and FRAME trial.

There were differences in the baseline characteristics of the populations in the ACTIVE trial and FRAME trial. The base case of the updated economic model was revised to incorporate the HRs from the updated NMA, which is considered to better account for the heterogeneity in the cross-trial populations. For completeness, the efficacy data from the ACTIVE trial and FRAME trial were included as a scenario analysis.

B22. CS Section B.3.3.2.4, Table 40. The data in this table for hip and other fractures for the abaloparatide and teriparatide treatment groups appear to have been taken from the nonvertebral fracture and MOF outcomes from Table 19. However, these tables report HRs not RRs. Please clarify if these are being applied as HRs or RR in the model. Please clarify why ‘nonvertebral fractures’ is applied to hip fractures and MOF to other fracture sites. The data in this table for vertebral fracture for the

abaloparatide and teriparatide treatment groups appear to be estimated by calculating 1-RRR from the RRR value reported for new vertebral fracture in Table 19. Please clarify if these are being applied in the model as HRs or RRs.

The model base case has now been updated using the HR from the updated NMA and a scenario utilising HR/RR applied as HR from the ACTIVE and FRAME trials has been included. The base case incorporates the HRs for hip, vertebral and non-vertebral fractures (for NHNV) from the updated NMA. The trial scenario uses data from ACTIVE and FRAME. Major nonvertebral fractures were used as a surrogate for hip fractures due to zero events of hip fracture in the abaloparatide and teriparatide arms.[9] This approach is recommended for economic evaluation in osteoporosis, which state that due to the lack of hip fracture data in RCTs, reduction in nonvertebral or clinical fracture can be used as a surrogate for reduction of hip fracture in the base case.[34] The FRAME trial reported HR for hip fractures, however, major nonvertebral fractures were also used to allow a fair comparison to ACTIVE. Nonvertebral fractures were used for NHNV in the model and new vertebral fractures were used for vertebral fractures.

B23. PRIORITY CS Section B.3.3.2.4 and Model: In column AZ to BB of the Simulation sheets for each treatment strategy (e.g. Simulation Abaloparatide), the Figures from Table 40 are subtracted from 1 before being multiplied by the absolute risk. This suggests that they are being applied as RRR i.e. (1-RR)=RRR. For example, during treatment the absolute risk for non-vertebral fracture for patients receiving abaloparatide is being multiplied by (1-0.31) =0.69. After treatment finishes this is adjusted linearly such that the multiplier at the end of the offset period is 1. However, this means that the full treatment effect is not being applied as the effective RR during treatment is 0.69 not 0.31, as per Table 40. Similarly, the RRR for vertebral fractures for abaloparatide vs placebo is given as 0.88 in Table 19 (equivalent to a RR of 0.12). But the absolute risk in the model, during treatment is multiplied by 0.88 not 0.12. If you set the data in the 'clinical inputs' cells E48 to E50 to 1, which would imply no treatment effect if these were RRs, then you get zero risk of fracture during the treatment period. Please correct the model or justify why the current approach is appropriate.

This approach was used because in the initial Company submission the estimates were modelled as relative risk reduction (RRR), therefore RR was subtracted from 1.

The model has been updated to use HR from the updated NMA (full details in the Appendix Section B.1.2), therefore, the calculation (see example below) now addresses the issue raised by the EAG ensuring that for the treatment duration, the full treatment effect is applied and after that the treatment effect wanes to that of no treatment. The base case now uses HR from the NMA. In the updated model, for all treatment strategies columns, AZ to BB calculate the HR-adjusted event risks.

The calculation has been updated in the model, using an example HR of 0.75 and where p1 = FRAX adjusted general population risk per cycle:

Event risk = -LN(1-(1-((1-(1-EXP(-p1)))^0.75

As can be seen from the data presented in Table 19, the updated model behaves as expected. Table 19 below shows that number of fractures in all the treatments are the same when HR = 1 for all treatments.

Table 19. Effects breakdown when HR=1 for all treatments

	Total			Incremental	
	Abaloparatide	Romosozumab	Teriparatide	Abaloparatide vs. Romosozumab	Abaloparatide vs. Teriparatide
Number of fractures	**20.720**	**20.720**	**20.720**	**0.00**	**0.00**
Hip	3.330	3.330	3.330	0.00	0.00
Vertebral	3.760	3.760	3.760	0.00	0.00
NHNV	13.630	13.630	13.630	0.00	0.00
Time to first fracture					
Hip	9.170	9.170	9.170	0.00	0.00
Vertebral	7.695	7.695	7.695	0.00	0.00
NHNV	3.595	3.595	3.595	0.00	0.00
Life years	**13.50**	**13.50**	**13.50**	**0.00**	**0.00**

Abbreviations: NHNV, non-hip non-vertebral; vs, versus

B24. CS Section B.3.3.2.4, Table 40. Please clarify the time period over which HRs/ RRs are applied. In particular, are they applied just for the period of abaloparatide/ teriparatide/ romosozumab treatment? If so, then what HRs or RRs are applied during the subsequent alendronate treatment period. Is any adjustment made to account for the fact that teriparatide is given for 24 months and not 18 months in the model so the HRs have been estimated over a time frame different from the period they are applied over in the model?

In the updated base case, the HRs from the updated NMA are applied for the initial duration of treatment for each therapy according to the label[6,7,10] (Table 20). For the subsequent alendronate treatment period (60 months), the HRs from Table 21 are applied.

In the scenario using clinical trial data (ACTIVE and FRAME), the HRs are applied for the full treatment duration of 60 months. Full details of this scenario are presented in the Appendix, Section B.2.2.2.4.2.

Table 20 NMA estimates used in the base case for the economic model

	Base case NMA estimates	
	vs. placebo	**HR (95% CrI)**
Hip	Abaloparatide (18 months)	[redacted]
	Romosozumab (12 months)	[redacted]
	Teriparatide (24 months)	[redacted]
Vertebral	Abaloparatide (18 months)	[redacted]
	Romosozumab (12 months)	[redacted]
	Teriparatide (24 months)	[redacted]
Non-vertebral	Abaloparatide (18 months)	[redacted]
	Romosozumab (12 months)	[redacted]
	Teriparatide (24 months)	[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta analysis

Table 21 NMA estimates for alendronate vs placebo in the base case - sequential treatment period

Base case NMA estimates	
	HR (95% CrI)
Hip	[redacted]
Vertebral	[redacted]
Non-vertebral	[redacted]

Abbreviations: CrI, credible intervals; HR, hazard ratio; NMA, network meta-analysis

B25. PRIORITY CS Section B.3.3.2.4, Table 41: Please explain how the figures in this table relate to the results presented in the forest plots from the NMA presented in CS, Section B.2.9.6.

The forest plots in the original NMA were constructed to show the efficacy of abaloparatide vs comparators. The original model scenario utilises RR for the abaloparatide, romosozumab and teriparatide vs placebo, therefore the forest plots and Table 41 do not align.

The NMA has been updated to include HR as the output, to include additional studies which were published before 2012 and the analysis has been conducted without pre-defined timepoints. Please see the Appendix, Section B.1.2 for full details, including the updated NMA results.

B26. CS Section B.3.3.2.4. The RRs for both abaloparatide and teriparatide are specified versus placebo in Table 40 and Table 53. Are these varied independently in the PSA? If the model does not provide results for a no treatment strategy, then it would be better to use the efficacy estimates for abaloparatide versus teriparatide from ACTIVE and sample this RR from a single distribution.

The model base case now utilises the HR estimates from the updated NMA rather than the ACTIVE trial, which was the base case in the original submission. In the PSA, the HRs are varied independently and sampled from Log normal distribution (as HR can range from 0 to infinity with positive domain) based on the uniform random number varied between 0 to 1. For example, if the HR was 0.74 with lower

and upper bound 0.38 and 1.43, respectively, and if the random number is 0.330194038, then the probabilistic value of HR can be calculated as follows:

LOGINV(0.330194038,LN(0.74),(LN(1.43)-LN(0.38))/(1.96*2)) = 0.637.

A scenario has been conducted with the trial data from the ACTIVE and FRAME trials, see the Appendix, Section B.2.10.1.3.

B27. PRIORITY Please provide an NMA that includes a romosozumab treatment strategy (this would be possible using the approach requested in Question A25). Please use CODA samples from that NMA to provide correlated estimates of the RRs/HRs for all three treatment strategies included in the model.

The NMA has been updated in response to the EAG's feedback to allow the incorporation of studies with different time durations, pre-2012 publications and where the relative treatment effects are modelled as hazard ratios. Full details of the updated SLR and NMA are provided in the Appendix, Section B.1.1 and Section B.1.2, respectively.

All cause mortality

B28. **PRIORITY** Model. 'Country specific data' worksheet, columns M and O (all cause mortality). Please clarify how 'Normal population mortality (per cycle)' was calculated in the model. We suspect that the formulation is incorrect because the cycle length is 0.5 years (6 months). Given that the data in column M is risk of death per annum, please consider applying the following correction to column O:

"=IFERROR(1-EXP(1)^(-1*(-LN(1-M6)/6)),1)"

would be changed to

"=IFERROR(1-EXP(-(-LN(1-M6)/1)*0.5),1)"

This issue has been resolved in the updated model by applying the formula as specified above.

B29. CS, section B.3.2.3, Table 37 and model. The company states regarding the time horizon that, "As such, a lifetime time horizon from the patient's age at treatment initiation to the age of 100 years or time of death (whichever comes first) was considered appropriate". Estimates of general population mortality are only available

up to age 100 but the time horizon implemented in the model does not appear to adjust to restrict the maximum age to 100. Even when using the mean starting age (69.9 years) the patient reaches age 100 within the time horizon and then the risk of death is fixed at the same risk from age 100. Please correct this so that the implementation of the time horizon in the model matches that described in table 37. Also, costs and QALYs appear to be restricted according to whether the analysis is within the timeframe using column F of the simulation sheet, but a similar restriction does not seem to apply when tallying up the number of fractures in cells AJ3:AL3. We believe that the number of fractures should also be counted within the time horizon in the model. Please check if it is correctly modelled.

In response to the concerns regarding the implementation of the time horizon in the original submitted model, revisions have been made to ensure alignment with the parameters detailed in CS, Section B.3.2.3, Table 37. Specifically, the formulas within columns AM to AP have been updated across all treatment sequences, which now accurately tally fractures occurring only within the defined lifetime horizon, ending as the patient's age reaches the cutoff of 100 years. The amended formula in column F serves as a conditional flag that restricts the counting of any further events or accrual additional costs or QALYs beyond this age threshold: The updated calculation is as follows:

=IF(M12>=100,0,IF(timeHorizon="Lifetime",1,IF(E12<=timeHorizon,1,0)))

This ensures that the model's calculations strictly adhere to the stipulated time horizon, providing a robust framework for accurately projecting costs and health outcomes.

Excess mortality following fracture

B30. CS, Section B.3.3.5, Table 44. Please clarify why an excess risk of mortality following fracture has been assumed for hip, vertebral and nonvertebral fractures when European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO)/International Osteoporosis Foundation (IOF) recommendations suggest only hip and vertebral fractures should be included. Please also provide a scenario in

which only hip fractures are associated with an excess risk of mortality as recommended by ESCEO/OIF.

To align with the recommendations of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and International Osteoporosis Foundation (IOF), for the conduct of economic evaluations in osteoporosis,[34] the model base case has been updated to model excess mortality after hip and vertebral fractures.

The updated model includes an option within the "Settings" sheet (cell "E29") to select the scenario where excess mortality is applied solely to hip fractures, as requested.

Full details of the updated model are presented in the Appendix Section B.2.10.1.3 and an overview of the results are presented in the Table 22 below.

Table 22 Results of the scenario analysis limiting excess mortality to hip fractures

Scenario	Description	Incremental costs	Incremental QALYs	ICER
Base case: romosozumab	NA	[redacted]	[redacted]	Dominant
Excess mortality applied on	Hip fracture only	[redacted]	[redacted]	Dominant
Base case	NA	[redacted]	[redacted]	Dominant
Excess mortality applied on	Hip fracture only	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life years

B31. CS, Section B.3.3.5, Table 44. Please clarify how long these increased risks of death following fracture are applied and justify why this is the appropriate duration. Is it applied from the time of the first fracture of that type onwards or only in the first cycle after the incident fracture because after that patients move to the 'at risk' health state? Does it apply a second time if a second fracture of the same type occurs? In the model that informed TA464 (Davis et al. 2016), it was assumed that excess mortality was limited to the first 6 months after hip and vertebral fracture. If the duration of excess

mortality fracture assumed in the model is longer than 6 months, please provide a scenario in which the increased risk is applied only for the 6 months.

The increased risk of death after fracture is applied for one cycle only (6 months). However, when a fracture persists for more than one cycle, the increased risk of death also persists for the same period. For subsequent fractures, the respective increased risk of death accumulates from the previous fracture. As requested by the EAG, a scenario in which the increased risk is applied only for 6 months has been included. This aligns with previous appraisals.[38]

Table 23 Results of a scenario analysis limiting the increased risk of death to 6 months post-fracture

Scenario	Description	Incremental costs	Incremental QALYs	ICER
Base case: romosozumab	NA	[redacted]	[redacted]	Dominant
Excess mortality risk after fracture persistence	Only 6-months	[redacted]	[redacted]	Dominant
Base case	NA	[redacted]	[redacted]	Dominant
Excess mortality risk after fracture persistence	Only 6-months	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life years

B32. CS, Section B.3.3.5, Table 44: Please clarify why the data from van Staa et al (2007). on excess mortality, used in the model that informed TA464 (Davis 2016), have not been applied as these provide estimates of absolute excess risk based on a UK source.

Due to a lack of country-specific data, it was assumed that the excess mortality based on Swedish data is generalisable to the UK. However, based on the EAG's suggestion, the excess mortality data sourced from van Staa et al 2007[39] has been included in the updated base case and is applied to hip and vertebral fractures.

Full details are presented in the Appendix, Section B.2.2.5.

B33. Model, 'Simulation' sheets for each treatment group, columns Q to S, headed 'Excess Mortality'. In previous models, it was assumed that only 30% of excess mortality was attributable to the incident fracture. In TA791, the RR was down adjusted by multiplying by 0.3 (TA791, committee slide 43). In columns Q to S of the simulation sheets for abaloparatide and romosozumab the excess risk estimated for the general population is being multiplied by (1-excess_mortality) where excess_mortality =0.3. Therefore it appears that 70% of excess mortality is being assumed to be attributable to the fracture rather than 30%. Please correct this or clarify why the current approach is appropriate.

The calculations have been modified and the component of subtracting 30% from 1 has been removed. Thus, 30% excess mortality (relating to the comorbidity adjustment factor) is applied on the incident fracture. This is consistent with previous technology appraisal.[4] has been included in the updated base case and is applied to hip and vertebral fractures.

The full results from updated economic model are presented in the Appendix, Section B.2.9 and Section B.2.10.

B34. PRIORITY Model, 'Simulation' sheets for each treatment group, columns Q to S, headed 'Excess Mortality': A RR approach is being used to capture excess mortality such that absolute risk after fracture is equal to the absolute risk in the general population multiplied by a RR which reflects the increased risk of death in people who have recently fractured compared to members of the general population. The adjustment for the proportion of excess risk attributable to fracture (30%) is then applied to this estimate of absolute risk after fracture. Therefore the total absolute risk of death after fracture is being adjusted for comorbidities and not the excess risk. In the 'other' fracture category, where the RR for fractured patients versus the general population is 1.23 (see CS, Table 44), this results in an absolute risk in the year following 'other' fractures that is lower than the risk of death based on general population characteristics. The EAG believes that the correct approach would be to apply the adjustment only to the excess risk, which is the part of the RR that is over 1. For example, if people with an incident fracture have a 23% higher risk of death in

the year following fracture than members in the general population, then the RR would be 1.23, but the absolute risk following fracture would be as follows:

General population risk x [(1.23-1)*0.3+1] = general population risk x 1.069

Please correct the model in line with the EAG's suggestion or clarify why the current approach is appropriate.

The calculation in the model has been updated according to the EAG's suggestions. The excess mortality is being applied in Q to S columns across treatment strategies.

B35. Model, 'Simulation Teriparatide' sheet. Please clarify the reason for any difference present in the formulae applied in the Simulation Teriparatide sheet to calculate the mortality risks in columns Q to S (headed 'Excess Mortality') in relation to those applied in the 'Simulation Abaloparatide' and the 'Simulation Romosozumab' sheets. This difference results in excess mortality only being adjusted down for the Teriparatide group after a hip fracture is sustained, which is not the case for the other two treatment strategies. Please correct any errors in the formulae so the same assumption for excess mortality following fracture applies across all three treatment strategies.

The model has been revised to ensure uniform application of the excess mortality risk formulae across all treatment strategies. This correction aligns the teriparatide treatment group with the standardised approach used for abaloparatide and romosozumab groups, ensuring that all groups now accurately reflect the intended model assumptions for excess mortality following a fracture. The model has been re-validated to confirm that these adjustments produce the expected outcomes and maintain the integrity of the comparative analysis across the treatment strategies.

Persistance

B36. CS, Section B.3.3.3. The company states that persistence on alendronate for patients following romosozumab is based on data from Morley et al. (2020). The data in the far-right column of Table 42 appear to match the data in the EAG report for TA791 (Table 4.13) in which the EAG provides the data from Morley et al. that they applied. These appear to match the data tabulated for non-naive patients starting oral bisphosphonates (Table 2 and Figure 4 of Morley et al.). However, the company used

the data from months 18 onwards suggesting that they interpret these figures as time since starting any treatment rather than time since starting alendronate. Please clarify why the data have not been applied according to time since starting alendronate (e.g. 31% persistence 6 months after starting alendronate) if they refer to persistence specifically on alendronate. Please provide functionality in the model to use the data in this manner.

An inconsistency in the application of the persistence data from Morley et al.[40] relating to alendronate post-anabolic therapy was identified. The data had been applied from the 18-month timepoint incorrectly, as it had been interpreted as the commencement of any osteoporosis treatment rather than the specific initiation of alendronate. It is acknowledged that this approach does not align with the EAG's application of the data or that used in pervious technology appraisals,[4] which is based on time since starting alendronate. To address this, the model has been adjusted to reflect persistence data beginning at the 6-month mark post-initiation of alendronate, ensuring that the methodology is consistent with the EAG's recommendations and more accurately represents patient persistence on alendronate therapy.

Full details are presented in the Appendix, Section B.2.2.3.

B37. Please clarify why it is appropriate to use data from clinical trials to model the persistence for alendronate following abaloparatide and teriparatide treatment and data from real world evidence to model the persistence on alendronate following romosozumab. Please provide a scenario analysis in which the Morley et al. data is applied for alendronate persistence across all three treatment arms.

The base case has been updated to use the Morley et al 2020[40] data for alendronate persistence across all three treatment arms in the 'Clinical Inputs' sheet.

Full details are presented in the Appendix, Section B.2.2.3.

B38. CS, Section B.3.3.3, page 115 and Table 42. The company states that "*The persistence rates for romosozumab were taken from a real-world study.[80]*" However, ref 80 by Söreskog et al. (2021) is an economic analysis of romosozumab in postmenopausal patients with severe osteoporosis at high risk of fracture in Sweden, which states that "*Romosozumab persistence for this economic evaluation was conservatively assumed to be 80% at 12 months*." Please clarify/justify the choice of

using persistence data from Söreskog et al. (2021) instead of data from other sources (e.g. the ARCH trial, if available)? Please clarify if any searches were conducted to identify real world evidence sources for romosozumab treatment persistence data.

The Söreskog et al. (2021)[32] study was chosen as it was the EAG's preferred source of data for romosozumab persistence in the romosozumab appraisal (TA791).[4] The ARCH trial[22] was not used as persistence in clinical trials is known to be significantly higher than in clinical practice, as patients know they are being observed. Söreskog et al. (2021)[32] was therefore used as clinical trial data can overestimate persistence and TA791[4] stated that there were no persistence data from RWE due to the recent UK launch of romosozumab. We did not conduct any literature searches to identify UK RWE sources for romosozumab treatment persistence data.

B39. CS, Section B.3.3.3, Table 42. The data from this table appear to be used directly to calculate the risk of stopping treatment in each 6-month cycle. However, these data are the cumulative risk of remaining on treatment and not the risk of discontinuation each cycle. In addition, the risk of being persistent appears to be sampled independently each cycle, such that patients can be non-persistent at an early time point and then sampled to be persistent with treatment with a later time point. This does not seem compatible with a time to event approach whereby patients are persistent on treatment until such time when they stop persisting. It also appears to lead to an increasing rather than a decreasing proportion being persistent on treatment between 1 year and 18 months in the 'Simulation Aggregation' sheet. We would suggest that it would be better to calculate the risk of stopping treatment for each cycle, given that they have persisted up to that point. The current approach may overestimate the discontinuation, which impacts on costs of drug.

To address this, the model approach has been refined. The calculations in columns U to AH for each treatment strategy have been corrected to ensure that the risk of stopping treatment is assessed accurately for each cycle, given persistence up to that point. The updated model calculates the probability of discontinuation in a manner that reflects cumulative persistence, rectifying the previous issue where patients could be incorrectly sampled as non-persistent and then persistent in subsequent cycles.

The revised model ensures that once a patient discontinues, they are not sampled for persistence in later cycles, consistent with a true time-to-event analysis. This

adjustment ensures that the proportion of patients persisting with treatment over time decreases in a realistic manner, aligning with the expected clinical scenario. These modifications have been applied retrospectively and prospectively in the model to ensure that the persistence data used is appropriate and that the impact on drug costs is now accurately represented.

B40. CS, Section B.3.3.3, page 115. The company states that, '*However, it was assumed that if a patient discontinues the initial treatment in a sequence before the maximum duration of initial treatment, then the patient will not be eligible to switch to alendronate. Sequential treatment was exclusively extended to those patients who fully adhered to the initial treatment protocol."* Please clarify the clinical rationale and validity for that assumption, and how this assumption was included in the model.

In the model, it was assumed that if a patient discontinues the initial treatment in a sequence before the maximum duration of initial treatment, then the patient will not be eligible to switch to alendronate. This is to ensure the optimal anabolic effect of abaloparatide, teriparatide and romosozumab were captured in the economic model. Treatment adherence helps to ensure that BMD increases are optimised before the antiresorptive is initiated. This effect is highlighted in ACTIVE,[8,9] where the greatest gain in BMD in the abaloparatide population was at 18 months, versus the 6- and 12-month timepoints.

Utilities

B41. CS, Section B.3.4.3 and model. Please clarify why the utility values for the UK general population were informed by Szende et al (2014), instead of usual data sources (e.g. Hernandez et al 2022). Please also clarify why the values in the model ('Country specific data' worksheet, column Q) do not match with the values reported in CS Table 46 or the EQ-5D measurements presented for the UK in the Szende et al study (2014). Please also clarify the rationale for picking the mean EQ-5D index values from the Szende et al study (2014) from the 'total' population instead of 'females'.

The base case has been updated to use Health Survey of England (HSE) 2014 female UK utility values from Hernandez et al 2022.[41] Hernandez et al states, their

recommendation to NICE is to use the most up to date information available that has direct observation of EQ-5D-3L from the HSE (2014). This is due to the 2020 survey data collection occurring during COVID lockdowns. For full details see the Appendix, Section B.2.3.3.

B42. How were the first year and subsequent year utility multipliers calculated from the various time points reported in ICUROS? Why do these differ from the values used by Davis et al. (2020).

The first and subsequent year utility multipliers were not calculated from the various timepoints reported in the International Costs and Utilities Related to Osteoporotic Fractures (ICUROS) Study; they were sourced from Söreskog et al 2021.[33] The values differ from those used in Davis et al 2020,[3] as the two publications cite ICUROS data from different timepoints, ICUROS data from 18 months[42] and 4 months,[43] respectively.

In the 'Clinical Inputs Sheet', the model has been updated to utilise the data from ICUROS at 18 months[42] and therefore now aligns with that reported in Davis et al 2020.[3] Full details are presented in the Appendix, Section B.2.3.3.

B43. PRIORITY Utility data in 'Simulation Romosozumab' and 'Simulation Teriparatide' sheets, columns CG to CJ, appear to be looking at columns AK to AM to assess fracture history rather than columns AJ to AL, (which are referred to in equivalent columns in the 'Simulation Abaloparatide' sheet). Please clarify if this is an error and either correct it or justify why the current approach is correct.

The issue has been resolved by linking columns CV to CY to columns AN to AP rather than to columns AO to AQ in the 'Simulation Romosozumab' and 'Simulation Teriparatide' sheets.

B44. PRIORITY Model, 'Simulation Teriparatide' worksheet, columns CG to CQ. The utility values, LYs and QALYs are not applied in the first row of these columns (row 7), whilst they are for the other two treatment groups (abaloparatide and romosozumab). Please clarify if this is an error and either correct it or justify why the current approach is correct.

This was an error which has been corrected by including row 7 of "Teriparatide Simulation" sheet in the calculations for utility values, LYs and QALYs, ensuring it is

aligned with the methods used in the 'Abaloparatide Simulation' sheet and Romosozumab Simulation' sheet.

B45. PRIORITY CS, Section B.3.4.3 and model. Please clarify if the 2nd and subsequent year utility values reported in CS Table 45 and model worksheet 'Clinical Inputs' are applied anywhere in the model, or if the utility value from the first year after fracture is applied to all subsequent years. If so, then this does not match what is stated on page 119 to 120 of the CS. Please correct the model to match what is described in the CS or provide a correct description of what is modelled. Please also provide evidence for the assumption that fractures have the same effect on HRQoL from the second 2 year after fracture onwards.

The model has been corrected so that the second and subsequent year utility values in columns CO to CR are applied for all treatment strategies to align with the description mentioned on page 119 and 120 of CS.

Evidence of long-term impact of fractures is reported in several studies, Adachi et al. 2011, Blomfeldt et al. 2005 and Ekström et al. 2009:[44–46]

- Adachi et al 2011 found that EQ-5D utilities remained lower than pre-fracture utilities after 3-years post-fracture.[44]
- Blomfeldt et al 2005 reported continuing steady decline in utility between months 4, 12, 24, and 48 post-displaced femoral neck fracture, which could be likely to continue.[45]
- Ekström provides evidence for a steady-state lower post-fracture utility at months 4, 12 and 24 post-subtrochanteric fracture.[46]

In economic assessments of osteoporosis treatment, it is often assumed that the impact on an individual's QoL persists over their lifetime following a fracture. In the recent assessment by NICE of non-bisphosphonates, the independent academic Assessment Group assumed that the quality-of-life multiplier was the same in the second year after fracture as in the subsequent years, with no restriction of duration of the impact[47] Many other economic evaluations have made the same assumptions, as identified by the systematic review in the aforementioned MTA.[47] Furthermore, the ESCEO/IOF guidelines for conducting economic evaluations in osteoporosis

recommend assuming QoL impact of fracture for first and subsequent years after fracture, separated by an acute and a chronic multiplier.[34]

These studies suggest that a long-term effect of fracture on HRQoL could be appropriate as the same lifetime chronic multiplier assumption was made in TA464 and the discontinued ID901,[17,47] it is proposed that this is a valid and accepted approach.

B46. CS, Section B.3.4.3. Please clarify how the utility multipliers were applied in the model to account for multiple fractures. For example, are they are accounted for in a multiplicative approach (more than one multiplier being applied at the same time). Please also clarify what utility is assumed if a second fracture of the same type occurs at a later date. If a multiplicative approach is used, please also add to the model the option of applying a different approach, such as a maximum disutility approach (whereby only the most impactful multiplier is applied).

In the model the multiplicative approach is utilised to account for multiple fractures of the same type, however for fractures of different types, the maximum disutility approach is used.

Resource use

B47. CS, Section B.3.5.1, Table 47. Please clarify regarding the drug acquisition costs:

a) Why the number of units for alendronate is given as 52.25 per year when each pack contains four tablets and therefore only 13.06 packs are required per year.

- The 'Cost Inputs' sheet in the model has been updated to incorporate 13 packs of alendronate per year.

b) Why 13 prefilled pens of teriparatide are required per year when each pen provides 30 doses and therefore the number of pens required per year would be 12.2. Even if it is assumed that every patient persists with treatment for 24

months, and there is wastage from unused doses, this would be covered by 25 pens not 26.

- Teriparatide pens provide 28 doses as per the SmPC,[7] therefore 13 pens are needed per year.

c) Table 47 states that each prefilled pen of abaloparatide contains 30 doses of 80 micrograms. But the drug's SMPC states that each pen contains 3mg, which would correspond to 37 doses. Please clarify how the number of annual doses for abaloparatide was calculated.

- Each prefilled pen of abaloparatide contains 3 mg of the drug. However, a common feature with many pre-filled pens is the inclusion of an "overage" amount of the drug, this also applies to the abaloparatide pen.
    - This "overage" serves several critical purposes:
        i. **Priming of the pen:** Before the first dose is administered, the pen requires priming to ensure its proper functionality. This involves one to two ejections of 40 µL each.
        ii. **Ensuring accurate doses**: The pen is designed to ensure that a full dose can be delivered every time. If the cartridge contains insufficient product, the pen will not function, hence a surplus is included to account for this.
        iii. **Product retention:** Due to the constraints of the cartridge design, not all of the product can be entirely extracted. This is a safety feature to ensure each dose delivered is complete and not partial.
- As the pens are stored at room temperature for 30 days from opening, any remaining unused product must be disposed of after 30 days. Therefore, this corresponds to 30 doses per pen as per the recommended posology. Theoretically, the pens contain 37 doses from the pen based on the total product volume, this is neither practically feasible nor medically advised due to the reasons outlined above.[12]

d) Please clarify if the company is assuming wastage for any of the drugs included in the model, and the calculations to estimate the annual number of pens/packs for each drug that generated the drug acquisition costs per cycle.

- In the model wastage is only assumed for abaloparatide, given the excess doses provided in the pre-filled pens. The calculations to estimate the annual number of pens/packs for each drug that generated the drug acquisition costs per year (the model incorporates annual drug costs not per cycle costs) are provided in Table 24.

Table 24 Calculations for the annual number of drug units in the updated model

Drug	Calculation for annual units
Alendronate	52/4=13
Teriparatide	365/28=13.04 = 13
Abaloparatide	18 months=~548 days, so 548/30 doses=18.3 pens, rounded up to 19 pens for 18 months. The annual number is (19/3)*2=12.67 pens.
Romosozumab	1*12=12

B48. CS, Section B.3.5.1.2. Please clarify what drug administration costs were assumed for drugs administered via subcutaneous injection other than abaloparatide? Is the one nurse visit per year for abaloparatide administration in addition to the disease management costs described in Table 49? Why is a nurse visit £6.45 in Table 49 and £9.00 in section B.3.5.1.2?

In the updated model, treatments are assumed to require one General Practice (GP) practice nurse visit for initiation of treatment (this is the administration cost) which is an annual cost therefore modelled as 0.5 per 6 month cycle. The GP practice nurse time for disease management have a different duration and frequency, therefore different cost to the administration visits.

Full details of the drug administration costs are provided in the Appendix, Section B.2.4.1.1 and Section B.2.4.2.2

B49. PRIORITY CS, Section B.3.5.2.1. Please clarify how the costs for long-term care (residential or nursing care) were estimated in the model. In particular;

a) The model includes data on % going into long term care after hip fracture in column S of the 'country specific data' sheet. These are described in the header for this column as "Proportion going to nursing home/long term care after hip fracture". Please clarify if these are applied to all fracture types equally (columns DL to DN of the simulation sheets). These data are referenced as being taken from Nanjayan 2014 but this paper is not cited in the submission. Please provide this paper and provide details on this data source and whether the incidence quoted relates to hip fracture or any fracture.

- The original model submitted to NICE used the data reported in Table 42 of the TA464 HTA[48] (which cited Nanjayan, 2014[49]) for 'proportion going to nursing home/long term care after hip fracture', however, as the data presented in the cited table was based on both genders, the model ('Country specific data' sheet, column S) has been updated to incorporate data for female patients discharged to long-term care after hip fracture only per Table 25 below. Nanjayan et al 2014[49] is provided in the reference pack. Nanjayan et al 2014[49] reported a UK observational study of the discharge destination of 1,503 patients after surgically-treated hip fracture.[48]

Table 25 Rate of admission for female patients to non-home institutional care setting after hip fractures[48]

Age band (years)	Odds ratio	% discharged from hospital to a non-home location, by age group
50–59	0.76	4
60–69	1.92	7
70–79	1.96	12
80–89	4.54	21
90–99	9.09	33

b) For vertebral and other fractures the cost of £173 is being applied to the proportion requiring long-term care, but the cost of £173 is applied as a per

cycle cost for 3 cycles and then no further long term care cost is applied. Please justify why long-term care is only required for 18 months. Please also justify why the cost of £173 is applied per cycle rather than per day when it is described as a daily cost on CS, page 121.

- See response below for c)

c) For hip fracture, the cost of £173 per cycle is applied for 3 cycles and then the cost per cycle increases such that the cost of £173 is applied daily. Please clarify why this change occurs at 18 months. If this is an error, please correct so that the daily cost is applied from the time of the fracture.

- The long-term care cost was linked with treatment duration in error and therefore for abaloparatide the long-term care cost was applied only up to 18 months after an incidence of fracture. The calculations have been modified for all the treatment strategies, and the long-term care cost is applied as a daily cost in the model. The per-cycle cost in the original model is £173*(365.25/2), however the costs have been updated per EAG suggestion in d). The assumption in the model is that this daily cost accrues until the patient dies.

d) Please clarify why UK costs from the PSSRU were not used to estimate long-term care costs as per the approach used in the model that informed TA464.

- The long-term costs were updated using PSSRU data for 2021–22 and inflated to 2023 (6.7% applied). The daily cost of long term care after hip fracture is now (1212/7)*1.067 = £185.

B50. PRIORITY Model, Simulation sheets for each treatment group, Columns DG to DI (Fracture related direct costs): It appears that only half the cost specified in the Table 48 of the CS is being applied at the time of an incident fracture and no costs are applied in subsequent years (except for long term costs). Please clarify if this is the case and please correct the model such that the modelling approach matches that described on CS pages 121 to 122, whereby costs are applied in the second and subsequent years for hip and vertebral fractures. Alternatively, please clarify where

the remainder of the fracture costs are applied or justify why the current approach implemented in the model is appropriate.

Cost allocation across cycles: In the updated model, a phased cost application strategy has been implemented, in which half of the annual cost of a fracture is applied in the cycle during which the incident occurs, with the remaining half applied in the subsequent cycle. This is because the table reports annual costs but the cycle length in the model is 6 months. For example, in the scenario of a hip fracture, which incurs an annual cost of £15,579. If a patient experiences their first hip fracture during cycle 24, half of this cost, amounting to £7,790, is applied in cycle 24 (as seen in cell DO54 of "Simulation Abaloparatide" sheet). The remaining £7,790, is then allocated to the next cycle, cycle 25 (refer to cell DO55 of "Simulation Abaloparatide" sheet).

Incorporation of subsequent years' costs: The model includes costs incurred in the second and subsequent years following a fracture, however, they are specifically applied to patients who have experienced at least one hip or vertebral fracture. at least one fracture of any type. The company modelling approach, as detailed above, is consistent with the descriptions provided on pages 121 to 122 of the Company submission.

B51. PRIORITY Model, Simulation sheets for each treatment group, columns CR to CU. The drug acquisition and administration costs are applied in full each cycle despite being provided in the parameter inputs as costs per year. Please correct this such that the cost per 6 months is applied each cycle or explain why the current approach is appropriate.

Changes have been implemented in the parameter sheet in cells G97:G100. The annual cost is now divided by 2 so that the annual drug acquisition and administration costs are converted to per cycle costs.

B52. Model, Simulation sheets for each treatment group, columns H to J. The discounting factor is set to 1 for the first 3 model cycles. Please correct this such that discounting is applied appropriately at a rate of 3.5% per annum from time zero.

The model has been updated to implement the 3.5% discount for costs and QALYs from time zero.

B53. Model, Simulation sheets. Please clarify if half-cycle correction has been applied and if not please justify why this is not necessary in this case.

Half cycle correction has not been applied in the model as they are not required in discrete-event simulation (DES) models. In addition, this is aligned with the previous TA464[48] and TA791[50] appraisals which were based on DES models.

Adverse events

B54. CS, Section B.3 and model, worksheet 'Cost inputs'. Adverse events are not described in the economic section of the CS, but the frequency of AEs is included in the 'Cost Inputs' sheet. However, zero costs are attributed to AEs in the results sheet and no QALY losses related to AEs are included in the model. Please clarify if adverse events are included in the company's base case or scenario analyses and if so, please fully describe the methods and input parameters used to incorporate them.

The costs for treating AEs were not included in the base case or scenario analyses. For clarity, the data for the frequency of AEs has now been removed from the model; however, the table and functionality is included to enable a full exploration by the EAG if required. Technical support documents for cost-effectiveness modelling using patient-level simulations for NICE also support the non-inclusion of AEs for treatments.[51]

B55. CS, Section B.3.11.1.3 and model, worksheet 'Cost inputs. Table 55 and Table 56 of the CS suggest that a scenario analysis which excludes 'Cardiovascular adverse events' were conducted. Please clarify how this was implemented, since the switch in the model worksheet 'Cost Inputs' which is labelled "Include cardiovascular events' appears not to connect with any other model cells when tracing dependents.

The original model had the option to exclude cardiovascular events, however, as there were no costs linked to the AE data, the result of the scenario was same as the base case. This scenario has been removed from the updated model for ease of navigation.

B56. Model worksheet. Please clarify the source for the incidence rates for AE events for patients receiving romosozumab (the spreadsheet refers to the ARCH study, but

the values in Table 2 of Saag et al 2017 do not match to the values reported in the model).

AEs of back pain and nasopharyngitis for romosozumab were sourced from the FRAME trial. The correct reference should be Cosman et al. 2016[20]. In the updated model, the costs for treating AEs were not included in the model due to the limited availability of AE data for the comparators.

Cost-effectiveness results

B57. CS, Appendix J, Tables 34 and 35, and model worksheet 'Settings'. Please clarify how it was established that 100 patients is a sufficient number to obtain stable unbiased estimates of costs and QALYs.

To determine the number of individual patients to simulate, a simulation was conducted to establish the number of patients in which the model stabilises. Graphical representations of the costs and QALYs were used to determine where the model stabilises and therefore the appropriate number of patients. This method to determine the appropriate number of patients can reduce the computational time required.

To further increase the stability of the results, the number of patients to simulate in the updated model was increased to 1,000.

B58. CS, Section B.3.11.1.2, Table 53. Please clarify:

a) why the scenario analyses reported in Table 53 do not always include the base case results within their range. For example, the ICER for abaloparatide versus romosozumab ranges from £10,079 to £6,924 when varying the price for abaloparatide either side of the base case value, but the base case results is that abaloparatide dominates romosozumab. Therefore, it would be expected that the range to include abaloparatide dominating when the price is decreased.

b) whether the upper value for the discount rate range for QALYs and costs in Table 53 should be 0.06 instead of 0?

The value was not zero but displayed as such due to the decimal place setting in excel.

c) the upper value of the range for the treatment effect for abaloparatide for vertebral and other fractures. Presumably these are not 0.

The value was not zero but displayed as such due to the decimal place setting in excel.

d) the upper value for health state utilities of the range for hip, vertebral and other fractures first year. Presumably these wouldn't be 1, since the value is higher than the equivalent utility for the general population.

The issues identified above were due to computational errors in the model. The model functionality and inputs have been updated, and these issues are no longer present.

Full results are presented in the Appendix, Section B.2.10.1.3

B59. CS, Section B.3.11.1.3, Table 55. Can you explain why excluding the FRAX based estimation from the model in the scenario analyses results in such a large change to the cost-effectiveness. Presumably this reduces the absolute risk of fracture, but does so for both the abaloparatide and the romosozumab treatment strategies. It seems counterintuitive that this makes abaloparatide more cost saving, suggesting it is preventing more fractures but results in lower QALY gains suggesting it is preventing fewer fractures.

In response to question B11, the model was updated to correctly reflect the RR values as estimated by FRAX, to ensure that values are greater than 1 for a high-risk population compared to the general population.

Full results presented in Appendix, Section B.2.10.1.3 and in Table 26.

Table 26 Results for scenario analysis: exclusion of FRAX

Scenario	Description	Incremental costs	Incremental QALYs	ICER
Base case: romosozumab	NA	[redacted]	[redacted]	Dominant
FRAX based estimation	Excluded	[redacted]	[redacted]	[redacted]
Base case	NA	[redacted]	[redacted]	Dominant

Scenario	Description	Incremental costs	Incremental QALYs	ICER
FRAX based estimation	Excluded	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life years

PSA

B60. CS, Appendix N and model 'Parameter sheet'. Please clarify which parameters were included in the PSA. Some parameters listed in Table 40 of Appendix N are set in the model not to be included in the PSA (column Q in 'Parameter sheet'), such as mean age and BMI, the baseline characteristics (mean age, BMI, and the other patients characteristics for FRAX), AEs incidence and costs, and costs of some tests and clinical visits. Please confirm if this was an error or justify why the current approach is appropriate.

The mean, age and baseline characteristics were not included in the PSA, as these values were sampled from the random numbers due to microsimulation nature of the model. The parameters which were included in the PSA are presented in Table 27.

Table 27 Parameters included in the PSA

Parameter	Inclusion in PSA
Discount rate in costs	Yes
Discount rate in Life-years	Yes
Discount rate in QALYs	Yes
Excess Mortality (fracture related)	Yes
Health state based utility: Hip 1st Year	Yes
Health state based utility: Hip 2nd and Subsequent Years	Yes
Health state based utility: Vertebral 1st Year	Yes
Health state based utility: Vertebral 2nd and Subsequent Years	Yes
Health state based utility: NHNV fractures 1st Year	Yes
Health state based utility: NHNV fractures 2nd and Subsequent Years	Yes

Parameter	Inclusion in PSA
Treatment effect of events abaloparatide hip	Yes
Treatment effect of events abaloparatide vertebral	Yes
Treatment effect of events abaloparatide NHNV fractures	Yes
Treatment effect of events romosozumab hip	Yes
Treatment effect of events romosozumab vertebral	Yes
Treatment effect of events romosozumab NHNV fractures	Yes
Treatment effect of events teriparatide hip	Yes
Treatment effect of events teriparatide vertebral	Yes
Treatment effect of events teriparatide NHNV fractures	Yes
Treatment effect of events alendronate hip	Yes
Treatment effect of events alendronate vertebral	Yes
Treatment effect of events alendronate NHNV fractures	Yes
Drug costs: Abaloparatide	Yes
Drug costs: Romosozumab	Yes
Drug costs: Teriparatide	Yes
Drug costs: Alendronate	Yes
Fracture related costs hip fracture	Yes
Fracture related costs vertebral fracture	Yes
Fracture related costs NHNV fractures	Yes
Fracture related costs hip fracture subsequent years	Yes
Fracture related costs vertebral fracture subsequent years	Yes
Fracture related costs NHNV fractures subsequent years	Yes
Cost of Long-term Hip fracture cost	Yes
Cost of Long-term Vertebral fracture cost	Yes
Cost of Long-term NHNV fracture cost	Yes
Initial administration	Yes

Abbreviations: HNV, non-hip non-vertebral; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years

Section C: Textual clarification and additional points

C1. Model, 'Parameter Sheet'. The information in columns E and F (parameter name and cell name) of the parameter sheet do not appear to match for some of the adverse event incidence data for rows 57 to 96. Please clarify if this discrepancy has any impact on any base case of sensitivity analysis results and please correct to allow full functionality.

Adverse events were not included in the base case or any scenario or sensitivity analyses (as described in the response to B54). The content related to AEs was included in the model so that the functionality could be utilised if needed.

C2. CS, Section B.3.3.4, Table 43. Please clarify if this is a typo in Table 43. We would expect the treatment duration for romosozumab/ alendronate to be 6 years (1 year romosozumab +5 years alendronate) and for teriparatide/alendronate to be 7 years (2 years teriparatide +5 years alendronate) as per Table 36. But the data on treatment duration in Table 43 appears to be the opposite to this.

This was an error, the data in Table 43 had been transposed so it did not align with that presented in Table 36 of the original Company submission. The data should have been presented as per CS, Section B.3.2.2, Table 36 of the original Company submission. The correction has been made to this table in the Appendix Section B2.2.4 as per Table 28.

Table 28 Base case maximum duration, offset time, and offset method used in the model

Treatment	Maximum duration	Offset period	Offset method
Abaloparatide/alendronate	6.5 years	6.5 years	Dynamic
Teriparatide/alendronate	7.0 years	7.0 years	Dynamic
Romosozumab/alendronate	6.0 years	6.0 years	Dynamic

See full details in the Appendix, Section B.2.1.2 and Section B.2.2.4.

C3. Appendix I.3.2 - Please clarify if the 'excel embedded' in "See Excel embedded in section D.3.2' refers to the model file or to another file.

The embedded excel in section D.3.2 presents the articles excluded from the clinical SLR. As 210 articles were excluded it was deemed appropriate to present the details in this way.

C4. Table 2. The company states that "List price of abaloparatide: £294.54 for one-prefilled pen with 30 doses in 1.5 mL solution Cost for a fixed-duration 18-month treatment (based on list price): £5,301.72." The EAG notes that the 18-month treatment was calculated by just multiplying the cost of a pack by 18, and does not account for the exact number of necessary doses for an 18-month treatment course.

The total costs for abaloparatide have been updated to £5,596.26 to consider the use of 19 pens over the 18-month treatment course.

C5. CS, Section B.3.5.2.2. Is Borgstrom et al (2004) as the source of the disease management costs for romosozumab a typo? Should it be the source for alendronate?

This was an error which has been updated to 'Assumption' for romosozumab and Borgstrom et al (2004) for alendronate. Please see Table 29 below, and Appendix Section B.2.4.2.2.

Table 29 Disease management cost and resource use in the model per cycle

Resource	Unit cost	Frequency per 6 months			
		Abaloparatide	Teriparatide	Romosozumab	Alendronate
BMD measurement	£40.00	0.25	0.25	0.25	0.25
GP practice nurse visit[a]	£7.45	1.0	1.0	1.0	1.0
One-off costs applied to all initial treatments					
Reporting to referrer	£0.76				
Specialist consultation	£143				
Source	PSSRU [52]	Assumption[4,34]	Assumption[4] and Hiligsmann et al 2019[34]	Assumption and Hiligsmann et al 2019[34]	Borgstrom et al 2004[49]

Abbreviations: BMD, bone mineral density; GP, general practitioner; PSSRU, Personal Social Services Research Unit

a. based on a 9.72 minute consultation for a GP practice nurse visit costed at £46 per hour

C6. PRIORITY Please provide a version of the model that: (i) fixes any errors listed in the questions above, (ii) is free of internal errors (free of error messages after some time opened), and (iii) that can be saved by the EAG after any alterations.

Please refer to the updated model. A detailed description of the model, assumptions, inputs, and results are presented in the Appendix.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture [ID882]

Section A: Clarification questions

December 2023

File name	Version	Contains confidential information	Date
ID882 abaloparatide_osteoporosis_Section A clarification responses [redacted]	V1.1	Yes	7th March 2024

Notes for external assessment groups (EAGs) and NICE

[TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Studies included in the indirect treatment comparison

A1. Company response to A19: Thank you for providing the de-prioritisation criteria. Please can you explain why studies that have not included North American or Western European participants are considered less relevant than those that included North American or Western European participants. The EAG's clinical experts have indicated that there are differences in the absolute risk of fracture across different ethnic groups (see Cauley 2011) but previous economic models (e.g. Davis 2016)

have assumed the relative risk for fracture is consistent across groups with different baseline risks. Is there any evidence that anti-resorptive or anabolic treatments for osteoporosis have greater or lesser efficacy in preventing fracture in particular ethnic groups or in groups recruited in particular regions? In your response to the previous round of clarification questions (A26) you stated that "*Ethnicity and prevalent vertebral fracture remain an area of investigation and discussion in relation to treatment effect and are not established treatment effect modifiers in osteoporosis."* If ethnicity is not expected to be a treatment effect modifier, then what is the rationale for excluding these studies?

A literature search was not conducted to determine if anti-resorptive or anabolic treatments for osteoporosis have greater or lesser efficacy in preventing fracture in particular ethnic groups or in groups recruited in particular regions. It is not clear if ethnicity is a treatment effect modifier, however, Cauley et al 2011[1] report that there is large ethnic and racial variability in hip and all fracture rates.[1] In addition, disparities exist among racial and ethnic groups in osteoporosis diagnosis, dual X-ray absorption (DXA) measurement, and access to treatment.[2] These issues along with, differences in fracture risk due to ethnicity,[2] suggest that race and ethnicity could be confounding factors in the NMA. Therefore, the rationale for the exclusion of studies conducted outside of North America/Western Europe was to align with the population in the NICE appraisal submission.

A2. PRIORITIY Company clarification response – Appendix B.3.1, Table 39: Thank you for providing the reasons for studies being excluded when they were previously included in the analysis reported by Davis et al. (2020). We note that several studies have been excluded on the basis of the BMD values being outside of the target range, with a T-Score <-2.5 SD being specified in the company's review inclusion criteria. We note that some of the key efficacy studies for bisphosphonates, e.g. Cummings 1998 and Lufkin 1998, were conducted before modern definitions of osteoporosis were available leading to populations being recruited in which some patients fell outside of the current standardised definition of osteoporosis (T-Score<-2.5SD). In some other studies, less stringent definitions were applied to recruit populations (e.g. T-Score <-2 SD in Greenspan 2002, Fogelman 2000 and Sambrook 2004, Kendler 2010) These studies have been previously combined in network meta-analyses with studies which used the modern standard definition of osteoporosis (T-Score <-2.5 SD) and studies

that specifically recruited higher risk populations (e.g. ARCH Saag 2017), and meta-regression found no evidence of treatment effect varying by baseline risk (Davis 2020). Please reconsider whether any of these studies can be included. If including the full population of these studies is still considered inappropriate, please consider whether any of these studies provide subgroup results for the T-Score<-2.5 population that could be included, as we believe to be the case for Cummings et al. 1998.

The T-score of ≤2.5 SD below the score for young female adult mean was chosen based on the threshold used for the diagnosis of osteoporosis as defined in the European Foundation for Osteoporosis and Bone Disease (subsequently the International Osteoporosis Foundation; IOF) guideline published in 1997.[3] The updated versions of these guidelines in 2008, 2013 and 2019 also use the same threshold for the diagnosis of osteoporosis.[4–6]

The guidelines also state that a BMD of -2.0 means low bone mass (osteopenia) and should not be considered as a disease category but is intended solely for the purpose of epidemiological studies. Therefore, we have not included the articles which have patient populations aligned with this less stringent definition of osteoporosis. The articles which were excluded based on the BMD values being outside of the target range, with a T-Score <-2.5 SD were rescreened for relevant sub-group data. As a result, data from Cummings et al. 1998[7] was added to the NMA.

A3. PRIORITY Company clarification response – Appendix B.3.1, Table 39: Please clarify why Ettinger 1999 (MORE study) is described as being excluded due to insufficient fracture data being reported when Davis et al. (2020) cite fracture data being available from the MORE study (Ettinger 1999 and Maricic 2002). The EAG can find no mention of Maricic 2002 being included or excluded from the company's searches. Please include the data for this study. It can be lifted directly from Davis et al. (2020) if required (see Tables 17 and Table 27 of Davis 2020).

Following full text review of the primary publication for the MORE study (Ettinger 1999)[8], the article is now included in the updated NMA. Maricic et al. 2002[9] was not included in the NMA as it reports duplicate data to that provided in Ettinger et al. 1999.[8]

Full results are available in the Appendix, section B.1.5.

A4. Company response to A22: Some of the studies were excluded from the original review for being published before 2012 (see company response Table 13). The EAG expected to see all of these studies either included in the updated review, or a reason being provided for their exclusion. However, for some of these studies, the EAG cannot find a reason given for their exclusion from the updated review within the documents submitted. Examples include the STAND (Kendler 2010) and DAPs studies (Kendler 2011 and Freemantle 2012), Hooper 2005 and Panico 2011. Please ensure that for every study in clarification response Tables 13 and 14 that was previously excluded because it was published pre-2012, there is a reason provided as to why it does not meet the criteria for the updated review.

Table 1 and Table 2 list all the records that were initially excluded due to their publication dates being prior to 2012. In these tables, the updated screening outcome for each publication is presented. The reasons for exclusion are provided for the publications that remain excluded in the updated NMA. Freemantle et al. 2012[10] was excluded from the systematic literature review (SLR) during title/abstract screening due to the study design not being of interest (open label, cross over study). Additionally, the population T-score did not meet the criteria specified in the SLR PICOS.

Table 1 Studies from Davis et al. 2016 that were originally excluded due to timeframe (pre-2012)

Reference number in Davis et al. 2016[11]	Author, year	Reason for exclusion from the original NMA submitted to NICE	Screening results
45	Chesnut 2004 (BONE)	Published before 2012	The article is now included in the updated NMA.
55	Black 1996 (FIT I)	Published before 2012	The article is now included in the updated NMA.
56	Black 2007 (HORIZON-PFT)	Published before 2012	The article is now included in the updated NMA.
58	Boonen 2009	Published before 2012	Population outside scope; male population. Subpopulation data is not presented.
60	Carfora 1998	Published before 2012	Study design out of scope; real world evidence data.
63	Cohen 1999	Published before 2012	Population out of scope; men and women with glucocorticoid-induced osteoporosis
64	Cummings 1998 (FIT II)	Published before 2012	The article is now included in the updated NMA.

Reference number in Davis et al. 2016[11]	Author, year	Reason for exclusion from the original NMA submitted to NICE	Screening results
65	Dursun 2001	Published before 2012	Deprioritised: sample size <200 and did not include population from N America/ W Europe.
66	Fogelman 2000 (BMD-MN)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
70	Harris 1999 (VERT-NA)	Published before 2012	The article is now included in the updated NMA.
72	Hooper 2005	Published before 2012	Deprioritised: did not include population from N America/ W Europe.
76	Liberman 1995	Published before 2012	The article is now included in the updated NMA.
77	Lyles 2007 (HORIZON-RFT)	Published before 2012	Population out of scope; male and female population. Subpopulation data is not presented.
81	Miller 2008 (MOTION)	Published before 2012	The article is now included in the updated NMA.
82	Muscoso 2004	Published before 2012	The article is now included in the updated NMA.
83	Orwoll 2000	Published before 2012	Population out of scope; male population.
85	Reginster 2000 (VERT-MN)	Published before 2012	The article is now included in the updated NMA.
86	Reid 2000	Published before 2012	Population out of scope; patients with glucocorticoid-induced osteoporosis
88	Reid 2009 (HORIZON)	Published before 2012	Population out of scope; patients with glucocorticoid-induced osteoporosis
89	Ringe 2006	Published before 2012	Population out of scope; male population

Abbreviations: BMD, bone mineral density; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis

Table 2 Studies from Davis et al. 2020 that were originally excluded due to timeframe (pre-2012)

Reference number in Davis et al. 2020[12]	Author, year	Reason for exclusion from the original NMA submitted to NICE	Screening results
41	Cummings 2009 (FREEDOM)	Published before 2012	The article is now included in the updated NMA.
46	Adami 2008	Published before 2012	Outcomes out of scope; fracture data not reported.

Reference number in Davis et al. 2020[12]	Author, year	Reason for exclusion from the original NMA submitted to NICE	Screening results
47	Morii 2003	Published before 2012	Deprioritised: did not include population from N America/ W Europe.
48	Liu 2004	Published before 2012	Deprioritised: did not include population from N America/ W Europe.
50	Silverman 2008	Published before 2012	The article is now included in the updated NMA.
51	Ettinger 1999 (MORE)	Published before 2012	The article is now included in the updated NMA.
52	Lufkin 1998	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
53	Mok 2011	Published before 2012	Population out of scope; patients with glucocorticoid-induced osteoporosis.
57	Orwoll 2003	Published before 2012	Population out of scope; male population.
58	Miyauchi 2010	Published before 2012	Population out of scope; mixed male and female population. Subpopulation data is not presented.
59	Miyauchi 2008	Published before 2012	Population out of scope; mixed male and female population outside N America/ W Europe.
62	Neer 2001 (FPT)	Published before 2012	The article is now included in the updated NMA.
63	Sethi 2008	Published before 2012	Outcomes out of scope; fracture data not reported.
66	Eastell 2009 (EUROFORS)	Published before 2012	Outcomes out of scope; fracture data not reported.
69	Brown 2009 (DECIDE)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
70	Kendler 2010 (STAND)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
71	Kendler 2011 (DAPS)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.

Reference number in Davis et al. 2020[12]	Author, year	Reason for exclusion from the original NMA submitted to NICE	Screening results
72	McClung 2006 (AMG 162 Bone Loss)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
76	Sambrook 2004 (EFFECT International)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
77	Luckey 2004 (EFFECT USA)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
78	Johnell 2002	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
79	Muscoso 2004	Published before 2012	The article is now included in the updated NMA.
80	Recker 2007 (EVA)	Published before 2012	The article is now included in the updated NMA.
81	Sanad 2011	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
82	Michalska 2006	Published before 2012	Outcomes out of scope; BMD and biochemical markers only reported.
84	McClung 2005 (FACT)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility criteria. Subpopulation data is not presented.
85	Saag 2009	Published before 2012	Population out of scope; patients with glucocorticoid-induced osteoporosis.
86	Panico 2011	Published before 2012	Deprioritised: sample size <200.
88	Anastasilakis 2008	Published before 2012	Outcomes out of scope; fracture data not reported.
93	Cosman 2011	Published before 2012	The article is now included in the updated NMA.
313	Rosen 2005 (FACT)	Published before 2012	Population out of scope; BMD T-score and age/fracture history do not meet eligibility

Reference number in Davis et al. 2020[12]	Author, year	Reason for exclusion from the original NMA submitted to NICE	Screening results
			criteria. Subpopulation data is not presented.

Abbreviations: BMD, bone mineral density; FPT, Fracture Prevention Trial; N, North; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; W, Western

A5. PRIORITY Company clarification response – Appendix B.3.4, Tables 42 to 44: Bone 2013, Bone 2017 and Cummings 2009 all appear to be reports of the FREEDOM study or extensions to the FREEDOM study. However, they appear to form 3 separate studies in the NMA (Figure 3). Please clarify how these studies relate to each other and how they have been included in the NMA to avoid duplication of data. For example, Table 44 which presents hip fracture data included in the NMA appears to include both Cummings 2009 and Bone 2013 and both appear to provide 3-year data. All three studies contribute to Table 43 (non-vertebral fractures), with two sets of data being identical. In addition, both Bone 2017 and Bone 2013 both provide data in Table 42 (new vertebral fractures).

Cummings (2009)[13], Bone (2013)[14] and Bone (2017)[15] all report data from the FREEDOM trial. The Bone (2013)[14] and Bone (2017)[15] publications also report data from the FREEDOM extension study. The NMA has been updated to ensure there is no duplication of data from the FREEDOM trial. Where available the data from the primary trial publication (Cummings 2009)[13] has been used in the NMA.

These updates are reflected in the updated NMA. Full results and details are available in the Appendix, section B.1.5.

Network meta-analysis methods and results

A6. PRIORITY. Section B.1.5.6.4. “Table 12 presents the HR from the updated NMA used in the base case of the economic model. Table 13 presents the HR used for the alendronate treatment period in the base case of the economic model.”

a) Please clarify the statistical model that was used (fixed/random effects). It looks like these match the results from the fixed effects model.
b) Please clarify where the results in Table 13 come from. Are these from the same updated NMA?

a) The results in Table 13 of the appendix submitted with the September 2023 clarification questions are from the fixed effects model, however, as requested by the EAG the economic model has been updated to utilise the hazard ratios (HRs) from the random effects model. See Table 3 below and Appendix, section B.1.5.6.4.1.

Table 3 NMA estimates used in the base case for the economic model (REM)

Fracture type	Base case NMA estimates	
	vs. placebo	HR (95% CrI)
Hip	Abaloparatide	[redacted]
	Romosozumab	[redacted]
	Teriparatide	[redacted]
Vertebral	Abaloparatide	[redacted]
	Romosozumab	[redacted]
	Teriparatide	[redacted]
Non-vertebral	Abaloparatide	[redacted]
	Romosozumab	[redacted]
	Teriparatide	[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; REM, random effects model

b) The HRs for alendronate are from the same updated NMA submitted with the September 2023 clarification responses. The NMA has been updated again in response to the clarification questions provided by the EAG in December 2023. The HRs for alendronate are presented in Table 4 below and further information relating to the NMA updates are described in the Appendix, section B.1.5.6.4.1.

Table 4 NMA estimates for alendronate vs placebo in the base case - sequential treatment period (REM)

Fracture type	Base case NMA estimates
	HR (95% CrI)
Hip	[redacted]
Vertebral	[redacted]
Non-vertebral	[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; REM, random effects model

A7. PRIORITY. Company clarification response – Appendix B.1.5.5 NMA methodology pg 25. It is stated, "*In the absence of a formal estimate of heterogeneity a fixed-effects model was deemed appropriate to allow for heterogeneity between studies*". Please clarify/review this sentence. The company has stated previously that

heterogeneity in the network is expected (p24) and that random effects models were assessed to accommodate this heterogeneity (company response B20). If fixed effects models are used for the economic model (see A6), how does this allow for heterogeneity? Please update using a random effects approach for all NMA estimates that inform the economic model.

The analysis was conducted using both fixed-effects and random-effects models. Model comparison using deviance information criterion (DIC) and posterior means of the residual deviance did not indicate a clear preference for a single model. Both models produced effect estimates that were equally plausible according to residual deviance and DIC statistics. However, the economic model has been updated to utilise the results from the random effects model as requested by the EAG. Table 3 and Table 4 present the data used in the updated economic model and further details are provided in the Appendix, section B.1.5.6.4.1.

A8. PRIORITY. Company clarification response – Table 13: The presented results for hip fractures indicate a different direction of treatment effect vs placebo for several of the comparators, compared to the previous MTA by Davis et al (2016). The only direct RCT evidence from Black et al 1996 suggests a relative risk (RR) of (11/1022)/(22/1005)=0.49 for alendronate vs placebo. This is inconsistent with the hazard ratio (HR) of 2.69 from the NMA. There are similar issues for other treatment comparisons. Please confirm that the NMA results are correct for all analyses used to inform the model, and there are no data input errors.

The NMA results are accurate for all analyses and there are no data input errors. The data extraction and collation of NMA inputs were performed in parallel by two independent reviewers, and a third reviewer reconciled any discrepancies. A quality control step was conducted by an independent reviewer. For transparency, the NMA inputs are presented in the Appendix, section B.3.4.

In the context of the efficacy of alendronate for hip fractures, the study by Muscoso et al. (2004)[16] contributed to the indirect comparison between alendronate and placebo. This study reports that the incidence of fractures in the alendronate arm is 0.30%, while no fractures were reported in the other arms (raloxifene and risedronate), indicating a disadvantage for alendronate. Additionally, Saag et al. (2017)[17] provides data which contributed to the indirect comparison of alendronate versus placebo. The

fracture rate in the alendronate arm is 1.07%, compared to 0.68% in the romosozumab arm, once again suggesting a disadvantage for alendronate. Notably, only one study (Black, 1996, FIT I)[18] offers a direct estimate for the alendronate versus placebo comparison, where it is shown that the fracture rate in the alendronate arm is 1.1%, compared to 2.2% in the placebo arm. In the updated NMA, with the addition of data from Cummings et al. 1998,[13] the alendronate HR for hip fractures has changed (see Table 4), and the result is in line with the expectation that alendronate would be superior to placebo. The updated NMA is described in the Appendix, Section B.1.5.

The HR for hip fracture for the denosumab biosimilar is greater than that of denosumab as the NCT03974100[19] trial showed that the biosimilar was inferior to the originator against prevention of hip fractures.

The update of the NMA, as requested by the EAG, has impacted the HRs for some outcomes. In addition, it is important to note that the NMA reported in the Davis et al. 2016[11] publication included a broader patient population including men and women as well as types of osteoporosis other than post-menopausal. These differences contribute to the differential inclusion of studies between the submitted NMA and that published in Davis et al. 2016.[11]

A9. Company response to A23: Thank you for broadening the criteria for studies to be included in the network. One of the advantages of having a more complete network is the ability to assess for inconsistency statistically. This is particularly important if the network is predicting that a treatment increases the risk of fracture when the direct evidence predicts that it decreases the risk (see A8). Please consider assessing inconsistency in the networks. If inconsistency is not formally assessed then please clarify why this was not conducted.

Inconsistency was not evaluated in the previous NMA; however, this analysis has been conducted for hip, new vertebral and non-vertebral fractures, in the newly updated NMA as requested by the EAG. This analysis was conducted on these outcomes as they contributed to the economic model.

Inconsistency was evaluated using the inconsistency parameter approach proposed by Lu and Ades[20] (Bayesian hierarchical model), which is a generalisation of the Bucher method. As shown in Table 5 no inconsistencies were observed within the

networks for hip, vertebral and non-vertebral fractures, signifying a considerable level of coherence and reliability in the dataset. Table 5 presents the results of the analysis and further details are provided in the Appendix, section B.1.5.5.

Table 5 Inconsistency results for triangular loops in hip, new vertebral and non-vertebral fracture networks

Loop	IF (95% CI)
Hip fracture	
Denosumab-placebo-zolendronate	[redacted]
Alendronate-placebo-romosozumab	[redacted]
Placebo-romosozumab-teriparatide	[redacted]
Alendronate-placebo-raloxifene	[redacted]
Alendronate-placebo-risedronate	[redacted]
Placebo-raloxifene-risedronate	[redacted]
Placebo-risedronate-teriparatide	[redacted]
Abaloparatide-placebo-teriparatide	[redacted]
Alendronate-raloxifene-risedronate	[redacted]
New vertebral fracture	
Alendronate-placebo-romosozumab	[redacted]
Placebo-risedronate-teriparatide	[redacted]
Abaloparatide-placebo-teriparatide	[redacted]
Alendronate-raloxifene-risedronate	[redacted]
Non-vertebral fracture	
Alendronate-ibandronate-placebo	[redacted]
Alendronate-placebo-raloxifene	[redacted]
Alendronate-raloxifene-risedronate	[redacted]
Placebo-romosozumab-teriparatide	[redacted]
Placebo-risedronate-teriparatide	[redacted]
Abaloparatide-placebo-teriparatide	[redacted]
Placebo-teriparatide-zolendronic acid	[redacted]
Alendronate-placebo-romosozumab	[redacted]

Abbreviations: CI, credible interval; IF, inconsistency factor

A10. Company clarification response – Table 21: For all random effect models please provide 95% Predictive intervals (PrI) in addition to the 95% CrI that are presented. Please also provide the estimate of the between study SD with 95% CrI

The NMA has been updated to include the HR with PrI as requested by the EAG (Table 6). HRs with credible intervals are also presented for comparison.

Table 6 Hazard ratios with predictive and credible intervals for all fracture outcomes

vs. placebo	HR (95% PrI)	HR (95% CrI)
Hip fracture		
Abaloparatide	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]
Denosumab biosimilar	[redacted]	[redacted]
Raloxifene	[redacted]	[redacted]
Risedronate	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]
Zolendronate	[redacted]	[redacted]
New vertebral fracture		
Abaloparatide	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]
Denosumab biosimilar	[redacted]	[redacted]
Ibandronate	[redacted]	[redacted]
Raloxifene	[redacted]	[redacted]
Risedronate	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]
Zolendronate	[redacted]	[redacted]
Non-vertebral fracture		
Abaloparatide	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]
Ibandronate	[redacted]	[redacted]
Raloxifene	[redacted]	[redacted]
Risedronate	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]
Zoledronic acid	[redacted]	[redacted]
Clinical fracture		
Abaloparatide	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]
Risedronate	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]
Major osteoporotic fracture		
Abaloparatide	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]

vs. placebo	HR (95% PrI)	HR (95% CrI)
Teriparatide	[redacted]	[redacted]
New or worsening vertebral fracture		
Abaloparatide	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]
Risedronate	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; PrI, predictive intervals

The estimates of the between study SD with 95% CrI are provided in Table 7.

Table 7 Estimate of between study SD for new vertebral, hip, and non-vertebral fracture NMAs

Outcome	Between-study SD (95% CrI)
Hip fracture	[redacted]
New vertebral fracture	[redacted]
Non-vertebral fracture	[redacted]

Abbreviations: CrI, credible interval; NMA, network meta-analysis; SD, standard deviation

A11. Please state the software used to implement the Bayesian NMA.

The Bayesian NMA was implemented using the WinBUGS software, version 1.4.3.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture [ID882]

Section B: Clarification responses

File name	Version	Contains confidential information	Date
ID882 abaloparatide_osteoporosis_Section B clarification responses_[redacted]	V1	Yes	5th February 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section B: Clarification on cost-effectiveness data

Risk of fracture

B1. PRIORITY The EAG is concerned that the company's model is providing estimates of fracture risk that lack face validity. The company's CSR describes the average FRAX risk in the ACTIVE study as being 13% (CSR addendum Table 6). That means that FRAX predicts an average 10-year risk of major osteoporotic fracture (MOF) of 13% across the ACTIVE trial cohort. But in the submitted model, the average number of fractures per patient in the 'Simulation Aggregation' sheet appears to be around 10 (sum of cells G12 to I12). Even when adjusting the model to use a time horizon of 10 years, the model predicts an average number of fractures per patient of 3. The EAG would expect a properly calibrated model to provide an average number of fractures over 10 years of around 0.13 per patient in line with the average FRAX score in the ACTIVE study of 13%. Please clarify if the EAG is misinterpreting the reporting of these results. The EAG has provided several suggestions (see questions B2 to B8) for areas where the model may need correcting which will hopefully resolve this calibration issue. If a revised model is submitted, please assess the calibration of the fracture risk predictions when validating the model and report the average number of fractures per patient over a 10-year horizon in response to this clarification question.

The model has been adjusted as requested by the EAG and described in questions B2 to B8. The outcomes from 5,000 simulations of the base case and scenarios are presented in Table 1, Table 2 and Table 3 to assess the face validity of the model findings.

In the updated model, the number of fractures possible for each fracture type were limited to one per bone (e.g. two hip fractures) and four vertebral fractures. This approach is aligned with the Davis (2020)[1] economic evaluation. In the Company model, non-hip-non-vertebral (NHNV) fractures includes forearm (distal forearm, distal radius and wrist) and "other" fractures (femur, pelvis, humerus, rib, clavicle, scapula, sternum). Therefore, a limit of ten fractures was applied for the NHNV fracture type.

To allow the EAG to explore the impact of this approach, a drop-down menu has been included to select the maximum number of fractures for hip, vertebral and NHNV.

Table 1 Total number of fractures in the base case results at a 10-year time-horizon

Total Number of fractures	[redacted]	[redacted]	[redacted]
Hip	[redacted]	[redacted]	[redacted]
Vertebral	[redacted]	[redacted]	[redacted]
NHNV	[redacted]	[redacted]	[redacted]

Abbreviations: NHNV, non-hip-non-vertebral

Table 2 Total number of fractures in the base case results, with no FRAX algorithm, at a 10-year time-horizon

Total Number of fractures	[redacted]	[redacted]	[redacted]
Hip	[redacted]	[redacted]	[redacted]
Vertebral	[redacted]	[redacted]	[redacted]
NHNV	[redacted]	[redacted]	[redacted]

Abbreviations: FRAX, Fracture Risk Assessment Tool; NHNV, non-hip-non-vertebral

Table 3 Total number of fractures in the base case results, with no FRAX algorithm and no imminent risk, in the base case at a 10-year time horizon

Total Number of fractures	[redacted]	[redacted]	[redacted]
Hip	[redacted]	[redacted]	[redacted]
Vertebral	[redacted]	[redacted]	[redacted]
NHNV	[redacted]	[redacted]	[redacted]

Abbreviations: FRAX, Fracture Risk Assessment Tool; NHNV, non-hip-non-vertebral

B2. PRIORITY The EAG believes that the data in columns E and H of the 'FRAX estimates' sheet have been taken from the files 'Chart_UK_hip_wom_bmd.pdf' and 'Chart_UK_ost_wom_bmd.pdf' downloaded from the 'Paper Charts' tab of the FRAX website [https://frax.shef.ac.uk/FRAX/charts.aspx]. Please confirm if this is a correct deduction. If this is the case then these data provide the absolute risk over 10 years for hip and MOF respectively in women with known BMD. They are not RRs and the method the company has used to estimate RRs in columns V to X of the 'Model Data' sheet is incorrect as the company has not compared these absolute risks to absolute risks in the general population. To do this it is necessary to estimate the FRAX score predicted for the general population for each age band (as the general population risks are age band specific). The company could do this by using the average T-Score by age band and assuming a zero incidence of risk factors in the general population. Average T-score by age band can be found in Table 1 of the 2007 report by Stevenson et al. For example, for a 70 year-old woman with a T-Score of -2.5, and a risk factor of current smoking, the FRAX prediction on the

‘FRAX estimates’ sheet is 19% for MOF (cell H334). But the average T-Score in that age group is -1.69 (Stevenson 2007). If we look up age 70 and T-Score of -1.5 (presuming you are rounding T-Scores in this direction), then the FRAX prediction for MOF is 9.2% (cell H347) when assuming zero risk factors on average in the general population. Therefore, the RR needed to adjust from the general population to the trial population is 19%/9.2%=2.1. This figure could be used directly in ‘Model Data’ columns W and X and a similar process could be used to calculate RRs for column V using column E of the FRAX estimates sheet. There are some limitations to this approach, the most obvious one being that it assumes that the average number of risk factors in the general population is zero. It is therefore likely to overestimate risk in the trial population because it is underestimating the FRAX score in members of the general population as there will be a non-zero prevalence of some risk factors in the general population.

The data in columns E and H of the ‘FRAX estimates’ sheet were originally taken from the files ‘Chart_UK_hip_wom_bmd.pdf’ and ‘Chart_UK_ost_wom_bmd.pdf’ downloaded from the ‘Paper Charts’ tab of the FRAX website [https://frax.shef.ac.uk/FRAX/charts.aspx]. In the updated model, the predicted FRAX score for the general population age bands are calculated using the UK average T-score from Stevenson et al. 2007[2] and assuming a zero incidence of risk factors in the general population.

The UK average T-score data have been added to columns L and M of the FRAX estimates sheet; based on the data, the FRAX score for hip and MOF are populated in columns N and O. These FRAX scores are used to calculate the FRAX based adjusted relative risk in column V to X of Model data sheet.

The updated formula in columns V to X of the model data sheet is:

```
(INDEX('FRAX estimates'!$E$4:$E$1158,MATCH(1,INDEX((IF(CEILING.MATH($F6,5)>120,120,CEILING.MATH($F6,5))='FRAX estimates'!$B$4:$B$1158)*($N6='FRAX estimates'!$C$4:$C$1158)*(CEILING.MATH($G6,0.5)='FRAX estimates'!$D$4:$D$1158),0,1),0)))/INDEX('FRAX estimates'!$N$3:$N$22,MATCH(CEILING.MATH($F6,5),'FRAX estimates'!$L$3:$L$22,0))
```

B3. PRIORITY Company clarification response – Appendix B.2.2.5 p44. The equation for total fracture risk, includes a term RR_{frax} where " RR_{frax} = *relative risk estimated by FRAX for a given patient profile excluding prior fracture as a clinical risk factor.*" The EAG understands this to be the RR that the company is intending to estimate in 'Model Data' columns V to X. However, in the latest model submitted, the current patient has a prior fracture at baseline and no other risk factors, leading them to be classed as having one clinical risk factor (CRF) in column N. This one CRF is then used when looking up their FRAX score on the 'FRAX estimates' sheet despite the definition of RR_{frax} being described as excluding prior fracture. Please clarify if prior fractures at baseline are used when estimating RR_{frax}. If this is the case, then what assumption is made when an incident fracture occurs? The EAG notes that there is no mechanism in the model to update the CRFs in column N and therefore the impact of any incident fractures must be calculated using later terms of the equation e.g. "MAX(RR_{frax_fx} | RR_{recent})." In which case, the EAG suspects that any increased risk at baseline captured in RR_{frax} is maintained lifelong and therefore a patient who has a fracture at baseline and an incident fracture will have the risk factor for prior fracture applied once within RR_{frax} and again within "MAX(RR_{frax_fx} | RR_{recent})." Please clarify if this is the case and if so please reconsider your approach. Alternatively if the intention was for RR_{frax} to exclude prior fracture at baseline then please correct column N to exclude prior fracture accordingly.

The Company acknowledge that in the previous model, prior fracture at baseline was not excluded while calculating RR_{frax} from column N. This has been addressed in the updated model by not counting the prior fracture at baseline in column N of the Model data sheet. Therefore, the updated RR_{frax} calculation excludes the clinical risk factor (CRF) of prior fracture at baseline.

In column N, a SUM function was applied to columns J to M (baseline clinical risk factors). Column N is further used to look at the FRAX score from the FRAX estimates sheet columns E and H. The updated formula in column N is =SUM(J6:M6).

B4. PRIORITY Company clarification response appendix – B.2.2.5 p44. The equation for total fracture risk includes a term "MAX(RR_{frax_fx} | RR_{recent})" which the EAG interprets as meaning that the maximum is taken of RR_{frax_fx} and RR_{recent}. In this situation, the EAG would expect RR_{frax_fx} to represent the additional RR according to

FRAX for someone with an incident fracture versus someone without an incident fracture. The EAG would expect this to be estimated by comparing the FRAX score for someone with the same CRFs as baseline plus one additional CRF versus the FRAX score for someone with baseline CRFs. So for the example patient described in B2 (age 70, smoker, T-2.5), RR_{frax_fx} would be 26%/19% = 1.37 (i.e. cell H335 divided by cell H334). Please consider using this approach to populate columns AD to AF of the 'Model Data' sheet which the EAG believe are being used to incorporate RR_{frax_fx}.

The term "MAX(RR_{frax_fx} | RR_{recent})" in the equation for total fracture risk indicates that the maximum is taken of RR_{frax_fx} and RR_{recent}. In response to the feedback from the EAG, the formula has been modified in columns AD to AF of the "Model data" sheet to account for the calculation of RR_{frax_fx}. RR_{frax_fx}, which represents the additional relative risk (RR) according to Fracture Risk Assessment Tool (FRAX) for someone with an incident fracture versus someone without an incident fracture. In the updated formula the numerator is the FRAX score for someone with the same CRFs as the baseline plus one additional CRF, and the denominator is the FRAX score for someone with only baseline CRFs.

The updated formula is:

```
((INDEX('FRAX estimates'!$E$4:$E$1158,MATCH(1,INDEX((IF(FLOOR.MATH($F6,5)>120,120,FLOOR.MATH($F6,5))='FRAX estimates'!$B$4:$B$1158)*(($N6+$I6)='FRAX estimates'!$C$4:$C$1158)*(FLOOR.MATH($G6,0.5)='FRAX estimates'!$D$4:$D$1158),0,1),0))))/((INDEX('FRAX estimates'!$E$4:$E$1158,MATCH(1,INDEX((IF(FLOOR.MATH($F6,5)>120,120,FLOOR.MATH($F6,5))='FRAX estimates'!$B$4:$B$1158)*(($N6)='FRAX estimates'!$C$4:$C$1158)*(FLOOR.MATH($G6,0.5)='FRAX estimates'!$D$4:$D$1158),0,1),0))))
```

The formula has been validated and calculates the same results as the example highlighted by EAG.

B5. Company response to B16. Thank you for clarifying that the maximisation of prior fracture according to FRAX and imminent fracture risk is operationalised in

columns BH to BJ. We note that there is an option to switch off the imminent risk in these columns by setting Settings!$E$47="No". However, when this happens the formula applies 1 rather than applying RR_{frax_fx}. Please clarify if this is an error. If so we would suggest a correction of the form:

BH7 =BD7*MAX('Model Data'!AD6,IF(Settings!$E$47="Yes",AV7,1))

The model has been corrected by updating the formula of columns BH to BJ of all treatment simulation sheets as per the suggestion by EAG. As a result, the updated formula is noted below:

=BD7*IF(SUM(AZ7,AW7,AT7)>0,**MAX('Model Data'!AD6,IF(Settings!$E$47="Yes",MAX(AV7, AY7, BB7),1)),1)**

B6. PRIORITY Company response to B16. It is unclear to the EAG how the formulae in columns BH to BJ of the simulation sheets operate when a person has not had an incident fracture (i.e. one occurring since baseline). The imminent fracture risks (RR_{recent}) default to 1 if someone has not had a fracture, but the RR_{frax_fx} coming from columns AD to AF of the Model Data sheet appear to be applied regardless, i.e. they are not dependent on either baseline or incident fractures. Please consider if this is correct and amend if necessary. One possible correction would be to make the application of the "MAX(RR_{frax_fx} | RR_{recent})" dependent on whether an incident fracture had occurred yet using fracture counts in columns AZ, AW and AT of the simulation sheets (e.g. Simulation Abaloparatide). Therefore, if accepting the previous correction also (see B5), then this would give BH7 = BD7*IF(SUM(AZ7,AW7,AT7)>0,MAX('Model Data'!AD6,IF(Settings!$E$47="Yes",AV7,1)),1). If however, the intention is for RR_{frax} to exclude prior fracture at baseline, and for this to be captured by RR_{frax_fx} then the application of RR_{frax_fx}, would also need to be dependent on whether a baseline fracture is present, which it currently is not. In addition, the prior fracture CRF would need to be excluded from RR_{frax}, as discussed in B3.

In line with the response in to Question B3, for the application of imminent risk in the model, the RR_{frax} calculation has been updated to exclude prior fracture at baseline. Furthermore, columns BH, BI, and BJ were updated to be dependent on AZ, AW, and AT in all the treatment simulation sheets based on whether an incident fracture has

occurred or not. Therefore, the imminent fracture risk will only apply after an incident fracture. The updated formula is noted below:

BD7*IF(**SUM(AZ7,AW7,AT7)>0**,MAX('Model Data'!AD6,IF(Settings!$E$47="Yes",MAX(AV7, AY7, BB7),1)),1)

B7. The columns BH:BJ in the model simulation sheets only refer to one specific site of fractures each, despite the fact that according to the original CS B.3.3.2.3, any first to third fracture could affect the future risk of hip, vert, and non-hip non-vertebral (NHNV) fractures. In addition, Table 2 of Söreskog et al. (2020), from which the data in the 'Imminent risk' sheet appear to have been taken, describe these as the adjustment for risk of major osteoporotic facture (MOF; that is any fracture at the hip, vertebra, forearm or humerus). Therefore, the imminent risk of fracture is not limited to the particular site of the previous fracture and any previous fracture can increase the risk of hip, vert, and NHNV fractures. Therefore, if considering fractures from all sites, BH7 should use max(AV7, AY7, BB7) instead of AV7 only as an imminent fracture risk. Similarly BI7 and BJ7 should also refer to max(AV7, AY7, BB7) instead of AY7 and BB7 respectively. Please reconsider your approach and correct accordingly.

The model has been updated as requested by the EAG. The formula in BH7, BI7 and BJ7 in all treatment simulation sheets has been updated to:

BD7*IF(SUM(AZ7,AW7,AT7)>0,MAX('Model Data'!AD6,IF(Settings!$E$47="Yes",**MAX(AV7, AY7, BB7)**,1)),1).

B8. Model, 'Simulation' sheets for each treatment group, columns BD:BF (event risks [HR adjusted]): In the formulas in these columns, for abaloparatide, it is looking at time (cycle in months, column D) at the same row, whilst for romosozumab and teriparatide, it is looking to time 4 rows after the current row. Please consider if these are errors and correct accordingly.

The model has been updated as requested by the EAG. The updated formula in columns BD to BF is:

-LN(1-(1-((1-(1-EXP(-'Model Data'!R6)))^IF(AJ7>0,1-((1-IF(**D7**<=Settings!$G$55,'Parameter Sheet'!$G$46,'Parameter Sheet'!$G$52))*AJ7),1)))),

The bold highlighted value has been changed from the previous model.

Efficacy of drugs after discontinuation

B9. PRIORITY Company clarification response – Appendix B.2.2:4: The EAG is concerned that there remains an error in the methods used by the company to implement the dynamic approach to the residual effect. In the model, 'Simulation' sheets for each treatment group, columns BD:BF, for adapting residual effect, the company used the below formulation:

Risk reduction from treatment=(HR_treatment)*(1+(1-dynamic effect multiplier))

Following the description in the CS, the EAG believes that the correction formulation should be**:**

Risk reduction from treatment=1-((1-HR_treatment)*dynamic effect multiplier).

The difference between the two approaches is demonstrated in Table 1 below using HR for NHNV for teriparatide as an example. Please reconsider your approach and correct it as appropriate.

Table 4 Demonstration of the difference between the company's approach and the EAG's proposed fix when using the RR for teriparatide for NHNV

Dynamic effect multiplier	(1+(1-dynamic effect multiplier)) from company's model	Relative risk for treatment from the company model	Relative risk for treatment as recommended by EAG
1	1	[redacted]	[redacted]
0.7	1.3	[redacted]	[redacted]
0.5	1.5	[redacted]	[redacted]
0.3	1.7	[redacted]	[redacted]
0	1[a]	[redacted]	[redacted]

[a]This is forced to 1 by the IF function

The model has been updated as requested by the EAG. The formula in columns BD to BF of all treatment strategies has been updated to form of 1-((1-HR_treatment)*dynamic effect multiplier).

"IF(AJ7>0,1-((1-IF(D7<=Settings!$G$53,'Parameter Sheet'!$G$45,'Parameter Sheet'!$G$54))*AJ7),1)"

An example output resulting from this change is presented in Table 5.

Table 5 Demonstration of the effect of the requested update to the model using the RR for teriparatide for NHNV

Dynamic effect multiplier	(1+(1-dynamic effect multiplier)) from company's model	Relative risk for treatment from the updated company model	Relative risk for treatment as recommended by EAG
1	1	[redacted]	[redacted]
0.7	1.3	[redacted]	[redacted]
0.5	1.5	[redacted]	[redacted]
0.3	1.7	[redacted]	[redacted]
0	1[a]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Assessment Group; NHNV, non-hip-non-vertebral; RR, relative risk

[a]This is formed by IF function in the formula IF(AJ7>0,1-((1-IF(D7<=Settings!$G$53,'Parameter Sheet'!$G$45,'Parameter Sheet'!$G$54))*AJ7),1)", which is in the form of 1-((1-HR_treatment)*dynamic effect multiplier)

Utilities

B10. PRIORITY Company clarification responses B45: The company states, *"The model has been corrected so that the second and subsequent year utility values in columns CO to CR are applied for all treatment strategies to align with the description mentioned on page 119 and 120 of CS."* However, whilst columns CP to CR do now update from acute (i.e. first year) to chronic (i.e. second and subsequent year) utility values appropriately, this has no impact of QALYs as patients move to the "at-risk" state one cycle after their fracture. In the "at risk" column (CO), which the patients move to in the cycle after a fracture, the utilities for the first year after fracture are applied in perpetuity. Please correct the model so that the 'acute' utility values apply for one year and the 'chronic' utility values apply thereafter.

The model has been updated as requested by the EAG, by changing the formula in column CO. In the CO column of all the treatment simulation sheets the updated formula is:

'Model Data'!AM6*IF(AND(SUM($AN$7:AN7)>0,OR(AU7=0,AU7=6)),'Parameter Sheet'!$G$37,IF(SUM($AN$7:AN7)>0,**'Parameter Sheet'!$G$38**,IF(AU7=-1,1,MIN('Parameter Sheet'!$G$37,**'Parameter**

Sheet'!$G$38**))))*IF(AND(SUM($AO$7:AO7)>0,OR(AX7=0,AX7=6)),'Parameter Sheet'!$G$39,IF(SUM($AO$7:AO7)>0,**'Parameter Sheet'!$G$40,IF(AX7=-1,1,MIN('Parameter Sheet'!$G$39,**'Parameter Sheet'!$G$40**))))*IF(AND(SUM($AP$7:AP7)>0,OR(BA7=0,BA7=6)),'Parameter Sheet'!$G$41,IF(SUM($AP$7:AP7)>0,**'Parameter Sheet'!$G$42**,IF(BA7=-1,1,MIN('Parameter Sheet'!$G$41,**'Parameter Sheet'!$G$42**)))).

Please note, the bold highlighted values are chronic utility multipliers.

To validate this, the multiplier of age-related utilities was set to zero in column Q of Country Specific Data sheet and the discounting set to zero in cell H10 of the Settings sheet. The results confirm that whenever an incident fracture occurred, the acute utility multiplier was applied at that time only and in the subsequent cycles, chronic utility multiplier was applied.

B11. PRIORITY Company clarification responses B46: When patients experience a second fracture of a different type, their utility in that cycle does not reflect any previous fractures because columns CP to CR only depend on fracture history for that fracture type. This means that a patient's utility can improve if they experience a more severe fracture followed by a less severe fracture. Please correct this so that no patient has an improved utility when experiencing an incident fracture.

The model has been updated as requested by the EAG. This has been validated so that no patient has improved utility when experiencing an incident fracture of any type.

In columns CP to CR the updated formula is:

'Model Data'!AM6*IF(AND(SUM($AN$7:AN7)>0,OR(AU7=0,AU7=6)),**'Parameter Sheet'!$G$37**,IF(SUM($AN$7:AN7)>0,**'Parameter Sheet'!$G$38**,IF(AU7=-1,1,MIN(**'Parameter Sheet'!$G$37,'Parameter Sheet'!$G$38**))))*IF(AND(SUM($AO$7:AO7)>0,OR(AX7=0,AX7=6)),**'Parameter Sheet'!$G$39**,IF(SUM($AO$7:AO7)>0,**'Parameter Sheet'!$G$40**,IF(AX7=-1,1,MIN(**'Parameter Sheet'!$G$39,'Parameter Sheet'!$G$40**))))*IF(AND(SUM($AP$7:AP7)>0,OR(BA7=0,BA7=6)),**'Parameter Sheet'!$G$41**,IF(SUM($AP$7:AP7)>0,**'Parameter Sheet'!$G$42**,IF(BA7=-1,1,MIN(**'Parameter Sheet'!$G$41,'Parameter Sheet'!$G$42**))))

In this formula, the highlighted bold values are fractures of different types, and it can be observed from the above formula that the utility multiplier is dependent on different sites of fracture, not only on a particular site of fracture. For example, the utility multiplier of vertebral fracture is also dependent on hip fracture and NHNV fracture.

B12. PRIORITY Company clarification responses B46: The company says that, "*In the model the multiplicative approach is utilised to account for multiple fractures of the same type, however for fractures of different types, the maximum disutility approach is used."* From the formulas in columns CO:CR, the EAG think it is the other way around (i.e. in the at-risk column [CO] a multiplicative approach is used to account for the cumulative impact of different types of fractures whereas in columns CP to CR for individual fracture types, the maximum disutility across the 1st year and subsequent year utilities is applied when a second fracture occurs). The EAG would suggest using the approach adopted by Davis et al. (2016) whereby, *" If more than one fracture has occurred then the chronic multiplier for each fracture is applied but no more than one acute utility multiplier is applied at any one time."* There are multiple way to achieve this in a patient level model but care should be taken to ensure that the approach implemented is achieving the desired results. This can be checked by setting age-related utilities to zero, and discounting to zero, and examining the QALYs in columns CV to CY under these conditions for patients with different fracture histories.

The model has been updated as requested by the EAG, in columns CO to CR of each treatment simulation sheet by applying the following formula:

The updated formula in columns CO to CR is:

'Model Data'!AM6*IF(AND(SUM($AN$7:AN7)>0,OR(AU7=0,AU7=6)),'Parameter Sheet'!$G$37,IF(SUM($AN$7:AN7)>0,'Parameter Sheet'!$G$38,IF(AU7=-1,1,MIN('Parameter Sheet'!$G$37,'Parameter Sheet'!$G$38))))*IF(AND(SUM($AO$7:AO7)>0,OR(AX7=0,AX7=6)),'Parameter Sheet'!$G$39,IF(SUM($AO$7:AO7)>0,'Parameter Sheet'!$G$40,IF(AX7=-1,1,MIN('Parameter Sheet'!$G$39,'Parameter Sheet'!$G$40))))*IF(AND(SUM($AP$7:AP7)>0,OR(BA7=0,BA7=6)),'Parameter Sheet'!$G$41,IF(SUM($AP$7:AP7)>0,'Parameter Sheet'!$G$42,IF(BA7=-1,1,MIN('Parameter Sheet'!$G$41,'Parameter Sheet'!$G$42))))

B13. Company response to B41: Thank you for incorporating utility values from the suggested source. Please clarify why population utility values are only updated every 10 years when values by year of age are available: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d.

The model has been updated so that utility values by year of age are included (column Q of the Country Specific data sheet) using the source requested by the EAG.

Mortality

B14. PRIORITY Company clarification responses - Appendix B.2.2.5.2: The excess mortality from van Staa et al. (2007) is described by the authors as "*Excess 1-year mortality in fracture cases (absolute difference in 1-year mortality between fracture cases and controls)"* It is therefore an absolute difference not a RR of death, i.e. an additional 2.4% of women aged 50 to 59 with a hip fracture die over and above the expected deaths that year in those without a hip fracture. In the model by Davis et al. these were applied as one-off absolute risks of death occurring at 3 months after fracture because the excess mortality risk was found to be low after 6 months. However, the company has incorporated the data by applying it like it is a standardised mortality risk (SMR) versus general population mortality, i.e. converted 2.4% to 1.024 in the 'Country specific data' sheet and then multiplied by general population mortality. Please correct the model to apply these data as an absolute risk of death over and above general population mortality or clarify why the current approach is appropriate.

In line with the recommendation by the EAG the Company model has been updated. For example, at age 50, the expected death in the general population is 2,234 per 1,000,000 (Cell M6 of Country-specific sheet)[3]. Using the excess mortality from van Staa et al[4], the excess mortality due to hip fracture is 2.4%, resulting in a total mortality rate of 26,234 per 1,000,000. The total mortality rate is then used to determine the relative risk of death compared to the normal population, as follows: 26,234/2,234 = 11.743. This has been applied in the model in columns I:K of the "Country Specific Data" sheet.

Applying excess mortality to hip and vertebral is recommended by Hiligsmann et al 2019.[5] Therefore, the model base case applies excess mortality to hip and vertebral fractures only, with a scenario included to model excess mortality for hip only. Excess

mortality is applied to the first six months of an incident fracture which is in line with published economic models.

Further information is presented in the Appendix, Section B.2.2.5.

B15. Company clarification response to B33 and Model, 'Simulation' sheets for each treatment group, columns Q to S, headed 'Excess Mortality': In columns Q to S of the simulation sheets for individual drugs (e.g. Simulation Teriparatide etc) the excess risk estimated for the general population is being multiplied by (1+excess_mortality) where excess_mortality =0.3. In TA791, the RR was down adjusted by multiplying by 0.3 (TA791, committee slide 43). Therefore it appears that 130% of excess mortality is being assumed to be attributable to the fracture rather than 30%. According to the response to clarification Q. B33, the company responded that they were consistent with the previous technology appraisal, but the EAG does not believe this is the case. The EAG believes that this adjustment is no longer necessary due to van Staa et al. (2007) already providing an estimate of excess risk versus matched controls. However, if it is still the company's intention to adjust excess mortality to 30%, please correct the calculation.

As requested by the EAG, this adjustment for excess mortality is completely removed from the model and the formulas in columns Q to S of all treatment simulation sheets have been modified. The updated formula becomes:

$O7*(((INDEX('Country specific data'!$I$6:$I$56,MATCH(M7,'Country specific data'!$D$6:$D$56))-1))+1)

B16. Please clarify what is meant by the following statement made in section B.2.2.5.2 (page 50): "When a fracture persisted beyond one cycle, the increased risk of death also persisted for the same period. For subsequent fractures, the respective increased risk of death accumulates from the previous fracture." The data from van Staa et al. are excess risks in the year after fracture and the literature suggest that the excess risks generally occurs in the first 6 months (see Davis 2016 page 229). Therefore, the excess mortality risks from van Staa et al. should apply be for a single cycle only.

As requested by the EAG, in the updated model the excess risk is only applied for the first 6-months of an incident fracture.

Persistence

B17. Company clarification responses B39 and Model 'Simulation' sheets for each treat group, columns U:AH (persistence): All the cells are now looking at the same random number ("'Random Numbers'!K7' - exception is teriparatide, cell AA13 [42 months] which is looking at L7). The EAG considers it reasonable in this case to use a single random number to estimate persistence across time as this would be akin to sampling a single random number to inform the hazard for an exponential distribution. However, using the same random number for different treatment strategies means that persistence is correlated across the drug strategies. So a high persistence sample for abaloparatide also occurs at the same time as a high persistence sample for teriparatide. This is not a reasonable assumption as the persistence on treatment for these two drugs should not be correlated. Please use a different random number when sampling persistence for each drug.

The common random numbers (CRN) approach was used to reduce simulation variance, ensuring that observed differences in persistence are directly attributable to the treatment effects rather than random variability or differences in the simulated patients.[6] The use of CRNs allows for a more efficient and transparent comparison of complex treatment strategies, including those for abaloparatide and teriparatide.

The model base case has been updated with UK real world evidence for teriparatide persistence[7], which was also applied to abaloparatide. This transferability of the persistence data was validated by UK clinical KOLs.[8] This enables the company model to incorporate RWE persistence in the company base case. Due to these changes, we propose that the use of CRNs is valid. To allow the EAG to explore the impact of this approach, a drop-down menu and scenario were included to simulate persistence with different random numbers.

Further information is presented in the Appendix, Section B.2.2.3

B18. The company states that sequential treatment with alendronate is limited to those who complete anabolic therapy. The NOGG Guideline states that "Any patient stopping denosumab, romosozumab or teriparatide requires a sequential therapy strategy usually involving an anti-resorptive drug, which should be planned at the time the initial therapy is instigated to avoid a gap in treatment." The EAG's clinical advisors

stated that they would want to move a patient on to an antiresorptive if they are coming off anabolic therapy whether or not they had received the full course. Please consider whether the model can be adapted to allow patients to be offered an antiresorptive if they do not complete their anabolic therapy. The current assumption lacks clinical face validity.

In the updated model, a patient receives antiresorptive treatment after anabolic therapy, irrespective of whether the patient has received the full course of anabolic therapy. This can be validated by looking into the formulas in columns U to AH of all treatment simulation sheets; there are no conditions implemented in the formulas to restrict the receipt of the sequential therapy.

In the updated model base case, the HR for abaloparatide, teriparatide and romosozumab, were applied to the baseline fracture risks and these HRs were maintained during the alendronate sequential treatment. This assumption is consistent with the findings in the ACTIVExtend trial[9] and has been validated by clinical KOLs.[8]

Resource use

B19. Company clarification responses B48: Please clarify why the cost for a general practice nurse to initiate treatment is applied as 0.5 per 6 month cycle, for all cycles that involve treatment. Since each drug has different maximum treatment durations, overall they would receive 1, 1.5 and 2 visits in total depending on the treatment received (if the patient doesn't discontinue). If the cost relates to treatment initiation then it should be a one off cost at the start of treatment for all anabolic therapies (and will therefore cancel out).

The model has been updated as requested by the EAG and the cost is now applied as a one-off cost in the first cycle for each treatment arm.

The updated formula in cell CZ is:

AM7*$F7*(IF($D7<'Parameter Sheet'!$G$27,'Parameter Sheet'!$G$98,IF($D7<'Parameter Sheet'!$G$28,'Parameter Sheet'!$G$100,0))+IF($D7<'Parameter Sheet'!$G$27,'Cost Inputs'!$F$33,IF($D7<'Parameter Sheet'!$G$28,'Cost Inputs'!$I$33,0)))*$H7*$AI7*DX7+(**'Parameter Sheet'!$G$124*T7**)

Please note, the bold highlighted part in the above formula depicts the one-off cost that has been added newly in the updated model.

B20. PRIORITY Model, simulation sheets, columns DN:DQ. The calculation for the fracture related direct costs does not seem to be multiplied (or constrained by) the health state occupation - so the costs of fractures in subsequent years seem to be applied indefinitely (even after the patient dies). Conversely the long term costs in columns DS to DV are constrained to be zero when a patient dies by checking that the QALYs are above zero across the available health states. Please check and correct to ensure that all costs are zero after patients die.

The model has been updated by adding a column (Column DX) with a flag variable which identifies whether the patient is alive (1) or dead (0), and as soon as the patient dies, all the outcomes (i.e. life-years, QALYs and costs) becomes zero. The DX column is further multiplied into columns CU: DK for all the treatment simulation sheets to ensure that no outcomes are accrued after the patient dies.

B21. Model simulation sheets, Column DT: The look-up for long-term care costs uses their current age not their age at the time of the fracture. The look-up should be used to determine the % who require long-term care using age at the time of the fracture and this % should be fixed thereafter. To use an example, if a 50 year-old has a hip fracture and recovers without needing long-term care, as their risk of needing long-term care at that age is low (4%), then they shouldn't have a high risk of long-term care at age 70 because they had a hip fracture at age 50. The high risk of needing long term care at age 70 (12%) should only apply if the fracture occurs at age 70.

Column DT across all treatment simulation sheets has been updated to reference the starting age of an index hip fracture instead of the current age of patient. The following formula has been implemented to calculate the index age in cell AU3 of all treatment strategies:

(INDEX ('Country specific data'!$S$6:$S$56,MATCH($AT$3,'Country specific data'!$D$6:$D$56,1)))*IF(SUM(AN$7:AN7)>0,1,0)*IF(SUM($CV7:$CY7)>0,1,0)*('Parameter Sheet'!$G$121*365.25/2)

This calculated index age is now utilised in column AT to determine the percentage of patients requiring long-term care.

Please note, the bold highlighted parts are the changes made in the formula.

Miscellaneous

B22. Company response to B49: Where does the 6.7% inflation rate come from? Information in the model appears to suggest that this is based on CPI from the ONS rather than a health specific inflation index.

The inflation rate of 6.7% was taken from the CPI from the ONS for 12 months to September 2023, to align with use of the CPI calculator for other fracture costs.[10] In the updated model, the inflation rate of 8.2% is taken from the health specific inflation index for 12 months.[11]

B23. T-Score in column G of Model Data sheet. Please clarify why age and CRFs are sampled to allow patient level heterogeneity in these variables, but T-Score at baseline is not sampled to allow patient level heterogeneity? Instead, it is being sampled on the parameter sheet with other variables included in the PSA. The PSA captures uncertainty in the average BMD and not patient level heterogeneity. Please also provide a source for the decrease in BMD over time which appears to be hard coded in the model as 0.041 per annum (cell AT3 on Model Data sheet).

In response to the feedback from the EAG, the T-score at baseline is now sampled to allow patient level heterogeneity. The decrease in T-score for osteoporosis patients was assumed to be equal to the general population decrease (4.19% annually) and is sourced from Stevenson et al. 2007[2]

B24. Company response to B52 and Model, 'Simulation' sheets for each treatment group, columns H to J: Please check the year when calculating the discount for costs and effectiveness. The formula is rounding the time up to a whole number of years meaning that 1 year discounting is applying at 0.5 years. It is possible to use the exact time e.g. t=0.5 for cycle 1 in the discounting formula without any rounding and this would be preferable.

The change has been made as requested by the EAG, the following formula 1/(1+cDR)^($E8) = 1/(1+3.5%)^(0.5) = 0.9829 has been applied to columns H to J across all treatment simulation sheets.

References

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2. Stevenson M, Davis S, Lloyd-Jones M, Beverley C. The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Health Technol Assess [Internet]. 2007 Feb [cited 2024 Jan 4];11(4). Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta11040/

3. National Life Tables, United Kingdom, period expectation of life, based on data for the years 2018-2020.

4. van Staa TP, Kanis JA, Geusens P, Boonen A, Leufkens HGM, Cooper C. The cost-effectiveness of bisphosphonates in postmenopausal women based on individual long-term fracture risks. Value Health. 2007 Oct;10(5):348–57.

5. Hiligsmann M, Reginster JY, Tosteson ANA, Bukata SV, Saag KG, Gold DT, et al. Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the US branch of the International Osteoporosis Foundation. Osteoporos Int. 2019 Jan;30(1):45–57.

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7. 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 Sep 29;17(11):1626–9.

8. Theramex data on file. Section B: Clarification questions UK KOL Interview Report – Supplementary Evidence. 2024.

9. ACTIVExtend CSR addendum (data on file).

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11. CPI annual and monthly inflation rates by division - Consumer price inflation tables (National Statistics) - ONS [Internet]. [cited 2023 Sep 15]. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/datasets/consumerpriceinflation

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Royal Osteoporosis Society
3. Job title or position	Osteoporosis Specialist Nurse- Clinical adviser
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Royal Osteoporosis Society (ROS) is the UK's only national charity dedicated to bone health and osteoporosis. We work to improve the bone health of the nation and support everyone with osteoporosis to live well through our support services and information. The ROS provides both printed and digital information to help people understand more about living with osteoporosis. There is also a dedicated nurse specialist helpline and support groups locally across the UK. We influence and shape policy and practice at every level through our work with healthcare professionals and policymakers. We are committed to our public mission to raise awareness and inspire action among the public and policy-makers, demanding change for the 3.5 million people who live with osteoporosis. We are driving research and working to reduce the 'care gap' – making sure people at the highest risk of fractures get the drug treatment, information and care they need to reduce the chance of fractures in the future. We fund our work through a range of income streams – including traditional fundraising activities such as appeals and community fundraising, our membership programme, and education and training events for healthcare professionals. Each year, we apply for funding to a range of national and regional charitable trusts and foundations which kindly contribute both to new projects and ongoing work. We also work with a small number of carefully selected corporate partners from the field of osteoporosis and bone health. In 2022, we raised just over £4,668,169. towards our work.

	In a typical year, around a half of our income (60% in 2022) comes from gifts in wills, and we are extremely grateful to supporters who choose to remember us in this way. Our membership programme, individual donations, and fundraising activities such as appeals, lotteries and challenge events contribute around a third of our funding. More detail can be found in our accounts and Trustees' Annual Report, which is available both on our website and on the Charity Commission site. A list of corporate partners can be found on our website. We currently have over 20,000 members
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**2022** 1.6% of total income was from pharmaceutical companies . [Amgen donated £10k to support policy and public affairs work to promote fracture liaison services from Jan-Dec 2022 UCB donated £10,675 in 2022 for similar work.] **2023** UCB donated £49,395 to support as above. In addition, the following are for Stands at a recent Conference for healthcare professionals: UCB £25k Amgen £25k Thornton & Ross £18.5k Flynn Pharma £6k Stirling Anglian Pharma £2k. Theramex did not support us in the last 12 months. Negotiations are underway for a further £10K from both UCB and Theramex later in 2023.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Our detailed Life with Osteoporosis 2021 survey was completed by over 3,200 people. The findings gave us the richest set of insights for many years into the realities of living with the condition. We collected further insights from our public and healthcare professional members, who helped us understand their priorities. We are fortunate to have the input of over 70 Volunteer Advocates, who represent the 3.5 million people with osteoporosis, and many of them bring their lived experience to direct our work. In addition, I have worked at the charity for 30 years, for much of this time managing the ROS specialist nurse team who provided our helpline and information service. Listening to people's views and concerns has been the foundation for the services we provide and I continue to be closely involved. We carefully evaluate and collect information from our members and service users. I also consulted directly with volunteer patient advocates on our Clinical & Research committee for their views.

What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Osteoporosis is a condition where bones lose strength, making people affected more likely to break a bone after a minor bump or fall. One in two women and one in five men over the age of 50 are expected to break a bone during their lifetime. Spinal fractures are the most common osteoporotic fractures. Those diagnosed with osteoporosis(low bone density compared to the average young adult) perceive this risk of breaking bones in a variety of ways. For some it has no impact on their lives, for others there is fear and concern about the possible future of living with fracture and their impact, especially if family members or close other have been affected, with a desire to prevent fractures if at all possible. For those with fractures, there is again a continuum of experience and impact. A single fracture may be significantly painful and inconvenient until healing and recovery is complete but for some people, especially those with multiple spinal fractures that change their spinal shape or for those with hip or multiple other fractures, there are lasting mobility and functioning problems that result in a permanent change in independent living and life quality. The impact can be devastating with lasting pain and distress. Pain, fear and fractures mean losing things in life they love. It means giving up activities, hobbies, friendships and work. People can become inactive, exacerbating the decline in their bone health. They can also struggle financially if they lose their income. People who experience height loss and spine curvature from multiple spinal fractures can hate the way they look, making them feel insecure and self-conscious. They may become breathless and struggle to eat. People who suffer hip and spinal fractures have a decreased life expectancy. Of those who survive a hip fracture, many can no longer carry out basic tasks for themselves such as dressing, feeding themselves and going to the toilet. A majority will never return home or be able to walk independently. Hip fracture is often the 'last straw' for living independently and this really matters to people affected. People can feel socially isolated. Relationships can become strained as people become more dependant. The impact of fractures can stop people from seeing family & friends.

	"I feel absolutely terrible. Very depressed. I can't get clothes to fit. I am embarrassed going out. It doesn't help that my husband calls me a hunchback. I feel worthless. " "It has further eroded my self esteem. I have felt for a long time I no longer serve a purpose in life." "It's a depressing life and we are only 64 and 68. I'm constantly stressed and depressed about our lack of quality of life because we haven't enough `." "I feel terrible. I cry most days... Being in constant pain is awful." For carers, who provide support, it can be physically and emotionally draining and exhausting. They tell us, it can be very difficult to watch their loved ones struggling with pain and disability as a result of fractures caused by osteoporosis. In some cases, they have to take on a new role as carer and undertake new tasks around the house and garden which may be new and unexpected to them. Osteoporosis 2021

7. What do patients or carers think of current treatments and care available on the NHS?	Experience on the helpline and questions and comments especially from our members tells us that patients who contact us (who are often those with concerns, questions and negative experiences) are frustrated by the lack of information they get about osteoporosis and the limited discussions they have about drug treatments. They experience, or are anxious about, side effects and especially long term health risks associated with their medications. They are worried about the availability of, or clarity about, drug treatments they need throughout older age especially as they may have a high risk of fracture long term. The research and recommendations often don't cover this and their doctors(if they are less well informed) may stop a drug treatment after a limited number of years without offering further options. Alternatively they may just be left on a drug for many years without any monitoring or discussion so they feel quite abandoned. More recently, they are frustrated by problems with waiting times to either contact their GP and or to get a specialist appointment if necessary. They worry about drug treatment safety especially with social media alarm – often exaggerated about adverse effects such as atypical fractures and osteonecrosis of the jaw and the confusing information about 'needing to get a dental check' before they start some treatments. They often face reluctance from dentists to offer necessary dental care like extractions or implants if patients are taking bisphosphonates, denosumab or romosozumab (even though guidance says this is still safe to do). Our Osteoporosis report 2021 found : Only 48% are confident they're on the right medication (and this is 10% fewer than in 2014) Only 54% feel the benefits and drawbacks of their medication are fully explained to them 57% are worried about the risks of taking their medication for prolonged periods of time 52% are worried about the potential side effects of their medication 26% don't feel that their doctor takes their osteoporosis seriously

8. Is there an unmet need for patients with this condition?	Patients need effective and safe drugs. There needs to be a range of effective options especially if they continue to have multiple fractures and the drug treatment they are taking doesn't seem to work(they continue to fracture) or if they can't tolerate it because of side-effects. There need to be a range of different treatment options to ensure those with a continuing high fracture have a range of options throughout later life. Currently, many available treatments are not prescribed long term without some restrictions. MHRA advise a treatment review at 5 years for bisphosphonates because of concerns about a rare, atypical thigh bone fracture side effect. There is also a lack of data about both safety and effectiveness for existing treatments beyond 10 years. But many people still have a high fracture risk and need to continue treatment long term These contradictions can be worrying and confusing for patients. They may be told to take a treatment 'pause' with bisphosphonates but they don't have certainty as to whether this will effectively reduce the risk of atypical fractures or whether they can move onto other treatment types with the same risk of atypical fractures. There is a lack of certainty but also a lack of other options. Having another treatment option available will help with treatment decisions for those who need a sequence of therapies.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients will hear that this treatment is 'bone building' and will perceive that the drug is 'better' than existing drugs. They want to know they are being prescribed the drug that will be most effective. Many existing available drugs are associated with the serious health risks, osteonecrosis of the jaw and atypical fractures. These are rare side effects but often cited by patients as an important reason for not starting or persisting with a treatment and as a result adherence to medication is poor. Patients incorrect perception of these risks as significantly high is strengthened by frequent discussions by health professionals about the need to see a dentist and some dentists refusing to offer invasive dental treatment because of the ONJ risk. Abaloparatide is not associated with these risks which will be perceived as an important advantage.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients are interested in whether it works to reduce all types of fractures. They will have concerns about any potential side effects or health risks which always contribute to low adherence. Patients who have had any radiotherapy or atrial fibrillation will have questions and concerns about potential 'bone cancer' or 'fast heart beat'. Having to wait to see a specialist to gain access to this medication may be perceived as a disadvantage. A patient and/or carer will have to be taught how to administer this subcutaneous injection where most other treatments involve taking a tablet, or the injection is administered by a Health Professional. This injection will be daily which may feel challenging. It may be confusing for patients/carers as they will be required to change onto a different treatment at the end of a course - ensuring this happens will be important.

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Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	• There are currently limited anabolic options for the treatment of post-menopausal osteoporosis with strict criteria for their use. Currently, only romosozumab is recommended by NICE as a first-line treatment and is not suitable for all women who might be recommended an anabolic treatment, particularly if they have a history of heart attack or stroke. • People having side effects or problems with one medication say they really welcome a second choice if they have side effects or contradictions to the treatment they are initially recommended. • An additional anabolic option is therefore important to ensure anabolic therapy is accessible to a broad range of women likely to benefit from this type of medication. • This drug treatment will be most useful for post-menopausal women with multiple vertebral fractures(fragility fractures in the spine)because they may benefit from the anabolic action of this drug which is potentially more effective. • We strongly ask for consideration of abaloparatide as a first line "anabolic" therapy for post-menopausal women defined as 'very high risk' of fractures and especially those who have had vertebral fractures. Data for drug treatments with a similar anabolic action(teriparatide and romosozumab) support anabolic-first sequence as providing a greater response. It will be important to consider if there is evidence with abaloparatide which will support the case to use it as a first line drug. • We also anticipate its use as a second line or third line therapy for post-menopausal women defined as 'high risk' (as opposed to 'very high risk') who cannot tolerate or have had a poor response to oral bisphosphonates. This would mean side effects, continued loss of bone density or further fractures.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	People with cognitive or physical disability who have problems with administration or those with an aversion to injections, will need consideration and support if this treatment is recommended and prescribed. Cultural beliefs and the acceptability of this medication including self-administering an injection will need consideration. Men and transgender men and women who have a high fracture risk who would benefit from treatment will be excluded. We hope that future changes in the market authorisation to include these groups would be accommodated within the guidance. NICE recommendations on romosozumab has led to the identification of a cohort of treatment naive patients who are eligible in terms of fracture risk for romosozumab but excluded on the grounds of their cardiovascular risk factors . Abaloparatide will be an alternative anabolic option to avoid inequality of access.

13. Are there any other issues that you would like the committee to consider?	One patient advocate told us that the crucial piece is understanding how this new treatment fits within the existing options, and how / why it would apply as part of an individual's lifetime osteoporosis management. 'I have no sense from my GP that they understand the various protocols fully, and this creates a level of concern about this perceived gap in my clinician taking a holistic, long-term view of treatment and guiding decision-making accordingly. What are the downside risks of this drug, and potential side-effects? How can these be most clearly explained to overcome concerns (real and imagined) and how does this drug treatment intersect with other medicines? What guidance will be issued to GPs to help patients prioritise their individual health considerations for multiple-morbidities.' She also said 'For the treatment to be successful, the clinician will need to create a sense of partnership with the patient, whereby the patient understands and commits to following the course of treatment for the duration – and what the risks are of non-adherence. Can the GP surgery accommodate the necessary support and what do patients need to do alongside to create conditions for successful treatment? How many injections will be needed for a full course of treatment? Are these self-administered or given by a practice nurse? I see multiple issues if the former, and likely lower adherence over time without the engagement of clinical support staff. The consultation should consider practicalities of patients with osteoporosis in travelling to a clinic – particularly in winter or icy conditions where the risk of slipping and breaking a bone is a very real risk. ' She made a further point, 'I am also concerned that the use is limited to women who've already fractured with high risk of repeat fracture. If there are drugs like this more effective that can prevent the first fracture more effectively than other available drugs then shouldn't these be available more widely?'. Consideration needs to be given to the use of the term 'osteoporosis' in the appraisal. There is a strict technical diagnosis of osteoporosis defined by bone density measurement (T score of -2.5 Standard Deviations below the average healthy adult range.) This is an important risk factor for fragility fractures. However, in the context of determining eligibility for osteoporosis treatments, ' 'high fracture risk' takes into account not only BMD, but also additional independent risk factors

	for fracture. Patients reaching this threshold for treatment as described in NOGG (referred to by NICE in CG 146) will usually, but not always, have had 'osteoporosis' diagnosed on a bone density scan. Conversely some patients, with osteoporosis diagnosed from a scan measurement, will not have a high enough fracture risk to need a treatment. People prescribed treatments have stressed to us that this confusion needs to be resolved in future guidance.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

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Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Some patients with a high risk of fracture especially with multiple spinal fractures need to be able to benefit from effective anabolic medications as a first -line treatment. • This will be an important treatment option for those who meet the criteria for romosozumab but cannot take it because of cardiovascular risks. • Patients need a range of effective and safe treatment options to meet their individual needs. • Adherence to (and therefore the success of) many existing treatments is poor often because of concerns about health risks/side effects not associated with this drug.

Thank you for your time.

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Single Technology Appraisal

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society for Rheumatology
3. Job title or position	Consultant Rheumatologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No, but the submission has been reviewed by the BSR Osteoporosis Specialist Interest group. Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Society for Rheumatology which is the UK's leading medical society for rheumatology and musculoskeletal professionals.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Accord Healthcare – sponsor of our Annual Conference and Case-based conference (£11,500) Amgen – funding for our RA Register, PsA register and Annual conference sponsor (£671,774) Eli Lily – funding for our RA register and sponsor of our Annual conference (£147,500) Novartis – sponsor of our Annual Conference and Case-based Conference (£135,100) Sandoz – sponsor of our Annual Conference (£25,300) UCB – sponsor of our Annual Conference (£45,200)
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To strengthen bone through increases in bone mineral density, and to lower the risk of further fracture
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in vertebral fracture risk of 30% or more would be equivalent or better than existing therapies.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Anabolic agents are currently limited to teriparatide or romosozumab. We have found only a small number of women are eligible or willing to have romosozumab (most frequent reason for not being eligible is not having a BMD of -2.5 or less). Teriparatide access is also currently restricted by age and T score. NICE guidelines. As far as I'm aware NICE doesn't stipulate a specific BMD cut-off for romosozumab but reserves the medication for those "with severe osteoporosis in those with a high risk of fracture" although limited to those who have had one of 4 types of fracture in the previous 2 years. However Romosozumab is usually limited due to co-morbidities such as cardiovascular risk factors. NOGG does recommend BMD cut-offs but as far as I'm aware NICE trumps NOGG.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Osteoporosis is managed by both primary and secondary care clinicians in a range of specialities – elderly care, rheumatology, endocrinology, biochemistry. Patients requiring parenteral and/or anabolic therapies are managed within secondary care.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	National osteoporosis Guideline Group NICE –for both Teriparatide (TA161) and Romosozumab (TA791). Guidance also for raloxifene (TA161), bisphosphonates (TA464) and denosumab (TA204).
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is variation in care and variation in specialities involved and pathways. Royal osteoporosis Society is campaigning for a fracture Tsar in each devolved nation to address variation in practice.
9c. What impact would the technology have on the current pathway of care?	The technology would easily be embedded within existing care pathways. It would fit in as follows: • In secondary care, as an alternative second-line option to existing parenterals • Ideally as a first line option in patients at particularly high risk (given evidence that anabolic drugs given before antiresorptive have better results than when antiresorptive are started first), and given safety/eligibility issues with romosuzumab which preclude use in some number of patents. • Possibly as competitor to teriparatide, depending on price
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	The technology is similar to existing technologies (teriparatide)
10b. In what clinical setting should the technology be used? (For example,	Secondary care

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Increase investment in osteoporosis specialist nurses and potentially DXA if T scores required for eligibility and fracture liaison services to proactively identify eligible patients.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, as anabolic agents have superior results to antiresorptive agents in people with spinal fractures yet there use is restricted as described above
11a. Do you expect the technology to increase length of life more than current care?	It is theoretically possible, through hip and spinal fracture prevention, but data confirming this is unlikely due to size and length of existing trials
11b. Do you expect the technology to increase health-related quality of life more than current care?	It is theoretically possible, through hip and spinal fracture prevention, but data confirming this is unlikely due to size and length of existing trials
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The subgroups as indicated in the scope, particularly those with priori spinal fractures who are at high risk of subsequent spinal facture

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Increased nursing, pharmacist and medical time needed to process homecare prescriptions and engage in shared decision making
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Possibly, depending on the extent to which the impact of vertebral fracture on quality of life (as opposed to the impact of hip fracture, which is well documented from a health economic perspective) is taken into account. A focus on hip fracture as an outcome may have led to previous under-valuation of osteoporosis prevention and treatment interventions.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
16a. Is the technology a 'step-change' in the management of the condition?	No
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, in those with side effects to teriparatide and unable to have romosozumab
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Given the short half life if patients experience disabling side effects that warrant discontinuation then one would expect these to resolve swiftly on treatment cessation.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	In the ACTIVE clinical trial participants reflected the characteristics of those seen in the UK with the exception of BMD. Bone mineral density had to be between or equal to -2.5 and -5 and in the UK clinical

	guidelines suggest osteoporotic treatment based on risk rather than bone density readings meaning about 50% of patients requiring osteoporotic medicines do not have BMD within these ranges.
18a. If not, how could the results be extrapolated to the UK setting?	Data is needed on efficacy in people with osteopenic BMD.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Fracture and BMD and adverse events, which were all included. Benefits to life expectancy or QoL would not be expected in the duration of clinical trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	BMD predicts further fracture risk
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance	NO

[TA791, TA464, TA204, TA161]?	
21. How do data on real-world experience compare with the trial data?	Abaloparatide Real-World Patient Experience Study - PMC (nih.gov) This paper reports high adherence and satisfaction. One of the major limitations of the paper is selection bias. The inclusion criteria on specifying patients had to be on treatment for one month, would have skewed the sample to people who were more satisfied and therefore continuing on treatment. The study characteristics suggests a well-educated, physically active group with good health insurance, and lower than expected alcohol intake. Various other studies have examined cost-effectiveness and safety in US medical databases which may have different characteristics to the UK population

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Men and women should both be considered Relying on a BMD defined diagnosis risks excluding people who are unable to have a scan due to local availability, or mobility issues or have unreliable BMD readings due to surgery or osteoarthritis for example.
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Abaloparatide offers an important additional choice to people at high fracture risk who have limited treatment options • Men and women should be considered for treatment. • Having a T score eligibility criteria will restrict access to high risk fracture patients – it is important to identify evidence of efficacy in people with T scores which are not osteoporotic • Abaloparatide fits well into existing secondary care pathways but may require small investment in clinician/practitioner time • Abaloparatide should be considered as a first line treatment for patients at high risk of fracture as defined by NOGG and consistent with NOGG recommendations for other anabolic therapies.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **26 March 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating osteoporosis in postmenopausal women and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Eugene McCloskey
2. Name of organisation	University of Sheffield
3. Job title or position	Professor of Adult Bone Diseases
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with osteoporosis? ☒ A specialist in the clinical evidence base for osteoporosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for osteoporosis in postmenopausal women? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim of most current pharmacological treatments is to maintain or improve bone strength and reduce future fracture risk.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Current evidence suggest that agents should be able to reduce vertebral and/or hip fractures by 40+% and other fractures (non-vertebral, non-hip) by at least 20%. Any new agent should show similar efficacy.
10. In your view, is there an unmet need for patients and healthcare professionals in osteoporosis in postmenopausal women?	There is a sizeable treatment gap in osteoporosis resulting from poor identification and assessment of those at increased risk of fracture, with subsequent poor initiation and persistence with well-proven therapies
11. How is osteoporosis in postmenopausal women currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The most well-established and supported guideline in the NHS in the UK is that provided by the National Osteoporosis Guideline Group (https://www.nogg.org.uk/). It was first launched in 2008 and most recently updated in 2022. It has the advantage of being linked to the fracture risk assessment tool, FRAX (https://frax.shef.ac.uk/FRAX/ and also a new beta website https://www.fraxplus.org/) which is approved by NICE for risk assessment. The NOGG intervention thresholds are also referred to by NICE. The pathway of care is well-defined with large consensus reflected in the wide participation of specialties endorsing the NOGG guideline. The stumbling blocks to better pathway implementation are: a) Lack of access to management of fracture risk in those presenting with fracture – fracture liaison services (FLS) are only available in about 50% of hospital trusts in England. b) Lack of awareness and time within primary care to identify and treat those presenting with less recent fractures or other clinical risk factors. c) A limited access to bone-forming treatments largely due to 'relative' expense (predominantly reflecting very inexpensive anti-resorptive treatments e.g. oral bisphosphonates). The current technology (abaloparatide) would add another option with proven efficacy to the bone-forming group of treatments. This would increase access for some patients intolerant to, or with contraindications to, current therapies. As a n additional competitor it would hopefully help to decrease the overall costs of

	bone-forming treatments over time, bringing this type of treatment more to the first line in patients with particularly high fracture risk.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology is similar to current care (with a slightly different mode of action) that would fit easily into current pathways of care. The efficacy and safety are comparable to other available treatments that mediate their effect through the PTH receptor. The gains in BMD, particularly at the total hip site which is under consideration as a surrogate of anti-fracture efficacy, are larger and more rapid for abaloparatide compared to teriparatide. Like teriparatide and biosimilars, this technology will be initiated in secondary or specialist care without any significant additional investment needed.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The technology will deliver similar or perhaps better clinical outcomes than currently available treatments acting through the PTH receptor. The clinical outcomes are primarily fracture outcomes that ware well-established to have detrimental, and in some cases (e.g vertebral or hip fractures) prolonged, impacts on individual's quality of life. While comparable efficacy was seen in the pivotal but relatively small clinical trial, subsequent real world evidence shows potentially greater reductions in fracture rates compared to teriparatide, with comparable safety profiles.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment would be targeted at those with highest fracture risk as espoused in recent clinical guidelines including the NOGG guideline in England and the UK.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	The use will be similar to existing technologies without any significant practical implications.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No specific rules required. Use will be similar to that of teriparatide and biosimilars.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Not that I am aware of.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The technology will provide impetus towards a step-change in the management of osteoporosis as it will provide an additional option in the area of bone-forming treatments. I would hope that increased options will lead to slow but steady decreases in treatment costs, enabling a wider range of higher fracture risk patients to have access to such treatments. The latter is a major unmet need in the treatment of such patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The efficacy and safety profiles are similar to existing therapies acting on the PTH receptor. The technology has a different, and potentially more favourable, effect on bone turnover with less of an increase in bone resorption compared to teriparatide. This appears to translate into a lower incidence of hypercalcaemia than seen with teriparatide.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The pivotal trial was the ACTIVE study, followed by ACTIVExtend. The study examine sequential therapy of abaloparatide followed by an anti-resorptive (oral alendronate), a commonly used sequence in the UK for bone-forming treatments. The patients selected reflect those at higher risk of fracture in UK clinical practice. For example, the mean age was 69 years, with almost two-thirds having either a prevalent vertebral fracture or a history of non-vertebral fracture within the past 5 years. During 18 months of intervention, the fracture rates were high in the placebo arms (4.2% and 4.5% for vertebral and non-vertebral fractures, respectively); this could be extrapolated to fracture rates of 28%-30% over 10 years reflecting the high incidence in this patient population.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not that I am aware.
22. How do data on real-world experience compare with the trial data?	I am aware of a real-world experience study that has shown high satisfaction with the use of abaloparatide amongst patients (in the USA). Ease of use and compliance were reported as very favourable. Within the field of osteoporosis, for the first time real-world evidence has actually contributed to the marketing authorization application (MAA) for the current technology in the EU and UK, combined with data from the pivotal clinical trial and other studies. Specifically, data from an observational study was used to support and complement the efficacy and safety data already available from the prospective randomized clinical trial. References are readily available and I can provide details on request if needed.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	There a number of inequalities that frequently and persistently arise in the treatment of osteoporosis, but most of which are probably beyond the remit and scope of this process. These include, for example, lack of access to treatment of high fracture risk in men as the studies are usually confined to postmenopausal women (of the three bone-forming agents potentially available including this technology, only one is currently approved for use in men). Another inequality is the disparate provision of risk assessment, identification

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	and initiation of treatment in patients at increased risk of fracture. Often described as a 'post code lottery' this is an inaccurate description and harder to address.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Abaloparatide is a safe, effective bone-forming treatment for the management of high fracture risk in postmenopausal women

Abaloparatide provides another option for patients requiring bone-forming treatment but have contraindications to, or are intolerant of, other bone-forming therapies

The totality of evidence, including real world evidence, suggests that the anti-fracture efficacy of abaloparatide is equal to or greater than that of teriparatide

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with osteoporosis or caring for a patient with osteoporosis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed patient and want to bring to the attention of the committee.

Patient expert statement

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **26 March 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Patient expert statement

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with osteoporosis

Table 1 About you, osteoporosis, current treatments and equality

1. Your name	Alison Smith
2. Are you (please tick all that apply)	☒ A patient with osteoporosis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with osteoporosis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Royal Osteoporosis Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I have knowledge of the experiences of others living with osteoporosis through involvement with ROS patient groups and RCP Patient Carer Panel (Falls and

	Fragility Fracture Audit Programme) Also of working with an organisation working with Asylum Seekers. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with osteoporosis? **If you are a carer (for someone with osteoporosis) please share your experience of caring for them**	Having retired from an academic career in 2012, I started out on an active new chapter but within months I had fallen, broken bones and been diagnosed with osteoporosis. I was fortunate to live in a part of the country where there is an effective Fracture Liaison Service (FLS) where I could benefit from early identification, assessment, diagnosis and treatment. My diagnosis came as a complete shock and as a result I became fearful of falling and increasingly anxious and withdrawn, being reluctant to go out as Winter approached. I realised, as a trained psychologist, that my mental health as well as my physical health was at risk and I relied heavily on the support and monitoring of the FLS and the explanation given by ROS re medication and lifestyle. Initially I had difficulty in both accepting my diagnosis and being compliant with treatment.
7a. What do you think of the current treatments and care available for osteoporosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I think that the current treatment and care is patchy across the country and is dependent on available resources across NHS Trusts. Treatment and care at present fall to a 'postcode lottery'. At best they are excellent but sadly many people suffer secondary and multiple fractures needlessly. I was fortunate but I have met several other people living with osteoporosis who suffered extensive pain before receiving diagnosis and an effective treatment e.g. someone I have known who experienced over 15 fractures before breaking her hip and then being diagnosed with low bone density, having osteoporosis. I have met others who remained on medication without it being monitored and who have

	stopped taking medication because of side effects, being unaware of the availability of alternatives.
8. If there are disadvantages for patients of current NHS treatments for osteoporosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The method of administration of drugs particularly those which tend to be prescribed as a first line therapy can be a challenging for patients. for example having to stand or sit upright for a prolonged period of time and consume a large quantity of cold water. I understand that this can be very painful, particularly when a patient has several vertebral fractures. Being involved in volunteering with an organisation working with different ethnic cultures and language, I understand that the protocols of administration are important to the adherence to treatment. Personally, I suffered hair loss when taking Alendronic Acid and when prescribed an alternative, Resonadrate but having read that hair loss was also a side effect with this, then I avoided treatment for a period, falsely declaring dental treatment needs as the cause. I was again fortunate to have the support of an FLS nurse who picked up on this and supported me back to treatment with an alternative medication, Triparatide For me, two years of a drug which required a daily self-administered injection, a drug which I had particular trust in as a bone building drug ,proved effective in promoting my adherence. Unfortunately, lack of primary care follow up and knowledge resulted in a year without any medication. Drug regime /process may need to be organised/timetabled by the patient. I now receive a six-monthly injection for which, I am required to book a blood test, receive results, request the injection to be ordered on the level of the result, collect it from

	the pharmacy and take it to the surgery fridge. Book an appointment, receive the injection and set up the procedure again six months later. For some patients this is a complex requirement.
9a. If there are advantages of abaloparatide over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does abaloparatide help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I do not have personal knowledge of abaloparatide
10. If there are disadvantages of abaloparatide over current treatments on the NHS please describe these. For example, are there any risks with abaloparatide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I do not have knowledge of abaloparatide
11. Are there any groups of patients who might benefit more from abaloparatide or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I do not have knowledge of abaloparatide

12. Are there any potential equality issues that should be taken into account when considering osteoporosis and abaloparatide? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I do not have knowledge of abaloparatide. However it is always important to be mindful of cultural, ethnic and language differences so that patients have understanding of their medication and needs.
13. Are there any other issues that you would like the committee to consider?	I am not aware of any at this stage Thank you

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- A patient's understanding of and confidence with a drug regime is important for adherence.
- A patient's understanding of side effects and co-morbidity issues are important are important in building trust.
- It is important that a patient knows that their progress is being monitored
- It is important for a patient to feel confidant in communicating about their treatment and to be aware there are alternative

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Single Technology Appraisal

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with osteoporosis or caring for a patient with osteoporosis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

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Patient expert statement

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with osteoporosis

Table 1 About you, osteoporosis, current treatments and equality

1. Your name	Philippa Russell
2. Are you (please tick all that apply)	☒ A patient with osteoporosis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with osteoporosis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Royal Osteoporosis Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with osteoporosis? **If you are a carer (for someone with osteoporosis) please share your experience of caring for them**	I was diagnosed with severe osteoporosis thirty years ago when at the age of 58. I had already lost two inches in height. Since then, I have sustained a number of fractures in my knee, forearm, spine, hip, foot and elbow. Apart from my hip fracture, I recovered from them after a few months. But the spinal fractures, which are especially painful, took nearly a year. During that time, I could not sit up enough to play my cello, I had to lean back on a cushion or a warm pad, and I still ache when I sit up. I have now lost nearly six inches in height; this is a nuisance for reaching things, and since it is mostly in my spine there is a shortage of space in my trunk. Bending down is uncomfortable, and I can't eat a large meal. I need a booster cushion at the hairdressers to get my head up to the basin. But the biggest change I have suffered is the result of the hip fracture. Complications meant that the muscles in my right thigh were destroyed by repeated operations, so I can't walk at all without something to hold on to. I use a rollator outdoors and a trolley or zimmer indoors. (Of course I can no longer carry an umbrella: I just get wet!). Another result of the hip surgery is that my thigh has shrunk by four inches; I need a built-up shoe, even to go to the loo at night to avoid falling. I am constantly afraid of falling, as are most people with osteoporosis, and can no longer walk with gay abandon. Long, country walks were previously a regular delight. But I'm one of the lucky ones, I'm not in great pain like many with this disease, I only ache.

7a. What do you think of the current treatments and care available for osteoporosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I have taken a variety of drugs since 1993: • HRT, • daily Fosamax, • weekly Fosamax/alendronic acid, • Preotact – daily injection (I was grateful to be allowed this expensive drug for two years and didn't find injecting a problem), • Zolendronic acid – yearly infusion. I tolerated all well and I did not suffer any noticeable side effects, but the most convenient is the zolendronic acid. I am very lucky to live in a part of Birmingham where my NHS treatment, since I was diagnosed in 1993, has been excellent in every way. But I hear from other people, and the ROS, that this is far from the case in other parts of the UK.
8. If there are disadvantages for patients of current NHS treatments for osteoporosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Patients need early diagnosis, information, and timely treatment which they are happy to continue with, if advised, long term. Some give up on weekly alendronic acid because they find it tiresome to take because they don't like having to sit or stand for at least half an hour before having their first cup of tea or their breakfast.
9a. If there are advantages of abaloparatide over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	I have no experience of abaloparatide.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does abaloparatide help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of abaloparatide over current treatments on the NHS please describe these. For example, are there any risks with abaloparatide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have no experience of abaloparatide.
11. Are there any groups of patients who might benefit more from abaloparatide or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	People from ethnic minorities, those with mental health issues and people living in deprived areas and struggling, should always be given priority when considering treatment. Also, it needs to be borne in mind that it has become difficult sometimes to contact a GP.
12. Are there any potential equality issues that should be taken into account when considering osteoporosis and abaloparatide? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	Not that I'm aware of.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No

Patient expert statement

Abaloparatide for treating osteoporosis in postmenopausal women [ID882]

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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Abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture [ID882]. A Single Technology Appraisal

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
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Date completed	Date completed (5/03/2024)

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Sarah Davis, Aline Navega Biz and SunHong Kwon critiqued the health economic analysis submitted by the company. Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company submission. Jean Hamilton critiqued the statistical aspects of the submission. Ruth Wong critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AEs	Adverse events
AESI	Adverse events of special interest
BGR	Brooks Gelman-Rubin
BMD	Bone mineral density
BMI	body mass index
BNF	British National Formulary
CEAC	Cost-Effectiveness Acceptability Curve
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
CPI	Consumer Prices Index
CQ	Clarification question
CRCQ	Company's response to clarification questions
CRF	Clinical risk factor
CrI	Credible interval
CS	Company Submission
CSR	Clinical Study Report
CV	Cardiovascular
DES	Discrete event simulation
DIC	Deviance information criterion
DSU	Decision Support Unit
DXA	dual X-ray absorptiometry
EA	Exploratory analysis
EAG	External Assessment Group
EQ-5D	EuroQol 5 dimensions
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis
FEM	Fixed effect model
FRAX	Fracture Risk Assessment Tool
GI	Gastrointestinal
GP	General practitioner
HCRU	Healthcare resource utilisation
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratios
IOF	International Osteoporosis Foundation

ITT	Intention-to-treat
IV	Intravenous
KOL	Key opinion leader
MACE	Major adverse cardiovascular events
MCMC	Markov chain Monte Carlo
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent-to-treat
MTA	Multiple technology appraisal
NHNV	Non-hip non-vertebral
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOGG	National Osteoporosis Guideline Group
NR	Not Reported
ONJ	Osteonecrosis of the Jaw
ONS	Office for National Statistics
PAS	patient access scheme
PrI	Predictive intervals
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QS149	Quality standard 149
RCT	Randomised Controlled Trial
RE	Random effect
REM	Random effect model
RR	Relative risk
RRR	Relative risk reduction
RWE	Real-world evidence
SA	Sensitivity analysis
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event

TRAE	Treatment-related adverse event
TSD	Technical support document
VBA	Visual Basic for Applications
WHO	World Health Organization
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This External Assessment Group (EAG) report assesses abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. This summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) when using list prices for comparator technologies. The cost-effectiveness results when using confidential comparator prices are included in a confidential appendix.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, and do not necessarily reflect the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

The company submission (CS) states that the most relevant comparators for abaloparatide are teriparatide and romosozumab and only these comparators are included in the economic analysis.[1] The term anabolic therapy is used in this report to refer to abaloparatide, teriparatide and romosozumab. Each of these anabolic therapies should be followed by an antiresorptive therapy and the company assumes that alendronate will be used for this purpose.

Key issues identified by the EAG that potentially impact on the cost-effectiveness estimates for abaloparatide versus teriparatide and abaloparatide versus romosozumab are summarised in Table 1.

Table 1: Overview of EAG's key issues

ID882	Summary of issue	Report sections
Issue 1	Generalisability of the model to the population likely to receive anabolic therapy in current practice	2.3, 3.13.2, 4.2.1, 4.3.4.2, 4.4.2.7
Issue 2	Presence of model implementation issues and minor coding errors	4.3.4.2, 4.4.2.1
Issue 3	Underestimation of uncertainty around differences in treatment effectiveness	3.10, 3.12, 3.13.2, 4.3.4.2, 4.4.2.2
Issue 4	Choice of treatment effect estimates for abaloparatide versus teriparatide	3.10, 3.12, 3.13.2, 4.3.4.2, 4.4.2.2
Issue 5	Assumptions and sources used for persistence rates	4.3.4.2, 4.4.2.3
Issue 6	Long-term care costs applied using a cohort approximation	4.3.4.2, 4.4.2.4
Issue 7	Utilities not applied for nursing home admission	4.3.4.2, 4.4.2.7
Issue 8	Resource use for disease management	4.3.4.2, 4.4.2.5

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

- The EAG has assumed that abaloparatide has the same efficacy as teriparatide for preventing hip fractures because the hazard ratios (HRs) from the network meta-analysis (NMA) for abaloparatide versus placebo are uncertain and are informed by very few events.

- The EAG has assumed that abaloparatide has the same efficacy as teriparatide for preventing non-hip non-vertebral (NHNV) fractures because the HRs from the NMA suggest a direction of treatment effect that is inconsistent with direction of treatment effect from the real-world evidence (RWE) study (a large anonymised US patients claims database, see Section 3.5).

- The EAG has used the CODA (convergence diagnosis and output analysis) samples from the NMA to represent the uncertainty around the HRs whereas the company has sampled each HR independently using a gamma distribution, using an arbitrary standard error, which provides narrower confidence intervals and does not capture any correlations between the HRs.

- The EAG has assumed a linear decline in treatment persistence for romosozumab across the 12 month treatment period to match the assumption applied to teriparatide and abaloparatide rather than assuming 80% treatment persistence at both 6 months and 12 months.

- The EAG adapted the model to simulate whether a new admission to long-term care occurred for each patient having a hip fracture, whereas the company used a cohort-level approximation for long-term care cost in which a proportion of the costs for long-term care to every patient experiencing a hip fracture is applied.

- The EAG applied alternative resource use and unit cost assumptions for initiating treatment and following up patients, with the main difference being more frequent follow-up appointments for patients on newer anabolic therapies (romosozumab and abaloparatide).

- The EAG made several corrections to the company's model.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

In the company's base case, the technology is modelled to affect QALYs by:

- Reducing the risk of fractures, which are associated with an acute reduction in health-related quality of life (HRQoL) during the first year after fracture and a chronic reduction in health-related quality of life thereafter

In the company's base case, the technology is modelled to affect costs by:

- Having [redacted] drug acquisition costs compared to teriparatide and romosozumab
- Reducing the risk of fractures, which incur costs substantial cost in the year after fracture and lower ongoing costs in subsequent years

The modelling assumptions that have the greatest effect on the estimates of incremental costs and QALYs are:

- The use of the CODA samples in the PSA to characterise uncertainty in the HRs instead of gamma distributions with an arbitrary standard error.
- The choice of HR estimates, in particular, whether the HRs from the NMA are applied for abaloparatide for hip and NHNV fractures or whether it is assumed that the efficacy for abaloparatide is similar to teriparatide.
- The treatment persistence estimates applied for romosozumab
- Whether costs for long-term care admission follow hip fracture are simulated individually or using a cohort-level approximation.
- Whether the baseline characteristics match those of the ACTIVE study or a higher risk cohort from the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) study in which all patients had a prior fracture.

1.3 The decision problem: summary of the EAG's key issues

The EAG had some concerns regarding the decision problem addressed in the CS. The company states that the population addressed in the CS is patients at 'very high risk of fracture' in whom the current standard of care would be either teriparatide or abaloparatide.[1] This is narrower than the licensed indication which is simply, "*postmenopausal women at increased risk of fracture*."[2] The CS states that the population at 'very high risk of fracture' would be consistent with the population eligible for recruitment to the key clinical effectiveness study, Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE).[1] However, the EAG notes that some patients eligible for recruitment to the ACTIVE study would not be eligible for either teriparatide or abaloparatide under current NICE guidance[3, 4] because they did not have a prior fracture at baseline. This also has implications for the cost-effectiveness analysis because the baseline characteristics of the ACTIVE study are used to

determine the characteristics of the modelled population. This is therefore further discussed in Section 1.5 below (see Issue 1).

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The key evidence of the clinical effectiveness and safety of abaloparatide is from the ACTIVE study.[5] The EAG had some concerns regarding the generalisability of the ACTIVE study population to patients likely to receive abaloparatide in the UK which included: the lack of UK centres in the study; the exclusion of patients with prior bisphosphonate treatment and the inclusion of patients without previous fractures (Section 3.2.1 and 3.2.4). The EAG was not able to assess the impact of these uncertainties on the ICER, but it considers that they should be taken into account when assessing the generalisability of the cost-effectiveness estimates to the population likely to receive abaloparatide in the UK.

The ACTIVE study was also considered to be at high risk of bias when assessed by the EAG using the Cochrane risk of bias tool (version 2). This was mainly due to the high proportion of post-randomisation withdrawals (see Section 3.2.2). The EAG was not able to assess the impact of this high risk of bias on the ICER, but it considers that this should be taken into account when assessing the robustness of the cost-effectiveness estimates.

Vertebral fractures were the primary outcome in the ACTIVE study. However there is considerable uncertainty for other outcomes, in particular hip fractures, in which one hip fracture was observed in the placebo arm and no fractures were observed in the abaloparatide and teriparatide arms (CRCQ2 NMA Appendix, Table 21). Although an NMA was conducted the results are extremely uncertain and should be viewed with caution. The impact of this uncertainty on the cost-effectiveness analyses is addressed in Section 1.5 (see Issue 2).

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG identified a number of key issues impacting the cost-effectiveness analysis which are described in full in section 4.3.4. Those issues that were found to have an important impact on the cost-effectiveness estimates are described in the following tables.

Issue 1 Generalisability of the model to the population likely to receive anabolic therapy in current practice

Report section	2.3, 3.13.2, 4.2.1, 4.3.4.2, 4.4.2.7
Description of issue and why the EAG has identified it as important	The company states that the population modelled is postmenopausal women 'at very high risk' of fracture, who would be likely to receive either abaloparatide or teriparatide under current practice. The company uses the population of the ACTIVE study to represent the characteristics of this target population. However, a substantial proportion of the patients recruited to ACTIVE would not have been eligible for either teriparatide or romosozumab under current NICE guidance as they did not have a prior fracture at baseline.
What alternative approach has the EAG suggested?	The EAG has conducted a scenario analysis using the patient characteristics from a trial of romosozumab (ARCH study) which was restricted to patients with a prior fracture at baseline.
What is the expected effect on the cost-effectiveness estimates?	The EAG found that incremental costs and QALYs were in the same direction, but the absolute cost savings and QALY gains were greater when modelling using a higher risk population (QALY gain: -0.016 versus teriparatide and 0.027 versus romosozumab) when compared with the results when using the population of the ACTIVE trial which is used in the EAG's base case (QALY gain: -0.005 versus teriparatide and 0.002 versus romosozumab).
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that the company could explore this issue more thoroughly by providing analyses that reflect the characteristics of the specific groups recommended for treatment with either teriparatide or romosozumab under current NICE guidance.

Issue 2 Presence of model implementation issues and minor coding errors

Report section	4.3.4.2, 4.4.2.1
Description of issue and why the EAG has identified it as important	The EAG identified several model implementation errors and minor coding errors. The correction that had the largest impact on the incremental QALYs related to the method used to sample patient characteristics within the company's model. The company's approach to sampling patient characteristics is overly complex and is providing a higher proportion of prior fractures at baseline than the proportion across the ACTIVE study (65.6% vs 58.5%). The correction that had the largest impact on the incremental costs was the assumption that 19 pre-filled pens would be required to provide a maximum of 18 months of treatment for abaloparatide. The other corrections had a smaller impact and a description of these can be found in section 4.3.4.2.
What alternative approach has the EAG suggested?	The EAG made a total of twelve sets of corrections to the company's model which are detailed in Section 4.4.2.1. These included using a simpler approach to sampling the patient characteristics and assuming 18 pre-filled pens are required to provide 18 months of abaloparatide treatment.
What is the expected effect on the cost-effectiveness estimates?	The EAG's corrected model provides results that are reasonably consistent with the company's base case model.
What additional evidence or analyses might help to resolve this key issue?	None identified.

Issue 3 Underestimation of uncertainty around differences in treatment effectiveness

Report section	3.10, 3.12, 3.13.2, 4.3.4.2, 4.4.2.2
Description of issue and why the EAG has identified it as important	The company has not used the CODA samples from the NMA to capture uncertainty around the estimates of treatment effect. Instead they have sampled the HRs for each treatment independently from a gamma distribution using an arbitrary measure of uncertainty (standard error =5% of the mean HR). The impact of this is to substantially underestimates the uncertainty around the HRs from the NMA within the economic model.
What alternative approach has the EAG suggested?	The EAG prefers to use the CODA samples from the NMA to reflect the uncertainty around the HRs.
What is the expected effect on the cost-effectiveness estimates?	The uncertainty in the cost-effectiveness estimates is expected to be substantially underestimated in the company's PSA. In addition, robust estimates of the average costs and QALYs can only be obtained when the uncertainty around the HRs is properly characterised with the PSA.
What additional evidence or analyses might help to resolve this key issue?	The company could correct their model to use the CODA samples from the NMA.

Issue 4 Choice of treatment effect estimates for abaloparatide versus teriparatide

Report section	3.10, 3.12, 3.13.2, 4.3.4.2, 4.4.2.2
Description of issue and why the EAG has identified it as important	The company has used the NMA outputs to capture the expected HRs for each treatment versus placebo. However, the EAG considered that the HRs for hip fracture for abaloparatide versus placebo were highly uncertain because they were based solely on the ACTIVE study in which only a single event was observed for placebo and zero events for abaloparatide. In addition, the EAG considered that the HRs for NHNV fractures for abaloparatide versus teriparatide based on the NMA were uncertain and the direction of treatment effect for the median HR, which is used in the deterministic analysis, was inconsistent with the findings of the RWE study.
What alternative approach has the EAG suggested?	The EAG prefers to assume that abaloparatide has the same efficacy as teriparatide for both the hip and NHNV fracture outcomes.
What is the expected effect on the cost-effectiveness estimates?	This had an important impact on the cost-effectiveness estimates because the estimate of incremental QALYs for abaloparatide versus teriparatide was in the opposite direction when assuming equal efficacy for the hip and NHNV fracture outcomes. This is due to the longer duration of treatment for teriparatide versus abaloparatide.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider that this issue is likely to be addressed by collecting additional evidence given that a RWE study comparing abaloparatide with teriparatide is already available and an RCT of the size required to detect a difference would be unlikely to be feasible.

Issue 5 Assumptions and sources used for persistence rates

Report section	4.2.4.4, 4.3.4.2
Description of issue and why the EAG has identified it as important	The company has taken the assumed treatment persistence of 80% for romosozumab at 1 year from a published model but has assumed that 80% are persistent with treatment (i.e. have not discontinued) at both 6 months and 12 months. This contradicts the approach taken for abaloparatide and teriparatide whereby a linear decline in treatment persistence has been assumed. In addition, the company has presented a scenario analysis incorporating a trial-based estimate of treatment persistence rather than RWE for abaloparatide and teriparatide, but in this scenario analysis it has continued to apply the assumed 80% treatment persistence for romosozumab rather than also using trial-based treatment persistence from ARCH.
What alternative approach has the EAG suggested?	The EAG prefers to assume a linear decline in treatment persistence from baseline to 12 months for romosozumab, which is consistent with the approach used for the other two anabolic therapies. In addition, in the EAG's scenario analysis exploring trial-based treatment persistence, the EAG has applied trial-based estimates for all three treatments by using the data from the ARCH trial for romosozumab.
What is the expected effect on the cost-effectiveness estimates?	The EAG's assumption of a linear decline in treatment persistence for romosozumab, resulted in incremental QALYs that were in the same direction, but which were numerically smaller. It also resulted in incremental cost that were in the same direction, but which were numerically [redacted] This is because it increases mean time on treatment with romosozumab meaning that both the HRs and the costs are being applied for a longer period. In the EAG's scenario analysis using treatment persistence from clinical trials for all three treatments, the incremental QALYs for abaloparatide versus romosozumab were in the opposite direction and the incremental costs were in the same direction but were numerically [redacted]. The results for abaloparatide versus teriparatide were very similar to the EAG's preferred base case.
What additional evidence or analyses might help to resolve this key issue?	It is clear that the cost-effectiveness of abaloparatide is dependent both on the relative efficacy and on the average time on treatment and therefore additional RWE on treatment persistence for all three anabolic therapies would be beneficial. The EAG notes that the company has not used any of the information from the US RWE study to quantify if treatment persistence is similar for abaloparatide and teriparatide and instead relies on the assumption that they will have identical persistence, applying treatment persistence estimates from a teriparatide RWE study.

Issue 6 Long-term care costs applied using a cohort approximation

Report section	4.3.4.2, 4.4.2.4
Description of issue and why the EAG has identified it as important	The company has used a patient-level state transition structure to simulate the fractures occurring in the lifetime of each individual rather than the proportion of the cohort experiencing a particular outcome. Costs and utilities are therefore applied according to the individual's specific fracture history. However, costs related to new admissions to long-term care following hip fracture are estimated using a cohort approach rather than an individual approach with a proportion of the costs allocated to every individual having a hip fracture rather than simulating whether the individual is admitted to long-term care.
What alternative approach has the EAG suggested?	The EAG has adapted the model to simulate whether or not a new admission to long-term care occurs for each individual experiencing a hip fracture.
What is the expected effect on the cost-effectiveness estimates?	Using an individual rather than a cohort-level approach resulted in incremental costs that were in the same direction but were numerically [redacted] in both pairwise comparisons.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider that additional evidence is needed to resolve this issue as it relates to a structural choice within the model.

Issue 7 Utilities not applied for nursing home admission

Report section	4.3.4.2, 4.4.2.7
Description of issue and why the EAG has identified it as important	The company's model does not account for any loss of HRQoL in patients whose hip fracture results in a new admission to long-term care (e.g. nursing home or residential care home) versus those who return to living in their own home.
What alternative approach has the EAG suggested?	The EAG's adaptation to allow long-term care admission to be modelled at the individual level (see Issue 6) allowed for a utility multiplier (0.625) to be applied to those admitted to long-term care. However, there is some potential for double counting if the estimate of utility applied in the second and subsequent years after hip fracture already accounts somewhat for the greater utility decrement in those admitted to long-term care. For this reason, the EAG has not included this change in their base case.
What is the expected effect on the cost-effectiveness estimates?	The absolute impact of this was small when applied to the EAG's base case because the difference in hip fracture incidence was small.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that this issue is resolved as this had a small impact on the cost-effectiveness estimates in the EAG's preferred base case. However, this has the potential to have a larger impact if the NMA estimates are applied for abaloparatide and therefore it remains a key issue.

The EAG also had alternative preferences for disease management costs, but these had a minimal impact on the ICER so the reader is referred to the description of Issue 8 in Section 4.3.4.2

1.6 Other key issues: summary of the EAG's view

The EAG identified a number of cost-effectiveness scenario analyses which generated the same ICERs when applying different HRs when using both the company and the EAG's model. The EAG is reasonably satisfied that this is related to the difficulty in estimating differences in outcomes between treatments in a patient level simulation when there are small differences in treatment efficacy. The EAG would therefore urge caution in interpreting the results for deterministic scenarios which generate small differences in QALYs. The EAG also noted some variability in the cost-effectiveness evidence when using different random number seeds (see Appendix 3). The EAG believes that it has minimised the impact of this issue on its base case estimate of cost-effectiveness by using a different set of random number seeds for each PSA run, thereby average the results across 200 sets of random number seeds, as well as averaging across 200 sets of parameter samples. However, this issue is not resolved within the company's base case analysis.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2: Summary of EAG's exploratory analyses and preferred base case scenario

	Abaloparatide versus teriparatide			**Abaloparatide vs romosozumab**		
Scenario	**Incr. cost, £**	**Incr. QALYs**	**ICER**	**Incr. cost, £**	**Incr. QALYs**	**ICER, £**
Company's base case	[redacted]	0.013	[redacted]	[redacted]	0.031	[redacted]
EAG EA1: Correction of model errors	[redacted]	0.008	[redacted]	[redacted]	0.024	[redacted]
EA2: EA1+ Use of same HRs for abaloparatide and teriparatide for hip and NHNV	[redacted]	-0.005	[redacted]	[redacted]	0.01	[redacted]
EA3: EA1+The persistence rate of romosozumab at 6 months	[redacted]	0.008	[redacted]	[redacted]	0.016	[redacted]
EA4: EA1+Long-term costs simulated individually	[redacted]	0.008	[redacted]	[redacted]	0.024	[redacted]
EA5: EA1+ Resource use for disease management	[redacted]	0.008	[redacted]	[redacted]	0.024	[redacted]
EAG-preferred base case (EAG EA1-5 combined), deterministic	[redacted]	-0.005	[redacted]	[redacted]	0.002	[redacted]
EAG-preferred base case (EAG EA1-5 combined), probabilistic	[redacted]	-0.005	[redacted]	[redacted]	0.015	[redacted]

Modelling errors identified and corrected by the EAG are described in full in Section 4.3.4 (EA1 with step by step result changes provided in Appendix 4). For further details of the exploratory and sensitivity analyses done by the EAG, see Section 4.4.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company submission (CS) describes osteoporosis as a "*progressive skeletal disease characterised by low bone mass and deterioration of bone structure, leading to an increase in bone fragility and risk of fracture*."[1] It states that osteoporosis is highly prevalent and that 50% of women will experience one or more fragility fractures in their lifetime.[1] The EAG notes that although the recent National Osteoporosis Guideline Group (NOGG) guideline is cited as the source for this in the CS,[6] the source cited in the guideline is a paper by van Staa *et al.* and this paper gives a lifetime risk of 53.2% based on analysis of a large general practice research database over the period 1988 to 1998, and may therefore not reflect current fracture risks.[7] More recent epidemiological estimates (for the year 2017) provide an estimated prevalence for osteoporosis in women aged ≥50 years of 21.8%, and an estimated lifetime risk of fragility fracture for a 50-year old women of 35%, including a 17.2% lifetime risk of hip fracture.[8]

The CS describes osteoporotic fractures as most commonly occurring in the vertebrae (spine), hip and wrists, but also occurring in the arm, pelvis, ribs and other bones.[1] Morphometric is a term used to describe fractures of the vertebrae which can be identified radiographically, which may or may not be associated with symptoms, whereas clinical vertebral fracture is the term used to describe only those associated with symptoms. The EAG notes that the term major osteoporotic fractures is often used when collectively describing fractures at the hip, wrist and humerus, and clinical vertebral fractures.[6, 9, 10]

The CS describes how postmenopausal women are at increased risk of fracture due to bone mineral density (BMD) being affected by declining oestrogen levels associated with menopause.[1] In addition to age, sex and menopausal status, various modifiable and fixed risk factors for osteoporosis are described in CS, Table 3.[1] The risk factors include coexisting health conditions, medications, family history, low body mass index (BMI), smoking status, alcohol consumption, sedentary lifestyle, poor nutrition and low intake of calcium and vitamin D. The EAG notes that frequent falls and previous fractures are also risk factors for future osteoporotic fractures.[11]

The CS describes the diagnostic criteria for osteoporosis using the WHO definition which is a BMD more than 2.5 standard deviation's (SDs) below the mean for a young adult reference population.[12] This is also referred to as having a T-Score of ≤–2.5 (NB: units for T-Scores are always SDs). People with a T-Score ≤–2.5 and a previous fracture are often described as having severe or 'established' osteoporosis. Whilst BMD is used to diagnose osteoporosis, the outcome of interest to patients is their risk of fracture and tools exist which provide an estimate of fracture risk, in the absence of a BMD measurement, based on the presence of clinical risk factors.[6] NICE clinical guideline 146 (CG146)

recommends that those eligible for fracture risk assessment, based on either age or the presence of risk factors, are first assessed using either the Fracture Risk Assessment Tool (FRAX®, without BMD) or QFracture risk assessment tools. It is recommended that BMD is then only measured in those whose risk is just below or above the intervention threshold for starting treatment.[13] This means that treatment can be started without a BMD scan in individuals assessed as being at sufficient risk when assessed using either QFracture or FRAX. This targeted use of BMD measurement, to allow a reassessment of fracture risk incorporating BMD in only those close to the threshold for intervention, makes more efficient use of the dual X-ray absorptiometry (DXA) scans used to measure BMD, than a policy of scanning all individuals with risk factors for osteoporosis.[6]

The CS describes fragility fractures as having an impact on both mortality and quality of life.[1] Hip fractures are associated with an excess risk of mortality which is greater at older ages.[14] The CS describes the absolute life-time risk of death from a hip fracture as being 2.8% for a 50-year old woman,[1] but this is based on an estimate from a 1989 publication and is therefore unlikely to reflect current risks.[15] The CS states that, "*In the first year after a hip fracture there is a 10–fold increased mortality risk with overall mortality reported as approximately 20%."*[1] However, the sources cited are webpages,[16, 17] which themselves cite numerous papers, and the EAG was unable to identify the specific sources for these estimates. The EAG notes that the National Hip Fracture Database reported a national average 30-day mortality rate following hip fracture ranging from 6.4% to 6.9% across 2022.[18] The EAG notes that care must be taken to assess the excess risk of mortality associated with hip fracture and to account for the proportion of that excess risk that is attributable to the fracture and not to other comorbidities present.[19] A fuller discussion on the excess mortality associated with fractures is provided in Section 4.2.

In terms of quality of life, the CS describes the high burden of osteoporotic fractures including chronic pain, disability and loss of independence and a reduction in health-related quality of life (HRQoL).[1] Vertebral fractures in particular are described as being a cause of chronic pain, loss of function, and disability from kyphosis (curvature of the spine).[1] Hip fractures are also described as causing permanent disability in 50% of patients, with 10 to 20% of patients moving to nursing homes.[1] The EAG notes that the CS cites a website,[16] which itself cites multiple sources for these estimates, so the EAG had difficulty identifying the exact sources and assessing the validity of these estimates. However, the EAG notes that the same website cited by the company also cites a more recent study (International Costs and Utilities Related to Osteoporotic Fractures Study [ICUROS] Europe) in which the proportion of community dwelling individuals moving into long-term care at 12 months after hip fracture rises from 2% for 50-60 year-olds to 35% for 90 year-olds and above, although the UK was excluded from these European estimates due to a lack of data.[8, 20] A fuller critique of the evidence regarding the impact of fractures on HRQoL and admission to residential/nursing care is provided in Section 4.2.

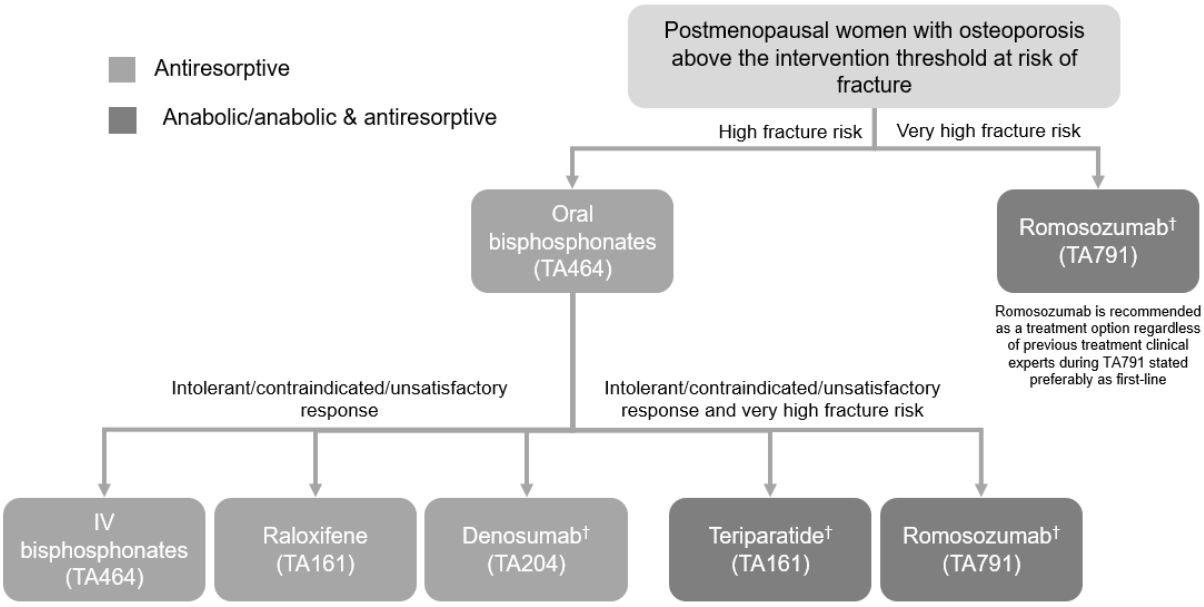
The EAG is broadly satisfied with the company's description of the health problem, although it noted that the CS frequently cites websites where information from multiple sources is collated rather than a specific published article, making it difficult for the EAG to validate the estimates used by the company to describe the burden of osteoporosis.

2.2 Critique of company's overview of current service provision

The CS summarised current practice in England and Wales using Figure 1 (reproduced from CS, Figure 4). In addition, CS Table 6 provides extracts from relevant NICE appraisals for all of the interventions included in Figure 1. The EAG considers that Figure 1 could make it clearer that raloxifene and teriparatide are restricted under NICE guidance to use in patients with a prior fracture (i.e. secondary prevention) because the NICE Technology Appraisal number 161 (TA161) only covered this population.[4] In addition, romosozumab is restricted to those with a prior fracture in the previous 24 months and is therefore only available for secondary prevention (TA791).[3] Therefore, for patients without a previous osteoporotic fracture, the only treatments recommended by NICE would be bisphosphonates and denosumab. The EAG also notes that the NICE recommendations for the use of raloxifene and teriparatide for secondary prevention in TA161, and the NICE recommendations for the use of denosumab as primary prevention in TA204, are restricted to certain combinations of age, T-Score and clinical risk factors, as presented in CS Table 6, which effectively restricts these treatments to higher risk patients. Similarly, the recommendations for bisphosphonates under TA464, refer to patients needing to be at 'higher risk' of osteoporotic fragility fracture, referring the reader to NICE's Osteoporosis Quality Standard (QS149), which provides thresholds for intervention using a 10-year probability of major osteoporotic fracture. It is unclear if this threshold from QS149 is the 'intervention threshold' referred to when specifying the population at the start of Figure 1, but the EAG notes that the intervention thresholds are not currently harmonised across the various NICE TAs. Further commentary is provided in Section 2.3.3 on the relevance of each treatment included in Figure 1 as a comparator for abaloparatide.

The company's description of current service provision in CS Section B.1.3.3 is focused on the treatments available and does not describe whether patients are primarily managed in primary or secondary care. However, the NOGG guideline,[6] which is referenced by the CS in Section B.1.3.3.4.2, does recommend considering referral for, "*very high-risk patients to an osteoporosis specialist in secondary care, for assessment and consideration of parenteral treatment.*"

Figure 1: Company's presentation of the current treatment pathway in England and Wales based on NICE guidance (reproduced from CS, Figure 4)



† Patients stopping denosumab, teriparatide or romosozumab require a sequential therapy strategy typically involving an antiresorptive drug
Abbreviations: IV, intravenous; TA, technology appraisal

2.3 Critique of company's definition of the decision problem

2.3.1 Population

The CS states that the target population for abaloparatide is postmenopausal women with osteoporosis at very high risk of fracture and that this is narrower than the licensed indication which describes the population as those "*at increased risk of fracture*". The CS states that the target population for abaloparatide is in line with the population of the pivotal phase 3 placebo controlled abaloparatide study (ACTIVE). The ACTIVE study recruited healthy ambulatory postmenopausal women aged 49–86 years with osteoporosis who were deemed to be at risk of fracture because they met one of the following three criteria:

- T-score ≤-2.5 and >-5.0 at the lumbar spine or femoral neck and radiological evidence of ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma non-vertebral fracture within the past 5 years
- Women aged >65 years with the above fracture criteria and T-score ≤-2.0 and >-5.0
- Women aged >65 years who did not meet the fracture criteria whose T-score was ≤ -3.0 and > -5.0

The mean 10-year risk of major osteoporotic fracture calculated using the FRAX algorithm for the population enrolled in ACTIVE was 13% with an interquartile range of 7 to 17% across all three study arms (CSR addendum Table 6).

The EAG notes that the intervention threshold for bisphosphonates in the NICE QS149 ranges from 7.2% in a 50-year-old to 20% in those aged 70 years and over and these intervention thresholds were based on those defined in the 2017 version of the NOGG guideline.[6, 21] In addition, the latest update to the NOGG guideline (2021 version) describes patients at very high risk as those with a risk that is 60% greater than the intervention threshold giving thresholds for very high risk which vary from 11.7% at 50 years to 32.5% at 70 years (NOGG 2021, Table 5). Therefore, whilst there is some overlap between the population recruited to ACTIVE and the group defined at very high risk of fracture in the NOGG guideline, the EAG does not consider that the population of ACTIVE as a whole would be classed as being at very high risk of fracture according to the NOGG guideline. The EAG's clinical experts also noted that whilst the latest NOGG guideline introduced a definition for the group of patients at 'very high risk' of fragility fracture, a definition of 'very high risk' is absent from existing NICE guidance for osteoporosis treatments.[3, 4, 21-23] NICE guidance for bisphosphonates refers to the intervention thresholds provided in QS149, whereas guidance for denosumab, raloxifene, teriparatide and romosozumab restricts treatment to patients with specific risk factors, which differ for each treatment.

The NICE scope specified various subgroups that should be considered if the evidence allowed (see Table 3 for details). The CS does provide some information on clinical effectiveness in subgroups defined using patient characteristics that predict fracture risk (e.g. age, previous fracture history, BMD and BMI) and for some factors which may affect the impact of fracture on costs or quality of life (e.g. age). However, subgroup analyses are not provided according to the predicted 10-year risk of fracture or for the subgroup with a history of major osteoporotic (spine, hip, forearm or humerus) fracture in the previous 24 months. This latter subgroup is important as this is the population eligible for treatment with romosozumab in TA791 (See Box 1). The economic analysis does not provide any subgroup analyses or explore the impact of varying baseline characteristics to generate cost-effectiveness results for patients with particular risk factors at baseline (e.g. prior fracture) or for patients with higher or lower baseline fracture risk.

The EAG notes that the ACTIVE trial excluded patients with prior bisphosphonate treatment in the previous 5 years, except those patients where the bisphosphonate usage was less than 3 months and they were intolerant to bisphosphonates. However, the company's proposal for the place of abaloparatide in the clinical pathway, illustrated in CS Figure 5, includes the positioning of abaloparatide for patients both with and without prior bisphosphonate treatment (i.e. alongside the two positions shown for romosozumab in Figure 1).

2.3.2 Intervention

Abaloparatide is a "*34 amino acid peptide that shares 41% homology to parathyroid hormone [PTH(1-34)] and 76% homology to parathyroid hormone related peptide [PTHrP(1-34)], and is an activator of the PTH1 receptor signalling pathway*".[2] The licensed dose for abaloparatide is 80 µg, given once daily by subcutaneous injection.[2] Patients and/or their caregivers should be trained to allow self-administration (or carer-administration), but the first dose given by the patient or carer should be performed under the guidance of a healthcare professional.[2]

In CS, Table 1, the company describes the intervention as abaloparatide for 18 months followed by alendronate for 5 years (the terms alendronate and alendronic acid are used interchangeably). The 18 months treatment duration for abaloparatide is consistent with the maximum duration of treatment specified in the Summary of Product Characteristic (SmPC). The SmPC also states, "*Following cessation of abaloparatide therapy, patients may be continued on other osteoporosis therapies such as bisphosphonates."* The EAG notes that the SmPC does not specify that the osteoporosis treatment used following abaloparatide treatment should be alendronate and that subsequent treatment with other bisphosphonates or indeed other osteoporosis therapies would be consistent with the wording of the SmPC.

The list price for abaloparatide is £294.54 for one-prefilled pen with 30 doses in 1.5 mL solution, which the CS states is equivalent to a cost of £5,301.72 for an 18-month course. The company has submitted a patient access scheme (PAS) proposal for abaloparatide, consisting of a simple discount of [redacted] on the list price, giving a cost per pre-filled pen of [redacted].

2.3.3 Comparators

The comparators addressed fully in the CS are teriparatide and romosozumab. CS, Table 1 describes the comparator treatment strategies as: teriparatide (24 months) followed by alendronate (5 years); romosozumab (12 months) followed by alendronate (5 years); and no treatment. However, the comparator strategy of no treatment is not included in the economic analysis as this was not considered to be a relevant strategy in people at very high risk of fracture. The EAG's clinical experts agreed that abaloparatide is most likely to be used in patients who would currently be offered either teriparatide or romosozumab. The EAG notes that teriparatide is only recommended by NICE in TA161 for patients with a prior fracture (i.e. secondary prevention) and only in those who are unable to receive bisphosphonates or who have had an unsatisfactory response to bisphosphonates (i.e. second-line). The recommendations in TA791 for romosozumab do not restrict it to second-line use but do require patients to have had a recent fracture and therefore it is restricted to secondary prevention. The EAG's clinical experts stated that teriparatide is generally used second-line for those who have fractured whilst

receiving a bisphosphonate, indicating an unsatisfactory response (see Box 1 for specific wording of recommendation including restrictions by T-Score and number of prior fractures). However, they noted that it was also sometimes used as a first-line treatment in individuals with a previous fracture who are considered to be at high risk of further fractures, although this would only be in accordance with NICE guidance if the individual was unable to take oral bisphosphonates (see Box 1). The EAG's clinical experts noted that there is currently an ongoing update to the NICE osteoporosis guideline (CG146) which is likely to update guidance on the use of teriparatide. In addition, the 2021 NOGG guideline recommends either teriparatide or romosozumab as first-line treatment options in *"postmenopausal women at very high fracture risk, particularly in those with vertebral fractures."* However, as discussed earlier, the current guidance for romosozumab and teriparatide does not use the NOGG definition for very high risk when specifying the populations eligible for these treatments (see Box 1).

Box 1: Summary of NICE guidance for romosozumab and teriparatide[a]

Romosozumab (TA791)

1.1 Romosozumab is recommended as an option for treating severe osteoporosis in people after menopause who are at high risk of fracture, only if:

- they have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture) and
- the company provides romosozumab according to the commercial arrangement.

Teriparatide (TA161)

1.4 Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to take alendronate and risedronate, or have a contraindication to or are intolerant of alendronate and risedronate (as defined in section 1.6), or who have had an unsatisfactory response (as defined in section 1.8) to treatment with alendronate or risedronate 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.

[…..]

1.6 For the purposes of this guidance, intolerance of alendronate or risedronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.

[….]

1.8 For the purposes of this guidance, an unsatisfactory response is defined as occurring when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below her pre-treatment baseline.

[a] *excerpts only - please refer to full guidance for prescribing purposes*

In terms of the population specified in the ACTIVE study, the EAG's clinical experts considered that the group who were enrolled in ACTIVE without a prior fracture, whose risk factors were being aged over 65 years and having a T-Score of ≤-3, would not be offered an anabolic treatment (e.g. teriparatide or romosozumab) based on NICE current guidance (see Box 1). The EAG also notes that patients with prior bisphosphonate use were excluded from ACTIVE, meaning that those patients who fracture whilst receiving bisphosphonates, and who would currently be offered second-line teriparatide in clinical practice, would not have been eligible for the ACTIVE trial.

The NOGG guideline describes how bone turnover increases and there is a fall in BMD in patients discontinuing either teriparatide or romosozumab and to avoid this sequential treatment with an anti-resorptive drug should be planned in advance to ensure that there is no gap in treatment and that the beneficial skeletal effects of the anabolic therapy are maintained.[6] In patients completing a course of anabolic treatment, the EAG's clinical advisors stated that they would usually offer an intravenous (IV) bisphosphonate (e.g. zoledronic acid, also termed zoledronate), although an oral bisphosphonate (e.g. alendronate) could be offered if the patient preferred this option based on their previous experience. They also stated that the duration of subsequent treatment with a bisphosphonate would be tailored according to the individual's previous exposure to bisphosphonates. However, in most cases it would likely be a further 5 years if using an oral bisphosphonate and a further 3 years if using an IV bisphosphonate, with a subsequent review to determine if additional treatment was needed. The EAG notes that the NOGG guideline states that treatment durations over 10 years for oral bisphosphonate or 6 years for IV bisphosphonates should be made on an individual basis in careful consultation with the patient. In patients contraindicated for bisphosphonates, the EAG's clinical experts stated that denosumab would be offered as the subsequent antiresorptive treatment. This heterogeneity in the choice of follow-on antiresorptive treatment was also identified in the company's own survey of key opinion leaders (KOLs) which stated that *"(3 out of 6) reported that the treatment of alendronate post-anabolic therapy ranged between three to eight years. The other KOLs stated that IV zoledronate or denosumab were more common post-anabolic therapy."*

The CS states that bisphosphonates and denosumab are not considered to be comparators as these antiresorptive treatments are used following treatment with an anabolic agent (abaloparatide, teriparatide or romosozumab) rather than instead of anabolic treatment. The EAG's clinical experts agreed that the patient group offered anabolic treatments in clinical practice is fairly distinct from the group likely to be offered oral bisphosphonates. The EAG's clinical advisors considered that IV bisphosphonates may be an alternative treatment in some people at high risk of fracture where oral administration of bisphosphonates was not tolerated or was associated with poor adherence.

The EAG's clinical experts noted that denosumab treatment was generally offered to those unable to receive bisphosphonates or anabolic treatments due to contraindication for renal function. In addition, once started on denosumab treatment, patients would either need to continue treatment or to be switched to another antiresorptive when stopping denosumab, therefore a long-term personalised osteoporosis management plan needs to be in place before denosumab is started. For this reason, the group currently offered denosumab in clinical practice would be a distinct population from those offered a time-limited anabolic treatment.

The company also states that raloxifene is not a relevant comparator because it is not specifically indicated for women at very high risk of fracture. The EAG's clinical experts agreed that raloxifene is only used in patients without any other treatment options as it is generally considered to have lower anti-fracture efficacy than other treatments. It would therefore not be considered a comparator in patients at very high risk of fracture.

The company states that strontium ranelate is not a relevant comparator because it is not currently marketed in the UK. The EAG's clinical experts agreed that strontium ranelate does not form part of current UK clinical practice. In addition, patients who would have been offered strontium ranelate in the past, because they were unable to tolerate oral bisphosphonates, would now be likely to be offered IV bisphosphonates.

Overall, the EAG agrees that the main comparators for patients likely to receive abaloparatide in clinical practice would be romosozumab and teriparatide. However, not all patients in the ACTIVE study would be eligible for romosozumab or teriparatide under current NICE guidance. Furthermore, the treatment sequences in the CS do not represent the fact that there is some diversity in clinical practice regarding the choice of antiresorptive treatment used, with both IV bisphosphonates and denosumab sometimes used as alternatives to alendronate in patients coming off anabolic treatment.

2.3.4 Outcomes

The key clinical outcomes addressed in the CS are osteoporotic fragility fractures, BMD and adverse events (AEs). The main fracture outcomes presented in the CS were:

- New morphometric vertebral fracture
- Non-vertebral fracture (excluding those of the spine, sternum, patella, toes, fingers, skull, and face and those with high trauma)
- Major osteoporotic fracture (upper arm, wrist, hip or clinical spine)
- Clinical fracture (all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine)

The primary outcome of the ACTIVE study was the incidence of new morphometric vertebral fractures, that is fractures of the vertebrae which can be identified radiographically, which may or may not be associated with symptoms. However, clinical vertebral fractures (i.e. those associated with symptoms) were included in the reporting of the clinical fracture and major osteoporotic fracture endpoints, both of which were exploratory endpoints.

The BMD outcomes reported in the CS were total hip, femoral neck and lumbar spine BMD. The CS also reported bone turnover marker outcomes, which were not specified in the NICE final scope. The NOGG guideline states that there are, *"presently no definitive data that link a potential threshold change in BMD or bone turnover markers during drug offset to clinically meaningful changes in fracture risk*." Therefore, whilst changes in BMD and bone turnover markers may be useful for physicians monitoring a patient's response to treatment, the primary outcome of interest to patients is a reduction in the risk of fracture.

Mortality reporting in the CS is limited to reporting of AEs leading to death. HRQoL life is not reported as a clinical outcome as it was not measured in the ACTIVE study. Overall, the EAG is satisfied that the CS covers the outcomes specified in the NICE final scope where these were available.

2.3.5 Other relevant factors

The NICE methods guide allows for a QALY weighting for severity to be applied for health conditions where there is large absolute or proportionate QALY shortfall for patients with the condition receiving current standard care compared to patients living without the condition.[24] However, the company states that they do not consider that a QALY weighting, on the basis of disease severity, will apply in this case (CS, Section B.3.6).

The scope did not identify any special considerations related to equity or equality, however, the CS identifies an issue related to gender equality. It states, "*although abaloparatide has a marketing authorisation for postmenopausal women, this should not prevent using abaloparatide for some people who have been through menopause but do not identify as a woman."* It notes that a similar issue arose in TA791 where the committee concluded that, *"romosozumab will be considered within its marketing authorisation but that the recommendation need not specify sex".* [3]

Table 3: The decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from NICE scope	EAG comments
Population	Postmenopausal women with osteoporosis at increased risk of fracture	Postmenopausal women with osteoporosis at very high risk of fracture The submission positions abaloparatide for use in a narrower population of the licensed indication who have the greatest unmet need, and for whom abaloparatide is expected to provide the most clinical benefit. This population is in line with the ACTIVE study and clinical practice, where current anabolic treatments (teriparatide and romosozumab) are reserved for patients at very high risk of fracture.	The EAG considers that whilst there is some overlap between the population recruited to ACTIVE and the group defined at very high risk of fracture in the NOGG guideline, the EAG does not consider that the population of ACTIVE as a whole would be classed as being at very high risk of fracture according to the NOGG guideline. Also, patients recruited to ACTIVE who did not have a prior fracture would not be eligible for teriparatide or romosozumab under current NICE guidance (see Box 1).
Intervention	Abaloparatide	Abaloparatide for 18 months, followed by alendronate Abaloparatide is licensed as an 18-month course of treatment. The SmPC for abaloparatide states that *"following cessation of abaloparatide therapy, patients may be continued on other osteoporosis therapies such as bisphosphonates".*	The EAG notes that wording of the SmPC for abaloparatide does not specify that alendronate should be the treatment of choice for patients completing a course of abaloparatide and that other osteoporosis treatments including other bisphosphonates may be alternative treatments.
Comparator(s)	• Bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium, zoledronic acid) • Non-bisphosphonates (denosumab, romosozumab, strontium ranelate, teriparatide, raloxifene) • No active treatment	• Teriparatide for 24 months followed by alendronate • Romosozumab for 12 months followed by alendronate • No active treatment Theramex would like to clarify that bisphosphonates and denosumab (antiresorptive agents) are not appropriate comparators to abaloparatide. In practice abaloparatide would be used as part of a sequential therapy for women at very high risk of fracture. This sequential therapy includes an antiresorptive agent (after an anabolic agent) as opposed to displacing them. As such, the relevant comparators are the anabolic agents (teriparatide and romosozumab) and no active	Whilst the EAG's clinical experts advised that teriparatide and romosozumab were the most relevant comparators in patients likely to receive abaloparatide, the EAG notes that patients recruited to the ACTIVE study would also be eligible for other comparators listed in the scope which were not adequately addressed in the CS. The EAG is concerned about the exclusion of IV zoledronate as a comparator because the EAG's clinical experts said that IV zoledronate would be used in some higher risk patients unable to take oral bisphosphonates. It may therefore be a relevant comparator in those patients recruited to the ACTIVE study who did not have prior fracture

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from NICE scope	EAG comments
		treatment, with the latter represented by the placebo arm of the ACTIVE study. Strontium ranelate and raloxifene are not considered as comparators. Strontium ranelate is no longer part of routine clinical practice in England and Wales. Raloxifene is indicated for the prevention and treatment of osteoporosis in postmenopausal women but is not specially directed to women at very high risk of fracture. No active treatment was not included in the model as the most relevant comparators for patients at very high risk of fracture in the UK are teriparatide and romosozumab.	and would therefore not be eligible for either teriparatide or romosozumab (see Box 1). The EAG considered that denosumab was a potential comparator treatment in higher risk patients unable to take bisphosphonates, but the EAG's clinical experts noted that treatment with denosumab needed to be continued long-term and therefore the group of patients offered denosumab may differ from those offered anabolic treatment. The EAG's clinical experts agreed that strontium ranelate and raloxifene are not relevant comparators in the patient group likely to receive abaloparatide in clinical practice.
Outcomes	• Osteoporotic fragility fracture • Bone mineral density • Mortality • Adverse effects of treatment • HRQoL	In line with the final scope	Mortality in the CS is limited to reporting of AEs leading to death. No HRQoL data were collected in the ACTIVE or ACTIVExtend studies Overall, the EAG is satisfied that the CS covers the outcomes specified in the NICE final scope where these were available.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal	The CS provides estimates of the incremental cost per QALY for two comparisons: • abaloparatide followed by alendronate versus teriparatide followed by alendronate • abaloparatide followed by alendronate versus romosozumab followed by alendronate The company's analysis takes into account the proposed PAS for abaloparatide but does not take into account any confidential discounts for romosozumab.	The company has not provided a fully incremental analysis of all three treatment strategies included in the economic model. Other aspects of compliance to the reference case are commented on in Table 48, Section 4.3.3.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from NICE scope	EAG comments
	guidance for the same indication, a cost comparison may be carried out. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	The company analysis takes into account the costs of generic alendronate and explores in scenario analysis the impact of taking into account the costs for various biosimilar formulations of teriparatide.	
Subgroups to be considered	If the evidence allows the subgroups at higher risk of fracture will be considered to include: • subgroups based on predicted risk of fracture over 10 years • subgroups based on patient characteristics that affect the impact of fracture on lifetime costs and outcomes • subgroups based on fracture history • subgroups based on history of major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture)	Subgroup analyses are presented for the clinical evidence for some factors likely to be predictive of future fracture risks (e.g. age, previous fracture history, BMD and BMI) and some factors which may affect the impact of fracture (e.g. age). However, subgroups are not provided according to the predicted 10 years risk of fracture or for the subgroup with a history of major osteoporotic fracture in the previous 24 months. For the economic analysis the company states that as the CS focuses on patients at very high risk of fracture, in line with the inclusion/exclusion criteria of the ACTIVE study, the company does consider any further subgroups analyses are appropriate (CS Section B.3.12).	The EAG does not consider that the company has adequately addressed all the subgroups specified in the scope and it is unclear if the reason for this is a lack of evidence. An economic analysis for the subgroup with a prior major osteoporotic fracture in the previous 24 months would be useful as this is the population specified for romosozumab.
Special considerations including issues related to equity or equality	None discussed in the scope.	Although abaloparatide has a marketing authorisation for postmenopausal women, this should not prevent using abaloparatide for some people who have been through menopause but do not identify as a woman. In NICE TA791 for romosozumab, the committee concluded that romosozumab would be considered	The EAG notes that the company has raised this issue for the committee to consider when formulating its recommendations.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from NICE scope	EAG comments
		within its marketing authorisation, but the recommendation need not specify sex.	

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services

3 CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS is comprised of:

- A systematic literature review (SLR) of clinical evidence for abaloparatide vs a principal comparator, teriparatide, in postmenopausal women with osteoporosis at high risk of fracture;
- Summary and results for the ACTIVE trial, its 24-month extension, ACTIVExtend, and a retrospective real-world evidence (RWE) study of abaloparatide and teriparatide in postmenopausal women with osteoporosis
- A network-meta analysis (NMA) of clinical evidence for abaloparatide vs a range of potential comparators in postmenopausal women with osteoporosis

This chapter summarises and critiques the company's review methods and clinical effectiveness data. Full details are presented in the Section B.2 of the CS and CS Appendix D and the company's responses to clarification requests from NICE.[1, 25, 26] It should be noted that two rounds of clarification were undertaken and this report refers to the first set of clarification questions as CQ1. The company's response to the first clarification request is referred to as CRCQ1 which included an appendix describing both an updated NMA and an updated economic model. The second set of clarification questions and the company's response to these are described as CQ2 and CRCQ2 accordingly. The latter included an appendix describing a further updated NMA and an appendix describing a further updated model.

3.1 Critique of the methods of review(s)

The clinical evidence presented in the CS was informed by a SLR of studies assessing the clinical efficacy and safety of abaloparatide and other therapies (alendronic acid, ibandronic acid, risedronate sodium, zoledronic acid, denosumab, romosozumab, teriparatide, raloxifene, no active treatment, placebo, vitamin D and calcium supplementation) for the treatment of osteoporosis in postmenopausal women at increased risk of fracture (CS, Appendix D.1.1.2, Table 1).[1] The SLR involved a systematic search of bibliographic and conference abstract databases only for clinical studies of treatments in this population up to April 2023 (CS, Appendix D.1.).[1]

The primary clinical evidence detailed in the CS comes from the ACTIVE trial (Abaloparatide Comparator Trial In Vertebral Endpoints) - an international phase III, multi-centre, partially open-label, three-arm randomised controlled trial (RCT) comparing abaloparatide (arm 1) with either placebo (arm 2) or teriparatide (arm 3, open-label) in postmenopausal women with severe osteoporosis at risk of fracture (NCT01343004).[5, 27] This trial had a 24-month, single-arm extension (ACTIVExtend) for patients in arms 1 and 2 exposed to abaloparatide or placebo, who all received the bisphosphonate alendronate (NCT0657152).[28, 29] Two published papers relating to the randomised phase of the trial[27, 30] and four papers relating to the extension[29, 31-33] were identified by the SLR (CS, Appendix D.3.1, Table

6). However, the principal data reported in the CS were extracted from the Clinical Study Reports (CSRs).[5, 28] This was because the data from two trial sites – originally included in the publications of ACTIVE - were excluded on advice of the Committee on Human Medicinal Products (CHMP), so only the re-analysed data from the remaining sites (and contained in the submitted CSR) were presented. The CS did not report on the nature of the advice that led to the exclusion of these two sites, [redacted]

The CS states that the current clinical management of postmenopausal women with osteoporosis at high risk of fracture and intolerant/contraindicated to, or with an unsatisfactory response to oral bisphosphonates is either romosozumab or teriparatide (CS, Section B.3.1.1.2, Figure 4; see Box 1 for specific wording of TA161 and TA791).[5] However, the ACTIVE trial used both placebo and teriparatide as comparators; no direct evidence vs romosozumab was presented. Clinical advice to the EAG suggests that teriparatide is a reasonable comparator for abaloparatide (see Section 2.3.3).

This evidence was supplemented with data from a 19-month RWE retrospective observational study (NCT04974723; BA058-05-028)[34], which used anonymised US patient claims data. This study provided efficacy and safety evidence on the real-world use of abaloparatide and teriparatide in a US population of women aged ≥50 years with ≥1 new prescription fill of abaloparatide or teriparatide during the identification period, ≥1 claim for a medical or hospital visit, and a pharmacy claim in the 12 months before the index date (CS, Section B.2.3.2).

Given the availability of a single head-to-head phase III RCT comparing abaloparatide with an acceptable comparator, and the absence of any similar, relevant trials, the EAG agrees with the CS that a meta-analysis was not necessary (CS, Section B.2.8).[1]

The safety evidence reported in the CS comprised a narrative summary of data from the ACTIVE trial and ACTIVExtend (CS, Sections B.2.10).[1]

3.1.1 Searches

The company performed an SLR to identify all clinical effectiveness and safety studies of abaloparatide or comparator treatments of postmenopausal women with osteoporosis at increased risk of fracture.

Limitations identified by the EAG relate to the following.

- Search reporting for non-electronic database sources
- Search translation by restricted MeSH term searching in Cochrane Library only

- Applied population exclusion terms limit
- Application of date search limit

The company searched several electronic bibliographic databases in April 2023 (Appendix D.1 Identification and selection of relevant studies): PubMed, MEDLINE in Process (via PubMed.com, EMBASE (possibly via Embase.com), Cochrane Central Register of Controlled Trials (via Wiley) Database of Abstracts of Reviews of Effects (via CRD), NHS Economic Evaluation Database (via CRD) and Health Technology Assessment database (via CRD). The company hand searched the bibliographies of relevant systematic reviews to identify other new studies for inclusion.

The company searched one trial register (WHO International Clinical Trials Registry Platform) in April 2023 for ongoing, completed or unpublished trials. The company searched three conference abstract websites: the National Osteoporosis Society, the National Osteoporosis Foundation, and the International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) congress. The company searched several health technology assessment agencies and health institute websites: the Canadian Agency for Drugs and Technologies in Health, NICE, Food and Drug Administration, European Medicines Agency / Committee for Medicinal Products for Human Use, and National Institute for Health and Care Research. Supplementary sources searched by the company include the PROSPERO for review protocols, the Medicines and Healthcare Regulatory Agency website, and TRIP databases.

The electronic databases search in the CS is partially reported, e.g. full search strategies for CRD HTA were not provided. In addition, the date of the web searches and terms applied in the congress website, HTA agency and other websites searched were not reported in the submission by the company.

The EAG sought clarification from the company regarding the reason for applying a date limit to the electronic database searches (PubMed, MEDLINE In-process, Embase and Cochrane Library). The company described using a pragmatic methodology to retrieve the study prior to 2012 (CRCQ2, A2). This involved examining studies from two reports describing previous systematic reviews and economic evaluation.[9, 35]

In the Cochrane Library electronic search for trials in CENTRAL, the company restricted the search for the population (post-menopause osteoporosis) to MeSH headings only. The search from both MEDLINE and Embase was not translated consistently to Cochrane Library. The lack of free-text searching can negatively impact the recall of the search.

Two clarification questions were raised by the EAG with the company (CRCQ1, A1 and A2) concerning the use of exclusion terms for different indications and the application of the date limit. The EAG questioned the company's approach of applying exclusion terms for specific populations (Paget's disease, hypercalcemia of malignancy, breast cancer, prostate cancer, rheumatoid arthritis, celiac disease, bulimia nervosa and anorexia nervosa) in both MEDLINE and Embase search strategies (CS Appendix D, Tables 21 and 22, respectively). The approach taken by the company would exclude studies that mention both osteoporosis and the excluded populations in all fields that were searched. The EAG would have recommended the following steps for both MEDLINE and Embase search (CS Appendix D, Tables 21 and 22):

- Statement #12 should be [All exclusion population (statement 11)] NOT [All exclusion population AND Osteoporosis (Statement 1)] i.e. #11 NOT (#11 AND #1).
- Statement #24 should be (#1 AND #23) NOT #12

The company in the clarification response could not confirm whether the original approach taken would not have excluded relevant studies (CRCQ1 A1, page 2). The impact of the limitations identified in the search is inconclusive.

3.1.2 Inclusion criteria for the SLR

The inclusion and exclusion criteria for the SLR are reported in Table 4 (reproduced from CS, Appendix, D.1.5, Table 5).[1] These criteria were consistent with the NICE scope with the exception of the potential comparator strontium ranelate, which was excluded from the SLR criteria (CS, Section B.1.1 Table 1). Clinical advice received by the EAG confirmed that strontium ranelate is not a relevant comparator (see Section 2.3.3).

The SLR criteria included the key effectiveness outcomes from the final NICE scope. These included: osteoporotic fragility fractures and BMD, as well as mortality and adverse effects of treatment and HRQoL(for patients and carers) (CS, Section B.1.1 Table 1).

Table 4: Inclusion and exclusion criteria for the SLR (adapted from CS, Appendix D.1.5, Table 5[1])

	Inclusion criteria	Exclusion criteria
Population	• Postmenopausal women with osteoporosis at increased risk of fracture **Osteoporosis is defined for this SLR as:** o BMD T score ≤ -2.5 OR o Age of patients ≥ 50 years AND mention of previous fragility fracture For trials that include a mixed population of participants where not all these inclusion criteria are fulfilled, such studies shall be excluded unless separate data are reported for the population of interest.	• Women with normal or unspecified BMD who have not been selected based on the presence of risk factors • Women with glucocorticoid-induced osteoporosis • Women with other indications for osteoporosis treatment e.g., Paget's disease, hypercalcaemia of malignancy, metastatic breast cancer • Men with osteoporosis
Intervention	Abaloparatide (Eladynos)	Not applicable
Comparators	• Bisphosphonates: – Alendronic acid, Ibandronic acid, Risedronate sodium, Zoledronic acid • Non-bisphosphonates: – Denosumab, Romosozumab, Teriparatide, Raloxifene • No active treatment/ placebo • Usual care: vitamin D and calcium supplementation	• Strontium ranelate • Odanacatib • Combination therapies (exception: usual care) • Interventions which are not administered in accordance with licensed indications
Outcomes	Studies reporting at least one of the following outcomes shall be included: • Osteoporotic fragility fracture: – New or worsening vertebral fracture – Clinical vertebral fracture – Non-vertebral fracture – Clinical non-vertebral fracture • Hip fracture • BMD (e.g., % change in BMD) • Mortality • Adverse effects of treatment	• Studies not reporting at least one prespecified outcome • Studies reporting any of the outcomes only as a part of the AE monitoring process (e.g., a BMD outcome study reporting fractures outcomes as AEs) • Studies reporting outcomes relating to fractures associated with major trauma (e.g., road traffic accidents). Studies that reported mixed trauma and/or non-trauma fracture, shall be included only if they have reported separate data for relevant non-trauma fractures
Study design	• Studies following parallel RCT design, also including: – Randomised dose finding and formulation trials – Either a placebo or active control arm – No limitation by study phase – Followed-up patients for at least 12 months • Extensions studies belonging to a study where all these inclusion criteria are fulfilled should also be included	• Systematic reviews • Pooled analyses of previously published studies • Secondary analysis, subgroup analyses, subpopulation analyses of previously published studies • Studies based on animal models • Pre-clinical and biological studies • Narrative reviews, letters, editorials, opinions, and other forms of non-primary studies • Case series, case reports
Language restrictions	English language records	Non-English language records
Date range	• For articles: 01 Jan 2012 to present • For conference abstracts: 01 Jan 2021 onwards	Older records

Abbreviations: BMD, bone mineral density; RCT, randomised controlled trial

3.1.3 Critique of study selection, data extraction and quality assessment

CS Appendix D.1.4 reports that, for all citations, both the title/abstract and full-text screening stages of study selection were undertaken independently by two reviewers, and any discrepancies were resolved by referral to a senior reviewer.[1] The EAG considers independent study selection by two or more reviewers, as conducted here, to be best practice in systematic reviewing. The results of the study selection process were detailed, as required, by a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (CS Appendix D. 2, Figure 1).

Data extracted from the included studies (and/or any related CSR) are presented in Sections B.2.3-2.7 and 2.9-2.10 of the CS.[1] CS Appendix D.1.6 reports that this process was undertaken by one reviewer, with data checked by a second reviewer. The EAG considers independent data extraction by two or more reviewers, followed by reaching consensus or referral to a third reviewer in cases of disagreement, to be best practice in systematic reviewing.

The EAG considers independent risk of bias/quality assessment by two or more reviewers, with referral to a third if necessary, to be best practice in systematic reviewing. Details of the quality assessment process were not provided in the CS. As a result, the EAG requested clarification of the decisions made and processes undertaken; the company response confirmed that best practice had been followed (CRCQ1, A9).[26]

3.1.4 Results of the company's SLR

The clinical SLR presented in the CS identified one phase III trial of abaloparatide that was relevant to the decision problem: ACTIVE (clinicaltrials.gov: NCT01343004) – an international phase III, multi-centre, partially open-label, 18-month, three-arm RCT comparing abaloparatide (arm 1) with placebo (arm 2) and teriparatide (arm 3, open-label) in postmenopausal women with severe osteoporosis at risk of fracture (n=2070).[5] Also included is the 24-month single-arm extension of the trial (ACTIVExtend) for patients in arms 1 and 2 exposed to abaloparatide or placebo, who all received the bisphosphonate alendronate (n=963) (NCT0657152).[28] The ACTIVE trial and its extension (ACTIVExtend) forms the key evidence within the CS for clinical effectiveness and safety of abaloparatide within this indication.

The CS reported results of the SLR search (n=60) with its broad inclusion criteria, to identify both direct evidence and any relevant trials for any potential indirect treatment comparison (CS, Appendix D.2, Figure 1; and D.3.1, Table 6).[1] However, the CS did not specify which publications related to which trial. This was clarified following a request by the EAG (CRCQ1, A19-A22).[26] It should be noted that the CS states that the publications identified for ACTIVE[27, 30] and ACTIVExtend[29, 31-33] were not the source of data for the SLR results presented in the CS. These data were provided by the CSRs[5, 28], which contained reanalysed data following the exclusion of two trial sites on the advice of the CHMP (CS,

B.2.2). The CSRs were not identified from the literature searches. The principal data reported in the CS were therefore extracted only from the unpublished CSR.[5]

The CS also presented, as supplementary evidence, data from a retrospective, US RWE study based on an administrative claims database for abaloparatide effectiveness and safety in postmenopausal women new to anabolic therapy over a 19-month period after treatment initiation (n=23,232) (CS, B.2.2).[34, 36] The aim of this study was to evaluate the real-world comparative effectiveness of abaloparatide vs teriparatide on non-vertebral fractures and cardiovascular safety in propensity score-matched cohorts. It was not made clear in the CS how this study was identified: it was not listed in the table detailing the 60 publications/records identified by the SLR search (CS, Appendix D.3.1, Table 6).[1] The EAG requested clarification on this from the company; the company confirmed that this was not identified by any searches but that the '*manufacturer/marketing authorisation holder sponsored the study and provided the details to the Company'* (CRCQ1, A17[26]).

The EAG believes that no additional relevant published phase III trials of abaloparatide in relevant patient groups have been omitted from the CS that could have provided data on safety and efficacy.

3.2 Characteristics of the ACTIVE trial of abaloparatide

3.2.1 Study design: ACTIVE trial

ACTIVE is a phase III, randomised, international, multi-centre, 18-month, partially open-label trial initiated in April 2011 and conducted in 28 centres (26 after the exclusion of two sites) across 10 countries (USA, Brazil, Argentina, Hong Kong, Czechia, Denmark, Estonia, Lithuania, Poland, Romania); there were no UK centres (NCT01343004).[5] ACTIVE is a three-arm efficacy and safety trial of abaloparatide compared with either placebo or teriparatide in postmenopausal women aged ≥50 years with severe osteoporosis and at risk of fracture. Details of study design, duration, settings and locations, inclusion and exclusion criteria, treatments, permitted and prohibited concomitant medications and relevant outcomes are reported in Table 5. The actual completion date was October 2014, (NCT01343004).

Overall, 5268 adult patients were enrolled and screened, and 2463 patients who satisfied all eligibility criteria were randomised 1:1:1 (abaloparatide:placebo:teriparatide).[27] However, the CS is based on the reanalysed data after the exclusion of 652 participants from two sites (CS, B.2.4.3).[1] The ACTIVE population reported here therefore consisted of the following: 4616 screened patients, and 2070 randomised patients, who satisfied all eligibility criteria. Participants therefore self-administered either daily subcutaneous (sc) injections of abaloparatide (80 µg), matching placebo, or teriparatide (20 µg). Abaloparatide and matching placebo were administered using a double-blind format, but teriparatide

was given open label because whilst it is also administered subcutaneously it could be administered only via its trademarked injection pen.

Table 5: Summary of the trial design of ACTIVE and ACTIVExtend (adapted from CS, Section B.2.3.1.2, Table 9)

Study	ACTIVE	ACTIVExtend
Study design	Phase 3, randomised, placebo- and active-controlled, multicentre international study (NCT01343004)	Open-label extension study to evaluate the effects of 24 months of treatment with alendronate following 18 months of treatment with abaloparatide or placebo in participants who completed the ACTIVE trial (NCT01657162)
Duration of study	Up to 2 months screening; 1 week pretreatment; observational period 19 months (18 months treatment plus 1 month follow-up)	1 month period between final ACTIVE visit and initiation of ACTIVExtend (for recruitment and consenting patients to ACTIVExtend); treatment period 24 months
Participant eligibility criteria	Key inclusion criteria: • Healthy ambulatory postmenopausal women aged 49–86 years with osteoporosis at risk of fracture: • T-score ≤-2.5 and >-5.0 at the lumbar spine or femoral neck and radiological evidence of ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma non-vertebral fracture within the past 5 years • Women aged >65 years with the above fracture criteria and T-score ≤-2.0 and >-5.0 • Women aged >65 years who did not meet the fracture criteria whose T-score was ≤ -3.0 and > -5.0	Key inclusion criteria: • Participants who received abaloparatide or placebo in the ACTIVE trial and successfully completed the study (with no serious treatment-related AEs) • Participants must have been ≤40 days from end of treatment in the ACTIVE trial
	Key exclusion criteria: • 4 mild or moderate vertebral fractures • Any severe vertebral fractures • <2 evaluable lumbar vertebrae • Unevaluable hip BMD measurement • Evidence of metabolic bone disease or malabsorption or taking medications that would interfere with bone metabolism • Use of bisphosphonate for >3 months in the past 5 years or denosumab within the past year • History of osteosarcoma	Key exclusion criteria: • Severe treatment-related AEs during the ACTIVE trial • Non-compliant or withdrawn from the ACTIVE trial for any reason
Trial drugs	Intervention: Abaloparatide subcutaneous 80 µg once daily Comparators: Placebo	Intervention: Oral alendronate (70 mg/week) in patients who received abaloparatide or placebo in the ACTIVE trial

Study	ACTIVE	ACTIVExtend
	Active: Teriparatide subcutaneous 20 μg once daily	
Concomitant medication	Permitted concomitant medication: • Calcium (500–1000 mg/day) and Vitamin D (400–800 IU/day) supplements, or a dose determined by investigator according to patient need, were required to be administered daily from the Pretreatment Period until the end of the Treatment Period and recommended through the Follow-up period • Stable doses of required concomitant medications (e.g., statins, hypertensives). any other required medications must have been discussed with the investigator and recorded on the case report form Prohibited concomitant medication: • Any medications except as specified above within 72 hours prior to dosing on day 1 • Oestrogens as HRT were allowed on entry but could not be initiated during the study except for low dose vaginal oestrogen • Chronic treatment with an anticonvulsant or heparin (patients requiring such treatment were discontinued)	Permitted concomitant medication: • Calcium (500–1000 mg/day) and Vitamin D (400–800 IU/day) supplements continued from the ACTIVE study • Stable doses of required concomitant medications (e.g., statins, hypertensives), any other required medications must have been discussed with the investigator and recorded on the case report form Prohibited concomitant medication: • Oestrogens as HRT were allowed on entry but could not be initiated during the study except for low dose vaginal oestrogen • Treatment with an anticonvulsant or chronic heparin (patients requiring such treatment were discontinued)
Primary outcomes	Incidence of new morphometric vertebral fractures in the abaloparatide group versus the placebo group	Percentage of patients who sustained one or more new morphometric vertebral fractures between the baseline of the ACTIVE study and after 24 months of alendronate in the ACTIVExtend study abaloparatide/alendronate group versus the placebo/alendronate group
Other outcomes used in the model/specified in the scope	• Non-vertebral fractures • Major osteoporotic fracture • Clinical fracture • Bone mineral density • Adverse effects of treatment	• Non-vertebral fractures • Major osteoporotic fracture • Clinical fracture • Bone mineral density • Adverse effects of treatment
Other outcomes of interest	• Change in bone turnover markers (s-P1NP and s-CTX)	• Change in bone turnover markers (s-P1NP and s-CTX)
Pre-planned subgroups	For selected primary and secondary efficacy endpoints: • Age (<65, 65 to <75, ≥75 years) • Years since menopause (<15, 15 to <25, ≥25)	For primary and secondary efficacy endpoints: • Age (<65, 65 to <75, ≥75 years) • Years since menopause (<15, 15 to <25, ≥25)

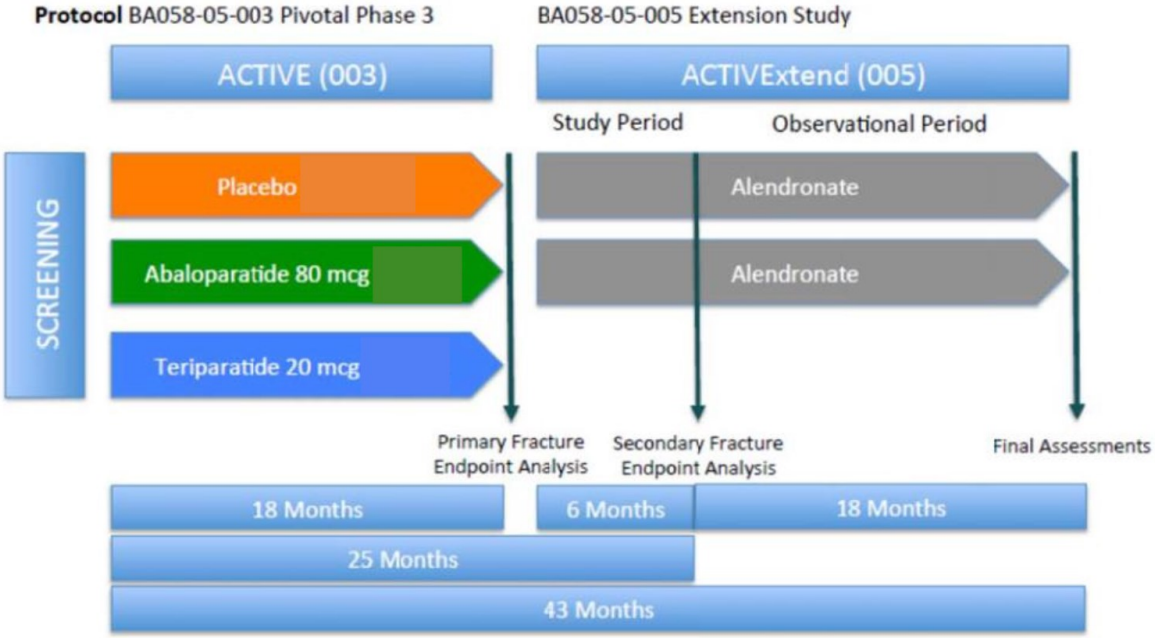
Study	ACTIVE	ACTIVExtend
	• Race (White, Black/African American, Asian, Other) • Region (North America, South America, Europe, Asia) • Any prior fracture (yes, no) • Any prior vertebral fracture (yes, no) • Any prior non-vertebral fracture (yes, no) • Prevalence of vertebral fracture at baseline (0, 1, ≥2) • Severe disease (least BMD T-score ≤–2.5 and prevalent vertebral fracture) at baseline (yes, no) • Lumbar Spine BMD T-score at baseline (≤–2.5, >–2.5) • Lumbar Spine BMD T-score at baseline (≤–3.0, >–3.0) • Total hip BMD T-score at baseline (≤–2.5, >–2.5) • Total hip BMD T-score at baseline (≤–3.0, >–3.0) • Femoral neck BMD T-score at baseline (≤–2.5, >–2.5) • Femoral neck BMD T-score at baseline (≤–3.0, >–3.0)	• Race (White, Black/African American, Asian, Other) • Region (North America, South America, Europe, Asia) • Any prior fracture (yes, no) • Any prior vertebral fracture (yes, no) • Any prior non-vertebral fracture (yes, no) • Prevalence of vertebral fracture at baseline (0, 1, ≥2) • Severe disease (least BMD T-score ≤–2.5 and prevalent vertebral fracture) at baseline (yes, no) • Lumbar Spine BMD T-score at baseline (≤–2.5, >–2.5) • Lumbar Spine BMD T-score at baseline (≤–3.0, >–3.0) • Total hip BMD T-score at baseline (≤–2.5, >–2.5) • Total hip BMD T-score at baseline (≤–3.0, >–3.0) • Femoral neck BMD T-score at baseline (≤–2.5, >–2.5) • Femoral neck BMD T-score at baseline (≤–3.0, >–3.0) • BMI (kg/m^2) at baseline (<25, ≥25)

Abbreviations: BMD, bone mineral density; BMI, body mass index; HRT, hormone replacement therapy

ACTIVExtend is an open-label, single-arm 24-month extension of the ACTIVE trial initiated in April 2011 and conducted in 25 centres (23 after the exclusion of two sites) across 10 countries (as ACTIVE); there were no centres in the UK (NCT01657162).[28] ACTIVExtend evaluates alendronate in ACTIVE participants who satisfied the following criteria: had received either abaloparatide or placebo in the preceding 18 months; had been >80% compliant with study medication during the ACTIVE study; and, in the opinion of the investigators, were appropriate candidates for treatment with alendronate (CS, B.2.3.1.2 and CSR).[1, 28] Overall, 1139 participants were enrolled and screened, but, after the exclusion of two sites, 963 were included (CS, B.2.3.1.2). The trial design for ACTIVE and its extension is presented in

Figure 2.

Figure 2: Overview of the ACTIVE / ACTIVExtend trial design (reproduced from CS, Section B.2.3.1.2, Figure 6[1])



A 1 month gap in treatment was allowed for reconsenting from ACTIVE to ACTIVExtend Participants received oral alendronate at a total dose of 70 mg once per week
Abbreviations: ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ACTIVExtend, Abaloparatide Comparator Trial In Vertebral Endpoints Extension Study

3.2.2 Quality assessment of ACTIVE trial

The CS performed a quality assessment of ACTIVE using the University of York's CRD checklist for RCTs (as per recommendations in the NICE user guide). The findings were reported in the CS (section B.2.5, Table 18)[1], but are reproduced in Table 6 together with the EAG judgements. This assessment is limited to the 18-month phase I period of the ACTIVE trial; the company's clarification response reported a separate assessment for ACTIVExtend (CRCQ1, A12[26]).

The stated overall judgement on the risk of bias in the ACTIVE trial in the CS was as follows: '*Overall, the included study for abaloparatide (ACTIVE, excluding Sites 131 and 132) was adjudged to pose a low risk of bias concerning randomisation, baseline characteristics, and statistical methodology'* (CS, section B.2.9.2).[1] No comment was provided on the remaining domains. In response to a request by the EAG, the company accepted that this was an oversight and provided an overall judgment using the CRD checklist: '*Overall, the included study for abaloparatide (ACTIVE) was judged to pose a low risk of bias concerning domains pertaining to randomisation, blinding and allocation concealment, baseline characteristics, measurement of outcomes, missing outcome data, and statistical methodology. An ITT [intention-to-treat] analysis was performed, and a logistic regression model was used to augment the data set by imputing the missing outcome multiple times'* (CRCQ1, A9 and A11[26]). The EAG only concurs with part of this assessment.

The EAG agrees with the company's responses to the number of the checklist's criteria: that adequate blinding applied only to the comparison of abaloparatide with placebo, but not to the abaloparatide/placebo comparison with teriparatide (which was open label); that there is no evidence of selective outcome reporting; and that an appropriate intention-to-treat (ITT) analysis was used. However, the EAG disagrees with the judgements that: randomisation was conducted appropriately and allocation concealment was adequate; the groups were similar at baseline in terms of prognostic factors, and that there was no unexpected imbalances in drop-outs between groups. The EAG assessed all of these checklist items as 'Unclear'. As stated in the CS, block randomisation was used and was appropriate, but no other details were provided regarding the randomisation and allocation concealment process for the blinded groups (e.g. the use of a form of central randomisation); the principal outcomes were assessed blinded, but some outcomes were not, e.g. certain safety outcomes; participants were not stratified by prognostic factors at randomisation and the balance of potential prognostic factors between groups, such as maternal fracture history and past falls[37], is not reported. There was also an imbalance between groups in terms of numbers of drop-outs (e.g. non-completers: abaloparatide (189/696=27.2%); placebo (157/688=22.8%); teriparatide (140/686=20.5%)), which was accepted by the company in a clarification response (CRCQ1, A10[26]), and it was not clear whether there was any resulting imbalance between groups, among the drop-outs, in terms of prognostic factors or other relevant characteristics.

Table 6: Quality assessment of the ACTIVE trial (adapted from CS, B.2.5, Table 18[1])

Questions	CS and EAG assessments
Was randomisation carried out appropriately?	**CS:** Yes. Patients were randomised using a permuted-block design with a block size of six in a ratio of 1:1:1 to 1 of the 3 treatment groups. **EAG**: Unclear. The actual process by which randomisation was performed (e.g. central randomisation) was not reported.
Was the concealment of treatment allocation adequate?	**CS:** Yes. Randomised distribution of participants was double-blind. **EAG**: Unclear: ACTIVE is an open-label study in terms of the active comparators abaloparatide and teriparatide. Blinding is restricted to the comparison between abaloparatide and placebo. The actual process by which allocation was concealed (e.g. by central randomisation) was not reported.
Were the groups similar at the outset of the study in terms of prognostic factors?	**CS:** Yes. Randomisation was not stratified by prognostic factors. **EAG**: Unclear. As noted, randomisation was not stratified by prognostics factors. However, participants across arms do appear to be well-balanced in terms of some prognostic factors, such as age and BMD, but less so for factors such as the presence of prevalent vertebral fractures: abaloparatide 20.8%, placebo 21.7%, teriparatide 26.5% (CSR, Table 6[5]). Other potential prognostic factors, such as past falls, maternal fracture history, levels of physical activity and left grip strength[37], were not reported.

Questions	CS and EAG assessments
Were the care providers, participants and outcome assessors blind to treatment allocation?	**CS:** Yes, for abaloparatide and placebo. The teriparatide device was a trademarked pen, it could not be reproduced, and the drug is not approved for dispensing from a different injection device to blind it. After opening the identical assigned study medication kit after randomisation day 1, it became apparent to investigators and patients whether open-label teriparatide or either double-blinded abaloparatide of double-blind placebo had been assigned. **EAG**: Partially. The only blinded treatments were abaloparatide and placebo, as stated, and most outcomes were either conducted by blinded assessment (e.g. radiographic evidence) or were objective measures. However, there was also unblinded assessment of some outcomes (e.g. some safety outcomes, including compliance.[27]
Were there any unexpected imbalances in drop-outs between groups?	**CS:** No **EAG**: Unclear.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**CS:** No. Reasoning clarified in response to request by EAG (CRCQ1, A10[26]) **EAG**: Agree. The trial protocol (Miller 2016[27]) and CSR[5] have been cross-checked and validated.
Did the analysis include an intention-to-treat analysis?	**CS:** Yes **EAG**: Agree
If such an analysis was included, was this appropriate and were appropriate methods used to account for missing data?	**CS:** Yes. To evaluate the statistical effect of missing data on incidence of new vertebral fractures, a sensitivity analysis was performed based on the multiple imputation method. This method used a logistic regression model to augment the data set by imputing the missing outcome multiple times to characterise the uncertainty of the imputation. **EAG**: Agree

Abbreviations: AE, adverse event; RCT, randomised controlled trial; SAP, statistical analysis plan.

The EAG also conducted a quality assessment using the Cochrane Risk of Bias tool (version 2)[38], which is the international standard for quality assessment of RCTs. This assessment is presented in Table 7. The risk of bias arising from both deviations from the interventions and selective reporting was judged to be 'Low'. However, the EAG judged there to be 'Some concerns' regarding aspects of the randomisation process (the actual process to conceal random allocation was not reported). The risks of outcome assessment bias was judged by the EAG to have 'Some concerns' due to the unblinded assessment of some outcomes (e.g. safety outcomes, including compliance[27]). There was a high rate of attrition (>20%) across all trial arms (but highest in the abaloparatide arm), and no data were presented on the prognostic characteristics of these missing patients; this resulted in a judgement of a high risk of bias for this domain. Overall, on account of the judgement of a high risk of bias in the missing data

domain, and some concerns in the domains of the randomisation process and outcome assessment, the EAG judges the level of risk of bias affecting the ACTIVE trial to be ‘High’.

Table 7: Cochrane Risk of bias v.2.0: ACTIVE[5, 27]

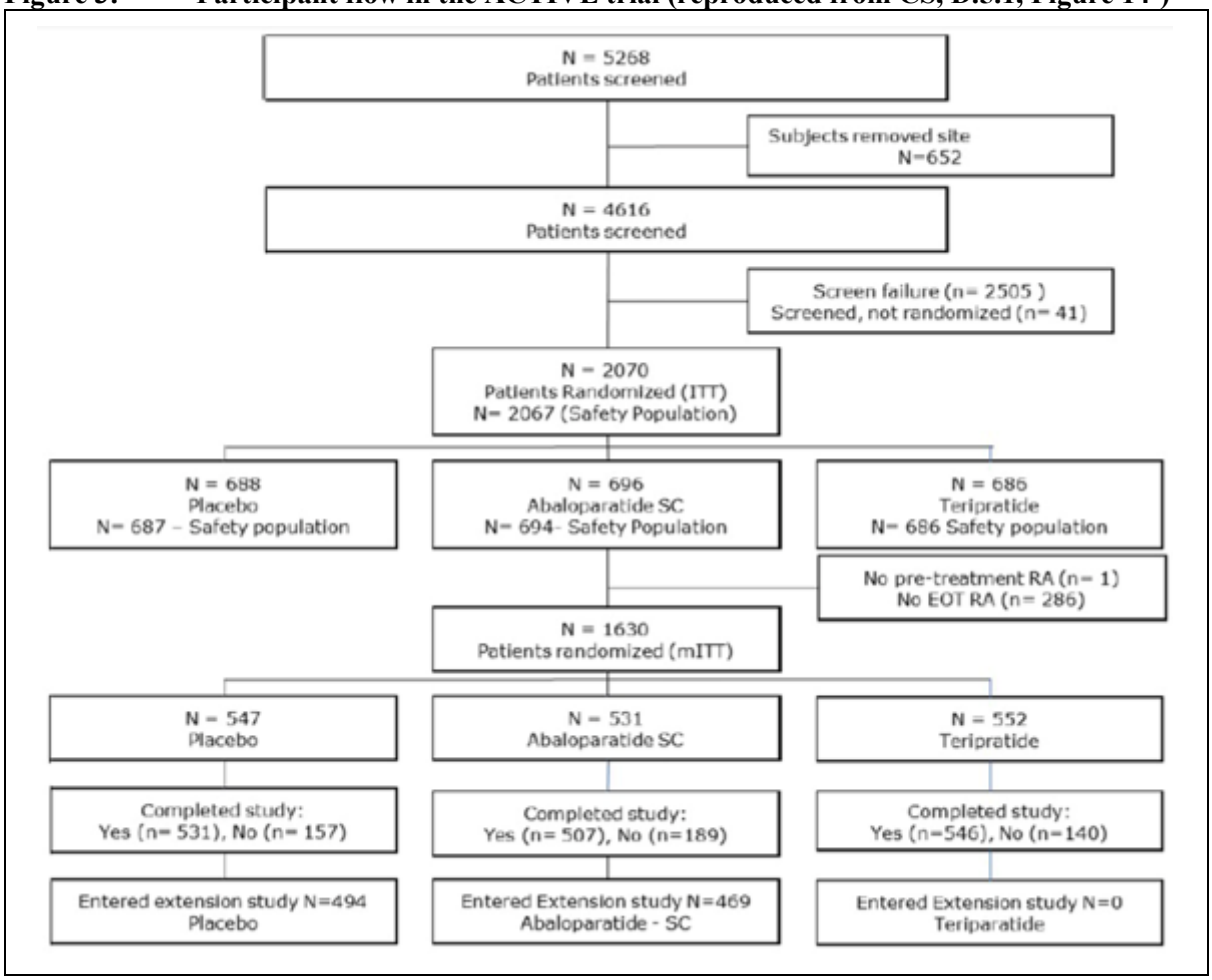
	Bias arising from the randomisation process: sequence generation, allocation concealment, balance between groups)	**Bias due to deviations from intended intervention (deviations with likely effect on outcomes)**	**Bias due to missing data (attrition)**	**Bias due to measurement of outcome (blinding of assessors, potential for differences between groups)**	**Bias in selection of reported results (prespecified outcomes, potentially different measures)**	**Overall risk of bias**
Assessment	Some concerns	Low	High	Some concerns	Low	High
Details	*'A balanced randomized block assignment will be utilized to insure [sic] that an approximately equal number of patients are assigned to each treatment group after a pre-specified block size has been achieved.'* (protocol supplement Miller 2016) Details of the randomization and allocation concealment process, other than block assignment and identical abaloparatide and placebo, are not reported. Arms were balanced at baseline for certain known prognostic factors, such as age and BMD, but less so for factors such as the presence of prevalent vertebral fractures: abaloparatide 20.8%, placebo 21.7%, teriparatide 26.5% (CSR, Table 6[5]). Other potential prognostic factors, such as past falls, maternal fracture history, levels of physical activity and left grip strength[37], were not reported.	There were no reported deviations from the intended intervention	ITT and mITT analyses were conducted, but the number of post-randomisation withdrawals was high, even in the principal mITT populations: abaloparatide (113/696=17.2%); placebo (88/688=12.8%); teriparatide (86/686=12.5%). Non-completers: abaloparatide (189/696=27.2%); placebo (157/688=22.8%); teriparatide (140/686=20.5%) (CSR, Table 1[5])	*'All radiographs will be viewed and assessed centrally by a blinded, independent assessor (radiologist) on the basis of existing baseline and study-acquired vertebral deformity, and fracture will be assessed according to the severity scale of Genant... A second blinded radiologist will confirm the assessment of the first reviewer for all patient radiographs in which an incident fracture has been identified. In the case of any disagreement, a third consensus assessment will be made to adjudicate the incident fracture.'* (protocol supplement[27]) Almost all outcomes were assessed blinded or were objective measurements, e.g. fractures and bone markers. This included some possible patient-reported outcomes for safety, e.g. nausea, pain, compliance.	The protocol, published as a supplement with the principal manuscript, reported all pre-specified outcomes.	As a result of the assessment of 'Some concerns' in two domains, and a 'High' risk of bias in one domain.

BMD: Bone Mineral Density; CSR: Clinical Study Report; ITT; mITT: modified intent-to-treat

3.2.3 Participant flow and analysis populations for the ACTIVE trial

A full CONSORT diagram of participant flow in the ACTIVE trial is presented in Figure 3. It should be noted that this participant flow diagram was provided by the company and is an amendment from the original trial conduct, following the post-randomisation exclusion of 652 patients from sites 131 and 132.[1] Of the 5268 patients screened, 2463 patients were randomised 1:1:1 to abaloparatide, matched placebo or teriparatide. Following the exclusion of all patients from two sites (see CRCQ1, A4[26] for reasons for exclusion), the number of patients randomised across all three arms, and included in the ITT analysis populations set for this submission was n=2070 (safety analysis set, n=2067). It should be noted that the number of patients with available data for the primary outcome (the mITT population) was n=1630 and the overall number of patients who competed the study was n=1584. A large proportion of participants from the abaloparatide and placebo arms, who completed the 18-month ACTIVE trial, entered the 24-month extension study (ACTIVExtend) (n=963/1038) and received alendronate. Participants in the teriparatide arm of ACTIVE were not eligible to enter the extension study.

Figure 3: Participant flow in the ACTIVE trial (reproduced from CS, D.5.1, Figure 14[1])



Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; SC, subcutaneous

The proportion of non-completers in the ACTIVE trial was high (>20% in any arm), with the highest rate in the abaloparatide arm (27.2% compared with 22.8% for placebo and 20.4% for teriparatide) (Table 8). Reasons for non-completion of the ACTIVE trial were reported by the CS and are presented in Table 8. Non-completion due to AEs was highest in the abaloparatide arm (as a proportion of non-completers: 38.1% compared with 26.1% for placebo and 31.4% for teriparatide), but non-completion due to withdrawal of consent and/or refusal of treatment were lowest in the abaloparatide arm (37.8% compared with 45.9% for placebo and 42.8% for teriparatide).

Table 8: Patient disposition - reasons for discontinuation for the ACTIVE trial (reproduced from CS, D.5.1, Table 16[1]).

Parameter	Placebo n (%)	Abaloparatide-SC n (%)	Teriparatide n (%)	Overall n (%)
Completed study [3, 6]				
Yes	531 (77.2)	507 (72.8)	546 (79.6)	1584 (76.5)
No	157 (22.8)	189 (27.2)	140 (20.4)	486 (23.5)
Primary reasons for non-completion [7, 8]				
Adverse Event	41 (26.1)	72 (38.1)	44 (31.4)	157 (32.3)
Withdrew Consent	46 (29.3)	45 (23.8)	43 (30.7)	134 (27.6)
Refusal of Treatment	26 (16.6)	26 (13.8)	17 (12.1)	69 (14.2)
Patient Died During Study	3 (1.9)	3 (1.6)	2 (1.4)	8 (1.6)
Lost to follow up	5 (3.2)	14 (7.4)	9 (6.4)	28 (5.8)
Inability to Complete Study Procedures	7 (4.5)	10 (5.3)	4 (2.9)	21 (4.3)
Non-compliance	9 (5.7)	4 (2.1)	9 (6.4)	22 (4.5)
Serious Intercurrent Illness	0	3 (1.6)	3 (2.1)	6 (1.2)
Protocol Violation	2 (1.3)	4 (2.1)	5 (3.6)	11 (2.3)
Continuing significant deterioration from baseline (>7%) of BMD at lumbar spine or hip (after confirmation of the findings)	11 (7.0)	1 (0.5)	0	12 (2.5)
Administrative Reasons	0	1 (0.5)	0	1 (0.2)
Hypercalcemia or Hypercalciuria	0	1 (0.5)	1 (0.7)	2 (0.4)
Treatment related SAE	0	0	2 (1.4)	2 (0.4)
Severe hypersensitivity to abaloparatide/placebo/teriparatide	1 (0.6)	0	0	1 (0.2)
Other	6 (3.8)	5 (2.6)	1 (0.7)	12 (2.5)

[3] Percentages based on number randomized.
[6] Study completion as indicated by the investigator on the End of Study CRF.
[7] Percentages based on the number of patients who did not complete the study.
[8] Primary reasons were exclusive; i.e., each patient had only one primary reason.

The proportion of non-completers in ACTIVExtend was 9.8% in the abaloparatide/alendronate arm and 10.9% in the placebo/alendronate arm (CS, Appendix D.5.2, Table 18).[1] In terms of reasons for non-completion, rates of AEs and refusal of treatment were higher in the placebo/alendronate arm (48.1% and 11.1% respectively) compared with the abaloparatide/alendronate arm (43.5% and 6.5%) (Table 9). However, non-completion due to continuing significant deterioration of BMD from baseline was much higher in the abaloparatide/alendronate arm (13%) compared with the placebo/alendronate am (3.7%) (Table 9).

Table 9: Patient disposition - reasons for discontinuation for the ACTIVE trial (reproduced from CS, D.5.2, Table 19[1]).

Parameter	Placebo /Alendronate n (%)	Abaloparatide-SC /Alendronate n (%)	Overall n (%)
Primary Reason for Non-Completion of Study BA058-05-005 [12, 13]			
Adverse Event	26 (48.1)	20 (43.5)	46 (46.0)
Refusal of treatment	6 (11.1)	3 (6.5)	9 (9.0)
Continuing significant deterioration from baseline (> 7%) of BMD at spine or hip (after confirmation of the findings)[14]	2 (3.7)	6 (13.0)	8 (8.0)
Inability to complete study procedures	4 (7.4)	1 (2.2)	5 (5.0)
Lost to follow up	3 (5.6)	2 (4.3)	5 (5.0)
Protocol violation	0	1 (2.2)	1 (1.0)
Patient died during the study	1 (1.9)	2 (4.3)	3 (3.0)
Withdrew Consent	11 (20.4)	11 (23.9)	22 (22.0)
Other	1 (1.9)	0	1 (1.0)

[12] Primary reasons were exclusive, i.e. each patient had only one primary reason
[13] Percentages based on the number of patients who did not complete the study
[14] Represents baseline from start of the ACTIVExtend study

The patient data sets analysed in ACTIVE and ACTIVExtend are described in Table 10Table 10 and Table 11. For ACTIVE, the principal analysis sets were the ITT set (consisting of all randomised patients who received a medication kit), and the mITT set (consisting of all ITT population patients with pre- and post-treatment radiographic data). The 'per protocol' (PP) set consisted of all mITT population patients without protocol violations. The safety analysis set included all randomised patients who received at least one dose of medication (Table 10). The same principles applied to the analysis sets in the ACTIVExtend trial period but from the ACTIVExtend baseline (Table 11).

Table 10: Analysis sets for the ACTIVE trial (reproduced from CS, B.2.4.2.1, Table 12[1]).

Analysis set	Definition	ACTIVE			
		Number of patients (excluding Sites 131 and 132), n (%)			
		Abaloparatide	Placebo	Teriparatide	Total
ITT	All patients who were randomised into the study by assigning the randomised study medication kit on Day 1	696	688	686	2,070
mITT	All patients with pretreatment and end of treatment evaluable radiological assessments (spine X-ray)	583	600	600	1,783
Per-protocol	Patients in the mITT population who complied with treatment and did not have any protocol violations	531	547	552	1,630
Safety	All patients who received ≥1 dose of study medication	694	687	686	2,067

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

Table 11: Analysis sets for ACTIVExtend (reproduced from CS, B.2.4.2.1, Table 13[1]).

Analysis set	Definition	ACTIVExtend		
		Number of patients (excluding Sites 131 and 132), n (%)		
		Abaloparatide / alendronate	Placebo / alendronate	Total
ITT – 24 months	All patients in the ACTIVE study who were enrolled in ACTIVExtend	469	494	963
mITT – 24 months	All patients with pretreatment and ≥1 ACTIVExtend post-baseline evaluable radiological assessments (spine X-ray)	457	489	946
Per-protocol	Patients in the mITT population who complied with treatment and did not have any protocol violations	436	444	880
Safety – 24 months	All patients who received ≥1 dose of alendronate	465	493	958

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

3.2.4 Baseline characteristics in ACTIVE

Participant baseline characteristics in ACTIVE are presented in Table 12 (and CS, Section B.2.4.4.1).[1] As noted in the CS, demographic and baseline characteristics were generally well-balanced among treatment groups. All patients were postmenopausal women aged 50–86 years, inclusive. The mean age

was between 69.3 years and 69.5 years, and ~65% aged between 65 and 75 years, across all arms. The mean number of years since menopause was between 20.6 years and 21.2 years across all arms. Three quarters (~75%) of patients were white and mean body mass index (BMI) between 24.8 and 25.0 across all arms.

Table 12: Characteristics of ITT population in ACTIVE at baseline (adapted from CS, B.2.4.4.1, Table 15[1] and CSR[5])

Characteristic	ACTIVE		
	Placebo n=688	Abaloparatide n=696	Teriparatide n=686
Age, mean (SD), years	69.3 (6.1)	69.5 (6.3)	69.4 (6.1)
Age groups n (%)			
<65 years	102 (14.8)	102 (14.7)	99 (14.4)
65 to <75	453 (65.8)	455 (65.4)	443 (64.6)
75 to <85	130 (18.9)	138 (19.8)	144 (21.0)
≥85	3 (0.4)	1 (0.1)	0
Time since menopause, mean (SD), years	20.6 (7.9)	21.2 (8.1)	20.9 (8.1)
Weight, mean (SD), (kg)	60.3 (9.8)	60.0 (9.7)	60.2 (10.2)
BMI, mean (SD), (kg/m^2)	24.9 (3.5)	24.8 (3.5)	25.0 (3.5)
Race, n (%)			
White	522 (75.9)	535 (76.9)	513 (74.8)
Asian	131 (19.0)	128 (18.4)	137 (20.0)
Black or African American	23 (3.3)	26 (3.7)	24 (3.5)
Other	12 (1.7)	7 (1.0)	12 (1.7)
Ethnicity, n (%)			
Hispanic or Latino	197 (28.6)	199 (28.6)	192 (28.0)
T-score, mean (SD):			
Femoral neck	–2.2 (0.7)	–2.2 (0.6)	–2.2 (0.7)
Total hip	–1.9 (0.8)	–1.9 (0.7)	–1.9 (0.8)
Lumbar spine	–3.0 (0.8)	–2.9 (0.9)	–2.9 (0.9)
Severe disease, n (%)[b]	127 (18.5)	113 (16.3)	142 (20.7)
BMD, mean (SD), g/cm^3:			
Femoral neck	0.730 (0.095)	0.730 (0.090)	0.736 (0.094)
Total hip	0.763 (0.099)	0.764 (0.091)	0.770 (0.095)
Lumbar spine	0.817 (0.096)	0.825 (0.106)	0.829 (0.107)
≥1 prevalent vertebral fractures, n (%)	149 (21.7)	145 (20.8)	182 (26.5)
≥1 prior non-vertebral fractures, n (%)[a]	302 (43.9)	308 (44.3)	271 (39.5)
Prior clinical fracture	334 (48.5)	334 (48.0)	307 (44.8)

Prior osteoporotic fracture	370 (53.8)	388 (55.7)	378 (55.1)
No history of prior fracture, n (%)	297 (43.2)	289 (41.5)	289 (42.1)

[a]Assessed based on fractures that occurred prior to visit 3 (study day 1). Excludes fractures of the spine, sternum, patella, toes, fingers, skull, and facial bones [b]Severe disease is defined as having at least one BMD T-score <= -2.5 measured at spine, femoral neck or total hip and prevalent vertebral fracture at baseline.

Abbreviations: BMI, body mass index; BMD, bone mineral density; ITT, intent-to-treat; SD, standard deviation

The percentage of patients with severe disease was slightly lower in the abaloparatide arm (16.3%) compared with the placebo (18.5%) and teriparatide arm (20.7%). There was a small difference between the abaloparatide (21.7%) and teriparatide (26.5%) arms in terms of ≥1 prevalent vertebral fractures, so the EAG requested information on the percentage of participants having 1, 2 or 3 prevalent vertebral fractures at baseline and information on the severity of vertebral fractures. The company provided these data (Table 13) (CRCQ1, A8[26]): there were almost twice as many participants in the teriparatide arm with ≥2 prevalent vertebral fractures (8.4%) and severe vertebral fracture (2.5%) as in the abaloparatide arm (4.6% and 1.4%, respectively).

Table 13: Baseline prevalent vertebral fracture (mITT population, excluding sites 131 and 132, CRCQ1, A8[26])

	Placebo n=600	**Abaloparatide-SC n=583**	**Teriparatide n=600**
Prevalent vertebral fracture, n (%)			
No. of prevalent vertebral fractures			
1	90 (15)	93 (16)	112 (18.7)
2	35 (5.8)	20 (3.4)	37 (6.2)
≥3	9 (1.5)	7 (1.2)	13 (2.2)
Grade of most severe vertebral fracture [1]			
Mild	85 (14.2)	74 (12.7)	92 (15.3)
Moderate	42 (7)	38 (6.5)	54 (9)
Severe	7 (1.2)	8 (1.4)	15 (2.5)
Unknown [2]	(0)	(0)	1 (0.2)

[1] The grade of the most severe vertebral fracture was assessed with the use of the Genant grading scale

[2] One subject had prevalent vertebral fracture, but corresponding Genant score is not available.

Abbreviations: mITT, modified intention-to-treat; SC, subcutaneous.

Clinical advice to the EAG was that patients contraindicated or intolerant to bisphosphonates or who have had an unsatisfactory response to bisphosphonates would be eligible for anabolic therapies, such as abaloparatide and its ACTIVE trial comparator, teriparatide (see Box 1 for NICE guidance on teriparatide). Therefore, the exclusion of patients with previous bisphosphonate treatment of > 3 months was a significant exclusion as previous treatment is needed to demonstrate an unsatisfactory response. Clinical advice to the EAG also confirmed that it is unlikely that patients with no prior history of fracture would be considered to be at 'very high risk of fracture' (the population designated by the company in

the submission): >40% of patients in the ACTIVE trial had no prior history of fracture (abaloparatide 41.5%, placebo 43.3%, teriparatide 42.1%).

The demographic and baseline characteristics reported in the CS for ACTIVExtend are based on the ACTIVE study baseline time-point for patients in the placebo and abaloparatide arms of that trial who completed ACTIVE and agreed to enrolment in ACTIVExtend (Table 14). These reported characteristics were generally well balanced between treatment groups.

Table 14: Characteristics of ITT population in ACTIVE at baseline (reproduced from CS, B.2.4.4.1, Table 16[1]).

Characteristic	ACTIVExtend[a]	
	Placebo/alendronate n=494[b]	Abaloparatide/alendronate n=469[b]
Age, years		
Mean (SD)	69.1 (5.9)	69.3 (6.3)
<65, n (%)	74 (15.0)	67 (14.3)
65 to <75, n (%)	331 (67.0)	310 (66.1)
≥75, n (%)	89 (18.0)	92 (19.6)
Time since menopause, mean (SD), years	20.4 (7.7)	20.9 (8.0)
BMI, mean (SD), (kg/m^2)	24.7 (3.4)	24.7 (3.5)
Race, n (%)		
White	360 (72.9)	344 (73.3)
Asian	106 (21.5)	101 (21.5)
Black or African American	18 (3.6)	19 (4.1)
Other	10 (2.0)	5 (1.1)
Ethnicity, n (%)		
Hispanic or Latino	137 (27.7)	124 (26.4)
Region, n (%)		
North America	7 (1.4)	9 (1.9)
South America	157 (31.8)	145 (30.9)
Europe	225 (45.5)	216 (46.1)
Asia	105 (21.3)	99 (21.1)
T-score, mean (SD)		
Femoral neck	–2.2 (0.7)	–2.2 (0.6)
Total hip	–2.0 (0.8)	–1.9 (0.7)
Lumbar spine	–3.0 (0.8)	–2.9 (0.8)
≥1 prevalent vertebral fractures, n (%)	107 (21.7)	96 (20.5)
≥1 prior non-vertebral fractures, n (%)[c]	209 (42.3)	206 (43.9)
No history of prior fracture, n (%)	225 (45.5)	196 (41.8)

[a]*Baseline and demographic characteristics are based on the ACTIVE study baseline time-point*

[b]*Treatment groups are based on randomisation in the ACTIVE trial*
[c]*Assessed based on fractures that occurred prior to visit 3 (study day 1). Excludes fractures of the spine, sternum, patella, toes, fingers, skull, and facial bones*
Abbreviations: BMI, body mass index; ITT, intent-to-treat; SD, standard deviation

3.2.5 Study endpoints in ACTIVE and ACTIVExtend

The primary efficacy endpoint in ACTIVE was the percentage of participants with one or more incidents of new morphometric vertebral fracture in the abaloparatide group vs the placebo group (and the teriparatide group vs the placebo group) at 18 months.

Key secondary efficacy endpoints included incident non-vertebral fractures at 18 months and percentage change from baseline in BMD at the total hip, femoral neck and lumbar spine at 6, 12 and 18 months. Other efficacy endpoints included changes in serum markers of bone turnover (procollagen type I N-terminal pro-peptide [s-P1NP] and carboxy-terminal cross-linking telopeptide of type I collagen [s-CTX]); these were evaluated in a subset of patients at 3, 6, and 12 months.

Prespecified exploratory endpoints (assessment of clinical fractures, incidence of fractures and time to event) included major osteoporotic fractures (fractures of the upper arm, wrist, hip or clinical spine) and clinical fractures (all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine fractures).

Safety endpoints included the incidence of hypercalcaemia (a prespecified safety endpoint), AEs and serious adverse events (SAEs), vital signs, electrocardiograms, incidence of hypercalciuria, clinical laboratory parameters, renal safety and bone histomorphometry.

The primary efficacy endpoint in ACTIVExtend was the percentage of patients with one or more new morphometric vertebral fractures between the baseline of the ACTIVE study and the end of ACTIVExtend (cumulative 43 months [18 months ACTIVE, 1 month treatment gap for rollover to ACTIVExtend, 24 months ACTIVExtend]) in the abaloparatide/alendronate group vs the placebo/alendronate group.
Secondary efficacy endpoints included the incidence and time to first event for non-vertebral, major osteoporotic, and clinical fractures; percentage change in lumbar spine, total hip, and femoral neck BMD from ACTIVE baseline through cumulative months of ACTIVExtend (25, 31, 37 and 43 months); and changes in serum markers of bone turnover in a subset of patients from ACTIVE baseline through cumulative months of ACTIVExtend (25, 31, 37 and 43 months).

Prespecified exploratory endpoints included the incidence and time to event of non-vertebral, clinical and major osteoporotic fractures from ACTIVExtend baseline to month 6 and 24; and the percentage

change from baseline in lumbar spine, total hip and femoral neck BMD from ACTIVExtend baseline to month 6 and 24. Safety endpoints included AE monitoring.

3.3 Clinical effectiveness of abaloparatide (ACTIVE trial)

Efficacy endpoints were presented and described for ACTIVE in CS, Section B.2.6.[1]

3.3.1 Fracture endpoints in ACTIVE: Primary and secondary efficacy outcomes

The 18-month results of the ACTIVE trial for the primary endpoint of vertebral fractures, the secondary endpoint of non-vertebral fractures, and the exploratory endpoints of major osteoporotic and clinical fractures, are presented in Table 15. It should be noted that the CS reports relative risk reduction (RRR) for the outcome of new vertebral fractures (where RRR=0 indicates no difference in the risk of fracture), but reports hazard ratios (HRs) for all other fracture outcomes (where HR=1 indicates no difference in the risk of fracture). Comparisons between abaloparatide and teriparatide were exploratory and were not reported for the primary outcome of new vertebral fracture as the sample size was too small to detect a treatment difference between these two active treatments.

3.3.1.1 New vertebral fractures

The ACTIVE trial found that abaloparatide significantly reduced the risk of new vertebral fractures compared with placebo (0.5% vs 4.2% respectively; relative risk reduction [RRR] = 88% [95% confidence interval (CI) 59–96%]; p<0.001) at 18 months. In the teriparatide group, the risk of new vertebral fractures occurred in 0.7% of patients, (RRR compared with placebo 84% [95% CI 54–94%]; p<0.001).

Table 15: ACTIVE | Fracture efficacy endpoints after 18 months of treatment[a] (excluding Sites 131 and 132) (adapted from CS, B.2.6.1.1, Table 19[1])

	Study participants with fracture, n (%)[a]			Abaloparatide vs placebo			Abaloparatide vs teriparatide[b]			Teriparatide vs placebo		
	Abaloparatide (n=696)	Placebo (n=688)	Teriparatide (n=686)	Risk reduction (95% CI)[c]	HR (95% CI)[d]	p-value[e]	Risk reduction (95% CI)[c]	HR (95% CI)[d]	p-value[e]	RR (95% CI)[c]	HR (95% CI)[d]	p-value[e]
Primary endpoint (mITT population[a])												
New vertebral fracture[a]	(n=583) 3 (0.5)	(n=600) 25 (4.2)	(n=600) 4 (0.7)	–3.65 (–5.59 to –2.00)	RRR, –0.88 (–0.96 to –0.59)[f]	<0.001				–3.50 (–5.45 to –1.82)	RRR, –0.84 (–0.94 to –0.54)[f]	<0.001
Secondary endpoint (ITT population)												
Non-vertebral fracture	15 (2.7)	21 (3.6)	12 (2.0)	ARR, –0.87 (–2.89 to 1.15)	0.74 (0.38 to 1.43)	0.368	ARR, –0.73 (–1.01 to 2.48)	1.30 (0.61 to 2.79)	0.49	ARR, –1.61 (–3.47 to 0.26)	0.56 (0.28 to 1.15)	0.11
Exploratory endpoints (ITT population)												
Major osteoporotic fracture	7 (1.2)	23 (5.4)	14 (2.2)	ARR, –4.48 (–7.80 to –0.56)	0.31 (0.13 to 0.72)	0.004	ARR, –1.04 (–2.50 to 0.42)	0.51 (0.21 to 1.27)	0.14	ARR, –3.14 (–6.84 to 0.56)	0.60 (0.31 to 1.17)	0.13
Clinical fracture	21 (3.8)	35 (7.4)	21 (3.4)	ARR, –3.64 (–7.63 to 0.35)	0.61 (0.36 to 1.06)	0.08	ARR, 0.33 (–1.82 to 2.47)	1.04 (0.57 to 1.90)	0.90	ARR, –3.97 (–7.91 to –0.03)	0.59 (0.35 to 1.02)	0.06
Major non-vertebral fracture[g]	10 (1.8)	19 (3.2)	11 (1.8)		0.54 (0.25 to 1.16)	0.1100		0.94 (0.40 to 2.21)	0.8849		0.57 (0.27 to 1.20)	0.1370

[a]The percentage of new vertebral fractures was calculated using the modified intent-to-treat population at 18 months (placebo, n=600; abaloparatide, n=583; teriparatide, n=600). The percentage of non-vertebral, major osteoporotic, and clinical fractures was cumulative Kaplan–Meier estimates using the intent-to-treat population at 19 months (the entire observational period including 18 months of treatment plus 1 month of follow-up)

[b]Comparisons vs teriparatide were exploratory. Comparison of abaloparatide vs teriparatide was not performed for the primary endpoint as a sample size of ~22,000 per treatment group would be required to provide 90% power to detect a treatment difference[1]

[c]The 95% CI for risk reduction for new vertebral fractures was calculated using the Newcombe method[68]; 95% CIs for risk reductions for non-vertebral, major osteoporotic, and clinical fractures used standard error by Greenwood's formula with the normal approximation
[d]Values are reported as HR (95% CI) unless otherwise indicated
[e]P values for new vertebral fractures were derived using the Fisher exact test. P values for non-vertebral, major osteoporotic, and clinical fractures were calculated using the log-rank test
[f]Values comparing abaloparatide vs placebo and teriparatide vs placebo are reported as relative risk reductions (95% CIs) for new vertebral fractures
Abbreviations: ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction
[g] Major non-vertebral includes clinical fractures of the pelvis, distal femur (upper leg [not hip]), proximal tibia (lower leg [not knee or ankle]), ribs, proximal humerus (upper arm or shoulder), forearm (wrist) and hip.

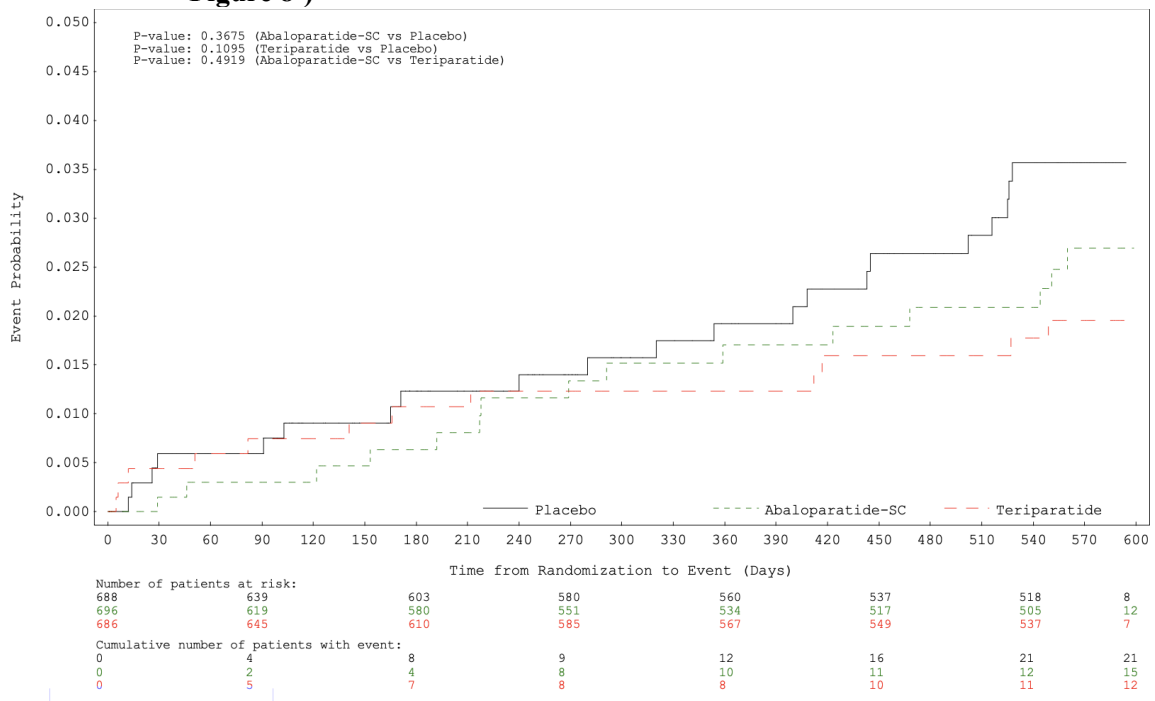
3.3.1.2 Non-vertebral fractures, major osteoporotic fractures and clinical fractures

The ACTIVE trial found that abaloparatide did not significantly reduce the risk of non-vertebral fractures compared with placebo (2.7% vs 3.6% respectively; HR = 0.74 [95% confidence interval (CI) 0.38-1.43]; p=0.368) at 18 months (Table 15 and Figure 4). In the teriparatide group, the risk of non-vertebral fractures occurred in 2.0% of patients, (HR compared with placebo 0.56 [95% CI 0.28–1.15]; p=0.11). No significant difference was found between abaloparatide and teriparatide for this outcome (see Table 15).

Major osteoporotic fractures and clinical fractures were prespecified exploratory analyses. The difference in major osteoporotic fracture (fractures of the wrist, upper arm, hip, and clinical spine) event rates was statistically significant for the abaloparatide group vs the placebo group (HR 0.31 [95% CI 0.13 - 0.72]; p=0.004) but not for clinical fractures (HR 0.61 [0.36 - 1.06]; p=0.08) (Table 15 and Figure 5 and

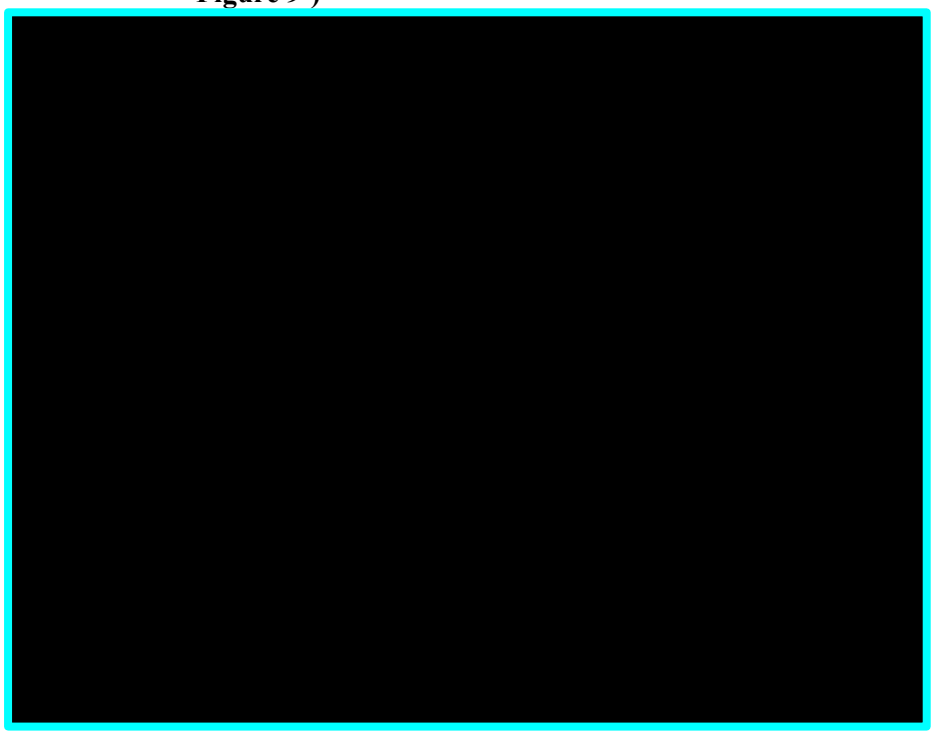
Figure 6). No significant difference was found between abaloparatide and teriparatide for the outcomes of major osteoporotic fractures and clinical fractures (see Table 15).

Figure 4: ACTIVE | Kaplan–Meier curves of time to event of non-vertebral fractures[a] through 19 months (excluding Sites 131 and 132; ITT population, CS, B.2.6.1.2, Figure 8[1])



[a]All comparisons with teriparatide were exploratory
Abbreviations: ITT, intent-to-treat; SC, subcutaneous

Figure 5: ACTIVE | Kaplan–Meier curves of time to event of major osteoporotic fractures[a] through 19 months (excluding Sites 131 and 132; ITT population, CS, B.2.6.1.2, Figure 9[1])



[a]All comparisons with teriparatide were exploratory

Abbreviations: ITT, intent-to-treat; SC, subcutaneous

Figure 6: ACTIVE | Kaplan–Meier curves of time to event of clinical fractures[a] through 19 months (excluding Sites 131 and 132; ITT population, CS, B.2.6.1.2, Figure 10[1])

[a]All comparisons with teriparatide were exploratory

Abbreviations: ITT, intent-to-treat; SC, subcutaneous

3.3.2 Fracture endpoints in ACTIVExtend: Primary and secondary efficacy outcomes

The findings for ACTIVExtend, at the end of the full 43-month treatment period (18 months treatment in ACTIVE, 1 month for recruitment and consenting to ACTIVExtend, 24 months treatment in ACTIVExtend), were entirely consistent with the findings for the ACTIVE trial. ACTIVExtend found that abaloparatide/alendronate significantly reduced the risk of new vertebral fractures compared with placebo/alendronate (0.9% vs 5.3% respectively; relative risk reduction [RRR] = 84% [95% confidence interval (CI) 53–94%]; p<0.001) (Table 16), but found that abaloparatide/alendronate did not significantly reduce the risk of non-vertebral fractures compared with placebo/alendronate (HR 0.61 [95% CI 0.35-1.08], p=0.088) at 43 months (Table 16 and

Figure 7A). Like the ACTIVE trial, the difference in major osteoporotic fracture event rates was statistically significant for the abaloparatide/alendronate group vs the placebo/alendronate group (HR 0.48 [95% CI 0.25-0.92], p=0.024) but this was not the case for clinical fractures (HR 0.68 [95%CI 0.24-1.10] p=0.119) (Table 16 and

Figure 7B & C).

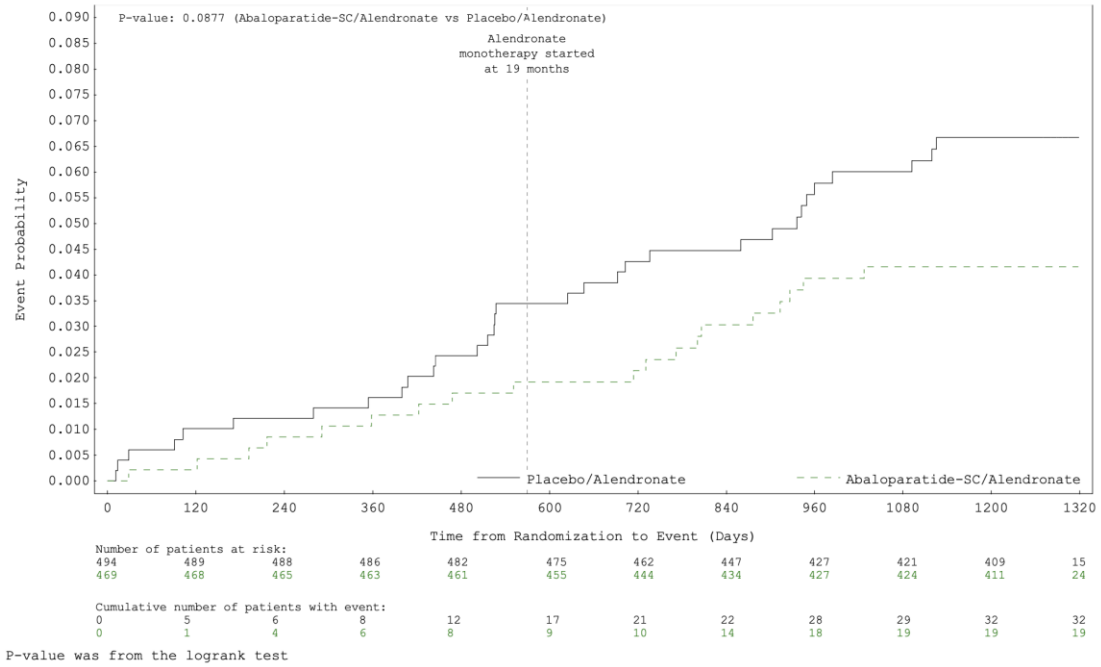
Table 16: ACTIVExtend | Fracture efficacy endpoints | Incidence of fractures from active baseline through 24 months of ACTIVExtend (Month 43; excluding Sites 131 and 132, CS, B.2.6.1.1, Table 20[1])

Endpoint	ACTIVExtend	
	Placebo/alendronate	Abaloparatide/alendronate
Primary endpoint (mITT population)	**n=489**	**n=457**
≥1 new vertebral fracture, n (%)	26 (5.3)	4 (0.9)
Risk reduction (95% CI)	–4.44 (–6.86, –2.30)	
RRR (95% CI; p value)	–0.84 (–0.94, –0.53; p<0.001)	
Secondary endpoints (ITT population): Kaplan–Meier estimates	**n=494**	**n=469**
≥1 non-vertebral fracture, n (%)	32 (6.7)	19 (4.2)
ARR (95% CI)	–2.53 (–5.42, 0.36)	
HR (95% CI; p value)	0.61 (0.35–1.08; p=0.088)	
≥1 major osteoporotic fracture, n (%)	28 (5.8)	13 (2.8)
ARR (95% CI)	–2.98 (–5.57, –0.38)	
HR (95% CI; p value)	0.48 (0.25–0.92; p=0.024)	
≥1 clinical fracture, n (%)	42 (8.7)	28 (6.1)
ARR (95% CI)	–2.61 (–5.97, 0.74)	
HR (95% CI; p value)	0.68 0.42–1.10; p=0.119)	

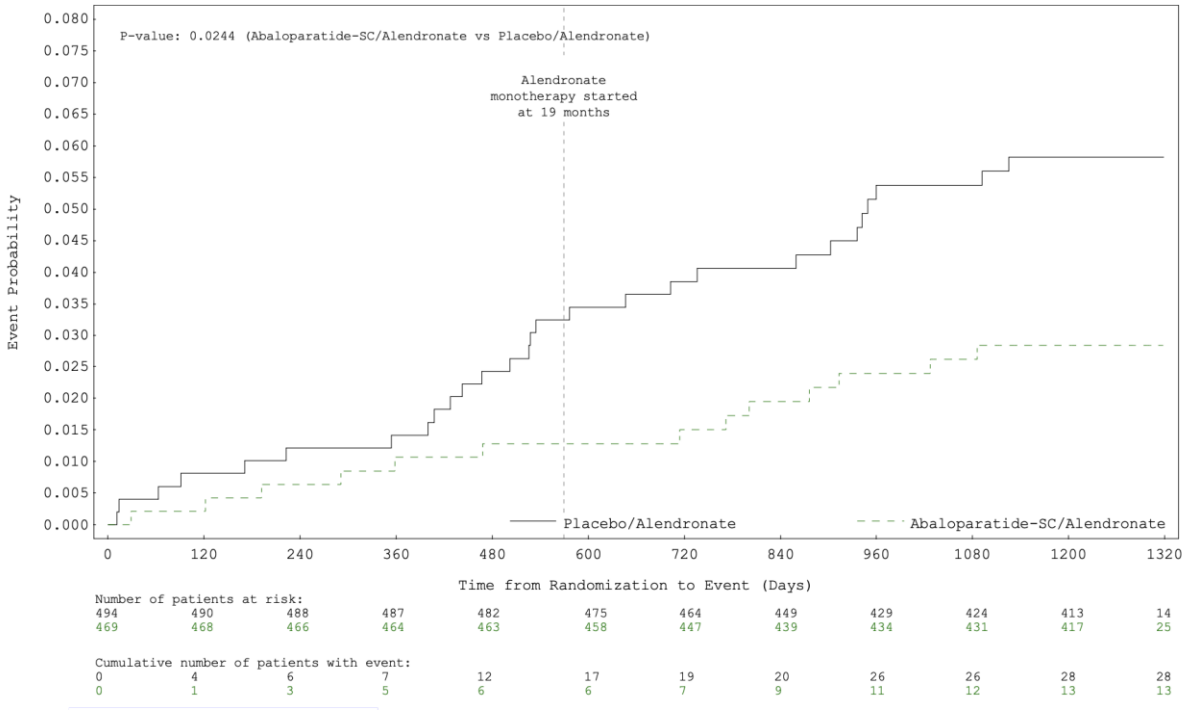
Abbreviations: ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints Extension study; ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mITT, modified intent-to-treat; RRR, relative risk reduction

Figure 7: ACTIVExtend | Kaplan–Meier curves of time to first incident A) non-vertebral, B) major osteoporotic and C) clinical fractures from ACTIVE baseline through 24 months of ACTIVExtend (Month 43; excluding Sites 131 and 132; ITT population, CS B.2.6.1.2, Figure 11[1])

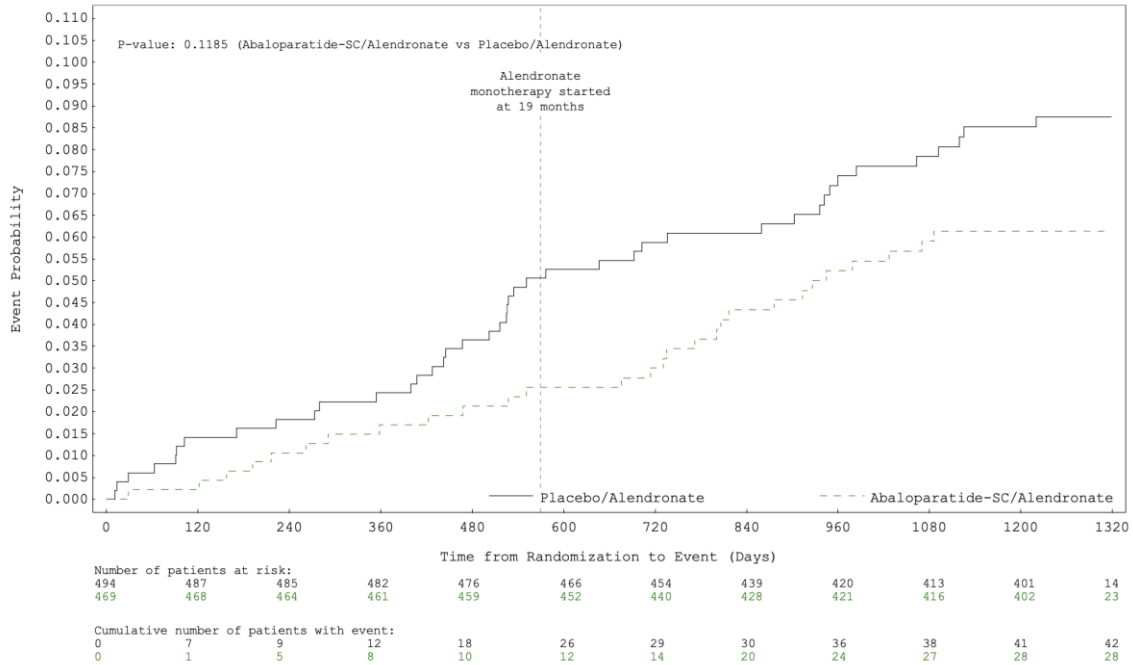
A)



B)



C)



Abbreviations: ITT, intent-to-treat; SC, subcutaneous

3.3.3 BMD endpoints in ACTIVE and ACTIVExtend

In ACTIVE, improvements in BMD were significantly greater with abaloparatide than with placebo at the total hip, femoral neck and lumbar spine at 6, 12 and 18 months ($p<0.001$ for all three sites; Table 17; Figure 8; exploratory analyses for 6 and 12 months). Abaloparatide showed a greater increase from baseline in BMD than was seen with teriparatide (exploratory analysis; nominal p values) [redacted]; at the total hip ([redacted] and p=0.021) and femoral neck ([redacted] and p=0.039) at 12 and 18 months, respectively; [redacted]. Increases in lumbar spine BMD were similar between abaloparatide and teriparatide at 18 months (p=0.786).

BMD improvements were sustained throughout ACTIVExtend and were statistically significant at all time points (all $p<0.001$) (Figure 9).

Table 17: ACTIVE | BMD endpoints for abaloparatide versus placebo and teriparatide after 6, 12, and 18 months of treatment using LOCF (excluding Sites 131 and 132; ITT population, CS, B.2.6.2, Table 21[1])

ACTIVE					
Time-point	% change from baseline in BMD, mean (SD)		Abaloparatide vs placebo	% change from baseline in BMD, mean (SD)	Abaloparatide vs teriparatide
	Abaloparatide (n=696)	Placebo (n=688)	p value	Teriparatide (n=686)	p-value[a]
6 months					
Total hip	2.04 (2.48) (n=694)	0.29 (2.09) (n=687)	<0.001[a]	[redacted]	[redacted]
Femoral neck	1.42 (2.93) (n=694)	–0.11 (2.77) (n=687)	<0.001[a]	[redacted]	[redacted]
Lumbar spine	5.88 (5.25) (n=695)	0.50 (3.35) (n=688)	<0.001[a]	[redacted]	[redacted]
12 months					
Total hip	2.79 (2.97) (n=694)	0.11 (2.48) (n=687)	<0.001[a]	[redacted]	[redacted]
Femoral neck	2.04 (3.38) (n=694)	–0.42 (3.08) (n=687)	<0.001[a]	[redacted]	[redacted]
Lumbar spine	8.06 (6.72) (n=695)	0.38 (3.52) (n=688)	<0.001[a]	[redacted]	[redacted]
18 months					
Total hip	3.33 (3.41) (n=694)	–0.03 (2.81) (n=687)	<0.001	2.96 (3.33) (n=686)	0.021[a]
Femoral neck	2.68 (3.97) (n=694)	–0.42 (3.55) (n=687)	<0.001	2.30 (3.46) (n=686)	0.039[a]
Lumbar spine	9.09 (7.59) (n=695)	0.47 (3.85) (n=688)	<0.001	9.20 (6.28) (n=686)	0.79[a]

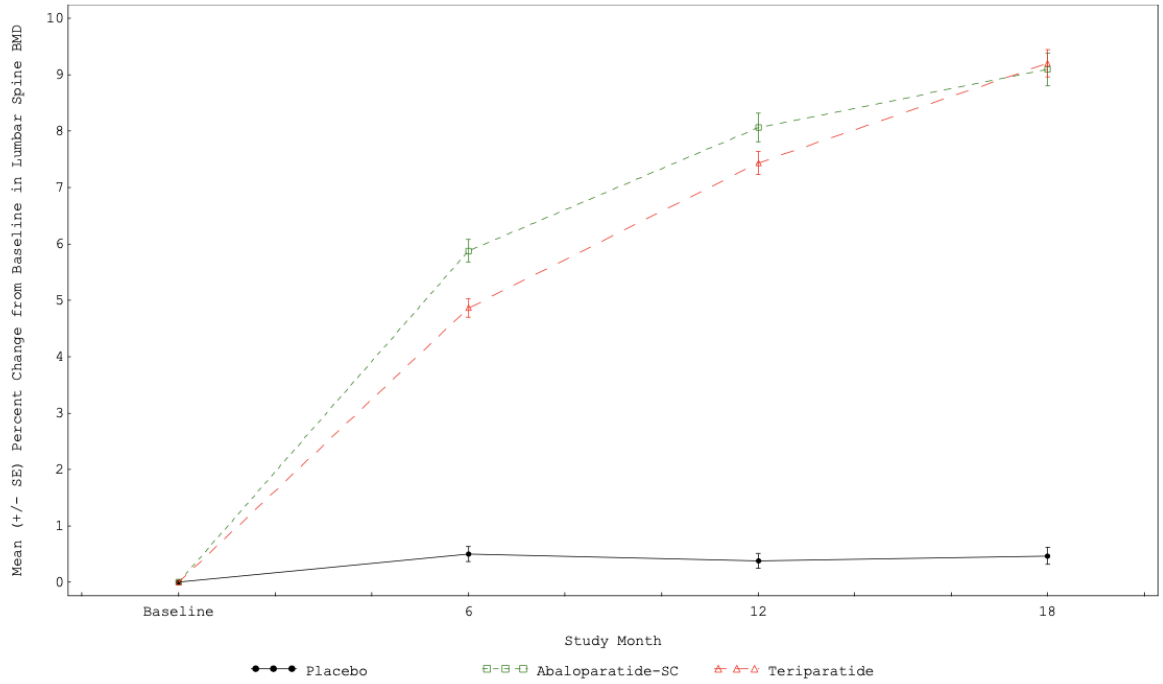
[a]*Nominal p values presented for exploratory analyses*
BMD, bone mineral density; ITT, intent-to-treat; LOCF, last observation carried forward; SD, standard deviation

Figure 8: ACTIVE | Change from baseline in BMD using LOCF through Month 18 (excluding Sites 131 and 132; ITT population, CS section B.2.6.2, Figure 12[1])

A) Total hip

B) Femoral neck

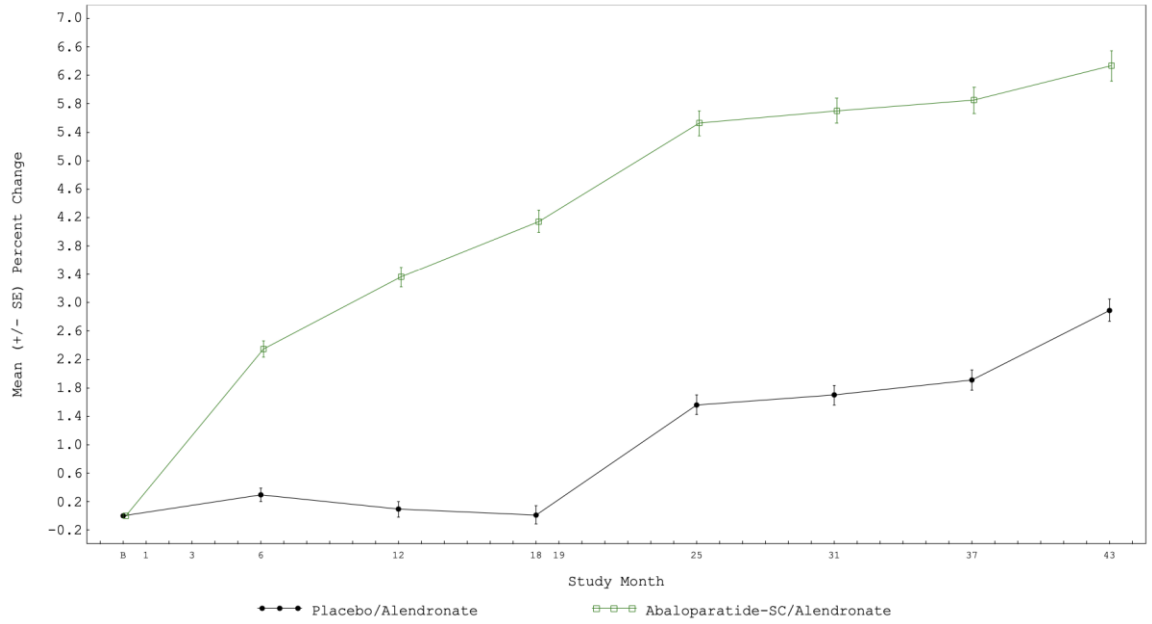
C) Lumbar spine



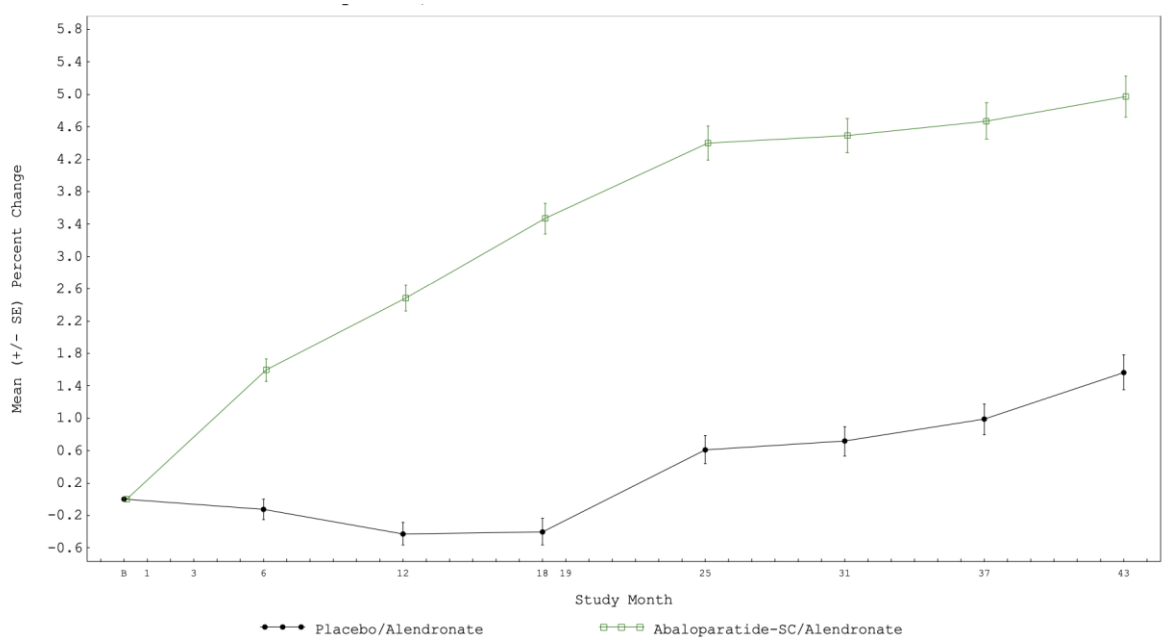
Abbreviations: BMD, bone mineral density; ITT, intent-to-treat; LOCF, last observation carried forward; SC, subcutaneous

Figure 9: ACTIVExtend | Percentage changes in BMD from ACTIVE baseline to end of ACTIVExtend (Month 43) using LOCF (excluding Sites 131 and 132; ITT population, CS, B.2.6.2, Figure 13[1])

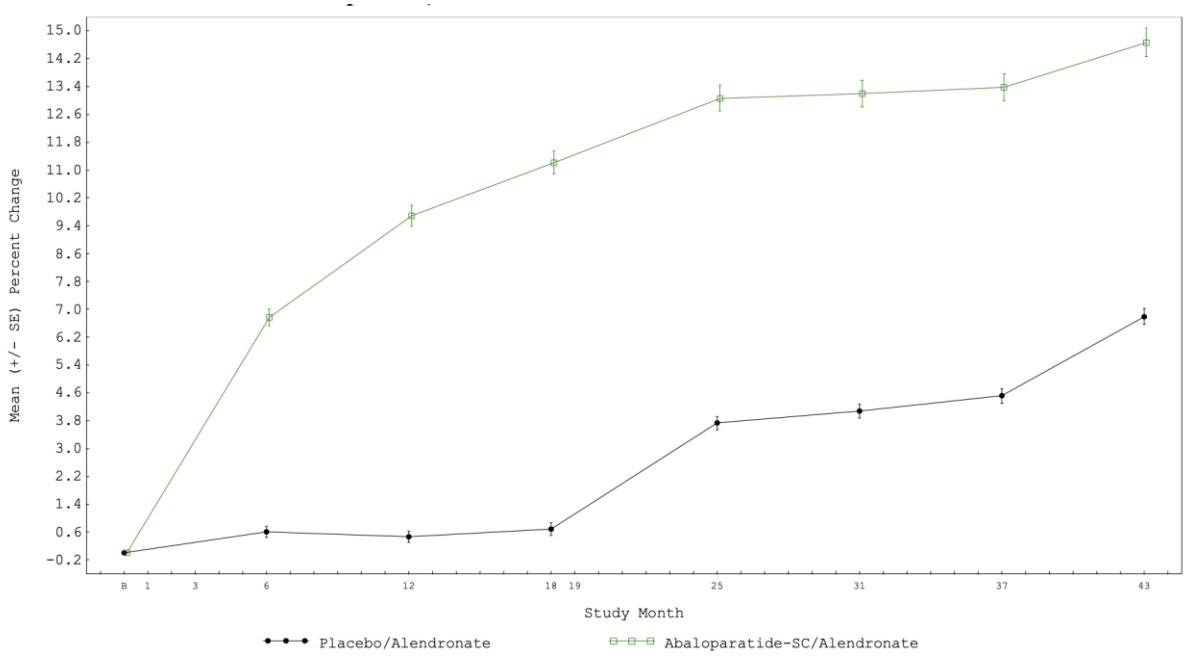
A) Total hip



B) Femoral neck



C) Lumbar spine



ITT, intent-to-treat; LOCF, last observation carried forward; SC, subcutaneous

3.3.4 Bone turnover marker endpoints in ACTIVE and ACTIVExtend

Bone turnover endpoints were not included as an outcome in the NICE scope and therefore the EAG has not presented these in full here but provides a brief summary in Appendix 1.

3.3.5 Subgroup analyses

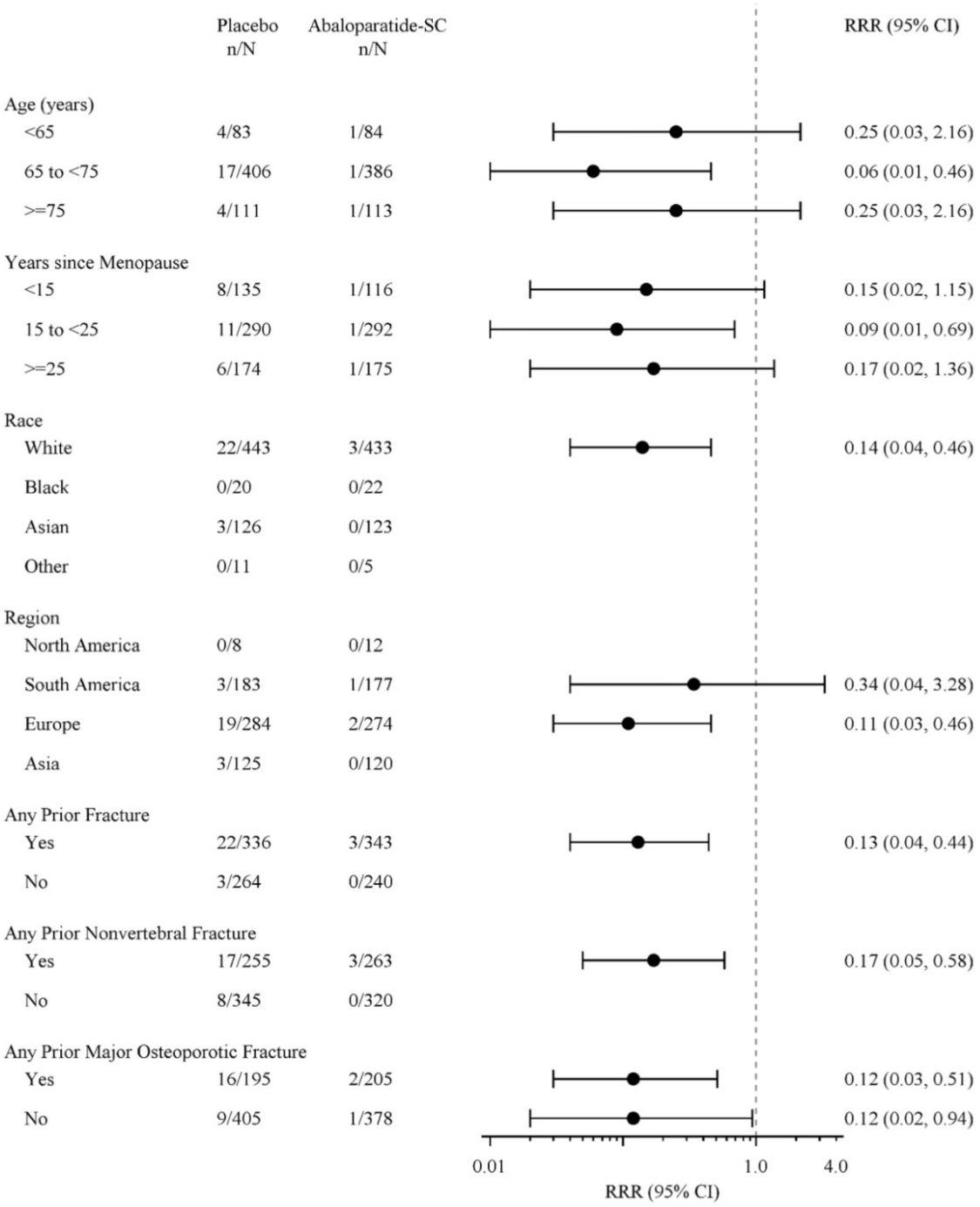
Pre-specified subgroups are reported in Table 5; the results of the analyses for the primary endpoint of new vertebral fractures were detailed in the CS (Section B.2.7 and Appendix E1).[1] These analyses are presented in

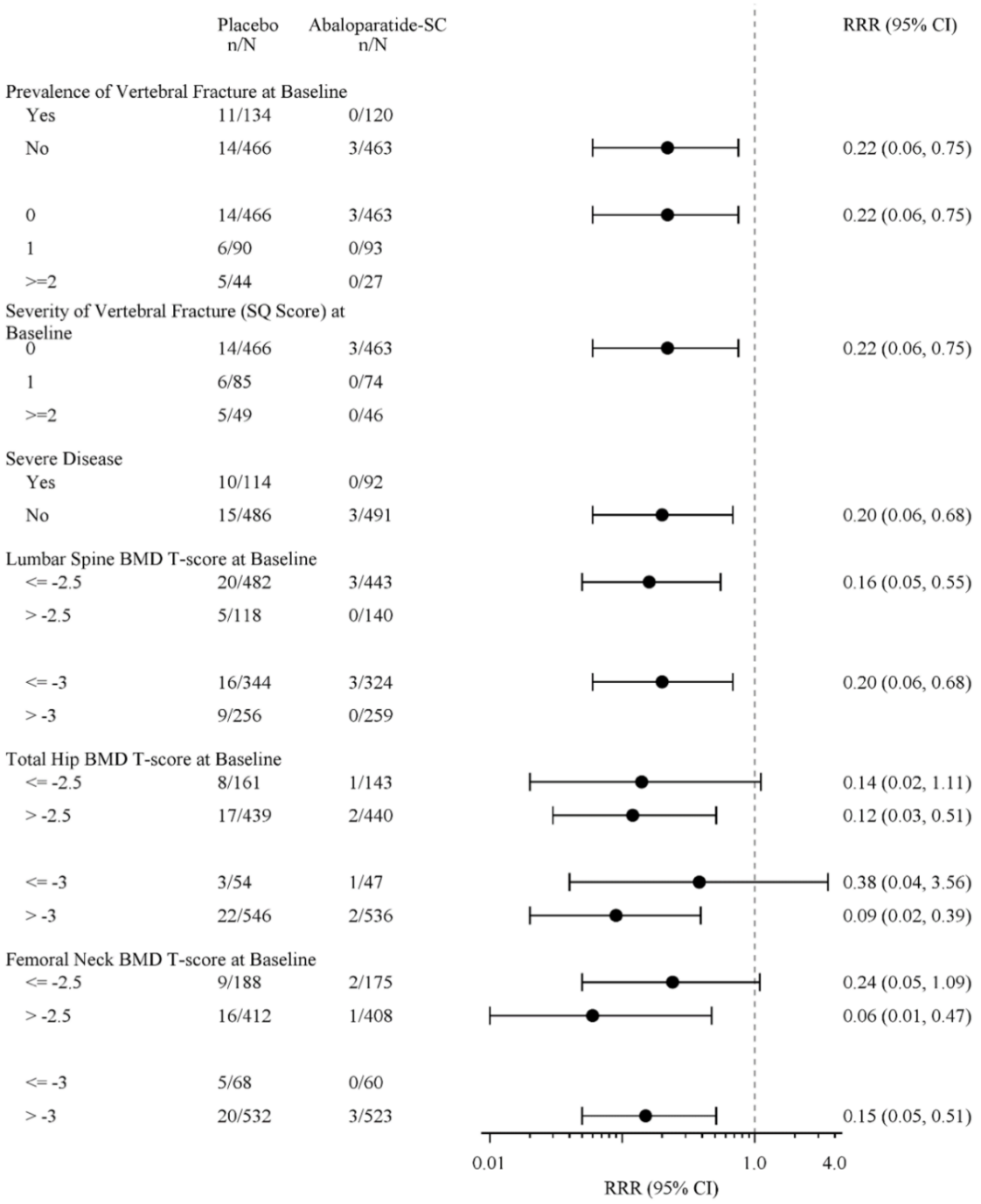
Figure 10. They indicate that the treatment effect of abaloparatide was consistent across the majority of pre-specified patient subgroups. It should be noted that in

Figure 10 the metric reported is described as ‘relative risk ratio’ and abbreviated to ‘RRR’. This is a relative risk (RR), where no difference in effectiveness between two treatments is indicated by 1, and not a relative risk reduction as reported in Table 15 where no difference in effectiveness between two treatments is indicated by 0.

The analyses conducted for ACTIVExtend also found no differences between subgroups (CS, Appendix E2, Figures 16-19).[1]

Figure 10: ACTIVE | Relative risk ratio of new vertebral fractures for abaloparatide vs placebo by subgroup (excluding Sites 131 and 132; mITT population, CS Appendix E1, Figure 15[1])





Abbreviations: BMD, bone mineral density; CI, confidence interval; mITT, modified intent-to-treat; RRR, relative risk ratio

3.4 Safety

3.4.1 Safety data reported for the ACTIVE trial

The CS presented data from the ACTIVE trial (18 months follow-up) and ACTIVExtend study (24 months follow-up) in section B.2.10.1.[1] The CS reported that the median treatment duration was 17.9 months for abaloparatide, 17.9 months for placebo and 17.8 months for teriparatide. (CS, Section B.2.10.1.1).[1]

Treatment-emergent AEs (TEAEs) for the ACTIVE trial at 18 months are reported in Table 18. There were generally no meaningful differences between arms in terms of severe or serious TEAEs or AEs leading to death. Serious TEAEs were reported in 62 patients (8.9%) in the abaloparatide group, 65 patients (9.5%) in the placebo group, and 64 patients (9.3%) in the teriparatide group. The only serious TEAEs to occur in ≥2 patients were osteoarthritis (<1% in any arm) and breast cancer (<1% in any arm) (CS, Section B.2.10.1.6).[1]

Table 18: Summary of AEs at 18 months in ACTIVE (reproduced from CS, B.2.10.1.1, Table 30[1])

Event, n (%)	ACTIVE		
	Abaloparatide n=694	Placebo n=687	Teriparatide n=686
All TEAEs	627 (90.3)	607 (88.4)	614 (89.5)
Treatment-related TEAEs	296 (42.7)	195 (28.4)	280 (40.8)
Severe TEAEs	38 (5.5)	37 (5.4)	36 (5.2)
Severe treatment-related TEAEs	7 (1.0)	2 (0.3)	4 (0.6)
Serious TEAEs	62 (8.9)	66 (9.6)	65 (9.5)
AEs leading to deaths[a]	3 (0.4)	3 (0.4)	2 (0.3)
AEs leading to discontinuation	68 (9.8)	42 (6.1)	47 (6.9)
Discontinuation due to a >7.0% BMD decrease[b]	1/189 (0.5)	11/157 (7.0)	0/140 (0)

[a]*Causes of death in the abaloparatide group: sepsis, bronchiectasis, ischaemic heart disease. Causes of death in the placebo group: bowel cancer, intestinal obstruction, sudden death. Causes of death in the teriparatide group: pancreatic cancer, cardio-respiratory arrest*
[b]*The denominator indicates the total number of subjects who discontinued study participation*
Abbreviations: BMD, bone mineral density; TEAEs, treatment-emergent adverse events

As noted above, a higher percentage of participants in the abaloparatide arm than the comparator arms discontinued due to AEs (9.8% compared with 6.1% placebo and 6.9% teriparatide) (CS, section B.2.10.1.2).[1] The most common TEAEs leading to study discontinuation in the abaloparatide group included nausea (n=11 [1.6%]), dizziness (n=10 [1.4%]), headache (n=8 [1.2%]), and palpitations (n=6 [0.9%]), which were generally mild to moderate in severity. Serious TEAEs leading to study discontinuation occurred in 14 patients (2.0%) in the abaloparatide group, 4 patients (0.6%) in the placebo group and 14 patients (2.0%) in the teriparatide group (CS, Section B.2.10.1.5).[1]

The most common TEAEs (≥5% for abaloparatide) for the ACTIVE trial at 18 months are reported in Table 19 (CS, Section B.2.10.1.3).[1] There were generally no meaningful differences between arms in terms of the most common TEAEs, with the exception of dizziness (11.1% abaloparatide compared with 7.1% placebo and 8.2% teriparatide), nausea (8.5% abaloparatide compared with 3.1% placebo and 5.4% teriparatide), and palpitations (5.6% abaloparatide compared with 0.4% placebo and 1.7% teriparatide). The incidence of severe TEAEs was very low across all arms. The incidence of the AE of

hypercalcaemia in the abaloparatide arm (3.3%) was higher than in the placebo arm (0.4%) but lower than the teriparatide arm (6.0%).

Table 19: Summary of TEAEs (in ≥5% of patients in the abaloparatide treatment group) at 18 months in ACTIVE (reproduced from CS, B.2.10.1.3, Table 31[1])

Event	ACTIVE					
	Abaloparatide n=694		Placebo n=687		Teriparatide n=686	
	Any Grade	Severe	Any Grade	Severe	Any Grade	Severe
Most frequently observed TEAEs (in ≥5% of patients in the abaloparatide treatment group), n (%)						
Hypercalciuria	93 (13.4)	0	73 (10.6)	0	101 (14.7)	0
Dizziness	77 (11.1)	2 (0.3)	49 (7.1)	1 (0.1)	56 (8.2)	0
Upper respiratory tract infection	65 (9.4)	0	61 (8.9)	0	65 (9.5)	0
Back pain	60 (8.6)	1 (0.1)	69 (10.0)	1 (0.1)	52 (7.6)	1 (0.1)
Headache	59 (8.5)	1 (0.1)	40 (5.8)	0	49 (7.1)	0
Nausea	59 (8.5)	1 (0.1)	21 (3.1)	0	37 (5.4)	0
Arthralgia	58 (8.4)	0	61 (8.9)	2 (0.3)	60 (8.7)	0
Hypertension	47 (6.8)	0	37 (5.4)	0	36 (5.2)	0
Influenza	43 (6.2)	0	21 (3.1)	0	23 (3.4)	1 (0.1)
Nasopharyngitis	43 (6.2)	0	56 (8.2)	0	43 (6.3)	0
Palpitations	39 (5.6)	1 (0.1)	3 (0.4)	0	12 (1.7)	0
Urinary tract infection	37 (5.3)	0	36 (5.2)	0	34 (5.0)	0
Hypercalcaemia[a] (prespecified safety endpoint), n/N (%)						
Hypercalcaemia[a]	23/692 (3.3)[b]	–[c]	3/685 (0.4)	–[c]	41/684 (6.0)	–[c]

Coded by MedDRA v17.1
[a]Hypercalcaemia was defined as albumin-corrected serum calcium of at least 10.7 mg/dL (2.67 mmol/L) at any time-point, which was a prespecified safety endpoint and was analysed using the χ2 test. Values are reported as n with hypercalcaemia/N with data in study group (%); [b]For abaloparatide and teriparatide vs placebo, p<0.001; for abaloparatide vs teriparatide, p=0.019; [c]The prespecified safety endpoint of hypercalcaemia was assessed based on any grade
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

Dizziness and nausea were also listed as two of the most common TRAEs (CS, Section B.2.10.1.4, Table 32).[1] Reported rates were only slightly higher for abaloparatide compared with teriparatide: nausea (7.3% abaloparatide compared with 2.6% placebo and 5.7% teriparatide); and dizziness (5.5% abaloparatide compared with 1.3% placebo and 3.6% teriparatide).

Adverse events of special interest (AESI)

Prespecified adverse events of special interest (AESI) data at month 18 in ACTIVE included hypercalcaemia, hypercalciuria, hypophosphatemia, hypersensitivity, orthostatic hypotension and renal impairment. There was no meaningful difference between active treatments for these AESIs (CS, section B.2.10.1.3, Table 33)[1], except for orthostatic hypotension and, to a lesser extent, palpitations and nausea; the incidence of these three AESIs was higher in the abaloparatide arm than the placebo or teriparatide arms (

Table 20).

Table 20: Summary of selected AESIs at 18 months in ACTIVE (modified from CS, B.2.10.1.3, Table 33[1])

AESI, n (%)	ACTIVE		
	Abaloparatide n=694	Placebo n=687	Teriparatide n=686
Orthostatic hypotension[a]			
≥1 TEAE	197 (28.4)	99 (14.4)	136 (19.8)
≥1 TRAE	112 (16.1)	34 (4.9)	71 (10.3)
≥1 severe TEAE	6 (0.9)	4 (0.6)	0
≥1 serious TEAE	2 (0.3)	2 (0.3)	4 (0.6)
≥1 AE leading to discontinuation	25 (3.6)	6 (0.9)	12 (1.7)
Palpitations			
≥1 TEAE	59 (8.5)	16 (2.3)	24 (3.5)
≥1 TRAE	35 (5.0)	4 (0.6)	13 (1.9)
≥1 severe TEAE	1 (0.1)	0	1 (0.1)
≥1 serious TEAE	1 (0.1)	0	2 (0.3)
≥1 AE leading to discontinuation	8 (1.2)	2 (0.3)	0
Nausea			
≥1 TEAE	62 (8.9)	24 (3.5)	44 (6.4)
≥1 TRAE	39 (5.6)	10 (1.5)	27 (3.9)
≥1 severe TEAE	1 (0.1)	0	0
≥1 serious TEAE	1 (0.1)	0	0
≥1 AE leading to discontinuation	11 (1.6)	2 (0.3)	4 (0.6)
Dizziness			
≥1 TEAE	77 (11.1)	49 (7.1)	57 (8.3)
≥1 TRAE	51 (7.3)	18 (2.6)	39 (5.7)
≥1 severe TEAE	2 (0.3)	1 (0.1)	0
≥1 serious TEAE	0	1 (0.1)	2 (0.3)
≥1 AE leading to discontinuation	10 (1.4)	3 (0.4)	8 (1.2)

Coded by MedDRA v17.1

[a] reported as orthostatic hypertension in the CS, but corrected to orthostatic hypotension by EAG after cross-checking with CSR

Abbreviations: AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

The safety data for ACTIVExtend were reported in the CSR.[28] There were no meaningful differences between the arms for TEAEs, TRAEs, serious TEAES or severe TRAEs (Table 21). In terms of those TEAEs with relatively higher frequencies in the abaloparatide arm than the comparator arms in the ACTIVE trial, only dizziness and nausea had an incidence of >1%, but there was no meaningful difference between patients previously treated with abaloparatide and patients previously treated with

placebo: dizziness 2.2% (placebo/alendronate) compared with 3.2% (abaloparatide/alendronate); nausea: 1.6% (placebo/alendronate) compared with 1.7% (abaloparatide/alendronate) (ACTIVExtend CSR Addendum, Table 21).[28]

Table 21: Summary of AEs at 24 months in ACTIVExtend (modified from ACTIVExtend CSR Addendum, Table 17[28])

Event, n (%)	ACTIVExtend		
	Placebo /Alendronate N = 493 n (%)	Abaloparatide-SC /alendronate N = 465 n (%)	Overall N = 958 n (%)
All TEAEs	397 (80.5)	377 (81.1)	774 (80.8)
≥1 Treatment-related TEAEs	70 (14.2)	77 (16.6)	147 (15.3)
≥1 Severe TEAEs	28 (5.7)	24 (5.2)	52 (5.4)
≥1 Severe treatment-related TEAEs	2 (0.4)	2 (0.4)	4 (0.4)
≥1 Serious TEAEs	43 (8.7)	50 (10.8)	93 (9.7)
≥1 AEs leading to deaths	1 (0.2)	2 (0.4)	3 (0.3)
≥1 AEs leading to discontinuation	28 (5.7)	24 (5.2)	52 (5.4)
≥1 TEAE Leading to Discontinuation	25 (5.1)	22 (4.7)	47 (4.9)

Abbreviations: TEAE, treatment-emergent adverse event.

3.5 Supporting evidence

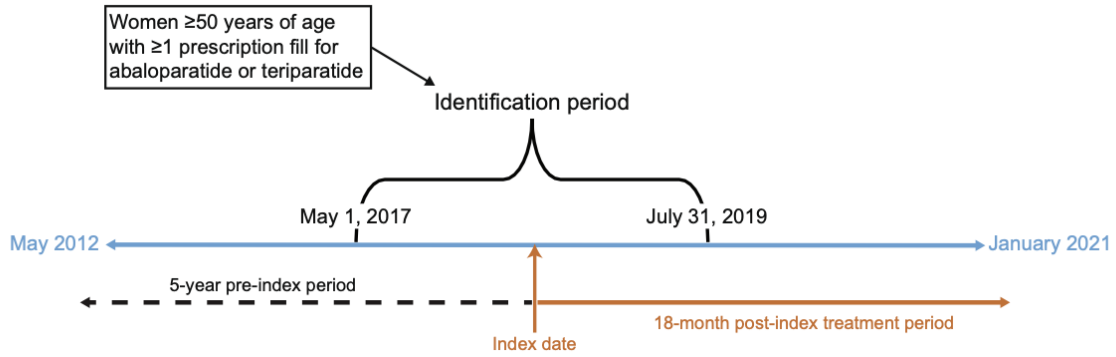
The CS also presented the findings of a large RWE study (anonymised US patient claims database) for abaloparatide effectiveness and safety in postmenopausal women new to anabolic therapy over a 19-month period after treatment initiation (CS, Sections B.2.2, 2.3.2 and Appendix D.5.3).[34, 36] These publications were not included in the 60 reports identified by the SLR search; it was unclear how the company had identified this study. The EAG requested clarification on this from the company; the company confirmed that this was not identified by any searches but that the '*manufacturer/marketing authorisation holder sponsored the study and provided the details to the Company'* (CRCQ1, A17[26]).

The aim of the study was to compare the real-world effectiveness of abaloparatide and teriparatide in propensity score-matched cohorts (n=11,616 per cohort) in terms of non-vertebral fractures outcome and cardiovascular safety outcomes. The primary efficacy endpoint, therefore, was the time to first non-vertebral fracture event, and time to first hip fracture was an exploratory effectiveness endpoint. Safety endpoints included time to the first composite endpoint of major adverse cardiovascular events (MACE; nonfatal myocardial infarction [MI], nonfatal stroke or cardiovascular death) with and without heart failure following hospitalisation.

This RWE study was a retrospective observational study (NCT04974723; BA058-05-028)[34, 36] and as such is subject to the increased risk of bias inherent in such study designs (e.g. selection bias). The

index date was defined as the date of initial prescription dispensed for either abaloparatide or teriparatide during the identification period of 1 May 2017 to 31 July 2019, following the 2017 US Food and Drug Administration approval of abaloparatide (Figure 11). Patients were assigned to a cohort based on their index therapy. Data regarding the medical and treatment history for each patient were also included from a 5-year pre-index period. Treatment effectiveness was evaluated from immediately after treatment initiation for 18 months plus 30-day follow-up after the index date. Cardiovascular safety outcomes were evaluated from immediately after treatment initiation and continued while on therapy for up to 18 months plus 30 days follow-up.

Figure 11: Real-world evidence (BA058-05-028) study design (reproduced from CS, B.2.3.2, Figure 7[1] and Cosman *et al*[36])



The matching of the cohorts is presented in the patient disposition table (Table 22). The key inclusion criteria were women aged ≥50 years with ≥1 new prescriptions of abaloparatide or teriparatide; exclusion criteria were a claim at baseline for Paget's disease of the bone or malignancy (except for non-melanoma skin cancers, carcinoma in situ of the cervix or ductal carcinoma in situ of the breast), Charlson Comorbidity Index score >10, prior index anabolic therapy, anabolic treatment switch after the index date.

Propensity score matching was used to create final abaloparatide and teriparatide treatment cohorts. A logistic regression propensity score model was used with variables including age, prior fracture history, chronic comorbidities, and prior osteoporosis medications. Details of the 73 matched categories are provided in the supplementary material. [36] One-to-one matching was conducted using a greedy matching algorithm with no replacement and a caliper width equal to 0.2 times the standard deviation of the logit of propensity. The post-match balance between the two treatment cohorts was evaluated to ensure that the standardised difference on each covariate was less than 0.1. Analyses were performed in R using the MatchIt package. [39]

The baseline characteristics of the population In the RWE study after matching are presented In

Table 23. The following differences with the ACTIVE trial should be noted: in the RWE only 25.6% of participants had no prior fracture compared with >40% in any arm in the ACTIVE trial; in the RWE only 64.1%-64.6% had a diagnosis of osteoporosis prior to the index date, whereas 100% of the ACTIVE trial participants had this diagnosis; finally, the following characteristics (and prognostic factors) were reported for the ACTIVE trial participants (mean weight, BMI, T-score and BMD); none of these was reported for the RWE study.

Table 22: Real-world evidence study | Patient disposition (reproduced from CS, Appendix, D.5.3, Table 20[1])

Parameter	Abaloparatide, N	Teriparatide, N
Women aged ≥ 50 years with ≥ 1 prescription claims for abaloparatide or teriparatide between 1 May 2017 and 31 July 2019	**17,958**	**61,914**
Of above, patients without Paget's disease	17,954	61,910
Of above, patients without malignancies[a]	17,226	60,536
Of above, patients with ≥12 months pre-index data[b]	13,172	45,737
Of above, patients with no anabolic[c] treatment before index date	12,062	23,565
Of above, patients with no anabolic[c] treatment, other than cohort medication, during 18 months plus 30-day follow-up after index date	11,618	22,820
Of above, patients with Charles Comorbidity Index ≤10	11,617	22,809
Of above, patients with propensity score matching	11,616	11,616

[a]*Except for nonmelanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ of the breast;*
[b]*≥1 medical or hospital claim, and a pharmacy claim any time within 12 months prior to the index date;*
[c]*Anabolic treatment includes abaloparatide, teriparatide and romosozumab*

Table 23: Real-world evidence study | Patient baseline demographic and disease characteristics (all population propensity score-matched) (adapted from CS, B.2.4.4.2, Table 17[1])

Characteristic	RWE study		
	Abaloparatide n=11,616	Teriparatide n=11,616	Standardised difference
Age, years[a,b]			
N	11,616	11,616	
Mean (SD)	67.3 (8.4)	67.5 (8.4)	0.023
Race/ethnicity[b], n (%)			
African American	152 (1.3)	151 (1.3)	0.001
Asian	104 (0.9)	98 (0.8)	0.006
White	4,368 (37.6)	4,505 (38.8)	0.024
Hispanic	682 (5.9)	551 (4.7)	0.050
Other	140 (1.2)	122 (1.1)	0.015
Unknown	6,170 (53.1)	6,189 (53.3)	0.003
Osteoporosis disease history			
Diagnosed osteoporosis prior to index date, n (%)	7,508 (64.6)	7,451 (64.1)	0.010
Years since first osteoporosis diagnosis in 5 years pre-index date			
N	7,508	7,451	
Mean (SD)	2.8 (2.2)	2.8 (2.2)	0.002
Fracture at any time pre-index, n (%)	2,968 (25.6)	2,973 (25.6)	0.001
Fracture in the year prior to index date, n (%)	1,876 (16.2)	1,863 (16.0)	0.003
Fall risk conditions[c], n (%)	8,413 (72.4)	8,561 (73.7)	0.029
Any cardiovascular risk factor, n (%)[d]	8,910 (76.7)	8,948 (77.0)	0.008
Prior osteoporosis medication, n (%)			
Alendronate	3,131 (27.0)	3,212 (27.7)	0.016
Ibandronate	859 (7.4)	840 (7.2)	0.006
Risedronate	723 (6.2)	725 (6.2)	0.001
Zoledronic acid	418 (3.6)	402 (3.5)	0.007
Denosumab	1,269 (10.9)	1,215 (10.5)	0.015
Hormone replacement therapy	2,837 (24.4)	2,797 (24.1)	0.008

[a]Due to the Health Insurance Portability and Accountability Act, age >80 years is recorded as 80. Age is matched at the group level (50–64, 65–74, ≥75)

[b]Variables not included in the propensity score matching covariates

[c]Includes stroke, history of falls, mobility issues, visual impairment, hearing impairment, Parkinson's disease, Alzheimer's disease, muscle weakness, atrophy, obesity, rehabilitation, dementia, depression, anxiety and sleep disorders

[d]Includes diagnosis of cardiovascular disease identified by the following terms: cardiac, coronary, pulmonary, cerebrovascular, peripheral arterial, vasculitis, venous, and hypertension; and cardiovascular risk factors of hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, type 2 diabetes, obesity
Abbreviations: SD, standard deviation; RWE, real-world evidence

The primary endpoint in the RWE study was time to first non-vertebral fracture and showed noninferiority of abaloparatide vs teriparatide (CS, Section B.2.6.4.1[1]; Cosman *et al*[36]). The estimated new non-vertebral fracture rate was similar for abaloparatide (2.9%) and teriparatide (3.2%; HR 0.89 [0.77-1.03], p=0.13) (Table 24;

Figure 12A). Noninferiority was established since the upper bound of the two-sided 95% CI of the HR between abaloparatide and teriparatide was 1.03 (<1.3). The CS reported that outcomes were consistent among all sub-populations in the sensitivity analyses (data not presented).[1] The risk of hip fractures (an exploratory endpoint) was reduced by 22% (0–33%) for abaloparatide vs teriparatide (new event rate, 1.0% vs 1.3%; HR [95% CI] 0.78 [0.62–1.00], p=0.04) (Table 24;

Figure 12B). When limiting the hip fracture sensitivity analyses to patients with >12 months of consecutive exposure to treatment, the HR (95% CI) still favoured abaloparatide (0.57 [0.35–0.94]).[1]

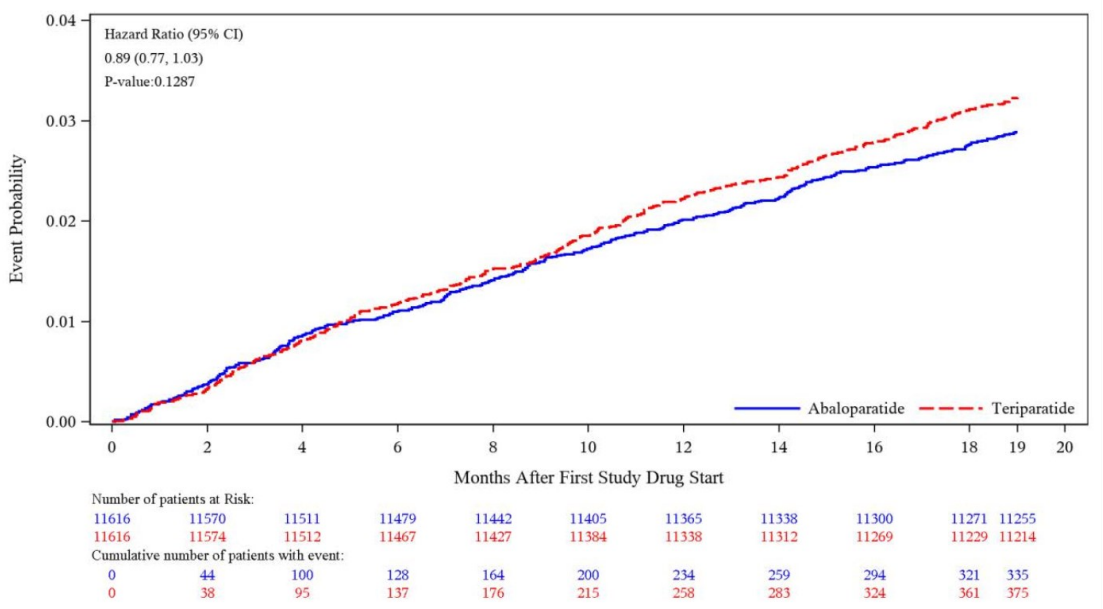
Table 24: Real-world evidence study | Time to first fracture event during 18 months after treatment initiation (all population propensity score-matched) (reproduced from CS, D.2.6.4.1, Table 22)

Time to event variable	Parameter	RWE study	
		Abaloparatide (n=11,616)	Teriparatide (n=11,616)
Primary endpoint			
Non-vertebral fracture	Number of patients with event, n (%[a])	335 (2.9)	375 (3.2)
	HR (95% CI) vs teriparatide[b]	0.89 (0.77–1.03)	–
	p-value vs teriparatide[c]	0.13	–
Exploratory endpoint			
Hip fracture	Number of patients with event, n (%[a])	121 (1.0)	154 (1.3)
	HR (95% CI) vs teriparatide[b]	0.78 (0.62–1.00)	–
	p value vs teriparatide[c]	0.04	–

[a]Percentage reported is Kaplan–Meier estimate at 19 months (observation period of 18 months [540 days] plus 30-day follow-up after the index date)
[b]Cox proportional hazard model was used to calculate the HR with teriparatide as the reference
[c]P values from the log-rank test
Abbreviations: CI, confidence interval; HR, hazard ratio; RWE, real-world evidence

Figure 12: Real-world evidence | Time to first incidence of A) non-vertebral fracture and B) hip fracture (overall propensity score-matched population) (reproduced from CS, B.2.3.2, Figure 16[1] and Cosman et al[36])

A)



B)

The intent-to-treat analysis observation period was from the index date to the 18 months plus 30 days follow-up
Patients at risk include all patients regardless of when treatment was discontinued, except those who had a fracture event or died.
Abbreviations: CI, confidence interval

The only safety evidence other than treatment duration reported for the RWE study was for the composite endpoint of MACE (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death); at 19 months after the index date, the risk of new MACE events was similar between the

abaloparatide (Kaplan–Meier estimate 3.0%) and teriparatide (3.1%) cohorts (HR [95% CI] 1.00 [0.84–1.20], p=0.97) (CS, section B.2.10.3.2).[1]

3.6 Ongoing studies

The CS reported that there are no relevant ongoing studies (Section B.2.11).[1] The EAG could not identify any relevant ongoing phase III trials of abaloparatide alone in the relevant population, but did identify the following trial: Phase IV trial of abaloparatide added to ongoing denosumab vs ongoing denosumab alone in postmenopausal women aged >45 years with osteoporosis (NCT04467983). This record listed an estimated trial completion date of January 2023.

3.7 Meta-analysis

The CS did not clarify the rationale for not conducting a meta-analysis (CS, section B.2.8)[1], but the EAG assessed that a meta-analysis is not appropriate given only a single relevant trial with a relevant population, intervention and one or more relevant comparators was identified (ACTIVE), and no similar, relevant trial has been missed.

3.8 Identification of studies for the indirect and mixed treatment comparisons

In the absence of head-to-head data, the CS presented an NMA in Section B.2.9.[1] to compare the efficacy of abaloparatide with the comparators of relevance to the decision problem in this evaluation, using published evidence identified from the clinical SLR. The CS stated that the efficacy outcomes considered in the NMA were based on the outcomes specified in the final scope issued by NICE, as well as the availability of data reported in the literature (Table 25).

Table 25: Outcomes for the NMA (CRCQ2, Table 5)

Outcome	Type of data or distribution	Output statistics of NMA
Efficacy outcomes: • New vertebral fracture • New or worsening vertebral fracture • Non-vertebral fracture • Clinical fracture • Hip fracture • Major osteoporotic fracture	Binomial	Relative risk, 95% CrI of the estimate

Abbreviations: CrI, credible interval; NMA, network meta-analyses

3.8.1 Identification and selection of relevant studies from the clinical SLR

The CS reported results of a SLR search with broad inclusion criteria, to identify both direct evidence and any relevant trials for a potential indirect treatment comparison (CS, Appendix D.2, Figure 1; and D.3.1, Table 6).[1] A total of 60 potentially relevant records or publications was identified from the initial screening following the criteria outlined in Table 26. An additional stage of eligibility screening was then applied: the application of 'de-priorisation' criteria based on sample size, geographical location and outcomes, specified in

Table 27. A 2012 cut-off date was also applied. The details and rationale for these 'de-prioritisation' criteria were provided by the company in a clarification response (CRCQ1, A19).[26] The original NMA included six publications, plus the CSR for the ACTIVE trial (CS, section B.2.91), with a large number of studies (n=20, CRCQ1 Table 12) excluded from the NMA because they did not report fracture outcomes at the specified time points (12 and 18 months). At the request of the EAG at CQ1, two revisions were made to the original NMA presented in the CS (section B.2.9): specified timepoints for outcome data were no longer required; and the previous timeframe limit (2012 onwards only) was removed (CRCQ1, B1.1).[26] The company took a pragmatic approach to identifying studies published pre-2012 and examined studies included in two published systematic reviews, to which the updated eligibility and de-prioritisation criteria were applied.[9, 35]

Table 26: Eligibility criteria for inclusion in the NMA (CRCQ1, Appendix, B.1.1, Table 2[26])

Domains	Eligibility criteria
Population	Postmenopausal women with osteoporosis at increased risk of fracture
Intervention	• Abaloparatide • Abaloparatide followed by Alendronate
Comparators	• Bisphosphonates: – Alendronic acid, ibandronic acid, risedronate sodium, zoledronic acid • Non-bisphosphonates: – Denosumab, romosozumab, teriparatide, raloxifene • No active treatment/ placebo
Outcomes	Efficacy outcomes:[a] • New vertebral fracture • Worsening vertebral fracture • New or worsening vertebral fracture • Non-vertebral fracture • Clinical fracture • Hip fracture • Major osteoporotic fracture • Fractures in other bones/regions
Language	English language records only

[a]*Based on feedback from EAG, studies which reported fracture data as safety outcomes were also included in the updated NMA*
Abbreviations: NMA, Network meta-analysis

Table 27: De-prioritisation of records prior to the NMA (CRCQ1, Appendix, B.1.1, Table 3[26])

Criteria	Description
Sample size	Exclude studies with a sample size less than 200 (n<200)
Geographic location	Exclude studies that do not include centres in North America or Western Europe
Language	Only include articles written in English language
Outcomes	Exclude articles with no mention of fracture risk†

†In the first iteration, articles that did not report fracture at specified time points (12 and 18 months) were also excluded
Abbreviations: n, number; NMA, network meta-analysis

In the updated review after CQ1, 27 publications were excluded during the 'de-priorisation' screen, principally based on the trials' sample sizes and/or location (CRCQ1, A22 and Table 12, and B.1.4, Figure 1[26]) (

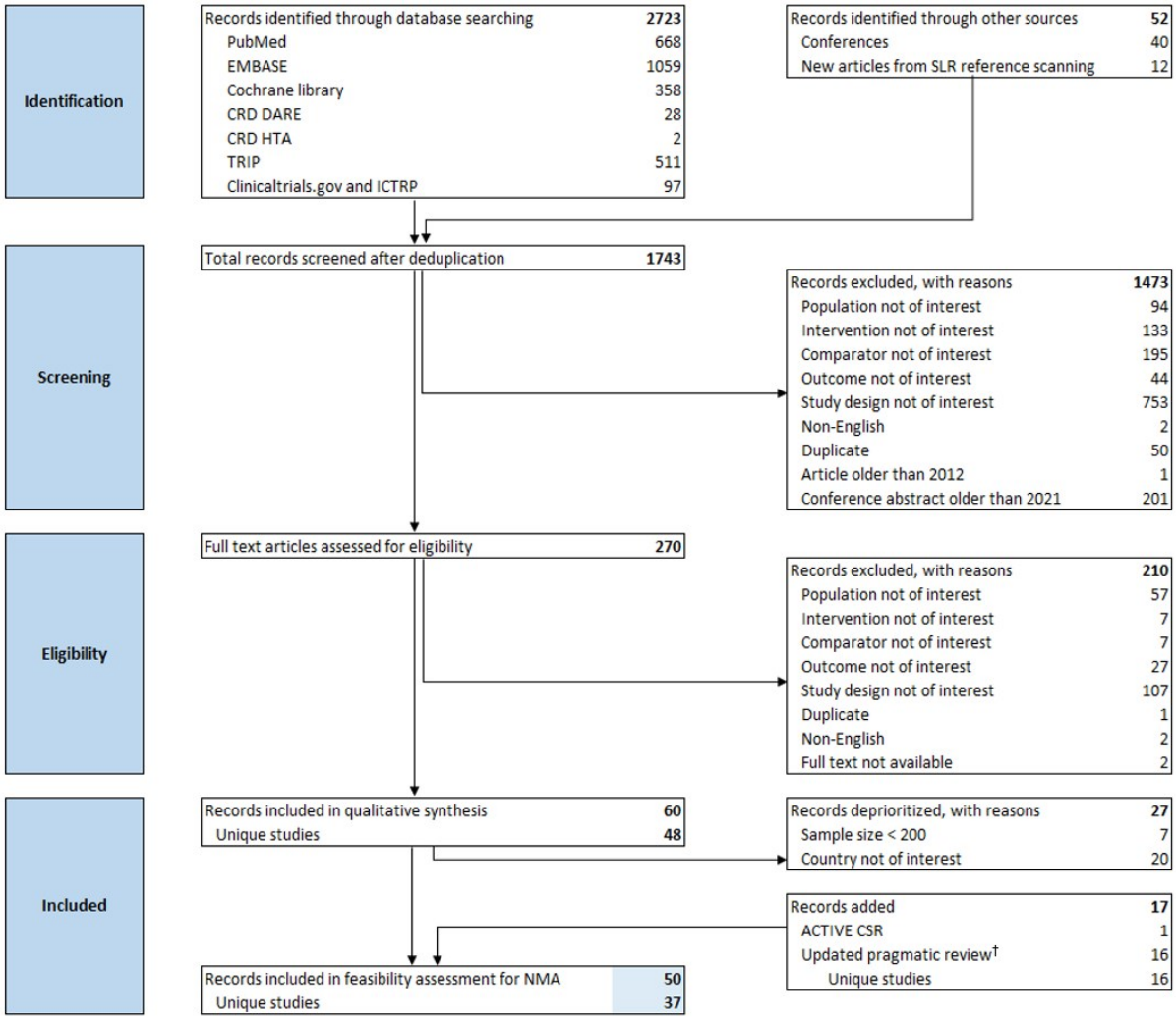
Figure 13). The remaining 33 records were supplemented with 22 records from a pragmatic review of records from two relevant reports[9, 35] (n=21) and the addition of the ACTIVE CSR.[5] The updated NMA after CQ1 therefore included 55 publications (42 studies). However, this was further revised by the company in response to CQ2 and a second, final iteration, the original 33 records were supplemented with records from a pragmatic review of records from two relevant reports[9, 35] (n=16) and the addition of the ACTIVE CSR.[5] The final result was 50 publications (37 studies) (

Figure 13). The 50 publications (and their sources) are provided in the Appendix to CRCQ2 (B.1.4.1.1, Table 4).[26]

Each iteration followed additional clarification questions from the EAG regarding the rationale for the exclusion of certain studies. The revisions principally led to the inclusion of trials from pre-2012 and trials with data other than from the previously specified time points of 12 and 18 months alone.

The final number of studies included in the NMA was 25, after the exclusion of 25 publications on account of their being disconnected records in the network (n=15), the absence of relevant fracture data (n=7), duplicate data from other publications (n=2), data from ACTIVE that was not from the CSR (n=1) (Appendix to CRCQ1, B.1.5.3).[26]

Figure 13: PRISMA flow diagram depicting the flow of records in the clinical SLR including updated literature review (Appendix to CRCQ1, B.1.4, Figure 1[26])



4. *The studies added from the pragmatic review contributed only to hip, vertebral and non-vertebral fractures, as other outcomes were not included in the economic model*
Note: The full methodology of the original clinical SLR and excel sheet with the reasons for the exclusion of 210 records are presented in the original company submission

Abbreviations: CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; HRQoL, health-related quality of life; HTA, health technology assessment; ICTRP, International Clinical Trials Registry Platform; SLR, systematic literature review

The EAG noted that the company's review had implemented several exclusion criteria that were not applied in the two previous published reviews which were used to identify pre-2012 studies. Some of these exclusion criteria, such as the exclusion of studies in men and people with steroid-induced osteoporosis, were consistent with restricting the review to studies of women with postmenopausal osteoporosis. This is consistent with the population specified in the decision problem, and seems entirely reasonable. The EAG had greater concerns regarding the exclusion of studies based on sample size and geographical region. The exclusion of studies with a sample size <200 seems pragmatic, given that large studies are generally needed to detect significant differences in fracture outcomes, but the EAG notes that every restriction that limits the studies contributing to the network will increase the risk

that the network is too sparsely populated to detect differences in fracture risk that may exist between treatments. The company also chose to restrict studies to those conducted in North American or Western European populations, with the rationale being to ensure relevance and applicability to the UK (CRCQ2 A1). Clinical advice to the EAG is that whilst the absolute risk of fracture may vary across different ethnic groups, the relative effectiveness of treatment is not expected to vary,[40] although data for subgroup analyses are generally limited to surrogate outcomes of BMD rather than fracture data.[41, 42] The company also made a point that differences may also exist among racial and ethnic groups in terms of health care provision, such as access to diagnostic investigations and treatment. However, the EAG notes that the application of this geographical restriction has also resulted in the exclusion of the study by Hooper et al.[43] which was conducted in Australia, a country in which access to healthcare is likely to be similar to many European countries. The EAG is concerned that the restriction by geographic region is likely to further limit the precision of the estimate provided by the network by reducing the amount of data contributing to the network. The company also applied a strict definition of osteoporosis and excluded studies which did not restrict recruitment to patients with a BMD <-2.5 or report a subgroup analysis for those with a BMD <-2.5. The EAG is not confident that such a restriction is necessary, as although BMD is a predictor of absolute fracture risk, previous analyses that included a broader network of studies, including studies that used a less severe BMD cut-off, found no evidence for an interaction between baseline risk and treatment effect.[44] However, the EAG accepts that given the focus of the CS on patients with 'very high fracture risk', a restriction to studies in patients meeting the strict definition of osteoporosis is pragmatic even though it will reduce the total evidence available to inform the NMA.

3.9 Critique of the indirect comparison and/or multiple treatment comparison

In response to CQ1 and CQ2 the company provided an updated NMA using the updated SLR described in Section 3.9 and using a different statistical model that allows the inclusion of studies with different study durations within a single synthesis. This provides a more comprehensive analysis than the original submission, which presented separate NMAs at each time point of assessment, resulting in sparse networks and a lack of evidence for key comparators. The EAG summary and critique concentrates on the final NMA presented in CQ2.

3.9.1 Summary of analyses undertaken

An NMA was performed to compare the treatment effects of abaloparatide to relevant comparators for seven outcomes. The results of three of these outcomes (vertebral (new only), hip and non-vertebral fractures) are used to inform the economic model and are summarised below. Separate NMAs were undertaken for each outcome.

The results of three further outcomes (vertebral (new or worsening), clinical, and major osteoporotic fractures) were also performed by the company (CRCQ2 Appendix Section B.3.5.1). Fractures in other bones/ regions was listed as an outcome for the NMA in the original CS (Table 23) but was excluded from Table 5 in the Appendix to the CRCQ2. Previous analyses have explored generating evidence networks for wrist and proximal humerus fractures, but these have often been sparsely populated leading to data from non-vertebral fractures being used in the economic analysis instead.[9] Therefore, the EAG is not overly concerned that specific results are not presented for wrist or proximal humerus fractures.

3.9.2 Methods for the NMA

The studies presented fracture data in terms of the number of individuals experiencing at least one fracture during the follow up period. The NMA was conducted in a Bayesian framework using a binomial likelihood and complimentary log-log link function that accounts for different lengths of follow up across the studies by assuming an underlying Poisson process for each trial arm, with a constant event rate (see NICE TSD 2 [45] for further details).

The company presented both fixed effects (FE) and random effects (RE) models. Standard reference priors, as recommended by NICE TSD2 [45], were used for all parameters. In CRCQ2 the company stated that the NMA was conducted in WinBUGS version 1.4.3. [46]

For all outcomes, a burn-in of 20,000 iterations of the Markov chain was used with a further 80,000 iterations retained to estimate parameters. Convergence was assessed visually and using the Brooks Gelman-Rubin (BGR) statistic[47] . The fit of different models to the same data was assessed based on the deviance information criterion (DIC). Lower DIC values are favourable and the CS states that differences of more than three were deemed relevant.

In response to CQ2 A9 the company assessed the networks for inconsistency of evidence using the inconsistency parameter approach proposed by Lu and Ades.[48] Results are presented as inconsistency factors for individual evidence loops in each of the three main networks. CRCQ1 A9 did not state whether FE or RE models were used. Overall measures of model fit (such as total residual deviance and DIC) and overall measures of inconsistency for each network were not provided.

Treatment effects are presented as HRs with a HR less than one reflecting a reduced risk of fracture relative to the comparator treatment. Results were summarised using posterior medians and 95% credible intervals (CrI). In the presence of heterogeneity the NICE TSD recommends that the predictive distribution, rather than the distribution of the mean treatment effect, better represents uncertainty about comparative effectiveness for a future rollout of a particular intervention. [49] The 95% predictive

intervals (PrI) were provided by the company in response to CQ2 as well as the estimates of between study standard deviation.

3.9.3 Results of NMA

A summary of the NMA results for the three outcomes used in the economic model is provided in Table 28. The model uses HRs compared to placebo for abaloparatide and the two comparators identified of interest in the decision problem (romosozumab and teriparatide). The HR for alendronate vs placebo is also used in some scenario analyses presented by the company but is not used in the company's base case (see Section 4.2.3). These key results are highlighted in Table 28.

The CS states that DIC and residual deviance were comparable for the FE and RE models and so both models were used to draw conclusions and results of FE models were used to inform the model. The EAG considers that RE models are more appropriate due to the stated concerns in heterogeneity between the studies and CRCQ2 was updated with RE models informing the cost-effectiveness.

The results of inconsistency checking are shown in CRCQ1 A9. None of the inconsistency factors were statistically significantly different from zero and the company concluded that this indicated a "*considerable level of coherence and reliability in the dataset*". The EAG agrees that no evidence is provided to suggest inconsistency in the networks but the provided results lacked details to assess this reliably. It was not stated whether FE or RE models were used. Overall measures of model fit (such as total residual deviance and DIC) and overall measures of inconsistency for each network were not provided.

Table 28: Summary of NMA results based on CRCQ2 Table 6 and Table 7 and CRCQ2 NMA appendix Figure 7-9, Table 14-16

Outcome	New vertebral fracture (S=20)			Hip (S=17)			Non-vertebral fracture (S=18)		
Comparator HR vs placebo	**FE model HR (95% CrI)**	**RE model HR (95% CrI)**	**95% PrI**	**FE model HR (95% CrI)**	**RE model HR (95% CrI)**	**(95% PrI)**	**FE model HR (95% CrI)**	**RE model HR (95% CrI)**	**95% PrI**
Abaloparatide									
Romosozumab									
Teriparatide									
Alendronate									
Denosumab									
Denosumab Bio									
Ibandronate									
Raloxifene									
Risedronate									
Zolendronate									
Model fit									
DIC									
Residual deviance									
datapoints									
Between study SD									

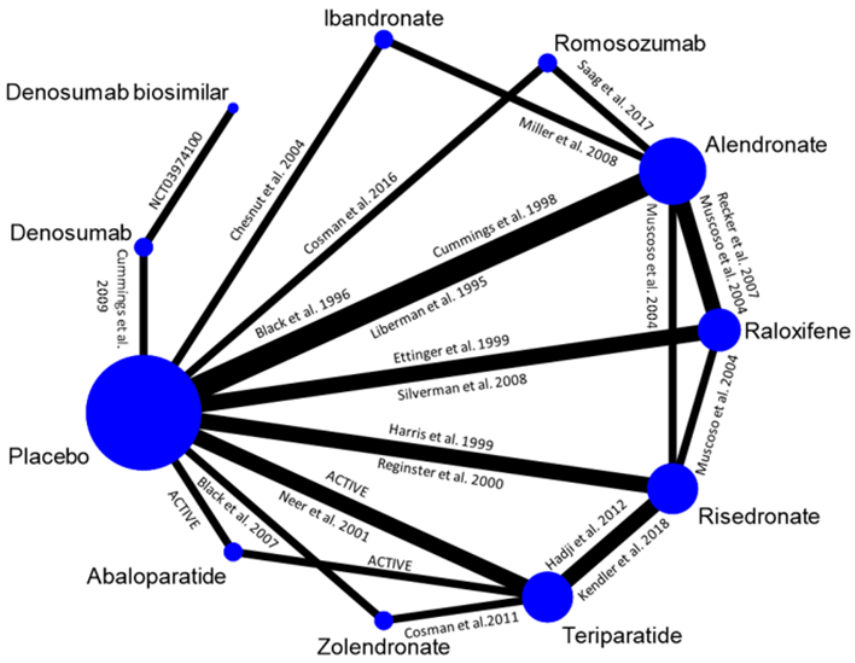
Cells in grey correspond to values that inform the company's model.
S: number of studies, FE: fixed effect, RE: random effect, HR: hazard ratio (median) , CrI: credible interval, PrI: prediction interval, DIC: deviance information criterion, SD: between study standard deviation, NR: not relevant.

New vertebral fractures

Twenty-one studies assessing 11 treatments contributed to the analysis for new vertebral fractures (although CRCQ2 Updated NMA Section B.1.5.6.1 states there are 20 studies assessing 12 treatments) and the network diagram is shown in Figure 14. Data contributing to the analysis is presented in CRCQ2 Updated NMA Section B.3.4.1.

All comparators demonstrated a reduced risk of new vertebral fractures compared with placebo (HR < 1). Abaloparatide was associated with the greatest reduction in fractures, HR [redacted] (95% CrI: [redacted] from the RE model). HRs vs abaloparatide are provided in company response to CQ2 Table 9 demonstrating statistically significant reductions in the number of new vertebral fractures for abaloparatide vs. placebo, alendronate, ibandronate, raloxifene and risedronate. The estimate of between study standard deviation from the RE model was [redacted] (95% CrI: [redacted]) suggesting mild heterogeneity in treatment effects between studies.

Figure 14: Network of studies contributing to the NMA for new vertebral fractures. Replicated from CRCQ2 Updated NMA Section B.1.5.6.1. Figure 4



Hip

Seventeen studies assessing 10 treatments contributed to the analysis for hip fractures and the network diagram is shown in

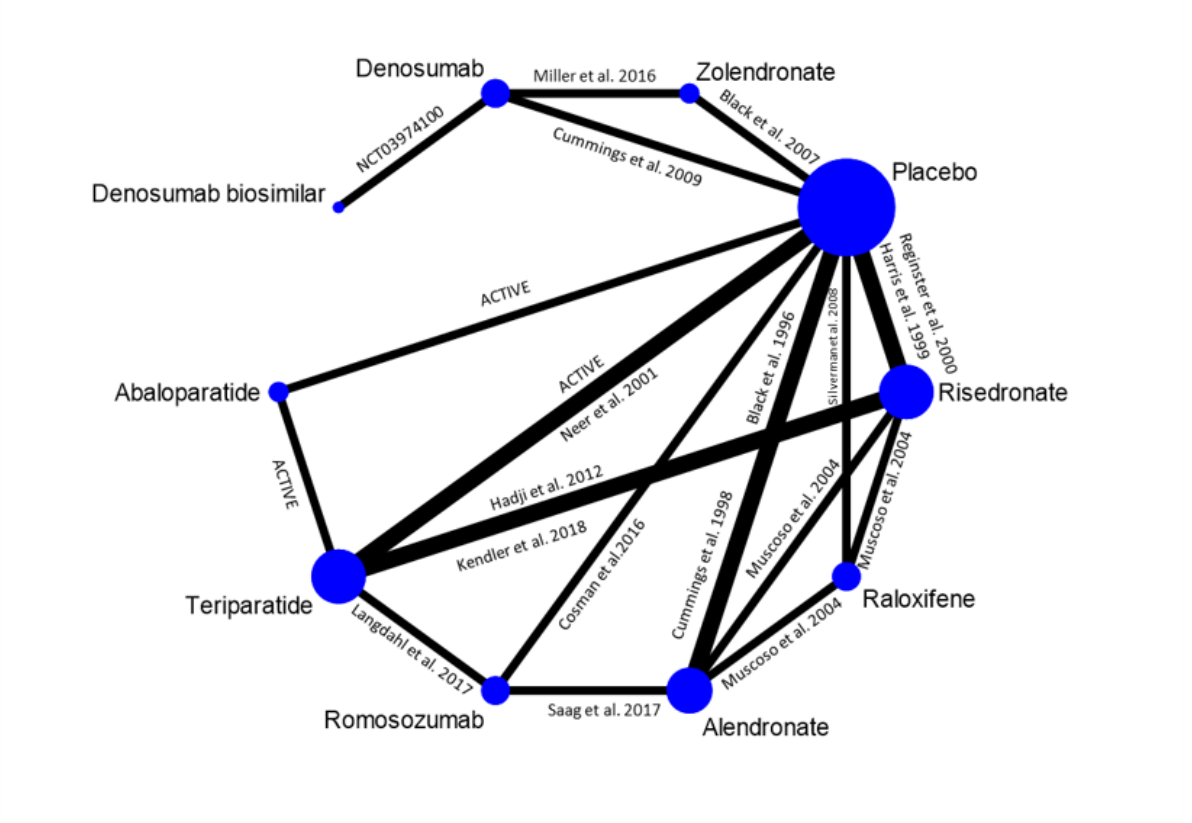
Figure **15**. Data contributing to the analysis is presented in CRCQ2 Updated NMA Section B.3.4.2.

All comparators apart from the denosumab biosimilar demonstrated a reduced risk of hip fractures compared with placebo. Abaloparatide was associated with the greatest reduction in fractures, HR [redacted] (95% CrI: [redacted] from the RE model) but the treatment effect was not statistically significant. HRs vs abaloparatide are provided in CRCQ2 Updated NMA Table 10 demonstrating reductions in the number of hip fractures for abaloparatide vs. all included comparators but with considerable uncertainty indicated by the wide credible intervals.

The considerable uncertainty is due to low numbers of hip fractures. Abaloparatide was evaluated in only one trial (ACTIVE [5]), in which one hip fracture was observed in the placebo arm and no fractures observed in the abaloparatide and teriparatide arms (CRCQ2 NMA Appendix, Table 21). When replicating the NMA the EAG found that the models (using standard reference priors as stated by the company) did not converge. Convergence was achieved by adding a constant value of 0.5 to the zero cells in order to obtain non-infinite estimates of the treatment effect and variance. The resulting treatment effects were in line with those reported by the company. However this approach is not generally recommended as it may produce biased estimates of treatment effects. [45] No adaptations to ensure convergence were reported by the company.

The estimate of between study standard deviation from the RE model was [redacted] (95% CrI: [redacted]) suggesting mild-moderate heterogeneity in treatment effects between studies.

Figure 15: Network of studies contributing to the NMA for hip fractures. Replicated from CRCQ2 Updated NMA Section B.1.5.6.1. Figure 5



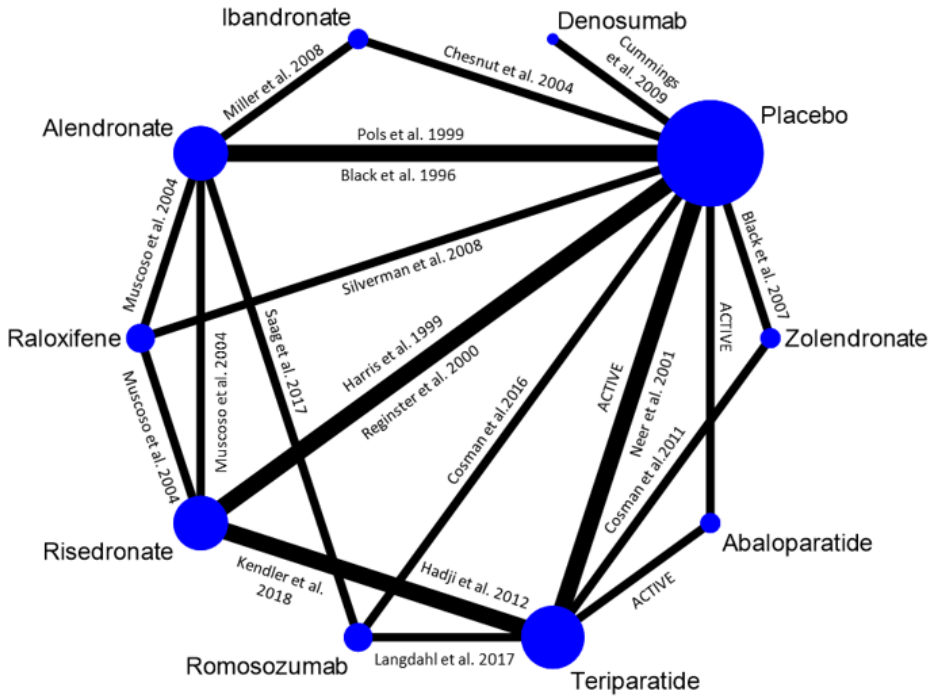
Non-vertebral fractures

Eighteen studies assessing 10 treatments contributed to the analysis for non-vertebral fractures (although CS Updated NMA Section B.1.5.6.1 states there are 19 studies) and the network diagram is shown in

Figure **16**. Data contributing to the analysis is presented in CS Updated NMA Section B.3.4.3.

All comparators except ibandronate demonstrated a reduced risk of non-vertebral fractures compared with placebo. Abaloparatide was associated with a reduction in non-vertebral fractures, HR [redacted] (95% CrI: [redacted] from the RE model) that was not statistically significant, whilst some other treatments achieved a statistically significant reduction (zoledronate, risedronate, romosozumab and teriparatide all had CrIs under 1 for the RE model). HRs vs abaloparatide are provided in CRCQ2 Updated NMA Table 11 and these fail to demonstrate statistically significant reductions in the number of non-vertebral fractures for abaloparatide vs. placebo and all active comparators. The estimate of between study standard deviation from the RE model was [redacted] (95% CrI[redacted]) suggesting mild heterogeneity in treatment effects between studies.

Figure 16: Network of studies contributing to the NMA for non-vertebral fractures. Replicated from CRCQ2, NMA Appendix, Section B.1.5.6.1. Figure 6



3.10 Additional work on clinical effectiveness undertaken by the EAG

NMAs were conducted by the EAG using a RE model for the three main outcomes (vertebral (new only), hip and non-vertebral fractures) to provide Markov chain Monte Carlo (MCMC) samples to inform the probabilistic sensitivity analysis (PSA) presented in Section 4.4.. For each of these outcomes the EAGs analyses used the same studies and data as presented by the company. As described in Section 3.9 the hip network data was amended by adding a constant value of 0.5 to the zero cells in order to obtain non-infinite estimates of the treatment effect and variance (as discussed in the NICE TSD[45]).

All analyses were conducted in the freely available software packages WinBUGS[46] and R,[50] using the R2Winbugs interface package. Convergence to the target posterior distributions was assessed using the Gelman-Rubin statistic, [47] for two chains with different initial values. The absolute goodness of fit was checked by comparing the total residual deviance to the total number of data points included in an analysis. For all outcomes, a burn-in of 50,000 iterations of the Markov chain was used with a further 20,000 iterations retained to estimate parameters using one chain and thinning every 5 iterations.

A summary of the NMA results for the three outcomes used in the economic model is provided in Appendix 2, Table 60. Results were similar to those presented by the company for all outcomes.

3.11 Summary of treatment effectiveness estimates from different sources

Table 29 provides a comparison of the treatment effect estimates for abaloparatide versus teriparatide between the direct evidence provided by the ACTIVE study and those provided by the RWE and the indirect comparison using the RE NMA. Overall it appears that abaloparatide provides a numerical reduction in fracture risk that is not statistically significant when compared with teriparatide, with the exception being the hip fracture outcome from the sensitivity analysis from the RWE study that used patients with more than 12 months treatment, where the difference was statistically significant.

For the comparison against placebo, both the direct evidence and the NMA provide a statistically significant reduction in vertebral fractures, but no statistically significant reduction in other fracture outcomes, although the risk is numerically lower for abaloparatide.

Table 29: Comparison of treatment effectiveness estimates from the ACTIVE study, the RWE and the NMA (RE model)

	Abaloparatide vs (HR and 95% CI unless otherwise stated)	
Outcome	**Placebo**	**Teriparatide**
Vertebral fracture (new only)		
ACTIVE	RRR= –0.88 (–0.96,–0.59) [equivalent to RR=0.12]	*Not estimated in CS RRR~ -0.23 [equivalent to RR ~ 0.77]
ACTIVExtend (including alendronate period)	RRR= –0.84 (–0.94, –0.53) [equivalent to RR=0.16]	
NMA (RE model)	[redacted]	[redacted]
Hip		
ACTIVE (HR not estimated, 0 abaloparatide events)	1 event	0 events
RWE study		0.78 (0.62–1.00)
RWE (>12 months consecutive treatment)		0.57 (0.35–0.94)
NMA (RE model)	[redacted]	[redacted]
Non-vertebral fracture		
ACTIVE	0.74 (0.38, 1.43)	1.30 (0.61 to 2.79)
ACTIVExtend (including alendronate period)	0.61 (0.35–1.08)	
RWE study		0.89 (0.77–1.03)
NMA (RE model)	[redacted]	[redacted]

CrI: credible interval

Informing the cost-effectiveness model

As there is no head-to-head evidence informing the comparative effectiveness of abaloparatide and romosozumab, NMA is required to inform this comparison. NMA allows a comprehensive analysis of all relevant treatments, combining direct and indirect evidence about treatment effects across studies that share at least one treatment in common with at least one other study.

For the comparison of abaloparatide and teriparatide there is direct evidence from the ACTIVE trial, as well as the ACTIVExtend extension study and RWE. Estimates from the NMA are preferred in the base case. This ensures consistency across comparisons and also provides the most comprehensive summary of the relevant evidence.

For vertebral fractures, the HR of abaloparatide vs placebo from the RE NMA of [redacted] is largely informed by the ACTIVE trial and so is similar to the estimated RR from the ACTIVE trial (RR =0.12 approximated by the EAG). The comparison of abaloparatide vs teriparatide is also informed by indirect evidence in the NMA. Point estimates of treatment effectiveness from the NMA differ slightly to the direct trial evidence but the sources are not inconsistent and indicate the same direction of effect (favouring abaloparatide)

For hip fractures there are very few observed events with one, zero and zero events observed in the placebo, abaloparatide and teriparatide arms respectively, of the ACTIVE trial. Treatment effects could not be estimated and although an NMA has been conducted, the results are highly uncertain and should be viewed with caution. Due to this uncertainty, and the observation of zero events in both active treatment arms, the EAG considers that for hip fractures an assumption of equal efficacy is appropriate for abaloparatide and teriparatide.

For non-vertebral fractures, the HR of abaloparatide vs placebo from the RE NMA of 0[redacted] is largely informed by the ACTIVE trial (HR 0.74 (95% CI 0.38, 1.43). The comparison of abaloparatide vs teriparatide is also informed by indirect evidence in the NMA but again, the estimates are similar (RE NMA HR: [redacted], ACTIVE HR: 1.30 (0.61 to 2.79)). The estimates show considerable uncertainty and the RWE suggests a different direction of effect. Due to this uncertainty, the EAG considers that for non-vertebral fractures an assumption of equal efficacy is appropriate for abaloparatide and teriparatide. This is a more optimistic assumption for abaloparatide than suggested by the point estimate of the NMA results.

3.12 Conclusions of the clinical effectiveness section

3.12.1. *Summary of principle findings*

The pivotal trial presented was ACTIVE – an international phase III, multi-centre, partially open-label, 18-month, three-arm RCT comparing abaloparatide (arm 1) with placebo (arm 2) and teriparatide (arm 3, open-label) in postmenopausal women with severe osteoporosis at risk of fracture (n=2070).[5] ACTIVE was conducted in 25 centres (23 after the exclusion of two sites) across 10 countries; there were no centres in the UK. Also included was the 24-month single-arm extension of the trial (ACTIVExtend) for patients in arms 1 and 2, who all received the bisphosphonate alendronate (n=963).[28] The ACTIVE trial and its extension (ACTIVExtend) form the key evidence within the CS for the clinical effectiveness and safety of abaloparatide within this indication. The EAG believes that no additional relevant published phase III trials of abaloparatide in relevant patient groups have been omitted from the CS that could have provided data on safety and efficacy.

In terms of efficacy, the ACTIVE trial reported data for the primary endpoint of new vertebral fractures, the secondary endpoint of non-vertebral fractures, and the exploratory endpoints of major osteoporotic and clinical fractures. ACTIVE found that abaloparatide significantly reduced the risk of new vertebral fractures compared with placebo at 18 months (0.5% compared with 4.2%; RRR -0.88 [95% CI -0.96, -0.59], p<0.001); teriparatide also significantly reduced this risk compared with placebo (RRR -0.84 [95% CI -0.94, -0.54], p<0.001). At 18 months, abaloparatide was not found to reduce the risk of non-vertebral fractures significantly compared with placebo (HR 0.74 [95% CI 0.38, 1.43], p=0.368). No significant difference was found between abaloparatide and teriparatide for this outcome (see Table 15). There was a significant difference in major osteoporotic fracture event rates (fractures of the wrist, upper arm, hip, and clinical spine) in favour of the abaloparatide group compared with the placebo group (HR 0.31 [95%CI 0.13, 0.72] p=0.004), but not for clinical fractures (HR 0.61 [0.36, 1.06] p=0.08). No significant difference was found between abaloparatide and teriparatide for these outcomes (Table 15). The efficacy findings for ACTIVExtend, at the end of the full 43-month treatment period, were entirely consistent with the findings for the ACTIVE trial for all of these outcomes. In ACTIVE, improvements in BMD were significantly greater with abaloparatide than with placebo at the total hip, femoral neck and lumbar spine at 6, 12 and 18 months. BMD improvements were also sustained throughout ACTIVExtend and were statistically significant at all time points up to month 43. Pre-specified subgroups indicate that the treatment effect of abaloparatide on new vertebral fractures was consistent across the majority of pre-specified patient subgroups.

In terms of safety, in ACTIVE, there were generally no meaningful differences between arms in terms of severe or serious TEAEs or AEs leading to death, or in terms of the most common TEAEs, with the exception of dizziness (11.1% abaloparatide compared with 7.1% placebo and 8.2% teriparatide), nausea (8.5% abaloparatide compared with 3.1% placebo and 5.4% teriparatide), and palpitations (5.6%

abaloparatide compared with 0.4% placebo and 1.7% teriparatide). The incidence of severe TEAEs was very low across all arms. The incidence of hypercalcaemia in the abaloparatide arm (3.3%) was higher than in the placebo arm (0.4%) but lower than the teriparatide arm (6.0%). A higher percentage of participants in the abaloparatide arm than the comparator arms discontinued due to AEs (9.8% compared with 6.1% placebo and 6.9% teriparatide). The most common TEAEs leading to study discontinuation in the abaloparatide group included nausea (1.6%), dizziness (1.4%), headache (1.2%), and palpitations (0.9%), which were generally mild to moderate in severity. The incidence of orthostatic hypotension and, to a lesser extent, palpitations and nausea was higher in the abaloparatide arm than the placebo or teriparatide arms, but otherwise there was no meaningful differences between active treatments for other AESIs, including hypercalcaemia, hypercalciuria, hypophosphatemia, hypersensitivity and renal impairment.

The CS presented supplementary data from a retrospective US RWE study based on an administrative claims database for abaloparatide effectiveness and safety in postmenopausal women new to anabolic therapy over a 19-month period after treatment initiation (n=23,232). The aim of this study was to evaluate the real-world comparative effectiveness on non-vertebral fractures and to compare the cardiovascular safety of abaloparatide vs teriparatide in propensity score-matched cohorts. Some baseline characteristics of the population in the RWE study differed from ACTIVE, e.g. proportion with prior fractures. Noninferiority of abaloparatide vs teriparatide was reported for the endpoints of new non-vertebral fracture rate and time to first non-vertebral fracture. The risk of hip fractures (an exploratory endpoint) was reduced for abaloparatide versus teriparatide (new event rate, 1.0% vs 1.3%; HR [95% CI] 0.78 [0.62–1.00], p=0.04). The only safety evidence other than treatment duration reported for the RWE study was for the composite endpoint of MACE (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death); at 19 months after the index date, the risk of new MACE events was similar between the abaloparatide and teriparatide cohorts.

The CS did not conduct a meta-analysis due to the absence of any similar, relevant trials. An NMA was conducted to compare the effects of abaloparatide to relevant comparators listed in the decision problem for seven outcomes. The results of three of these outcomes (vertebral (new only), hip and non-vertebral fractures) are used to inform the economic model. Twenty-one studies assessing 11 treatments contributed to the NMA for new vertebral fractures. All comparators demonstrated a statistically significant reduced risk of new vertebral fractures compared with placebo. Abaloparatide was associated with the greatest reduction in new vertebral fractures, HR [redacted] (95% CrI: [redacted] from the RE model). Seventeen studies assessing 10 treatments contributed to the NMA for hip fractures. All comparators apart from the denosumab biosimilar demonstrated a reduced risk of hip fractures compared with placebo. Abaloparatide was associated with the greatest reduction in hip fractures, HR [redacted] (95% CrI[redacted] from the RE model) but the treatment effect was not statistically

significant. Results for the hip fracture network are extremely uncertain due to the low number of events in ACTIVE study (one hip fracture was observed in the placebo arm and no fractures observed in the abaloparatide and teriparatide arms). Eighteen studies assessing 10 treatments contributed to the NMA for non-vertebral fractures. All comparators except ibandronate demonstrated a reduced risk of non-vertebral fractures compared with placebo. Abaloparatide was associated with a reduction in non-vertebral fractures, HR [redacted] (95% CrI: [redacted] from the RE model) that was not statistically significant, whilst some other treatments achieved a statistically significant reduction (zoledronate, risedronate, romosozumab and teriparatide all had CrIs under 1 for the RE model)

The estimate of between study standard deviation from the RE model was [redacted] (95% CrI: [redacted]), [redacted] (95% CrI: [redacted]) and [redacted] (95% CrI: [redacted]) from the new vertebral, hip and non-vertebral networks respectively, suggesting mild, moderate-mild, and mild heterogeneity in treatment effects between studies.

3.12.2 Uncertainties surrounding the reliability of the clinical effectiveness

The EAG identified a number of uncertainties and limitations in the clinical effectiveness evidence for abaloparatide. The EAG conducted a quality assessment of ACTIVE using the Cochrane Risk of Bias tool (version 2).[38] On account of the judgement of a high risk of bias in the missing data domain, and some concerns regarding the domains involving the randomisation process and outcome assessment, the EAG judged ACTIVE overall to be at 'High' risk of bias, following the Cochrane algorithm.

The EAG noted that patients with prior alendronate treatment were excluded from the ACTIVE trial which is significant given that an unsatisfactory response to alendronate is one of the possible reasons for patients being eligible for teriparatide in current UK practice (see Box 1 for specific recommendations for teriparatide). Therefore the EAG is concerned about the generalisability of the ACTIVE trial to some patients likely to be offered anabolic therapies in the UK. There was also a lack of UK centres in ACTIVE. In addition, clinical advice to the EAG also confirmed it is unlikely that patients with no prior history of fracture would be considered to be at 'very high risk of fracture' (the population designated as eligible by the company in the submission): >40% of patients in the ACTIVE trial had no prior history of fracture (abaloparatide 41.5%, placebo 43.3%, teriparatide 42.1%).

Abaloparatide was evaluated in only one trial (ACTIVE [5]), in which one hip fracture was observed in the placebo arm and no fractures observed in the abaloparatide and teriparatide arms (CRCQ2 NMA Appendix, Table 21). Although an NMA was conducted the results are extremely uncertain and should be viewed with caution. The impact of this uncertainty on the cost-effectiveness analyses is addressed in Sections 4.3 and 4.4.

Inconsistency checking was performed by the company (CRCQ1 A9) and no inconsistency between direct and indirect evidence was identified. However, the provided results lacked key details. The networks have a maximum of two studies per comparison and low event numbers from several studies so may have limited power to detect inconsistency statistically.

4 COST EFFECTIVENESS

This chapter provides a summary and critique of the company's health economic analyses of abaloparatide for the treatment of postmenopausal women with osteoporosis at increased risk of fracture in the UK. Section 4.1 summarises and critiques the company's review of existing cost-effectiveness evidence. Section 4.2 presents a detailed description of the methods and results of the company's submitted economic evaluation. Section 4.3 presents the EAG's critical appraisal of the company's model. Section 4.4 presents the methods and results of additional exploratory analyses undertaken by the EAG.

4.1 EAG's comment on company's review of cost-effectiveness evidence

The company carried out two SLRs, with the following objectives:

- To identify published cost-effectiveness studies and cost/healthcare resource utilisation (HCRU) studies for treatments for postmenopausal women with osteoporosis at high risk of fracture (CS Appendix G)[1]
- To identify utilities related to target population (CS Appendix H)

Limitations identified by the EAG relate to the following.

- Search reporting for non-electronic database sources
- Applied population exclusion terms limit
- Economics and cost studies filter
- Application of date search limit

4.1.1 Searches performed for cost effectiveness review

The data sources used in the company's review are summarised in Table 30, based on CS Appendices G and H. The described methods for the SLR process were not reported clearly in the CS. For example, Cochrane library was presented as one of the databases included in the searches in the review for published cost-effectiveness studies; however, this database was not shown in the PRISMA flow diagram (CS Appendix G Figure 20). In the SLR for utilities presented in CS Appendix H, the company referred to Appendix D 1.1 for a complete list of databases searched for identification of HRQoL studies. However, there were some discrepancies between the list presented in D 1.1 and the databases shown in the PRISMA flow diagram (CS Appendix H Figure 21). In addition, although the company mentioned searches conducted in HTA websites, Figure 21 (PRISMA flow chart) does not show any bibliographic records identified from HTA websites. It is unclear if the company searched any HTA websites. It is also unclear to the EAG why some sources listed in the company's cost-effectiveness

searches (CS Appendix G) applicable for finding HRQoL studies (CEA registry, SCHARRHUD, EQ-5D websites) were not searched (Table 30).

Table 30: Data sources searched as reported in PRISMA flow charts in CS[1]

	Cost-effectiveness and cost/resource use	Utility
Database	• EMBASE® • PubMed: MEDLINE®, MEDLINE In-Process Citations, Epub Ahead of Print & Daily Update • CRD: Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, National Health Service Economic Evaluation Database (NHS EED) • International HTA (INAHTA) • Cost-effectiveness Analysis (CEA) registry • ScHARR Health Utilities Database (ScHARRHUD) • EQ-5D publications database	• EMBASE® • PubMed: MEDLINE®, MEDLINE In-Process Citations, Epub Ahead of Print & Daily Update • Cochrane: Cochrane Central Register of Controlled Trials (CENTRAL) • CRD: Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database • TRIP databases • ClinicalTrials.gov • World Health Organisation International Clinical Trials Platform (WHO ICTRP)
Conference proceedings	• International Osteoporosis Foundation (IOF): WCO-IOF-ESCEO congress • European Calcified Tissue Society (ECTS) • The American Society for Bone and Mineral Research (ASMBR) • Fragility Fracture Network (FFN) • International Society for Pharmacoeconomics and Outcomes Research (ISPOR) • European Alliance of Associations for Rheumatology (EULAR)	• National Osteoporosis Society (NOS): getting redirected to Royal Osteoporosis Society (ROS) • National Osteoporosis Foundation (NOF): getting redirected to Bone Health & Osteoporosis Foundation (BHOF) • International Osteoporosis Foundation (IOF): WCO-IOF-ESCEO congress
HTA website	• The National Institute for Health and Care Excellence (NICE) • Scottish Medicine Consortium (SMC) • All Wales Medicines Strategy Group (AWMSG) • National Centre for Pharmacoeconomics, Ireland (NCPE)	

CRD - Centre for Reviews and Dissemination; HTA – health technology assessment

Searches were run in April 2023. The company provided search strategies only for a limited number of databases as following:

- SLR for economic evidence: Pubmed, Embase and CRD DARE-NHSEED-HTA
- SLR for utilities: Pubmed, Embase, Cochrane library and CRD DARE

It is unclear why the conference sources search differed from the SLR clinical effectiveness review (CS Appendix D). Details of the searches in conference and other health economic specific resources, including date, search terms and URLs, were not reported in the CS. Search strategies in other databases were missing.

The company used two search filters for economic evaluation and costs in the PubMed and Embase search strategy (CS Appendix G, Tables 21 and 22). The free-text terms used in the economic evaluation versus costs search filters are almost indistinguishable: In PubMed, two more MeSH headings are added to the cost search filter ("costs and cost analysis"[MeSH Terms] OR "resource allocation"[MeSH Terms]). By contrast, in Embase, the additional free text terms are added to the cost search filter ('resource allocation':ab,ti OR 'value for money':ab,ti OR 'health resources':ab,ti OR 'incremental cost':ab,ti). Furthermore, there is a lack of consistent translation of free-text terms used in the economic evaluations filter across the PubMed and Embase database searches e.g. “resource allocation” and “health resources:ab,ti. Other free-text terms could be included in the filters (e.g. “quality adjusted life year*” or (resource NEXT/2 (utilit* or usage)) to improve search sensitivity.

According to CS Appendix G Table 21, the company used Mesh and free text terms without title/abstract restriction in the PubMed. This approach is generally acceptable, but it can lead to exclude some references because the company used NOT in the use of Boolean logic to exclude population subject to exclusion criteria.

For reasons explained earlier in the clinical effectiveness review search critique (EAG report section 5.1.1.), the EAG recommends the following steps when applying the population exclusion filter in both MEDLINE and Embase search strategies (CS Appendix G, Tables 21 and 22).

- Statement #12 should be [All exclusion population (statement 11)] NOT [All exclusion population AND Osteoporosis (Statement 1)] i.e., #11 NOT (#11 AND #1).
- Statement #24 should be (#1 AND #23) NOT #12

The EAG considers that the economic filter applied in the CRD DARE-NHSEED-HTA search strategy (CS Appendix G, Table 23) was inappropriate because the NHS EED database has an inbuilt economic evaluations search filter (https://www.crd.york.ac.uk/crdweb/searchstrategies.asp).

In the SLR for utility studies, the company limited the population into postmenopausal women and used it as a search term. The EAG found one study (ICUROS) that was not retrieved and therefore excluded by the company. The EAG further investigated the reasons for the exclusion of this study at the search stage. The company restricted population terms by including the terms "postmenopausal" or "perimenopausal" in the title and abstract fields. In the title, abstract full-text and full-text of the ICUROS study, there is no mention of the term “postmenopaus*”, although patient inclusion is >50 years (Fig 1). Similarly, any studies where the terms "postmenopausal" or "perimenopausal" are not present in the title and abstract are excluded from the records retrieved from the electronic database searches. Understandably, if the company had removed these terms, they would screen ten times more records (e.g. 2.5K records in PubMed as opposed to <400). If the company had not limited the population to postmenopausal women, the ICUROS study, which the company used as a source of utility, would have been retrieved by the SLR.

There were discrepancies in the use of free terms for search across the databases, shown in CS Appendix H Tables 27 to 29. For example, the term ‘EQ-5D’, which is widely used in its abbreviated form, was only searched for in the Cochrane library and MeSH only searching for osteoporosis was applied in the Cochrane Library search strategy.

4.1.2 The inclusion and exclusion criteria used in the study selection

Inclusion and exclusion criteria for review of cost-effectiveness studies and utilities were presented in CS Appendix G.1.3 Table 24 and CS Appendix H.1.3 Table 31. The EAG agrees that the eligibility criteria are overall suitable to fulfil the company’s objective to identify cost-effectiveness studies and utility studies. Based on the information reported in CS Appendix G, the EAG considers it unlikely that this review would have missed any studies meeting the stated inclusion criteria.

However, it is unclear why the company included novel models from a selection of countries (UK, US, Australia, Canada or any European country) but restricted non-novel models to UK only. The company included articles published since 2012 and conference abstracts from 2021 to present. The rationale for the date restriction was not clearly provided and earlier studies reporting the cost-effectiveness of some comparators, such as raloxifene,[51] denosumab[52] or teriparatide[53] in the UK have been excluded. Searches were limited to English language articles, so language bias is possible.

4.1.3 Findings of the cost effectiveness review

The company’s searches identified 23 studies regarding cost-effectiveness and cost/resource use. Among these studies, 17 were cost-effectiveness studies, five were healthcare resource utilisation/cost studies, and one combined both. In Appendix G Table 25, the company summarised nine published

cost-effectiveness studies but the reason why only these nine were selected from the 17 included cost-effectiveness studies was not clearly explained. For example, Murphy *et al*. (2012),[54] which examined teriparatide versus bisphosphonates in a Swedish setting, was not included in the table even though other studies comparing bone forming agents to antiresorptive and other studies in a Swedish setting[55] were included. In the CS Section B.3.1, the company described two studies[55, 56] out of the nine studies summarised in Appendix G, and the NICE appraisal for romosozumab (TA791)[3] as being the "*most relevant for informing the abaloparatide economic analysis.*" However, the company did not describe why these studies are more relevant than other studies identified in the review. For example, Davis *et al*. (2020)[9] analysed the cost-effectiveness of romosozumab but the company did not comment on why it did not consider Davis *et al*. (2020) to be relevant. The company needed to explain more clearly how it narrowed down the number of relevant studies from 17 to 9 and then to three.

A total of 29 studies were included in the SLR for utilities, where five reported utility values from EQ-5D data; however, the company did not consider these studies to be suitable sources for utility values for the model because three were conducted outside of the UK and two did not report fracture sites of interest. The EAG has concerns whether the SLR was appropriate and comprehensive because the ICUROS study, which the company chose as its source of utility values for their model, was not captured through their SLR. The EAG cannot rule out the possibility that other relevant studies were missed.

4.1.4 Conclusions of the cost effectiveness review

The selection of databases was comprehensive. However, full details of the searches conducted, including the search strategies used, were not clearly reported. In the SLR for utility studies, it is unclear which databases were searched. The EAG therefore had concerns regarding the transparency of the company's searches and free text terms of commonly used abbreviations were missed. There is a risk that appropriate studies were missed as demonstrated by the ICUROS study being missed in the review. The company needed to clearly state and rationalise if no relevant studies were found or included studies were not relevant. The EAG notes that cost/utilisation studies were not mentioned in the CS Section B.3.5 which describes costs and resource use data used in the model, although they were included in the SLR in Appendix G. The EAG did not find an overview of the cost-effectiveness studies what were referenced in the CS and the CS did not formulate specific conclusions based on the studies identified in the cost-effectiveness review.

4.2 Summary of the company's submitted economic evaluation

As part of their submission to NICE,[1] the company submitted a fully executable health economic model of abaloparatide programmed in Microsoft Excel®. As part of the clarification process, the company has submitted two sets of responses to the questions raised by the EAG (CRCQ1 and CRCQ2),[26, 57]

updated versions of the model and new descriptions of the economic analysis undertaken (CRCQ1 appendix and CRCQ2 appendix).[25, 58] This discussion reflects the version of the model submitted at CRCQ2, with references to the original and CRCQ1 versions of the model where necessary.

4.2.1 Model scope

The scope of the company's economic analysis is summarised in Table 31.

Table 31: Scope of the company's economic analyses

Population	Postmenopausal women with osteoporosis at very high risk of fracture
Time horizon	Lifetime (maximum of 50 years)
Intervention	Abaloparatide
Comparator	• Teriparatide • Romosozumab
Economic analysis approach	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs
Price year	2023*

QALY - quality-adjusted life year; NHS - National Health Service; PSS -
**Drug costs were priced at 2023 values, whilst costs obtained from the literature, previous TAs and PSSRU 2022 were uplifted to 2023 values.*

The company's economic analysis assesses the incremental cost-effectiveness of abaloparatide versus teriparatide and romosozumab in postmenopausal women with osteoporosis at very high risk of fracture in terms of the incremental cost per quality-adjusted life year (QALY) gained from the perspective of the NHS and PSS over a lifetime horizon (up to 50 years). Costs are valued at 2023 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

4.2.1.1 Population

The population within the model relates to female postmenopausal patients with osteoporosis and classified as being at very high risk of fractures, which is consistent with the mITT population enrolled into the ACTIVE study (excluding sites 131 and 132).[5] The company notes that this population is narrower than the population defined at the final NICE scope and the marketing authorisation for abaloparatide (of postmenopausal women with osteoporosis at increased risk of fracture).[2, 58, 59]

The EAG has previously noted in Section 2.3.1 that whilst there is some overlap between the group who would be defined as being at very high risk based on the NOGG guideline, the EAG does not consider that the ACTIVE trial population as a whole would be classed as being at very high fracture risk based on the 10 year FRAX risk reported for the study cohort (mean 13%; IQR of 7% to 17%) and the inclusion of some patients with a prior fracture.

It should also be noted that patients were excluded from ACTIVE if they had *"use of bisphosphonate for >3 months in the past 5 years or denosumab within the past year,"* and not all patients had a prior fracture at baseline due to the inclusion criteria.[1] For these reasons, the EAG questions whether the whole ACTIVE study population is representative of patients likely to receive romosozumab or teriparatide in clinical practice (see Section 2.3 for further discussion).

4.2.1.2 Interventions and comparators

The intervention included in the company's economic analyses is abaloparatide, which is assumed to be administered via subcutaneous (SC) injection at a dose of 80 µg daily for a maximum duration of 18 months. After stopping abaloparatide, patients are assumed to receive further active treatment with alendronate (a bisphosphonate antiresorptive therapy), administered orally at a dose of 70 mg once weekly for a maximum duration of 60 months (5 years).

The company's economic analyses include two comparators: teriparatide and romosozumab. Teriparatide is assumed to be given via SC injection at a daily dose of 20 µg up to 24 months, whilst romosozumab is assumed to be administered once monthly at a dose of 210mg via SC injection (two injections of 105mg) for up to 12 months. Patients in both treatment groups are assumed to subsequently receive alendronate at the same dosage and duration as for the abaloparatide group.

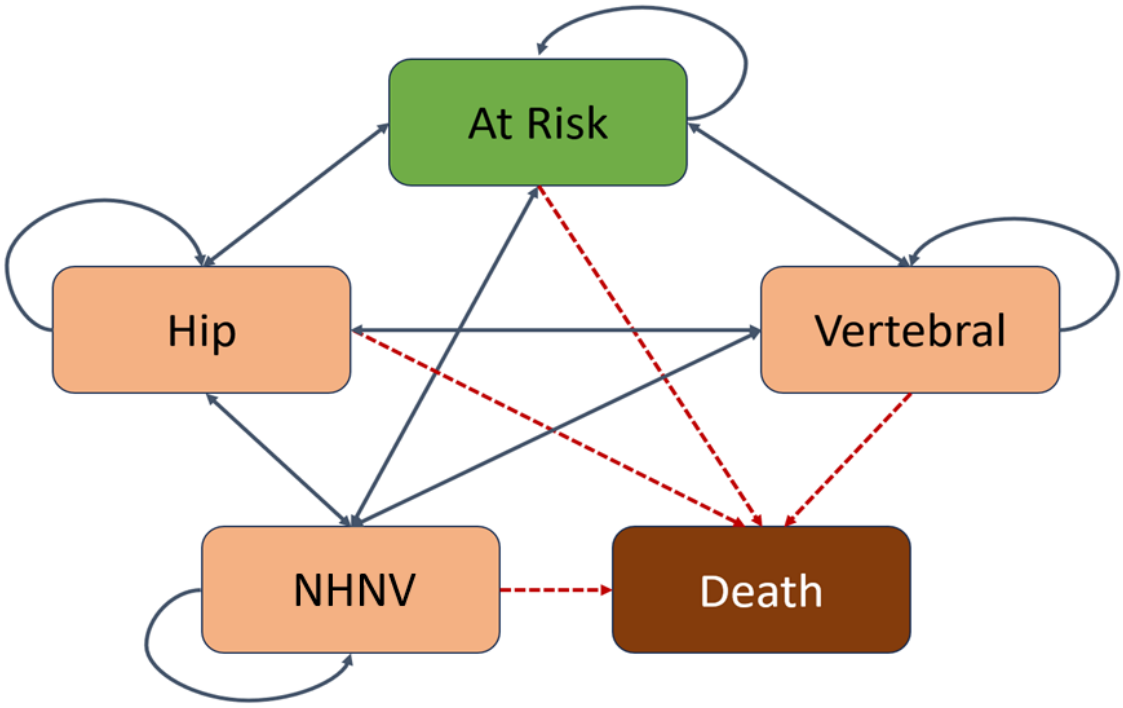
The final NICE scope[59] lists other comparators, divided in three groups: (i) bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium, and zoledronic acid); (ii) non-bisphosphonates (denosumab, strontium ranelate, raloxifene); and (iii) no active treatment. According to the CS,[1] the bisphosphonates options and denosumab were excluded from the economic analyses as they would not be appropriate comparators to abaloparatide, since antiresorptive agents would form part of the treatment sequence rather than replacing anabolic therapy. Strontium ranelate, raloxifene and no active treatment were not considered appropriate comparators by the company for different reasons, respectively: no longer used in UK clinical practice, not used in women at very high risk of fracture, and teriparatide and romosozumab being the relevant comparators in this population. The EAG's concerns about the comparators included in the company's economic analyses are further discussed in Section 2.3.3 of this report.

4.2.2 Model structure

The general structure of the company's model is presented in Figure 17.[58] The model adopts a state-transition patient-level microsimulation approach, with a structure which is comprised of four alive mutually-exclusive health states: at risk of fractures, hip fracture, vertebral fracture, and non-hip-non-vertebral (NHNV) fracture. The model also includes an additional state for death. It should be noted

that whilst one of the health states is named 'at risk of fractures,' patients are at risk of fracture in all states except the death state.

Figure 17: Company's model structure (reproduced from the CRCQ2 appendix, Figure 10)[58]



NHNV: non-hip-non-vertebral

The model logic operates as follows. Patients enter the model in the 'at risk of fracture' health state and receive treatment with either abaloparatide, teriparatide or romosozumab. The model tracks each patient individually within the model, where the initial characteristics and state occupation and events are processed by a set of calculations based on uniformly distributed random numbers and data distributions for each parameter (see section 4.2.4). For any time *t*, patients can either remain at the 'at risk' state or transition to one of the states related to a type of fracture (hip, vertebral and NHNV), or die (absorbent state). In the latest version of the model submitted at CRCQ2, the number of fractures a patient can incur is limited to two hip fractures, four vertebral fractures and ten NHNV fractures (CRCQ2, question B1).[57, 58] There are no restrictions to the order of the fractures incurred; patients who have had a fracture return to the 'at risk' state after one cycle unless they incur a new fracture or die. The company justified the choice of approach by its ability to capture an individual patient's fracture risk based on their history of events including the possibility for recurrent events which are characteristic of chronic conditions such as osteoporosis.[25] The company also mentions that this structure was based on the model structure from NICE TA791,[3] which is aligned with the International Osteoporosis Foundation (IOF)/European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) guidelines for osteoporosis modelling, and was previously validated under the NICE Preliminary Independent Model Advice (PRIMA) process.[58]

In the model, the risk of death captures both all-cause mortality and fracture related deaths, and is given by the age and sex-matched mortality risks of the general population in the UK and an increased risk related to the event of hip and vertebral fractures based on relative risks (RR) from van Staa *et al.* (2007).[14] These are described in detail in section 4.2.4.2.

The probability of incurring a hip, vertebral or NHNV fracture at any time *t* is given separately by: (i) the risk of fractures in the general population; (ii) an increased risk of fractures relative to the general population associated with the individual's baseline characteristics, calculated based on the FRAX algorithm;[60] (iii) an increased risk of subsequent fractures for individuals, after the occurrence of an incident fracture based on age- and gender-matched RRs from the literature which are described as capturing the 'imminent risk';[61] and (iv) a reduction in the risk of fractures related to the treatment effect. These are described in more detail in section 4.2.4.3.

Treatment discontinuation is included in the model by the estimated 6-month probabilities of remaining on treatment (treatment persistence) for each assigned therapy, based on a UK-based RWE study (Arden *et al.*),[62] and discontinuation rates from Söreskog *et al*. (2021a and 2021b)[55, 56] and Morley *et al*.[63] These are detailed in section 4.2.4.4.

HRQoL is assumed to be determined by a combination of age- and sex-matched general population utilities (Hernández Alava *et al*. 2022),[64] and a fracture-related utility multiplier that captures the impact of fractures which is based on estimates from the literature (ICUROS study).[65] This fracture-related multiplier depends on the number and type of fractures experienced and whether they occurred more than 1 year previously. The company's updated analyses do not explicitly include HRQoL losses associated with treatment AEs (CRCQ1, question B54).[26]

The model includes costs associated with: (i) drug acquisition and an initial administration of treatment during which the patient is trained to self-administer; (ii) drug acquisition for subsequent treatment with alendronate; (iii) disease management (follow-up and monitoring); and (iv) fracture-related costs (short and long-term costs including new admissions to a long-term care facility). Costs related to management of AEs were not included in the model. Costs are described in detail in Section 4.2.4.5.

The analyses presented in the CS,[1] CRCQ1 and CRCQ2 appendices[25, 58] and in this EAG report include the confidential Patient Access Scheme (PAS) price for abaloparatide and list prices for other drugs included in the model, which is consistent with NICE guidance. Results of key analyses using the discounted prices for the other drugs are presented in a confidential EAG addendum to this report.

The incremental health gains, costs and cost-effectiveness for abaloparatide versus teriparatide and romosozumab are estimated using 6-monthly cycles over a lifetime time horizon (up to 50 years – from patient's starting age until patient's death or until patients reach 100 years old, whichever comes first). Half-cycle correction is not applied in the model (CRCQ1, question B53).[26] No subgroup analyses are presented in the CS or in CRCQ1 or CRCQ2 appendices.[1, 25, 58]

4.2.3 Key assumptions employed in the company's model

- A cohort of patients with heterogeneous characteristics is simulated and each patient's progress through the model is simulated once for each treatment option. The events the patient experiences are dependent on a set of random numbers which is maintained across treatment arms so that differences between the treatment arms only occur due to differences in treatment effectiveness or persistence.
- The modelled comparisons against romosozumab and teriparatide are assumed to be generalisable to patients who are treatment naïve or have received prior treatment with bisphosphonates as per the proposed positioning of abaloparatide (see CS, Figure 5).[1]
- The model assumes no changes are made to the patient's attributes (e.g. risk factors) between fracture events, with exception of age which, increases by 0.5 years each cycle, and T-score, which is assumed to decline by 0.021 SDs per cycle until the minimal value in the scale (-4.0 SD) is reached.
- The model includes hip, vertebral and NHNV fractures and deaths as the main clinical events; the different types of fractures are modelled as independent events. In the latest version of the model submitted, the number of fractures patients can experience was limited to two hip fracture, four vertebral fractures and ten NHNV fractures (CRCQ2, question B1).[57]
- There are no constraints on the sequence in which the fractures can occur.
- Fracture risks are dependent on the patient's baseline characteristics, and are therefore heterogeneous within the cohort, and are updated according to age, BMD and incident fractures during the individual's lifetime.
- Both all-cause mortality and fracture-related mortality are included. An increased risk of death following hip or vertebral fracture is applied for 6 months following an incident fracture (CRCQ2 question B16).[57]
- Reductions in fracture risks due to anabolic treatment are assumed to apply in full for the duration of the anabolic therapy, and in patients competing anabolic therapy, for the duration of follow-on antiresorptive treatment (alendronate).[58]
- A treatment benefit is also assumed to be applied for a period after patients discontinue therapy known as the offset period. In the company's base-case, the offset period is assumed to be equal to the duration of the total treatment received including both anabolic and follow-on

antiresorptive treatment. A linear reduction in the treatment effect is assumed during the offset period until there is no remaining treatment effect at the end of the offset period.

- The model includes stopping rules for all drug therapies, whereby patients who are still receiving them at the maximum treatment duration point are assumed to discontinue therapy at: 18 months for abaloparatide, 24 months for teriparatide, 12 months for romosozumab, and 60 months for alendronate.
- Patients may discontinue treatment (i.e. become non-persistent with treatment) before reaching the maximum duration of treatment. Treatment persistence is modelled jointly for the initial and subsequent therapies (see section 4.2.4.4).
- Maximum duration of treatment and persistence rates for patient receiving follow-on treatment with alendronate were assumed to be the same for all treatment groups.
- The model is not half-cycle corrected therefore all events are assumed to occur exactly at the start of a new cycle.
- The model does not allow for drug wastage as a result of patients dying or becoming non-persistent with treatment mid-cycle.
- The model includes 6-monthly costs associated with disease management which were assumed to be the same for all treatment groups, and to be applied only whilst patients are receiving treatment.
- Costs associated with the first administration in which patients are taught to self-administer are described as being included as a one-off cost for all patients receiving abaloparatide, teriparatide and romosozumab (CRCQ2 question B19).[57] Patients receiving alendronate are assumed not to incur any administration costs.
- The model assumes patients experiencing fractures incur treatment costs related to acute care such as hospitalisations in the first-year post-fracture for all fracture types; for hip and vertebral fractures costs associated with chronic symptoms are assumed to be incurred in the second year after fracture and to continue until the patient dies.
- Patients experiencing a hip fracture are assumed to be at risk of a new admission to long-term care (e.g. residential or nursing care). These costs are unaffected by the occurrence of subsequent fractures and are incurred in addition to acute fracture costs occurring in the first and subsequent years after hip fracture.
- HRQoL is determined by age and fracture history and not by treatment received.
- Patients not experiencing any incident fractures are assumed to have the same HRQoL as age- and sex-matched members of the UK general population.
- Patients experiencing incident fractures are assumed to experience a HRQoL reduction in the first year after fracture (acute multiplier), and a continued but smaller HRQoL reduction in

subsequent years (chronic multiplier); they are assumed never to return to the same HRQoL as the general population.

- The model does not account for losses in HRQoL in patients who are institutionalised after hip fractures, nor in patients who have a prior fracture at baseline.
- The impact of AEs on costs or QALY losses are not included in the company's model, and therefore are assumed to impact all treatment groups similarly.

4.2.4 Evidence used to inform the company's model parameters

Table 32 summarises the evidence sources used to inform the model's parameters in the company's base case analyses. These are discussed in detail in the subsequent sections.

Table 32: Summary of evidence used to inform the company's model parameters

Parameter group	Parameter	Source
Patient characteristics	Age	Patients in the abaloparatide treatment arm enrolled in ACTIVE study[5] (mITT population, excluding sites 131 and 132 of the study). T-score annual variation based on Stevenson *et al.*[66]
	FRAX characteristics at baseline	
Mortality	General population mortality	Age- and sex-matched mortality rates from National life tables for the UK population 2018-2020.[67]
	Excess mortality related to fractures	Relative risks capturing the excess mortality related to hip and vertebral fractures based on van Staa *et al*.[14]
Risk of fractures	Risk of fractures in general population	Fracture incidence rates by fracture type from Singer *et al*.,[68] Kanis *et al*. (2000)[69] and NICE previous appraisal for romosozumab (TA791).[3]
	Increased risk of fracture for modelled population relative to general population	RRs estimated from 10-year probability of hip and major osteoporotic fractures obtained from the FRAX algorithm, applied to baseline risk of fracture of the general population.
	Risk of imminent fractures after incident fracture	RRs by age group, number of previous fractures and type and time since first fracture estimated from Söreskog *et al*. (2020)[61]
	Risk reduction due to treatment effect	Treatment-specific HRs obtained from the company's updated NMA (CRCQ2).[58]
Treatment persistence		Treatment persistence estimated based on data from Arden *et al.*, Söreskog *et al.*(2021a and 2021b)[55, 56] and Morley *et al.*[63]
HRQoL	General population and 'at risk' state utilities	Age- and sex-matched general population utilities based on published UK values from Hernández Alava *et al.*[64]
	Utility multipliers for fracture states (hip, vertebral and 'other')	Utility multipliers for first and for second and subsequent years after fracture occurrence were taken from the ICUROS study.[65]
	QALY losses related to AEs	Not included.
Costs	Drug acquisition – initial treatment (abaloparatide,	Unit costs from manufacturer[1] and BNF;[70] dosing schedules from SmPCs[2, 71, 72] and assumption.

Parameter group	Parameter	Source
	teriparatide and romosozumab)	
	Drug acquisition – subsequent treatment (alendronate)	Unit cost from BNF,[70] dosing schedule from SmPC.[73]
	Drug administration costs – all groups	Unit cost from PSSRU 2022,[74] and assumption.
	Disease management costs – follow-up and monitoring	Frequencies from NICE appraisal TA791[3] and Borgstrom *et al.*[75] and assumptions. Unit costs taken from NHS Reference Costs 2021/22,[76] PSSRU 2022[74] and NICE TA791.[3]
	Costs of fractures – acute care	Annual costs for the first and subsequent years of care by fracture type taken from Gutierrez *et al.*[77, 78] and Davis *et al.* (2015)[35] and assumption; values were uplifted to 2023 using Consumer Price Index (CPI).[79]
	Costs of fractures – long term	Proportion of patients receiving institutionalized long-term care based on NICE previous appraisal TA464.[35] Unit costs from PSSRU 2022.[74]
	AEs costs	Not included.

Abbreviations: AE - adverse event; CPI, consumer price index; HR - hazard ratio; ICUROS - International Costs and Utilities Related to Osteoporotic Fractures Study; IFO - International Osteoporosis Foundation; NMA - network meta-analysis; ONS - Office for National Statistics; PSSRU - Personal Social Services Research Unit.

4.2.4.1 Patients' characteristics

The patients' baseline characteristics are informed by the patients enrolled into the abaloparatide treatment arm in the mITT population of the ACTIVE study[5] (excluding sites 131 and 132 of the study). The model assumes all patients are females with a mean age of 69.5 years (constrained to between 50 and 100 years). Patients are assumed to have a baseline femoral neck T-Score of -2.19 SD. The other risk factors that can be present at baseline are history of previous fractures, prior use of glucocorticoids, smoking status, alcohol use status and rheumatoid arthritis. Table 33 summarises the baseline characteristics included in the model (based on Table 19 of the CRCQ2 appendix).[58] The patient characteristics at baseline are sampled independently, meaning that any possible correlations between patient characteristics will not be captured. The model considers different combinations of age, femoral neck T-score and the number of various independent clinical risk factors present to determine the risk of fractures using the Fracture Risk Assessment Tool (FRAX, see Section 4.2.4.3). Once the patient characteristics have been sampled at baseline, the only characteristics that are updated during the model are age and the T-score, regardless of the treatment being simulated and the occurrence of fractures. The initial T-score is assumed to decline 0.021 SDs per cycle until the minimal value in the scale (-4.0 SD) is reached, based on the annual variation on the average T-score for patients 50 to 89 years from Stevenson *et al.*[66] (NB: The need to have a minimum T-Score value of -4.0 appears to be due to the company using the paper tables for FRAX which only provide results for a limited set of scenarios, whilst the online FRAX calculator provides differing results for -4.0 versus lower T-Scores). The EAG

notes that the company's approach to estimating the T-Score decline per annum results in a decline of 0.0419 per annum, whereas the data from Stevenson *et al.* show a decline of 0.0512 per annum.[66]

Table 33: Baseline patient characteristics in the model base case (adapted from Company's CRCQ2 appendix, Table 19*)[25]

Baseline characteristics' parameter	Mean Value
Gender (female, %)	100.00
Mean age (years)	69.50
Mean femoral neck T-score	-2.19
Any prior fracture (%)	58.50
Tobacco use status (used tobacco in the past 5 years, %)	12.10
Prior glucocorticoid use (%)	1.30
Rheumatoid arthritis (%)	0.30
Alcohol use status (≥ 3 units/day, %)	0.10

**Table 19 of the CRCQ2 Appendix includes other baseline characteristics that are not directly used in the model, which were therefore omitted here.*

4.2.4.2 Mortality

In the 'at risk' health state, patients are assumed to experience the same age- and sex-matched mortality risks as the general population in the UK. The UK's age and gender-specific all-cause mortality rates were taken from recently published lifetable data from ONS (UK National lifetables 2018–2020).[67]

When patients experience a hip or vertebral fracture, an increased risk of death related to the occurrence of fractures is assumed to be incurred for one cycle from the point of fracture occurrence (CRCQ2, question 16 and appendix).[57, 58] The company modelled the increased mortality risk by applying a fracture type-specific RR of death, compared with the non-fractured population, to the general population all-cause mortality risk. (CRCQ2, question 15 and appendix).[57, 58] The excess mortality rates related to hip and vertebral fractures used in the updated version of the model submitted upon CRCQ2 to estimate the RRs are presented in Table 34, which were sourced from van Staa *et al.*[14] and were also used in Davis *et al.*(2020).[9]

Table 34: Excess mortality risks by fracture type used in company's model (adapted from CRCQ2 appendix, Table 28)[58]

Age group (years)	Excess mortality risks (%)		
	Hip	Vertebral	NVNH
50–59	2.4	2.3	0
60–69	4.4	3.5	0
70–79	7.5	5.2	0
80–89	11.4	6.7	0
≥90	13.6	6.6	0

NHNV, non-hip, non-vertebral

The approach chosen by the company to incorporate increased risks of death only for hip and vertebral fractures was based on the ESCEO/IOF guidelines[19] recommendation, due to lack of evidence on NHNV fractures. Similar approaches were used in NICE TA464,[22] Davis *et al.* (2020)[9] and TA791 (the latter after company's response to clarification),[3] where an increased risk of death following hip and vertebral fracture and no increased risk for fractures at other sites were assumed. The EAG notes that one of the clinicians consulted by the EAG mentioned that the mortality risk could be higher after other fractures occur, especially after fractures of femoral shaft or pelvis. This issue is further discussed in Section 4.3 (Issue 17). The company presents a scenario analysis where the increased risk of mortality is applied only to hip fractures (see Section 4.2.6.4).

The EAG also notes that in the original model submitted by the company at CS,[1] the total mortality risk also included a comorbidity adjustment factor, based on the ESCEO/IOF recommendations on the conduct of economic evaluations in osteoporosis, to account for the fact that it is estimated that only around 30% of the excess mortality following fracture is attributable to the fracture.[19] This approach was also used in NICE TA791.[3] However, the company's updated model after CQ2 used the excess mortality risks from van Staa *et al.* which have already been adjusted for comorbidity. Therefore this adjustment has been removed by the company at CRCQ2 (question B15 and appendix).[57, 58]

4.2.4.3 Risk of fractures

The model calculates separately the total risk of fractures for each type of fracture (hip, vertebral and NHNV). The model submitted by the company follows a similar structure to Söreskog *et al.* (2021a and 2021b)[55, 56] regarding the risk of fractures, where the risk of incurring a fracture in an individual patient is based on four different factors:

a) The baseline risk of fractures for the general population;
b) An increased risk of fractures for the modelled population (i.e. a population at high risk of fracture) compared to the baseline risk in the general population, based on the patient's individual risk of fracture as estimated by the FRAX algorithm;[60]
c) An increased risk of fracture following an incident fracture (described as capturing 'imminent risk'), based on the number of previous fractures and time since the incident fracture;[61] and
d) A reduction in the risk of fractures associated with the drug therapy received.

The multiplicative approach to calculate the total risk of factor is summarised by the following formula, adapted from the CRCQ2 appendix:[58]

$$Total\ risk\ of\ fracture\ in\ individual\ patient = Baseline\ risk_{general\_population} * RR_{frax_{nofx}} * MAX\ (RR_{frax_{fx}}, RR_{imminent}) * HR_{treatment\_benefit}$$

Where:

RR_{frax_nofx} = RR estimated from the absolute risk calculated by FRAX for individual patient's characteristics excluding prior fracture as a clinical risk factor, compared to the absolute risks for the general population

RR_{frax_fx} = RR associated with any prior fracture; calculated as the FRAX risk for an individual with the patient's characteristics including prior fracture as a clinical risk factor, compared to the FRAX risk for a patient with the same characteristics excluding prior fracture as a clinical risk factor.

$RR_{imminent}$ = RR of an imminent fracture based on the excess risk of having a new fracture after the occurrence of one, two or three previous fractures of the same or other types.

$HR_{treatment\_benefit}$ = HR for treatment versus placebo

It should be noted that when calculating the increased risk of fracture for the modelled population compared to the general population (i.e. RR_{frax_nofx}), the risk attributable to prior fracture at baseline is excluded to avoid double counting this risk when an incident fracture occurs, as this is reflected by applying either RR_{frax_fx} or $RR_{imminent}$, whichever is largest.

In the latest version of the model submitted by the company (CRCQ2, question B1 and appendix),[57, 58] the number of fractures a patient can experience is limited to two hip, four vertebral and ten NHNV fractures, but there are no constraints on the sequence in which these fractures occur. This approach is in line with the approach described in TA464[22] and Davis *et al.* (2020),[9] where the model evaluating non-bisphosphonates limited the maximum number of fractures that could be experienced to *"one per bone (i.e. two hip fractures), with an additional limit of four vertebral fractures, four rib fractures and two pelvic fractures."*

Risk of fractures in the general population

The CRCQ2 appendix[58] reports the risk of fractures in the general population as being based on incidence data of hip, vertebral and NHNV fractures from Singer *et al*.[68] and Kanis *et al.* (2000)[69] The overall incidence of fractures and the per cycle probability of incurring a fracture used in the model by age group and type of fracture are shown in

Table **35**. The approach is described by the company as being similar to those used in NICE TA791[3] and Hernlund *et al*.,[80] the latter being a report published by the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA).

Table 35: Incidence of fractures per 100,000 people in the UK and per cycle probability by age group used in the model, per fracture type (adapted from Table 20 in CRCQ2 appendix and model)[58]

Age group	Incidence of fractures (annual, per 100,000 people)			Probability of incurring a fracture (per cycle)		
	Hip	Vertebral	NHNV*	Hip	Vertebral	NHNV*
50-54	33	84	633	0.0014	0.0050	0.0069
50-59	51	142	813	0.0022	0.0085	0.0089
60-64	81	143	979	0.0035	0.0086	0.0108
65-69	132	192	1,425	0.0057	0.0116	0.0159
70-74	282	397	1,928	0.0123	0.0245	0.0218
75-79	619	602	2,891	0.0279	0.0382	0.0334
80-84	1,236	777	3,876	0.0594	0.0506	0.0459
85+	2,255	1,061	5,958	0.1229	0.0721	0.0748

NHNV – non-hip, non-vertebral
** NHNV fractures includes forearm fractures (distal forearm, distal radius and wrist) and "other" fractures (femur, pelvis, humerus, rib, clavicle, scapula, sternum) (CRCQ1, question B8 and appendix).[25, 26]*

The EAG notes that, although previously used in TA791 and Söreskog *et al.* (2021),[56] it is unclear how the estimates for hip fractures were originally estimated from the data presented in Singer *et al*.[68] Nonetheless, the values presented in

Table **35** are reported in Svedbom *et al*.,[81] even though it is unclear if this would be the original source of the data used by the other models.

The CS[1] and CRCQ1 and CRCQ2 appendices[25, 58] also report that for vertebral and NHNV fractures, due to the lack of data from the UK, estimates were obtained, respectively, by: (i) applying the ratio of vertebral to hip fractures in the Sweden population from Kanis *et al.* (2000)[69] to the incidence of hip fractures in the UK; and (ii) combining the incidence of forearm fractures in the UK from Singer *et al.* to the ratio of 'other fractures' and hip fractures in the Sweden population obtained from Kanis *et al.* to the incidence of hip fractures in the UK.[68, 69] The company also clarified in response to CRCQ1 question B8 that forearm includes *"distal forearm, distal radius and wrist"* fractures, and "other" fractures include *"femur, pelvis, humerus, rib, clavicle, scapula and sternum*" fractures.[25]

Increased baseline risk of fractures associated with osteoporosis

The increased risk of fractures associated with osteoporosis is modelled using the FRAX assessment tool, an algorithm-based tool available online which generates the 10-year probability of hip and major osteoporotic fractures based on a number of personal and clinical characteristics, such as age, sex, BMD at the femoral neck (T-Score), and a combination of clinical risk factors (history of prior fractures, smoking and alcohol consumption status, use of glucocorticoids, and diagnosis of rheumatoid arthritis).[60] The FRAX algorithm also includes parental history of hp fracture and secondary osteoporosis but the company does not include these risk factors in the model due to a lack of information on their prevalence in the ACTIVE cohort (CRCQ1 B6 and CRCQ2 Appendix p41). The company's model includes the calculations of the increased risk of fractures via two separate factors: RR_{frax_nofx} and RR_{frax_fx}.

RR_{frax_nofx} corresponds to the increased risk relative to the general population, for the individual patient based on their baseline characteristics and CRFs excluding prior fracture. The company used the 10-year absolute risks of hip and major osteoporotic fractures generated by FRAX by age groups, number of CRFs (excluding previous fracture, 0 to 4) and BMD T-score (from -4.0 SD to 1.0 SD by increments of 0.5 SDs) and compared these to the absolute risk in the general population from FRAX based on average T-scores in the general population from Stevenson *et al.*,[66] assuming no presence of CRFs and the same age group and T-score, to estimate RRs for each type of fractures per cycle (CRCQ2, question B2).[57] The absolute risks generated by FRAX for the general population is shown in Table 36.

The model also assumes that the risks of major osteoporotic fractures are equally applicable to vertebral and NHNV fractures when using the FRAX algorithm to adjust general population risks to those expected in the modelled population. The estimated RR_{frax_nofx} are then applied to the general population baseline risk of fractures, generating an adjusted risk of fractures per cycle.

Table 36: Average T-scores and absolute risks of fractures in general population in the UK by age group used in the model, per fracture type (adapted from CRCQ2 Table 21 and model)[58]

Age group	Average T-score	Absolute 10-year risk (%)		
		Hip	Vertebral*	NHNV*
50-54	-0.66	0.1	3.3	3.3
50-59	-0.92	0.2	4.1	4.1
60-64	-1.17	0.4	5.4	5.4
65-69	-1.43	0.6	7.0	7.0
70-74	-1.69	1.4	9.2	9.2
75-79	-1.94	2.0	9.9	9.9
80-84	-2.2	4.2	13.0	13.0
85-89	-2.45	5.7	15.0	15.0
90+	-2.45	6.0	14.0	14.0

NHNV – non-hip, non-vertebral
** The absolute risk of fractures for major osteoporotic fractures is assumed to be applicable to vertebral and NHNV fractures*

RR_{frax_fx} corresponds to the increased risk of fractures taking into account the presence of an additional CRF (previous fracture), relative to the risk for an identical patient excluding prior fracture in the CRF count, using estimates of absolute risks from FRAX using individual patient's characteristics. In the version of the model submitted at CRCQ2,[58] RR_{frax_fx} is included from the point a fracture of any type is experienced, where the maximum risk between RR_{frax_fx} and the imminent risk of fractures ($RR_{imminent}$) is applied.

Imminent risk of fracture

The company also included in the model estimates of individual imminent risk of fractures, intended to capture the increased risk of a subsequent fracture in the first five years after the occurrence of a prior fracture. Age- and gender-matched RRs for the risk of major osteoporotic fractures after having one, two or three fractures of the same type were obtained from Söreskog *et al.* (2020)[61] This retrospective observational cohort study included data from women aged ≥50 years from the Swedish National Patient Register who had incurred at least one previous fragility fracture, and estimated the adjusted risk of subsequent major osteoporotic fracture by number of previous fractures (1-3) compared with no fractures, by index fracture site and time since index fracture. The adjusted risks were included in the model as RRs from the point a fracture of any type occurs and are updated as the patient ages and every time a fracture occurs. The formula used to estimate fracture risks take the maximum of either $RR_{imminent}$ or RR_{frax_fx}. This maximisation ensures that as the $RR_{imminent}$ wanes over time, the increased fracture risk attributable to having a prior fracture never wanes below that predicted by the FRAX algorithm.

The EAG notes that in the updated version of the model submitted at CRCQ2 and in response to CRCQ2 question 7,[57, 58] the imminent risk of fracture is not limited to the particular site of the previous fracture and any previous fracture increases the risk of hip, vert, and NHNV fractures.

Treatment effect

A reduction on the risk of fractures related to the treatment received is included in the model, by applying HRs for each drug therapy (abaloparatide, romosozumab and teriparatide) to the risk of fracture estimated for the individual based on their characteristics and fracture history. In the company's updated base-case submitted at CRCQ2, the HRs were obtained from the company's updated NMA (see section 3.10),[25, 26] and HRs for the initial therapies are assumed to be applicable during the whole period of treatment (initial treatment with anabolic therapies plus period of subsequent therapy with alendronate). This approach is based on the clinical opinion from six key opinion leaders (KOL) consulted by the company in January 2024 and presented as supplementary evidence at CRCQ2. These KOL stated that the treatment benefit experienced in terms of improvement in BMD and bone biomarkers (surrogates for reduction in fracture risk) would be maintained whilst patients receive alendronate.[58]

The model also assumes a residual treatment effect which applies for an additional period after the patient discontinue therapy (referred to as the offset period). This is a usual feature of cost-effectiveness models for osteoporosis, which intends to capture the fact that any bone remodelling occurring during treatment does not immediately reverse the day that treatment stops (Hiligsmann *et al.*).[19] In the base-case analysis, the company applies a dynamic approach, where the treatment effect declines linearly for the same amount of time that the patient has received treatment (e.g. patients discontinuing treatment after 3 years observe a declining effect for another 3 years whereas those receiving 5 years of treatment observe a declining effect for another 5 years).

The company also presents three scenario analyses where: (i) an alternative approach for the offset period is applied which uses a fixed duration regardless of the length of treatment actually received, equivalent to the maximum treatment duration for both initial and subsequent therapies (6.5, 7 and 6 years for abaloparatide, teriparatide and romosozumab, respectively); (ii) alternative HR estimates are used for abaloparatide and teriparatide based on the 18-month data from ACTIVE[5] and for romosozumab from the FRAME study 12 month follow-up,[82] and the HRs for the initial therapies are assumed to be applicable during the whole period of treatment; and (iii) the HR estimates from the company's NMA are applied with separate HRs applied for alendronate during the period of alendronate treatment and for the offset period. The HRs used in the base-case and scenario analyses are presented in

Table 37

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The company notes in the updated description of the scenario analyses that, due to the lack of hip fracture events in the ACTIVE trial and to ensure consistency across the treatment groups, for this fracture type the treatment effect on major non-vertebral fractures (see Table 15) were used as a proxy for all treatment groups (CRCQ2 appendix).[58] This approach would be in line with the ESCEO/IOF guidance for economic evaluations in osteoporosis,[19] which recommends the use, in the absence of efficacy data from treatment for hip or wrist sites, of *"the reduction in non-vertebral or clinical fracture rate with treatment as a surrogate for reduction in hip fracture rate in the base case".* The guidance also recommends that "*This assumption should be tested in sensitivity analyses and observational studies or systematic reviews of multiple RCTs (with preference for using pooled individual level analysis) would be interesting to confirm it."* No sensitivity analyses have been presented by the company specifically regarding this issue.

Table 37: Relative risks for each treatment by fracture type used in the base-case (adapted from on Tables 22 to 24 of the CRCQ2 appendix and model)[58]

Analysis type	Base-case (company's NMA assuming anabolic treatment effect persists during antiresorptive phase)				Scenario 1 (ACTIVE and FRAME studies)				Scenario 2 (company's NMA allowing different treatment effect for antiresorptive phase)			
Fracture type	**Abalop.**	**Terip.**	**Romos.**	**Alend.†**	**Abalop.**	**Terip.**	**Romos.**	**Alend. †**	**Abalop.**	**Terip.**	**Romos.**	**Alend.**
Hip	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0. 670	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertebral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.270	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NHNV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.750	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abalop. – abaloparatide; NHNV – non-hip non-vertebral; NMA – network meta-analysis; Romos. – romosozumab; Terip. – teriparatide.
†In the base-case and scenario 1, the HR values used for the alendronate phase of treatment correspond to the HRs of the correspondent anabolic treatment given as initial therapy. For brevity, these are not shown in the table since already displayed in the correspondent initial therapy's columns.

4.2.4.4 Treatment persistence

Treatment persistence is the term used in the CS to describe the proportion of patients continuing to take the prescribed therapy. A patient becomes non-persistent with treatment if they discontinue treatment for reasons other than finishing the treatment course. All patients are assumed to initiate treatment with one of the anabolic therapies at the first cycle and are at risk of becoming non-persistent (i.e. discontinuing treatment) each subsequent cycle. The model does not allow for patients to stop and restart treatment. Persistence rates used in the updated base-case and scenario analysis at CRCQ2 are presented in Table 38. In the new base-case presented by the company, the rates for abaloparatide and teriparatide were obtained from the observed proportion of patients receiving teriparatide still persisting with treatment at 18 months (79%) in a UK RWE study (Arden *et al.)*.[62] The persistence rates for romosozumab were taken from Söreskog *et al*. (2021a and 2021b),[55, 56] cost-effectiveness studies of romosozumab in Sweden and UK which in turn assumed a persistence rate of 80% for the 12 months of treatment.[55, 56]

A new scenario analysis was presented by the company at CRCQ2, where the persistence rates for abaloparatide and teriparatide were based on the proportion of patients in the randomized population of the ACTIVE trial[5] who did not complete the study (27.2% and 20.4%, respectively). These were assumed to be a proxy for the discontinuation rate at 18 months and a linear extrapolation was assumed to estimate treatment persistence at 6 and 12 months, and at 24 months for teriparatide. The persistence rates for romosozumab in the scenario analysis were the same as in the base-case, i.e. based on the assumption from Söreskog *et al*. (2021a and 2021b).[55, 56] This scenario corresponded to the company's base case in the original submission.

As part of the response[26] to CRCQ1 question B38 around the source choice for romosozumab, the company states that "*The ARCH trial[22] was not used as persistence in clinical trials is known to be significantly higher than in clinical practice, as patients know they are being observed. Söreskog et al. (2021)[32] was therefore used as clinical trial data can overestimate persistence and TA791[4] stated that there were no persistence data from RWE due to the recent UK launch of romosozumab*". The EAG notes that this choice creates inconsistency across the different treatment groups in the approach adopted for the scenario analysis, and that the same issues should affect the estimates for abaloparatide and teriparatide obtained from ACTIVE.

In the model, all patients are assumed to receive alendronate after the initial anabolic therapy if they persist for the maximum duration period of the anabolic therapy. Persistence rates for alendronate for all three treatment groups (CRCQ2 version) are based on data from non-naive patients starting oral bisphosphonates from Morley *et al.,*[63] in the company's base-case analysis. The company also presents a scenario analysis using data from ACTIVExtend, based on linear calculation using the persistence rates at the end of each anabolic therapy and the completion rate of the abaloparatide plus alendronate arm from ACTIVExtend (CQCR2 appendix, Table 26).[58] In response to CRCQ2 question B18,[57] the company states that the updated version of the model no longer assumes that sequential treatment with alendronate is allowed only for patients who received the initial treatment for the maximum duration. However, the EAG disagrees with the company's view on how persistence is currently applied in the model (see more details in Section 4.3.4.3).

Table 38: Persistence rates used for each drug treatments in the company's model base-case and scenario (adapted from CRCQ2 appendix, Tables 25 and 26)

Analysis type	Base-case (CRCQ2)						Scenario analysis (CRCQ2)					
Drug/ treatment group	Abalop.	Terip.	Romos.	Alendronate after			Abalop.	Terip.	Romos.	Alendronate after		
Time (months)				Abalop.	Terip.	Romos.				Abalop.	Terip.	Romos.
6	93.0%	93.0%	80%	–	–	–	[redacted]		80%	[redacted]		
12	87.0%	87.0%	80%	–	–	–			80%			
18	79.0%	79.0%	–	–	–	30.6%			–			
24	–	71.0%	–	30.6%	–	19.2%			–			
30	–	–	–	19.2%	30.6%	14.4%			–			
36	–	–	–	14.4%	19.2%	11.3%			–			
42	–	–	–	11.3%	14.4%	9.0%			–			
48	–	–	–	9.0%	11.3%	8.0%			–			
54	–	–	–	8.0%	9.0%	7.0%			–			
60	–	–	–	7.0%	8.0%	6.0%			–			
66	–	–	–	6.0%	7.0%	5.0%			–			
72	–	–	–	5.0%	6.0%	4.0%			–			
78	–	–	–	4.0%	5.0%	–			–			
84	–	–	–	–	4.0%	–			–			
Source	Arden *et al.*[62]		Söreskog *et al*. (2021a and 2021b)[55, 56]	Morley *et al.*[63]			ACTIVE study[5]		Söreskog *et al*. (2021a and 2021b)[55, 56]	ACTIVExtend study[28]		

Abalop. – abaloparatide; Romos. – romosozumab; Terip. – teriparatide.

Data on persistence for each drug treatment is applied as the cumulative risk of remaining on treatment in each cycle. Treatment costs are assumed to be applied up to the point that patients discontinue, but the risk of fracture continues to be reduced during the offset period that follows (see Section 4.2.4.3). As a dynamic offset period is applied, the offset period is shorter for those who discontinue treatment early. The EAG notes that in the original version of the model submitted by the company at CS, persistence was sampled independently each cycle, which led to some potential inconsistencies such as patients who have already discontinued being sampled as persistent at later time point. This error was fixed by the company in the version submitted at CRCQ1 (CRCQ1, question B39).[25, 26] The EAG also flagged that persistence rates for the three treatment groups was being sampled based on the same common random number (CRCQ2 question B17).[57] The company has reiterated their view that this is appropriate in CRCQ2 but included a scenario analysis where different random numbers are used to sample persistence for each of treatment groups.[58] The company has also included a scenario analysis where persistence rates are removed from the analysis (see Section 4.2.6.4).

4.2.4.5 HRQoL

The ACTIVE and ACTIVExtend trials did not collect HRQoL data, and the company reported that none of the studies identified in the SLR were suitable sources for utility values for the model (See Section 4.1.3). Therefore, the company's economic analysis used a similar approach to TA791,[3] where utility multipliers for fractures from the ICUROS[65] study were used as the main source of HRQoL data, which were combined with general population utility values from Hernández Alava *et al.*[64]

The ICUROS study is an osteoporosis research project that was carried out across 11 countries (including the UK) and involved over 5,400 participants, which aimed to estimate the impact of fractures on patients' HRQoL and costs. Svedbom *et al.*,[65] one of the resulting publications from the study, estimated the impact on HRQoL of hip, vertebral, or distal forearm fractures and explored the determinants of accumulated HRQoL loss by fracture type. The EQ-5D-3L was used to evaluate the impact of fractures on HRQoL at different time intervals, including immediately after the fracture, regardless of treatment, and at 4 months, 12 months, and 18 months post-fracture. In the updated version of the model submitted at CRCQ1 and CRCQ2, utility multipliers for the initial year and subsequent years post-fracture were based on the utility multipliers for 0-12 months and subsequent years in the study (CRCQ1 question B42),[26] respectively. The EAG notes that the model assumes that the multiplier for 'distal forearm fracture' is a proxy for the impact of NHNV fractures.

The EAG has concerns regarding the company's searches, as it is unclear how the ICUROS study has been retrieved by the SLR. These concerns were addressed in more detail in Section 4.1.3. Nonetheless, the company has included data from ICUROS study as the main source of HRQoL data in the model. These values were also used by Söreskog *et al.* (2021a and 2021b)[55, 56] and by Davis *et al.* (2020),[9]

which evaluated the cost-effectiveness of romosozumab and non-bisphosphonates (denosumab, raloxifene, romosozumab and teriparatide), respectively. The utility multipliers applied in the company's model and in key previous appraisals (except TA791 which were described as being based on ICUROS but were redacted), are summarised in Table 39. The EAG is satisfied with the company's choice of utility multipliers which are consistent with those applied by Davis et al. (2020).

Table 39: Utility multipliers used by the company and in key previous appraisals in osteoporosis*

Health state	Company's model	ID901 Non-bisphosphonates (Davis *et al.* 2020)	TA464 Bisphosphonates (Davis *et al.* 2016)
First year			
Hip	0.55	0.55	0.69
Vertebral	0.68	0.68	0.57
NHNV	0.83	Humerus: 0.78 Distal forearm: 0.83	Shoulder: 0.86 Wrist: 0.88
Subsequent years			
Hip	0.86	0.86	0.85
Vertebral	0.85	0.85	0.66
NHNV	0.99	Humerus: 1.00 Distal forearm: 0.99	Shoulder: 1.00 Wrist: 0.98

NHNV – non-hip non-vertebral
** Utility data used in TA791 were redacted*

In the CRCQ2 version of the model, the utility multipliers for each type of fracture are applied in the model to the UK general population utility values by age estimated by Hernández Alava *et al*.[64] (CRCQ2, question B13).[57] The utility multipliers are assumed to be independent of treatment group and to reflect the impact of different fracture types in the first year and in subsequent years after a fracture occurrence. Patients in the 'at risk' health state who have not incurred any fractures are assumed to experience the same age- and sex-matched general population utilities from Hernández Alava *et al.*.[64] For patients who have incurred at least one fracture, the corresponding utility is applied depending on the type of fracture and time since the fracture occurred.

For multiple fractures, according to the company's response to CRCQ1 question B46,[26] the model was intended to account for disutility of multiple fractures of the same type by using a multiplicative approach, whilst using a maximum disutility approach to account for different fracture types. The EAG notes that in the updated version of the model submitted at CRCQ2,[58] a multiplicative approach is used

to account for the cumulative impact of different types of fractures, whilst a second fracture of the same type does not impact on the total disutility.

The model does not include any HRQoL decrements associated with AEs for abaloparatide, teriparatide, romosozumab or alendronate. The model also does not include any utility decrement for patients admitted to long-term residential or nursing care following hip fracture, which has been included in previous cost-effectiveness analyses[9] (see Section 4.3.4.2, issues 11 and 16)

4.2.4.6 Resource Costs

The model includes costs associated with: (i) drug acquisition and an initial administration of treatment during which the patient is trained to self-administer; (ii) drug acquisition for the subsequent treatment with alendronate; (iii) disease management (follow-up and monitoring); and (iv) management of fractures (acute care for first and subsequent years, and long-term care at residential or nursing care facilities). Costs related to the management of AEs are not included in the model. Table 40 and Table 41 summarise the costs applied within the model.

Table 40: Summary of drug acquisition, follow-up costs and adverse events costs applied in the company's model by treatment arm

Cost parameter	Therapy/fracture type	Abaloparatide	Teriparatide	Romosozumab
Drug acquisition costs (per 6-months cycle)*	Initial therapy	List price: £1,865 With PAS: [redacted]	List price: £1,767	List price: £2,566.50
	Subsequent therapy (alendronate)	£13	£13	£13
Drug administration costs (one-off cost)	Initial therapy only	£12	£12	£12
Disease management – follow-up and monitoring (per 6-month cycle)	Both initial and subsequent therapies	£17	£17	£17
Grade 3+ AEs (once-only)	Any therapy	Not included	Not included	Not included

NHNV - non-hip non-vertebral; PAS - Patient Access Scheme; AE - adverse event
**Drug acquisition costs do not include RDI adjustments or wastage*

Table 41: Summary of fracture costs applied in the company's model (same across all treatment arms)

Cost parameter (per 6 month cycle)	Hip	Vertebral	NHNV
Acute care in the first year after fracture (two cycles)	£7,790	£1,706	£1,192
Acute care for subsequent years (until death)	£68	£218	£0
Long-term care costs for patients newly admitted to long-term care following fracture (until death)	£33,739	Not included	Not included

Drug acquisition and administration costs – initial therapy

Drug acquisition costs for abaloparatide, teriparatide and romosozumab are modelled as a function of the planned treatment doses and frequency schedules based on each drug's SmPC,[2, 71, 72] and unit costs (Table 42). Treatment schedules involve a maximum period of treatment for each of the initial treatment drugs of 18, 24 and 12 months, respectively. Per cycle drug acquisition costs for the initial therapies are applied in the model (CRCQ2 version) in every model cycle according to patients' persistence rates (see Section 4.2.4.4), until the maximum duration of treatment is reached.

Based on its list price informed by the company, the cost per pre-filled pen with 3mg of abaloparatide is £295. The company has an agreed PAS which takes the form of a simple price discount of [redacted]; the discounted price per pack of abaloparatide is therefore [redacted]. Patients are assumed to receive 80µg of abaloparatide daily via SC injections. According to abaloparatide's SmPC,[2] each pre-filled pen must be used within 30 days after the first dose; therefore, in the model each pre-filled pen is assumed to contain 30 days' supply (CRCQ1, question B47c).[26] The model assumes the use of approximately 12.67 pens per year and estimates an annual treatment cost of £3,731 ([redacted] with PAS).

The company has provided results that do not include confidential discounted prices for other drugs (that reflect comparator PAS [cPAS], Commercial Medicines Unit [CMU] agreements or prices from the drugs and pharmaceutical electronic market information tool [eMIT]), which is consistent with NICE guidance. Drug prices were taken from the British National Formulary (BNF).[70] Patients are assumed to receive every month two injections, each containing 105mg of romosozumab. The cost of each pack with two pre-filled pens of romosozumab is £428. Each pre-filled pen must be used within 30 days after the first dose;[72] the model assumes 12 packs/pens of the drug are used per year of treatment. The annual cost of treatment with romosozumab was estimated to be £5,133.

The cost of one pre-filled pen with 600µg of teriparatide varies between £235 and £272, depending on the brand. The model includes the functionality to use one of four brands: Forsteo (originator); Movymia (bio-similar); Sondelbay (bio-similar); and Terrosa (bio-similar). The company's base case analysis uses the costs for Forsteo (reference drug brand). Patients are assumed to receive 20µg of teriparatide via SC injections once daily. Teriparatide's SmPC states that each pen contains 28 doses of the drug; the model assumes 13 pens per year of treatment and estimates an annual cost of £3,534. The company mentions in the CS that the results of scenario analyses are presented using the costs for teriparatide from bio-similar brands, for which estimated annual costs vary between £3,055 and £3,534; however, these were not presented neither in the CS, nor in CRCQ1 or CRCQ2 appendices.

Table 42: Dosing, treatment schedules and drug cost per cycle for treatments included in the company's model

Regimen	Regiment component	Admin route	Dosing schedule	Maximum duration (months)	Pack size (per pack/pen / injection)	Estimated number of packs per year‡	Annual drug costs	Drug costs per cycle	Admin costs (one-off cost)‡
Abaloparatide	abaloparatide	SC	80 µg daily	18	3 mg	12.67	Without PAS: £3,731 [redacted]§	Without PAS: £1,865 [redacted]§	£12
Teriparatide	Teriparatide (Forsteo®)*	SC	20 µg daily	24	600 µg	13.00	£3,534	£1,767	£12
	Teriparatide (Movymia®)†	SC	20 µg daily	24	600 µg	13.00	£3,055	£1,528	£12
	Teriparatide (Sondelbay®)†	SC	20 µg daily	24	600 µg	13.00	£3,534	£1,767	£12
	Teriparatide (Terrosa®)†	SC	20 µg daily	24	600 µg	13.00	£3,110	£1,555	£12
Romosozumab	Romosozumab	SC	2 injections of 105mg each (210mg total), once monthly	12	210 mg (2 pens of 105mg each)	12.00	£5,133	£2,567	£12
All treatment groups	Alendronate	Oral	One 70mg tablet once weekly	60	280 mg (4 70mg tablets)	13.00	£25	£13	Not included

Admin – administration; SC - subcutaneous
§Includes PAS for abaloparatide.
**Brand chosen for the company's base-case.*
† Biosimilar, results using this value were not used in any analyses presented by the company.
‡ The EAG believes that there are some minor errors in the calculation for abaloparatide, teriparatide and alendronate; please see Section 4.3.4.2 for more details.
‡ The EAG notes that the administration costs is only applied if a patient has persisted treatment in the first 6 months.

The EAG believes the company's approach to calculate the annual number of doses required for a complete course of abaloparatide is incorrect but the error has a minor impact on the cost-effectiveness (see Section 4.3.4.2 – Issue 2e). The company's model assumes that patients receive all of the intended doses until they become non-persistent with treatment or complete the treatment course.

The model includes administration costs of £12 per cycle for all the SC drugs in the model, which is assumed to account for one nurse visit of 15 minutes at the GP practice per year *"for initiation of treatment"* (CRCQ1, question B48).[26] Unit costs were obtained from the Personal Social Services Research Unit (PSSRU) 2022.[74] The EAG notes that in the updated version of the model submitted at CRCQ2,[58] this cost is applied as a one-off-cost to patients that have persisted with treatment in the first 6 months (see Section 4.3.4 for more details).

The EAG also notes that the SmPCs for the intervention and comparators state that patients, whilst on the anabolic therapies, should be supplemented with calcium and vitamin D if necessary. The EAG notes that, although the inclusion of costs for calcium and vitamin D supplementation are not mentioned in the CS, the approach taken by the company is in line with Davis *et al.* (2015),[35] where all patients were assumed to equally receive calcium and vitamin D supplementation regardless of the treatment received, so these costs were not included in the model. The SmPC for abaloparatide and romosozumab also states that patients with additional risk factors for hypercalcaemia (abaloparatide),[2] or with severe renal impairment or receiving dialysis (romosuzumab), are subject to monitoring for serum calcium whilst receiving these treatments.[72] The SmPC for teriparatide states that regular monitoring for calcium levels during therapy is not required.[71] Costs for serum calcium monitoring is not explicitly included in the model for any of the anabolic therapies, but the EAG does not consider the exclusion of these costs to be a major issue.

Drug acquisition costs – subsequent therapy with alendronate

The model includes the costs associated with treatment with an oral bisphosphonate (alendronate) after treatment with the initial anabolic therapy is ceased. These include the costs of drug acquisition, which is based on unit costs from BNF,[70] the drug's treatment schedule from alendronate's SmPC[73] and its maximum duration of treatment of five years (60 months). Each pack with four tablets containing 70mg of alendronate are assumed to cost £2; patients are assumed to receive one 70mg tablet once weekly; the model assumes the use of 13.00 packs of alendronate per year of treatment, which leads to an annual cost of £25. The estimated costs for alendronate are summarised in Table 42, and in the latest version of the model[58] these are applied in every model cycle according to patients' probabilities of persisting treatment after the maximum duration with the initial therapy is reached (see sections 4.2.4.4 and 4.3.4). No administration costs associated with alendronate's treatment were included in the model, since it is an oral treatment.

Similarly to the initial therapy drugs, no wastage was considered in the model for alendronate. The EAG also notes that there are lower unit costs available in BNF for the same dosage of alendronic acid, and that the calculation of the number of annual doses in the original version of the model submitted includes a minor error. These issues are described in more detail in Section 4.3.4.

Disease management costs

Resource use and unit costs related to disease management (monitoring and follow-up) included in the model are summarised in Table 43. In the updated version of the model submitted as part of CRCQ2,[58] disease management costs include two yearly visits to nurses at GP practice per year, and a biennial diagnostic imaging procedure BMD measurement. Resource use assumptions were based on NICE TA791[3] and Hiligsmann *et al*.[19] Unit costs of GP practice nurse visits assumed a Band 5 GP practice nurse (excluding qualifications) lasting 9.72 minutes and were obtained from PSSRU 2022.[74] Unit costs of BMD measurements were assumed to correspond to the costs of a DEXA scan taken from NICE TA791.[3] The model assumes that patients receiving abaloparatide, teriparatide, romosozumab and alendronate incur the same disease management costs related to follow-up and monitoring of £17 per 6-months cycle whilst they receive drug therapy.

Table 43: Summary of health state resource use and costs (per 6-month cycle)

Resource component	**Resource Use (per 6-month cycle)**				**Unit costs**	**Total Costs**
	Initial treatment			**Subsequent treatment**		**All treatments**
	Abaloparatide	**Teriparatide**	**Romosozumab**	**Alendronate**		
Nurse visits	1.00	1.00	1.00	1.00	£7	£7
BMD measurement	0.25	0.25	0.25	0.25	£40	£10
Total (per 6-month cycle)						**£17**

BMD – bone mineral density

The EAG notes that the unit costs for BMD measurement of £40.00 was taken from the NICE TA791 committee papers, where in turn the EAG mentions being sourced from the National Tariff Workbook 2020/2021.[83] In this submission for abaloparatide, the model uses the same value without uplifting it to current values or updating it using the costs available from NHS Reference Costs 2021/22[76] (code RD50Z, £95 if using 'total HRG' estimate). The EAG also notes that in Table 33 of the CRCQ2 appendix,[58] the company includes the costs of 'reporting to referrer (referral letter)' and 'Specialist consultation' as part of disease management costs as 'one-off costs applied to all initial treatments'. However, these resources are not included in the cost calculations for each treatment group. It is also unclear why the duration of the nurse visits is different from the duration used in the drug administration costs. These and other issues related to disease management costs are discussed in Section 4.3.4.

Costs of fractures

The costs associated with treating hip, vertebral and NHNV fractures included in the model consider three separate sets of costs for each type of fracture:

(i) First year acute care costs: per cycle costs which correspond to procedures related to the initial treatment of each type of fracture. The unit costs are based on values reported in Gutierrez *et al.* (2011 and 2012),[77, 78] which were updated to 2023 using a third-party online calculator based on the Consumer Price Index (CPI).[79] The company estimated annual costs of hip, vertebral and NHNV fractures were £15,579, £3,412, and £2,384, respectively and these are split evenly in the model across the two 6-month cycles following an incident fracture.

(ii) Subsequent years acute care costs: ongoing cycle costs which are assumed to correspond to the costs of fractures from the second year after the fracture's occurrence onwards; these are assumed to apply only to hip and vertebral fractures. The costs estimates were based on values reported in the NICE MTA for bisphosphonates (Davis *et al.* 2015),[35] which were updated using the same CPI online calculator.[79] Davis *et al.* (2015), in its turn, used resource use data from Gutierrez *et al.* (2011 and 2012),[77, 78] which included *"examined hospitalisations, accident and emergency (A&E) visits, referrals, prescriptions and GP contacts"*, and unit costs from NHS Reference costs and PSSRU. The annual costs for hip and vertebral costs were estimated at £136 and £436, respectively (see Table 44) and are applied in the model from the second year after a fracture occurrs until the patient's point of death (CRCQ2, question B20).[57]

(iii) Long-term care costs: these are ongoing costs assumed to be incurred only by patients experiencing a hip fracture that results in a new admission to long-term care (e.g. nursing or residential care home). In the updated version of the model submitted at CRCQ2, the total cost per cycle was based on a weekly cost of £1,212 associated with the establishment cost per permanent resident per week in a nursing home from PSSRU 2022,[74] which was converted to a daily cost and uplifted to 2023 values using CPI (12-month rate specific for health sector; CRCQ2 question B22).[57] The age-specific proportions of patients who are assumed to incur this cost was taken from the rate of new admissions to long-term care following hip fracture estimated from Nanjayan *et al.*[84] (Table 45).[58] The estimated daily cost of £187 (corresponding to a 6-month cost of £34,213) is applied in every cycle from the point of occurrence of a hip fracture until the patient's death.

These costs are applied to all patients that suffer fractures, regardless of treatment received. The annual and per cycle costs of each type of fractures are summarised in Table 44, as reported by the company in CRCQ2 appendix and currently applied in the latest version of the model.

Table 44: Fracture management cost (annual costs, adapted from CRCQ2 appendix Table 31 and model)[58]

Fracture type	Annual costs (CRCQ2 appendix)		
	Cost of fracture acute care		Cost of chronic long-term care
	1st year	2nd+ years	1st+ years
Hip	£15,579	£136	£ 68,426
Vertebral	£3,412	£436	£0
NHNV	£2,384	-	£0

CRCQ2 – clarification response 2; NHNV – non-hip, non-vertebral.

Table 45: Admission rates to institutional care setting for community dwelling individuals experiencing hip fractures in the model, by age group (adapted from CQCR2 appendix, Table 32)

Age group (years)	Proportion of patients admitted to institutional care setting after hip fracture
50–59	0.04
60–69	0.07
70–79	0.12
80–89	0.21
90–99	0.33

AE costs

Costs related to the management of AEs are not included in the CS, CRCQ1 and CRCQ2 appendices or updated version of the model.[1, 25, 58] The EAG notes that the current version of the economic model submitted by the company includes the functionality to include costs associated with treatment-related AEs; however, the frequency of AEs and unit costs are all set to zero. In response to CRCQ1 question B54,[26] the company limited to state that *"The costs for treating AEs were not included in the base case or scenario analyses"*, with the justification that the NICE Decision Support Unit (DSU) technical support document 15 (cost-effectiveness modelling using patient-level simulation) supports the non-inclusion of AEs costs for this type of model structure.[26] The EAG notes that this is an erroneous statement as it refers only to the specification of a simplified example model included in the TSD for teaching purposes. Previous models of osteoporosis treatments developed by Davis *et al.* (2020) to inform NICE guidance[9] have included AEs and this point is further discussed in Section 4.3.4.2 (Issue 16).

4.2.5 Model validation and face validity check

The CS (pages 131-132),[1] CRCQ1 (pages 62-63)[25] and CRCQ2 (page 65) appendices describe the company's model validation activities, which involved various checks for errors in cells links and formulas, checking for errors and debug in Visual Basic for Applications (VBA) coding, and testing the model on extreme values ("pressure testing"). The company states that validation was conducted by a

'validator', but no details were provided about this agent, nor was supporting evidence presented regarding the outputs of these activities in terms of external validity, apart from mentioning that minimal discrepancies and no impactful model calculation errors were raised and addressed, and that post-validation model was used to generate the final results presented by the company.

4.2.6 Company's cost effectiveness results

4.2.6.1 Company's central estimates of cost-effectiveness (deterministic and probabilistic)

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted at CRCQ2.[58] Table 46 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of abaloparatide versus romosozumab and teriparatide. The company provided pairwise comparisons between abaloparatide and each comparator.

The probabilistic version of the updated model suggests that abaloparatide is expected to generate [redacted] additional life-years (LYs), 0.01 additional QALYs and cost [redacted] per patient compared to teriparatide. Compared to romosozumab, abaloparatide is expected to generate [redacted] additional LYs, 0.03 additional QALYs and cost [redacted] per patient compared to romosozumab. Therefore, the model indicates that abaloparatide dominates both comparators. The deterministic version of the company's base-case analysis produces similar results.

Table 46: Company's base case results - abaloparatide versus romosozumab and teriparatide (generated by the EAG based on the CRCQ2 version of the model, pairwise against each of the comparators)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model (based on 200 iterations)							
Abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.01	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.03	[redacted]	[redacted]
Deterministic model							
Abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.01	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.03	[redacted]	[redacted]

**Undiscounte*

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year

The results of the company's PSA using 200 iterations are presented in Figure 18 as CEACs for abaloparatide versus romosozumab and versus teriparatide. The probability that abaloparatide generates more net benefit than romosozumab and teriparatide is expected to be approximately [redacted], for both willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained. The cost-effectiveness

plane showing the results of abaloparatide compared to each of the comparators using the 200 iterations is presented in

Figure 19.

Figure 18: CEACs, abaloparatide versus romosozumab and versus teriparatide (generated by the EAG based on the CRCQ2 version of the model, pairwise comparison)

Figure 19: Cost-effectiveness plane, abaloparatide versus romosozumab and versus teriparatide (generated by the EAG based on the CRCQ2 version of the model, pairwise comparison)

4.2.6.2 Company's DSA results

The company has presented revised results for the one-way deterministic univariate sensitivity analyses following the clarification process (CRCQ2 appendix, pages 60 to 62).[58] These included changing the parameter values for the following groups (each parameter was varied individually): (i) discount rates (0% to 6%); (ii) HRs for the treatment effect on risk of fractures (hip, vertebral and NHNV, varied using 95% CIs); (iii) drug acquisition, drug administration, disease management and fracture costs (varied by 5% of the mean); and (iv) utility multipliers (hip, vertebral and NHNV, varied by 5% of the mean). The company presents the results only in terms of net monetary benefits; for brevity, these results are not displayed here. However, the EAG comments that the parameter with most influence on the results were the treatment effect on the risk of hip fractures for abaloparatide, teriparatide and romosozumab, the treatment effect on the risk of vertebral and NHNV fractures for abaloparatide, the discount rates for costs and QALYs, and the drug acquisition costs.

4.2.6.3 Company's scenario analyses

Table 47 presents a summary of the updated results of the company's scenario analyses of abaloparatide versus romosozumab and abaloparatide versus teriparatide provided at CRCQ2 appendix.[58] Across all of the scenarios assessed, abaloparatide [redacted] regardless of the scenario adopted. Abaloparatide [redacted] for most of the scenarios, except S1, S7 and S11, where the results suggest abaloparatide generates less QALYs and costs, with ICERs in the south-west quadrant of [redacted], [redacted] and [redacted] per QALY lost, respectively. The EAG notes that

S7 and S11 provide identical results and the EAG had some concerns regarding this model behaviour which are further explored in the EAG's validation of the model in Section 4.3.1.

Table 47: Company's scenario analyses – pairwise comparisons of abaloparatide versus romosozumab and abaloparatide versus teriparatide (generated by the EAG based on the CRCQ2 version of the model), deterministic

Scenario analysis set	Scenario description	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Abaloparatide versus teriparatide					
BC	Company's base case (deterministic)	[redacted]	0.013	[redacted]	[redacted]
S1	Exclusion of FRAX based estimation of risk of fractures	[redacted]	-0.001	[redacted]	[redacted]
S2	Exclusion of imminent risk of fracture	[redacted]	0.012	[redacted]	[redacted]
S3	Exclusion of persistence	[redacted]	0.087	[redacted]	[redacted]
S4	Duration of treatment effect after discontinuation set to 'fixed' method	[redacted]	0.010	[redacted]	[redacted]
S5	Drug administration costs excluded	[redacted]	0.013	[redacted]	[redacted]
S6	Excess mortality risk applied only to hip fractures	[redacted]	0.013	[redacted]	[redacted]
S7	Treatment effect source from separate trials and publications	[redacted]	-0.003	[redacted]	[redacted]
S8	Maximum treatment duration reduced to 5 years for all treatment groups	[redacted]	0.013	[redacted]	[redacted]
S9	Persistence rates source from separate trials and publications	[redacted]	0.069	[redacted]	[redacted]
S10	Different treatment strategies persistence rates sampling from different random numbers	[redacted]	0.013	[redacted]	[redacted]
S11	Treatment efficacy based on sequential treatment efficacy	[redacted]	-0.003	[redacted]	[redacted]
Abaloparatide versus romosozumab					
BC	Company's base case (deterministic)	[redacted]	0.031	[redacted]	[redacted]
S1	Exclusion of FRAX based estimation of risk of fractures	[redacted]	0.003	[redacted]	[redacted]

S2	Exclusion of imminent risk of fracture	[redacted]	0.026	[redacted]	[redacted]
S3*	Exclusion of persistence*	[redacted]	0.107	[redacted]	[redacted]
S4	Duration of treatment effect after discontinuation set to 'fixed' method	[redacted]	0.030	[redacted]	[redacted]
S5	Drug administration costs excluded	[redacted]	0.031	[redacted]	[redacted]
S6	Excess mortality risk applied only to hip fractures	[redacted]	0.031	[redacted]	[redacted]
S7	Treatment effect source from separate trials and publications	[redacted]	0.012	[redacted]	[redacted]
S8	Maximum treatment duration reduced to 5 years for all treatment groups	[redacted]	0.031	[redacted]	[redacted]
S9	Persistence rates source from separate trials and publications	[redacted]	0.073	[redacted]	[redacted]
S10	Different treatment strategies persistence rates sampling from different random numbers	[redacted]	0.022	[redacted]	[redacted]
S11	Treatment efficacy based on sequential treatment efficacy	[redacted]	0.002	[redacted]	[redacted]

DM – decision modifier; ICER – incremental cost-effectiveness ratio; LYG – life year gained; QALY – quality-adjusted life year; S – scenario; SW – South West Quadrant.
**The EAG notes that the results for abaloparatide versus romosozumab for scenario S3 (treatment persistence excluded) produced different results from the ones generated by the company as reported in Table 39 of the CRCQ2 appendix. The exact source of this discrepancy is unclear, but the EAG notes that the difference is small and does not change the interpretation of the results.*

4.3 Critique of company's submitted economic evaluation by the EAG

4.3.1 Methods for reviewing the company's economic evaluation and health economic model

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's economic analyses and the underlying health economic models upon which these are based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[85, 86]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Checking the model's programming to fully assess the logic of the model structures, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.

- Examination of the correspondence between the company's executable models and their description in the CS[1] and CRCQ1[25] and CRCQ2[58] appendices.
- Replication of the results of the company's base case, PSA, DSAs and scenario analyses reported in the CS and CRCQ1 and CRCQ2.
- Where possible, checking key parameter values used in the company's models against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the models.
- Conducting additional scenario analyses exploring the impact of changing the random number seeds and using alternative HRs (see Appendix 3).

During the process of checking the original and first updated version of the model submitted at CRCQ1, the EAG identified several programming errors, which were flagged by the EAG and resolved by the company during the clarification process. Additional programming errors were identified by the EAG in the latest version of the model at CRCQ2; these are discussed in further detail in Section 4.3.4. Overall, the EAG believes the company's CRCQ2 version of the model to be generally well programmed despite these errors, and that the version of the model used by the EAG after correcting these errors are appropriate for the decision problem. The EAG did have a remaining concern regarding some unexplained behaviour identified in the company's scenario analyses, and replicated in the EAG's validation exercises, whereby the model produces identical results for abaloparatide versus teriparatide in several scenarios using different HRs (see Appendix 3). The EAG is reasonably satisfied that this is related to the difficulty in estimating differences in outcomes between treatments in a patient level simulation when there are small differences in treatment efficacy. The EAG would therefore urge caution in interpreting the results for deterministic scenarios which generate small differences in QALYs.

4.3.2 Correspondence of the model inputs and the original sources of parameter values

Where possible, the EAG also checked the company's model inputs against their original sources including published sources and additional sources provided by the company such as the CSR of the ACTIVE and ACTIVExtend trials. The EAG noted some inconsistencies, which were flagged during the clarification process and fixed by the company. No other inconsistencies were identified in the model submitted at CRCQ2.

4.3.3 Adherence of the company's model to the NICE reference case

The company's economic analysis is generally in line with the NICE Reference Case[24] (see Table 48). Each element is discussed in further detail within the EAG report, in particular in Section 4.3.4.2.

Table 48: Adherence of the company's economic analysis to the NICE reference case

Element	Reference case	EAG comments
Population	The scope developed by NICE	While there may be some overlap between the individuals recruited to ACTIVE and those classified as being at very high risk of fracture in the NOGG guideline, it does not mean that the entire population of ACTIVE would meet the criteria for being considered at very high risk of fracture according to the NOGG guideline.
Intervention	As listed in the scope developed by NICE	According to the SmPC for abaloparatide, it was not specified that alendronate is the preferred treatment option for patients who have completed a course of abaloparatide. Therefore, other osteoporosis treatments including other bisphosphonates may be alternative treatments.
Comparator(s)	As listed in the scope developed by NICE	Many comparators in NICE final scope are not addressed in the CS. The EAG's clinical experts stated that IV bisphosphonates, such as zoledronic acid would be used for patients who are unable to take oral bisphosphonates and this would be a more relevant comparator in those patients enrolled in the ACTIVE study who did not have a prior fracture and therefore would not be eligible for either teriparatide or romosozumab.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The company's approach is consistent with the NICE reference case. Health gains accrued by patients are valued in terms of QALYs gained. Health impacts on carers are not included.
Perspective on costs	NHS and PSS	The company's base case analysis adopts an NHS and PSS perspective. This is therefore consistent with the NICE reference case.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The model is evaluated using a cost-utility approach. However, the company has not provided a fully incremental analysis against each of the comparators specified in the NICE scope. They have only provided two pairwise comparisons against teriparatide and romosozumab.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A 50-year horizon has been adopted. This is considered by the EAG to be consistent with the NICE reference case in this population.
Synthesis of evidence on health effects	Based on systematic review	Health outcomes are modelled using HRs from the NMA.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health gains are valued in terms of QALYs. Utility multipliers for first year after fractures were taken from the ICUROS study and was combined with general population utilities. The company used age- and sex-matched general population utilities based on published UK

Element	Reference case	EAG comments
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	values.[64] Although the methods for identifying the data should be systematic and transparent, the company did not identified the ICUROS study for utility multipliers through an SLR.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The company's base case cost-effectiveness analysis generally used appropriate estimates of resource use and unit costs that were consistent with the NICE reference case.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum. This is consistent with the NICE reference case.

EAG - External Assessment Group; EQ-5D - Euroqol 5-Dimensions; HR – hazard ratio; ICUROS - International Costs and Utilities Related to Osteoporotic Fractures Study; NICE - National Institute for Health and Care Excellence; NOGG - National Osteoporosis Guideline Group; PSS – Personal Social Services; SmPC - Summary of Product Characteristic; QALY - quality-adjusted life year

4.3.4 Key issues identified by the EAG's critical appraisal

4.3.4.1 EAG Critique of the modelling performed by the company

Many of the issues raised during clarification were addressed by the company in their updated model provided after CQ2. The model provided in the CRCQ2 was considered broadly suitable by the EAG, although the EAG did identify some unexpected model behaviour suggesting that the model was failing to capture changes in the HRs for scenarios where treatments are assumed to have similar efficacy (see Section 4.3.1 and Appendix 3). The EAG also identified a number of remaining issues which are discussed in section 4.3.4.2.

4.3.4.2 The main issues identified by the critical appraisal

The main issues identified from the EAG's critical appraisal are summarised in Box 2. These are discussed in further detail in the subsequent sections.

Box 2: Summary of the main issues identified within the company's health economic model

Issue 1 – Generalisability of the model to the population likely to receive anabolic therapy in current practice
Issue 2 – Presence of model implementation issues and minor coding errors
Issue 3 – Underestimation of uncertainty around differences in treatment effectiveness
Issue 4 – Choice of treatment effect estimates for abaloparatide versus teriparatide
Issue 5 – Assumptions and sources used for persistence rates
Issue 6 – Long-term care costs applied using a cohort approximation
Issue 7 – Utilities not applied for nursing home admission
Issue 8 – Resource use for disease management

Issue 1 – Generalisability of the model to the population likely to receive anabolic therapy in current practice

The EAG agrees that abaloparatide is most likely to be used in patients who would otherwise be offered either teriparatide or romosozumab in current clinical practice. However, the characteristics of the model population are based on the cohort recruited to the ACTIVE trial and the EAG's clinical advisors were unclear whether all of these patients would be classified as being at very high risk as discussed in Section 2.3.1. The EAG would prefer the company to have presented scenario analyses in which the patient characteristics were based on the populations specified by NICE recommendations for either teriparatide or romosozumab. The EAG has addressed this by including an additional scenario analysis exploring a higher risk subgroup (see Section 4.4.2.7).

Issue 2 – Presence of model implementation issues and minor coding errors

The EAG identified a number of implementation issues, which they considered to be errors. These are further described below, but briefly they related to: (a) the sampling of patient characteristics; (b) the double-loop approach to PSA; (c) the impact of prior fractures at baseline; (d) the impact of multiple fractures; (e) drug acquisition costs per course, (f) incorrect inflation of costs. In addition, the EAG identified a number of minor coding errors described further in (g) to (k). All errors discussed within Issue 2 were corrected by the EAG in their exploratory analyses (see Section 4.4.2.1).

(a) Sampling of patient characteristics

The company's approach of using a binomial distribution to sample whether individual patients had various risk factors at baseline (prior fracture, current smoking, glucocorticoid steroid use, rheumatoid arthritis, alcohol use of ≥ 3 units per day) did not provide a cohort with the correct proportion of patients for each of these risk factors when compared against the intended proportions based on the ACTIVE trial cohort. This EAG is unsure why this was the case but has used an alternative sampling approach as part of their model corrections (see Section 4.4.2.1).

The EAG notes that although the company states that the updated model allows for BMD to vary within the sampled cohort (CRCQ2, B23) this is not the case and every patient in the sampled cohort has the same T-Score. However, this T-Score does vary within the PSA. The EAG did not attempt to introduce patient level heterogeneity for BMD as to do this properly would require some consideration of the correlation between BMD and the various risk factors for fracture. In addition to age being a strong predictor of BMD, the EAG also considered that the recruitment criteria for the ACTIVE would be likely to introduce further correlations with both age and prior fracture. Therefore, the EAG would prefer to see the heterogeneity in patient characteristics within the modelled population represented using patient level data from the ACTIVE study that properly captures these correlations.

(b) Double-loop approach to PSA

The PSA has not been implemented using the double-loop approach which is the standard approach for implementing a PSA in a patient-level simulation. In the standard double-loop approach, a set of parameter samples is obtained and then outcomes are simulated for the whole cohort using this set of parameter samples (referred to as the inner loop). This process is then repeated multiple times using a new set of parameter samples each time (referred to as the outer loop). This double-loop approach requires the parameter samples to be fixed when the model is re-calculated to simulate each subsequent patient in the cohort, but the company has not included a mechanism to hold the parameter samples constant during the inner loop. Therefore, the company's model applies a different set of parameter samples to each patient within the cohort. In a model that does not include any patient interaction or resource constraints, using different parameter set for each patient in the cohort can be a legitimate

approach to estimate the mean costs and QALYs, but further analyses would be required to estimate measures of uncertainty such as the cost-effectiveness acceptability curves (CEAC). However, this does not appear to be what the company intended to do in this case, and the company's method for calculating CEACs suggests that they intended to use a standard double-loop approach. The EAG has corrected this error in the model in their exploratory analyses (see Section 4.4.2.1). The EAG has also allowed the random number seeds that determine the random number array for each patient to change for each PSA run to ensure that any variation due to the random number seeds is averaged out over the PSA.

(c) Prior fractures at baseline

Although the company allows for patients to have a prior fracture at baseline this does not impact on their estimated fracture risk or their baseline utility. The latter potentially means that the QALY gains are overestimated as patients starting the model with prior fractures may already have lower utility compared to general population norms. This is likely to be especially true in those with multiple prior vertebral fractures or a prior hip fracture, both of which have a long-term utility decrement which the company includes in the model for incident fractures occurring after baseline. The EAG was not able to correct the model to include the impact of prior fracture at baseline on utility because the company's model does not sample the site of prior fracture, only the presence or absence of a prior fracture. However, the EAG was able to correct the model to incorporate the additional risk in those with a prior fracture at baseline and this was included as one of the EAG's model corrections (see Section 4.4.2.1).

(d) Utilities not applied for second fracture of same type

The multiplicative approach for accounting for the impact of multiple chronic or acute fractures has been used in previous appraisals. However, in the updated model submitted at CRCQ2, a second fracture of the same type does not impact on the utility. If we consider the example of a patient who experiences a hip fracture at year 2, followed by two NHNV fractures in years 4 and 6 respectively. When the first NHNV fractures occurs in year 4, the overall fracture-related utility multiplier (0.7138) is derived from multiplying the utility multiplier for a hip fracture in subsequent years (0.86) with the utility multiplier of NHNV fracture in the first year (0.83). In year 5, the subsequent year multiplier for NHNV (0.99) is applied instead of the first-year utility and therefore the multiplier increases to reflect recovery from the NHNV fracture (0.86*0.99= 0.8514). However, any further NHNV fractures do not impact utility at all in the company's base case. The EAG notes that the CS does not address the reason why the impact of incident fractures is restricted to only the first fracture at each site. The EAG agrees with the company's multiplicative approach, but considers that a second incident fracture of the same type should impact utility in the year after that fracture. For example, a patient who has largely recovered from a broken wrist happening over a year ago would still have an acute drop in utility from a shoulder fracture. The EAG has addressed this issue in their exploratory analyses (see Section 4.4.2.1.

(e) Drug acquisition costs per course

In the CRCQ2 version of the model, the company assumes that each patient would use 12.67 pre-filled pens of abaloparatide, 12 packs (of two injections each) of romosozumab, 13 pre-filled pens of teriparatide, and 13 packs of alendronate per year. The company stated in response to CRCQ1 question B47[26] that wastage in the model is only assumed for abaloparatide, where the number of total pens needed for a 18-month course of abaloparatide was rounded up from 18.3 to 19 pens (and therefore 12.67 pens per year). However, the EAG considered it would be more likely that clinicians would be pragmatic and prescribe 18 pens over 18 months, as prescribing 19 pens would potentially breach the maximum treatment period of 18 months.[2] The EAG has therefore corrected the model accordingly (see Section 4.4.2.1).

The model also does not account for other types of wastage, such as if a patient dies or discontinues part-way through a treatment cycle. However, this is likely to be a minor issue that affects each treatment equally as all are dispensed in packs covering 28 to 30 days of treatment. Therefore, the EAG has not adapted the model to address this issue.

The EAG also noted that the company was not using the lowest cost available for generic alendronate which was a cost of £0.18 per pack, provided by the eMIT. The EAG also noted that the company was basing the cost for teriparatide on the list price for the original branded formulation (Forsteo, £272) rather than the list price for the lowest cost biosimilar (Movymia, £235). The model presented by the company includes the functionality to use list prices for each of the teriparatide biosimilars (Movymia, Sondelbay, and Terrosa). However, the EAG notes that results using any of these options for teriparatide have not been presented at CS, CRCQ1 or CRCQ2. The EAG has therefore corrected the model to use these lower acquisition costs for both alendronate and teriparatide. (NB: The impact of confidential prices for romosozumab and CMU prices for teriparatide is addressed in the confidential appendix).

(f) Incorrect inflation of costs

The EAG notes that the acute costs incurred in the first year after fracture were, in the last instance, based on estimates from Gutierrez *et al.* (2011 and 2012).[77, 78] However, these studies do not report costs for subsequent years of treatment, so Davis *et al.* (2015)[35] reported using the incremental costs for medications as a proxy for ongoing costs beyond the first year post-fracture, which were reported as £106, £332 and £70 for hip, vertebral and NHNV fractures respectively (also in 2007 values).

The company stated in their submission[1] that the values from these two studies have been used to inform the costs of fracture in the model, but these have been updated to account for inflation using a web calculator from a chartered surveyors practice that inflates costs according to CPI.[79] The EAG had some uncertainties regarding exactly how this was done, however, the EAG believes that the first-year cost

estimates were updated from 2007 to 2023 values, whilst the estimates for costs in the second year after fracture were only uplifted from 2015 to 2023 because the company sourced them from Davis (2015). A summary of the costs' estimates used by the company and original sources are shown in Table 49.

Table 49: Cost estimates of fracture acute care (annual costs) for first and subsequent years by fracture type and sources (original from publications and uplifted to 2022 by EAG using NHSCII)

Source	Used by the company at CRCQ2 (2023 values)‡		Original values from Gutierrez *et al.* 2011 and 2012 (2007 values)		Values from Gutierrez et al 2011 and 2012 uplifted by the EAG to 2022 values using HCHS and NHSCII indices	
Type of fracture	1st year	2nd+ years	1st year	Medication costs in 1st year	1st year	2nd+ years
Hip	£15,579	£136	£9,936*	£106	£13,342	£142
Vertebral	£3,412	£436	£2,180	£332	£2,927	£46
NHNV	£2,384	-	Humerus:1390 Wrist: £1604	£70	£2,154	£94

HCHS - Hospital and community health service; NHSCII - NHS Cost Inflation Index; NHNV – non-hip, non-vertebral
**includes rehabilitation*
†The EAG believes the took the average of these values to estimate a cost of £1,497 for NHNV
‡ The EAG believes the company uplifted the costs of the first year from 2007 to 2023, whilst for the subsequent years from 2015 (year of publication of the Davis et al. 2015 report).

The EAG notes that the company has not used the recommended inflation index, the NHS Cost Inflation Index (NHSCII) pay and prices (and the Hospital and community health service [HCHS] pay and price for periods pre-2016), to update the original cost estimates and that all costs should have been updated from 2007 to 2022 (last year available in PSSRU). The updated costs of each type of fracture using the correct index are presented in Table 49. The EAG notes that in order to obtain the inflation indices for all years between 2022 to 2007, it had to use previous versions of PSSRU (up to 2016). The EAG has included the updated costs estimates in their exploratory analysis (see Section 4.1.3).

The estimate of costs for those requiring long-term care following hip fracture, was based on unit costs taken directly from PSSRU 2022[74] (weekly cost per permanent resident in a nursing home), which was also uplifted to 2023 values using CPI (specific 12-month rate for health sector; CRCQ2 question B22). The EAG notes that since the 2022 version of the PSSRU manual costs is the last available at the time of this appraisal, the company did not have to uplift this unit costs. The EAG has included the original value of £1,212 per week (£173.14 per day) as the unit costs for the long-term care of hip fracture in its exploratory analysis (see Section 4.1.3).

(g) Use of wrong age to calculate the costs of long-term hip fracture care

The EAG notes that as part of CRCQ2 response to question B21,[57] the company updated the formulas in the simulation spreadsheets used to look-up the proportion of patients who require long-term care due to a hip fracture (institutionalised patients) and consequently calculate the costs of long-term care,

to use the age at the first fracture instead of current age. However, upon model verification, the EAG noted that the model applies this correction by checking the age at the time of the first fracture of any type, instead of the age at the time of the first hip fracture. This is important as the risk of new admission to long-term care after hip fracture increases with age (see Table 45). The EAG has addressed this issue in their exploratory analyses by correcting the model to look to the age of the first hip fracture occurrence when estimating the probability of needing long-term care (see Section 4.4.2.1).

(h) Incorrect implementation of administration costs

The cost associated with teaching patients to self-administer should be incurred as a one-off cost for each patient starting treatment. However, whilst this cost is now only applied once for each patient, it is only applied in those persistent on treatment at 6 months. The EAG considers this to be an error and has corrected it as described in Section 4.4.2.1.

(i) Use of incorrect reference for fracture number to determine imminent fracture risks

There is a minor issue in the submitted model where the formula used to determine the increased risk attributable to a recent fracture was using time since last hip fracture instead of hip fracture count to control which HRs should be applied when there are 3 or more prior fractures. The EAG fixed the affected formulas in the simulation sheet for each treatment strategy (see Section 4.4.2.1).

(j) Incorrect numbers of cycles on treatment

The formula used to estimate whether the patient has reached the maximum treatment duration for the treatment sequence (anabolic followed by alendronate) for the purposes of determining when to apply the HRs for treatment was incorrectly assigning 13, 14, and 15 cycles of treatment for romosozumab, abaloparatide and teriparatide, whereas these should have been 12 for romosozumab (i.e. 2 six month cycles of romosozumab followed by 10 six month cycles of alendronate), 13 for abaloparatide and 14 for teriparatide. The EAG has corrected this (see Section 4.4.2.1).

(k) Transition matrix not allowing any fracture in first cycle

The first row of the transition matrix is set up to ensure that all patients stay in the same state rather than using the calculated risks of fracture and death during the first cycle. This means that the fracture risks calculated for the first cycle are not applied in the model. It also means that the treatment efficacy in the first cycle is effectively not applied once the number of cycles on treatment has been corrected. This may explain why the company added an additional cycle on treatment to ensure the correction duration of treatment efficacy, but the EAG prefers to correct both errors rather than assuming no fractures occur in the first cycle.

(l) Decline in BMD per annum.

The EAG notes that the company's approach to estimating the T-Score decline per annum results in a decline of 0.0419 per annum, whereas the data from Stevenson *et al.* show a decline of 0.0512 per annum.[66]

Issue 3 – Underestimation of uncertainty around differences in treatment effectiveness

The HRs for abaloparatide versus teriparatide and abaloparatide versus romosozumab from the company's NMA have credible intervals crossing 1 for the outcomes of vertebral, hip and non-vertebral fractures (see

Table 50). The credible intervals for hip fracture in particular are very wide suggesting a high degree of uncertainty regarding which is the most efficacious anabolic treatment for preventing hip fractures. However, this uncertainty is not adequately captured in the company's PSA because the company samples the HRs versus placebo independently from a gamma distribution and assumes that the SE is 5% of the median HR (the median being the estimate used in the deterministic analysis) (NB: The approach used in the model differs from the stated approach in CRCQ1 B26). The 95%CIs from the corresponding gamma distributions used in the PSA are shown in Table 51, which also shows for comparison the 95%CrIs from the company's RE NMA. It can be seen that whilst the company's NMA provides 95%CrIs that overlap between the various anabolic therapies, the 95%CrIs for the various gamma distributions used in the PSA are much narrower, especially for the outcomes of hip and vertebral fractures for abaloparatide as they are based on 5% of the median HR. This means that abaloparatide is sampled as having better efficacy for hip fracture than both romosozumab and teriparatide in at least 95% of the PSA runs which does not reflect the uncertainty in the company's NMA for this outcome where only 65% of the CODA samples provide better efficacy for abaloparatide. The EAG has addressed this issue in its exploratory analyses by adapting the model to use the CODA samples for the HRs versus placebo from their re-run of the company's NMA directly within the PSA.

Table 50: NMA estimates of effectiveness for romosozumab and teriparatide versus abaloparatide (CRCQ2, Appendix Tables 9, 10 and 11).

Abaloparatide vs.	FEM			REM		
	Median HR	LCrI	UCrI	Median HR	LCrI	UCrI
New vertebral fractures						
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hip fracture						
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-vertebral fracture						
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 51: Credible intervals (95%) for the HRs versus placebo for the company's NMA (REM) and the gamma distributions used to sample the HRs versus placebo in the PSA

Outcome	Vertebral fracture		Hip fracture		Non-vertebral fracture	
Treatment	NMA	Gamma	NMA	Gamma	NMA	Gamma
Abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Issue 4 Choice of treatment effect estimates for abaloparatide versus teriparatide

As discussed previously in section 3.12, the EAG considered that there was considerable uncertainty in the relative effectiveness of abaloparatide and teriparatide for both the hip and non-vertebral fracture outcomes. The EAG was concerned that incorporating the hip fracture HRs for abaloparatide from the NMA was potentially biasing the cost-effectiveness estimates because the risk of hip fractures for abaloparatide in the NMA was based solely on an estimate of zero events in the ACTIVE study. The EAG considered whether it would be reasonable to use the HRs for the non-vertebral fracture outcome in the model for hip fracture. The company had taken a similar step in their scenario analysis using trial-based HRs, in which they used major non-vertebral outcomes for hip fracture. However, the EAG noted that the median HR from the NMA for non-vertebral fractures favoured teriparatide over abaloparatide (see

Table 50). This contradicted the evidence from the RWE study which found a significant reduction in hip fracture risk for abaloparatide versus teriparatide in patients with more than 12 months treatment (see

Table 29). Therefore, the EAG decided that a pragmatic solution would be to assume equivalent efficacy for abaloparatide and teriparatide for hip fracture. As the teriparatide node of the NMA was supported by more studies, this assumption of equivalent efficacy was implemented in the model by using the HR for teriparatide versus placebo from the NMA in the abaloparatide arm for hip fractures.

Having made this decision, the EAG considered the uncertainty in the non-vertebral fracture outcomes for abaloparatide versus teriparatide. Whilst the confidence intervals are not as wide as for hip fracture, and the direction of effect was similar between the ACTIVE study and the NMA, a median HR greater than 1 suggesting better effectiveness for teriparatide for non-vertebral fracture was not supported by the RWE. It therefore decided to also apply the HR for teriparatide versus placebo in the abaloparatide arm, noting that this was potentially favourable to abaloparatide.

The EAG continued to use the outcomes from the NMA for abaloparatide for the outcome of new vertebral fracture. The rationale for this is that vertebral fractures were the primary outcome in the ACTIVE study and many other studies informing the NMA, meaning there was less concern about the sparsity of events in the NMA. There is also more consistency between the NMA outcomes and the findings from the ACTIVE study for the vertebral fracture outcome with both suggesting a midpoint HR under 1.

The EAG noted that there was also significant uncertainty in the relative cost-effectiveness of abaloparatide versus romosozumab due to the lack of any direct trial comparison. However, it considered that the HRs from the NMA were already similar for romosozumab and teriparatide meaning that they would be similar for romosozumab and abaloparatide when assuming equivalent efficacy for hip and non-vertebral fracture for abaloparatide and teriparatide. However, to explore the issue further, the EAG also conducted an exploratory analysis in which they assumed equivalent outcomes for all fracture types across all anabolic therapies. This can be considered to be equivalent to conducting a cost-comparison scenario with the only difference in fractures being driven by differences in treatment persistence (see exploratory analyses in Section 4.4.2.7).

A summary is provided in

Table **52** of the HRs applied in the EAG's base case and its cost comparison scenario versus those applied in the company's base case.

Table 52: Relative risks for each treatment by fracture type used in the company's base-case, the EAG base case and the EAG's cost comparison scenario (adapted from Tables 22 of the CRCQ2 appendix)[58]

Analysis type	Company base case			EAG base case			EAG cost comparison scenario		
Fracture type	Abalop.	Terip.	Romos.	Abalop.	Terip.	Romos.	Abalop.	Terip.	Romos.
Hip	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
Vertebral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
NHNV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	

Abalop. – abaloparatide; NHNV – non-hip non-vertebral; NMA – network meta-analysis; Romos. – romosozumab; Terip. – teriparatide.

Issue 5 –Assumptions and sources used for persistence rates

In the company's updated base-case analysis at CRCQ2, persistence rates for abaloparatide and teriparatide are based on data from Arden *et al.*,[62] an RWE study that evaluated the use of teriparatide in the UK; the company assumed the rates for teriparatide would also apply for abaloparatide. In contrast, persistence rates for romosozumab were taken from Söreskog *et al.* (2021a and 2021b);[55, 56] these cost-effectiveness studies evaluating romosozumab in Sweden and UK report having assumed a persistence rate of 80% at 12 months for romosozumab. The EAG notes that the company's approach in its base case is inconsistent between the treatment groups because it is making the assumption that the RWE for teriparatide apply to abaloparatide, but it is relying on an assumption to model real-world persistence for romosozumab. In addition, the EAG believes that the persistence rate for romosozumab at 6 months could have been linearly adjusted based on data at 12 months, and in line with the approach taken for teriparatide at 24 months. The EAG has addressed this issue in their exploratory analyses by applying a linear approach for romosozumab (see Section 4.4.2).

The company also presents a scenario analysis where the persistence rates for patients receiving abaloparatide and teriparatide are based on completion rates of the ACTIVE study at 18 months, whilst using the same base-case values for romosozumab. The company justified not using persistence data for romosozumab from the ARCH trial *"as persistence in clinical trials is known to be significantly higher than in clinical practice, as patients know they are being observed,"* in addition to stating that RWE data from the UK for romosozumab have not been identified in NICE TA791 or by the company (CRCQ1 Question B38).[26] However, the EAG considers that in this scenario analysis, the company could have used persistence data for romosozumab from the ARCH study as reported in Saag *et al.* (2017),[87] where 89.3% have completed 12 months of the trial. The EAG has addressed this issue in their additional scenario analysis using trial-based persistence data (see section 4.4.2).

In the latest version of the economic analyses,[58] the company used Morley *et al.*[63] as the source of persistence rates for alendronate after treatment with the three anabolic therapies, which corresponded to the subgroup of patients that received an oral bisphosphonate after previous treatment experience (non-naïve). The EAG noted that the committee in TA791 considered in their decision making both a scenario applying the data from Morley *et al*. to both arms and a scenario assuming higher persistence on alendronate for patients having anabolic therapy.[3] The EAG's clinical expert agreed that based on personal experience higher persistence might be expected for patients taking alendronate therapy after an anabolic treatment than for patients starting alendronate after other therapies. Therefore, the persistence estimates assumed in the company's base-case model for alendronate may be pessimistic, because they are not specific to a post-anabolic treatment group. The company's scenario analysis incorporating persistence data from the clinical trials provides an analysis in which the persistence on alendronate is higher than in Morley *et al.* because it allows for persistence to decline linearly from the end of the trial period. The EAG therefore considers that this issue is captured in its scenario analysis using the trial-based persistence estimates.

The EAG also notes that although the company's model allows persistence to vary within the sampled cohort, the uncertainty around the estimates of persistence is not captured in the PSA for any of the treatment groups. The EAG were not able to update the model to correct this issue, but it notes that the decision uncertainty will have been underestimated due to the exclusion of persistence data from the PSA.

Issue 6 – Long-term care costs applied using a cohort approximation

The EAG notes that, although using a patient-level state transition structure in the model, costs related to new admissions to long-term care following hip fracture are estimated using a cohort approach rather than an individual approach. The EAG has adapted the model to simulate whether new admission to long-term care occurs or not following each incident hip fracture. This is described further in EAG exploratory analyses (see Section 4.4.2.4).

Issue 7 – Utilities not applied for nursing home admission

The CS includes costs related to hip fractures that lead to a new admission to long-term care such as a nursing home or residential care home (see Section 4.2.4.6). However, the model does not include any detrimental impacts to HRQoL related to institutionalisation in nursing homes for patients suffering hip fractures.

In previous appraisals in osteoporosis, the impact to HRQoL associated with the residential status of patients has been considered. In TA464, the DES model built by the assessment group incorporated utilities based on a combination of *"gender, age, fracture history and residential status (community*

dwelling or institutionalised)," where the utility values accrued by an individual patient were updated at the occurrence of an event, and an estimated utility multiplier for nursing home admission following fracture of 0.625 was applied.[35] A similar approach was used in Davis *et al.* (2020).[9] It is unclear if including QALY losses due to institutionalisation was considered in TA791 since there were no mentions in the summary of the company'submission or in the EAG report (available in the committee papers).[3] The company mentions in the clarification response that "*One HRQoL survey found that 80% of older women would rather be dead than experience the loss of independence and QoL that results from a hip fracture and subsequent admission to a nursing home, valuing nursing home admission at 0.05 on a scale of 0–1, where death is equal to 0.*[14]" but no further mentions about its inclusion in the model were found.

The EAG considers that the impact of new admissions to long-term care following hip fracture are likely to be underestimated in the model presented by the company. The inclusion of an estimate of QALY loss using similar approach to TA464 and Davis *et al.* (2020) may have a considerable impact on QoL accrued by patients in each of the treatment groups, given the larger impact of hip fractures on health outcomes than other fracture types (which has been already noted by the EAG in TA791).[3] However, as discussed later in the EAG critique (see Issue 13), the model presented by the company was structured to account only for impacts of long-term care following hip fractures using a cohort approach rather than an individual approach. However, after amending the model to use an individual approach to determine whether or not patients enter a long-term care following a hip fracture (see Issue 6), the EAG were able to adapt the model to include a utility decrement for those entering long-term care. The methods used to do this are further described in Section 4.4.2.

Issue 8 - Resource use for disease management

The resource use assumed for disease management in the company's model did not reflect the advice received from the EAG's clinical experts with regard to frequency of DXA scans, nurse visits or specialist consultations. In addition, application of costs for specialist consultations and reporting back to the referrer at treatment initiation were described as being included in the analysis, but were not implemented in the model. The EAG has therefore explored alternative assumptions that more closely matched the advice from their clinical experts in its exploratory analyses.

The EAG did not consider it likely that patients would receive a DXA scan every other year. Clinical advice to the EAG was that taking a baseline DXA scan before starting an anabolic treatment and another DXA scan on completion of anabolic treatment is more representative of current practice. The EAG have tried to reflect this in their scenario analysis, although this is difficult to achieve as in the model DXA scans are attributed to time spent on treatment rather than to the events of starting and stopping treatment. The EAG assumed a DXA scan before initiating anabolic treatment as a one-off

cost for all model arms and then applied an annualised DXA scan cost to give 1 scan on average over the duration of treatment (i.e. 0.5, 0.33 and 0.25 per 6-month cycle for planned treatment durations of 1, 1.5 and 2 years respectively). The EAG recognises that this may marginally underestimate DXA scan costs due to imperfect persistence on anabolic treatment, meaning that the average time on anabolic treatment is less than the intended course duration, but this will affect all arms to a similar degree.

All patients are assumed to have one specialist outpatient appointment as an upfront cost at the start of treatment which is the same for all anabolic treatments as the company stated that they had included this, but it wasn't implemented in the model. The EAG's clinical advisors stated that they would usually also see patients at the end of teriparatide treatment, with one also offering a follow-up mid treatment. The EAG has therefore assumed one specialist consultation each year for teriparatide (i.e. 2 over the treatment course). For romosozumab, one expert said they would have the same number of visits but compressed over the shorter time romosozumab treatment timeframe, whereas the other expert said they would have more follow-up visits as romosozumab is a newer drug. The EAG has therefore assumed one specialist consultation every 6 months for romosozumab and has assumed the same would apply for abaloparatide as both are newer therapies. Both experts said that they would schedule a nurse visit once during early treatment. The EAG has assumed one nurse visit over the course of the anabolic treatment but has included this in the upfront cost one-off cost as it is likely to occur in the first cycle. This is in addition to the one-off cost for the first administration which the company already applies. The EAG has also included cost for reporting to the referrer in its one-off up-front cost for patient initiating an anabolic treatment as the company reported including this cost but it was not implemented in the model. For patients having follow-on alendronate therapy, the EAG's clinical advisors stated that they would usually see them once during their treatment course. The EAG has implemented this a $1/10^{th}$ of a specialist consultation per 6-month cycle, but acknowledges that this annualised approach may underestimate costs given that not all patients complete the 5 years of bisphosphonate treatment. The EAG acknowledges that these resource use assumptions are unlikely to capture the exact resource use in clinical practice especially given that there is likely to be variation in how patients are followed-up in different secondary care centres with some offering more or less frequent follow-ups or making more or less use of nurse-led or non face-to-face consultations. However, the EAG wanted to capture the potential for some increased resource use for abaloparatide and romosozumab versus teriparatide given that there is less clinical experience of using these newer anabolic therapies in many centres.

In addition, the EAG disagrees with some of the unit costs used by the company. The cost of the BMD measurements should have been sourced from NHS Reference Costs 2021/22 using the same code as in TA791 (code RD50Z, DEXA scan, total HRG £95.45),[76] instead of the same value from TA791 (£40.00, from the National Tariff Workbook 2020/2021).[83] The initial and follow-up appointments with specialist should correspond to a consultant-led non-admitted face-to-face attendance to endocrine

services in outpatient care (£220.74, code WF01A, service code 302 from 'OP' worksheet in NHS Reference Costs 2021/22),[76] whilst an initial follow-up visit with nurse after treatment initiation with a nurse correspond to non-consultant-led non-admitted face-to-face attendance to endocrine services in outpatient care (£134.83, code WF01A, service code 302 from 'OP' worksheet in NHS Reference Costs 2021/22).[76] As anabolic therapies are prescribed in secondary care, the EAG prefers to assume that the first supervised administration occurs as an additional task within a secondary care outpatient visit rather than being delivered by a primary care nurse, as assumed by the company. The EAG therefore assumes that the additional nurse time to demonstrate how to operate the treatment injections should correspond to a band 7 hospital-based nurse (assuming a 15 min appointment and using hourly cost of £64 from PSSRU 2022).[74] However, the EAG's clinical advisor noted that where anabolic therapies are delivered via a healthcare at home provider, the training on self-administering treatments can be provided as part of that service. Table 53 summarises the differences in the company's and EAG's approaches to disease management costs.

Table 53: Summary of health state resource use and costs (one-off cost and per 6-month cycle) used by the company in CRCQ2 and EAG's analyses*

	Resource component	Company's model at CRCQ2		EAG model			
		Initial treatment	Subsequent treatment	Initial treatment	Subsequent treatment	Initial treatment	Subsequent treatment
		Abaloparatide /romosozumab /teriparatide	Alendronate	Abaloparatide	Romosozumab	Teriparatide	Alendronate
Drug admin cost (one-off, at treatment initiation)		£12	£0	£16	£16	£16	£16
Disease management (one-off, at treatment initiation)	Nurse visits	£0	£0	£135	£135	£135	£0
	BMD measurement	£0	£0	£95	£95	£95	£0
	Specialist consultation	£0	£0	£221	£221	£221	£0
	Reporting to referrer	£0	£0	£1	£1	£1	£0
Total one-off-cost		**£12**	**£0**	**£468**	**£468**	**£468**	**£0**
Disease management (on-going per cycle costs)	Nurse visits	£7	£7	£0	£0	£0	£0
	BMD measurement	£10	£10	£32	£48	£24	£0
	Specialist consultation	£0	£0	£221	£221	£110	£22
Total ongoing cost (per cycle)		**£17**	**£17**	**£253**	**£268**	**£134**	**£22**

BMD – bone mineral density
**The costs from the company's estimates include the original unit costs, whilst the EAG's estimates includes the changes in unit costs described above*

4.3.4.3 Remaining areas of uncertainty

The EAG noted that there were a few issues identified for which it was unable to provide an estimate of the likely impact and these were therefore considered to be areas of remaining uncertainty.

Restriction of follow-on antiresorptive treatment to alendronate

As discussed in Section 2.3.3, the clinical advice to the EAG was that patients would usually receive IV zoledronate following an anabolic treatment, with denosumab being used in patients contraindicated for bisphosphonates. This is also supported by the company's own KOL survey, with the majority of respondents (KOLs 1, 2, 4, 5 and 6) reporting use of IV bisphosphonates in place of oral alendronate in at least one of their responses.

There are no data in the CS on whether the BMD or fracture outcomes would be similar when using IV zoledronate instead of alendronate as the follow-on treatment after an anabolic therapy. In TA464, the committee concluded that efficacy estimates for oral and IV bisphosphonates could be pooled as they were considered to be clinically interchangeable in terms of efficacy. The EAG would therefore expect that similar clinical outcomes would be achieved when using IV bisphosphonates instead of oral bisphosphonates as the follow-on antiresorptive treatment. However, the committee for TA464 also concluded that each bisphosphonate treatment would differ in terms of persistence, administration costs and AEs.

Incorporating IV zoledronate as the follow-on antiresorptive treatment in the model would be expected to increase the costs of treatment over the lifetime of the patient for both abaloparatide and the comparator anabolic therapies. However, as each anabolic treatment has different persistence data, it is not clear that the additional cost for using IV instead of oral bisphosphonates as the follow-on treatment would be equivalent when using different anabolic treatments. If it can be assumed that the percentage starting antiresorptive treatment would be the same regardless of the choice initial anabolic treatment and that it would not be affected by differing degrees of persistence to anabolic treatment, then any additional cost is likely to be similar across the different model arms.

The EAG also notes that the CS does not address the treatment pathway for patients who are contraindicated for bisphosphonates who may have denosumab treatment as their antiresorptive follow-on treatment after anabolic therapy. This is potentially a significant omission given that teriparatide is currently recommended as a second-line treatment for patients with a contraindication for bisphosphonates. Therefore if abaloparatide is offered as an alternative to patients currently offered teriparatide, it is likely that some patients will require a non-bisphosphonate follow-on treatment.

The restriction of the economic model to using alendronate as the follow-on antiresorptive therapy is a limitation of the company's economic model that the EAG were unable to address in the time available as it would require significant adaptations to the company's model to incorporate costs, efficacy and persistence data for both IV zoledronic acid and denosumab.

Modelling of antiresorptive therapy in patients stopping anabolic treatment early

The company states in response to question CQ2 B18 that in its updated model, follow-on treatment with alendronate is not restricted to those who receive the full course of anabolic therapy. However, the efficacy and costs of treatment are tied to a column that records whether the patient is 'on treatment' or not. If the patient is recorded as being off treatment during the anabolic phase of treatment, then they remain off treatment for the rest of the model and therefore no costs or benefits of alendronate treatment are applied to those patients. This is because a single treatment persistence curve is applied for the whole treatment sequence. Therefore, if the patient is sampled as being not persistent with treatment during the anabolic phase of treatment, then they do not start treatment with alendronate. The EAG's clinical experts considered that follow-on treatment with an antiresorptive would be required even if patients had not completed their anabolic therapy due to the potential for increased bone turnover when coming off an anabolic therapy and due to the fact that patients would need to be a high risk to start anabolic therapy and therefore an alternative treatment would be needed to prevent fracture. The EAG explored whether it was possible to correct the model in this respect, but the application of the single treatment persistence curve meant this was not possible without a significant restructure of the model which could not be achieved in the time available.

Non-inclusion of impact of AEs

In the latest versions of the model at CRCQ1 and CRCQ2, the company has not included any impact on costs and HRQoL related to AEs associated with abaloparatide, teriparatide, romosozumab or alendronate. The AEs originally included in the model submitted at CS,[1] using frequency of AEs from ACTIVE[5] and FRAME[82] studies are provided in Table 54 for reference. Costs and QALY losses were not applied to these adverse events in the original model and they were removed entirely at CRCQ1 meaning that no AEs are modelled for any drugs included in the cost-effectiveness analysis.

Table 54: Incidence of AEs included in original model at CS[1] (reproduced from company's model)

	Treatment group		
AE (incidence in %)	**Abaloparatide**	**Romosuzumab**	**Teriparatide**
Hypercalciuria	[redacted]		[redacted]
Dizziness	[redacted]		[redacted]
Upper respiratory tract infection	[redacted]		[redacted]
Back pain	[redacted]	10.5%	[redacted]
Headache	[redacted]		[redacted]
Nausea	[redacted]		[redacted]
Arthralgia	[redacted]		[redacted]
Hypertension	[redacted]		[redacted]
Influenza	[redacted]		[redacted]
Nasopharyngitis	[redacted]	12.8%	[redacted]
Palpitations	[redacted]		[redacted]
Urinary tract infection	[redacted]		[redacted]
Cardiac disorders†	[redacted]	6.3%	[redacted]
Vascular disorders†	[redacted]		[redacted]

**The EAG believes this is a typo and it should be [redacted] according to CSR addendum table 18.*
† Based on values in Table 15 of the CSR addendum for abaloparatide and teriparatide, the EAG is unclear from where the value for romosozumab was obtained.

The EAG notes that the cost-effectiveness analysis conducted to inform TA464 included gastrointestinal side effects for oral bisphosphonates (e.g. alendronate) and flu-like symptoms for IV bisphosphonates. The analysis by Davis et al. (2020) extended this list to include osteonecrosis of the jaw (ONJ) for bisphosphonates and denosumab and cellulitis for denosumab. No adverse effects were included in the modelling by Davis et al. (2020) for either teriparatide or romosozumab. In NICE TA791, the company base-case submitted at the CS accounted only for GI AEs in patients receiving oral bisphosphonates, using similar assumptions to TA464. At the clarification response stage, based on the EAG's request, costs and QALY losses related to cardiovascular (CV) AEs were included as part of a scenario analysis for patients without a contraindicating history of prior MI or stroke. The frequencies, cost and utility values applied in previous appraisals are summarised in Table 49 for reference.

Clinical advisors consulted by the EAG have stated they would expect patients receiving abaloparatide to experience similar AEs to teriparatide, such as hypercalcaemia, nausea and muscle spasms/cramps. They also stated that romosozumab is generally well tolerated, although it is being avoided in patients with risk of CV events other than age. The EAG's clinical experts noted that AEs leading to patients seeking medical attention or requiring hospitalisation would be more likely to significantly impact costs and HRQoL. The EAG note that the data in Table 54 are not restricted to serious or severe AEs and

these were rare in the ACTIVE study suggesting that the exclusion of AEs may not be a significant issue for the cost-effectiveness analysis. The EAG also notes that the limited report of AEs of interest in ARCH and FRAME for romosozumab limits its comparisons and is likely to disadvantage abaloparatide and teriparatide. Therefore, and since the inclusion of oral bisphosphonates as subsequent treatment in the model adopts similar assumptions and source of persistence data for all treatment groups, the EAG has not explored the inclusion of AEs in the model given its likely minor impact in the results.

The EAG notes that the model does not include any direct utility decrement attributable to the discomfort of daily or monthly injections. This may fail to capture differences between the anabolic therapies in terms of the duration of time over which patients are required to continue with a subcutaneous treatment and differences between abaloparatide and romosozumab in terms of the requirement for daily rather than monthly dosing.

Table 55: AEs included in previous key osteoporosis appraisals

	Bisphosphonates model (TA464)				Non-bisphosphonates model (Davis *et al.* 2020)				Romosozumab appraisal (TA791)			
AE type	**AE rate**	**Cost**	**QALY loss**	**Applied to**	**AE rate**	**Cost**	**QALY loss**	**Applied to**	**AE rate**	**Cost**	**QALY loss**	**Applied to**
GI	3%	£47	0.0075	oral BPs	3%	£47	0.0075	oral BPs	3%	£40	0.0075	oral BPs
Flu-like	14%	£0	0.005	IV BPs	14%	£0	0.005	IV BPs	-	-	-	-
Serious cellulitis	-	-	-	-	0.2%	£4,467	0.005	Den†	-	-	-	-
ONJ	-	-	-	-	0.022%	£166	0.206	Oral BP	-	-	-	-
					0.007%			IV BP				
					0.052%			Den				
CV	-	-	-	-	-	-	-	-	redacted	£4,994 (6 mo); £2,460 (6mo+)	Multiplier of 0.910 (y1); 0.95 y1+)	Romo

BP – bisphosphonates; Den – denosumab;IV – intravenous; mo – months; Rlx – raloxifene; Romo – romosozumab; y – year.
† per year of exposure to treatment

Issue 17– Grouping of fractures into hip, vertebral and NHNV

The EAG notes that the model assumes the same cost and HRQoL implications for all NHNV when NHNV covers a heterogeneous group of fractures (distal forearm, distal radius, wrist, femur, pelvis, humerus, rib, clavicle, scapula, sternum) which might have heterogenous impacts. This is in contrast to the approach taken in a previous model by Davis *et al.*, in which femoral shaft fractures were grouped with hip fractures to reflect the expectation that they would have similar costs and HRQoL implications.[9, 44] The company's approach may therefore underestimate the cost and HRQoL implications of femoral shaft fractures by assuming they are similar to those of wrist or shoulder fractures. The EAG has not explored this issue in their exploratory analyses given the significant restructure of the model necessary which could not be achieved in the time available.

4.4 Exploratory analyses undertaken by the EAG

4.4.1 Overview of the EAG's exploratory analyses

The EAG undertook exploratory analyses (EAs) using the updated version of the model provided in the CRCQ2. All EAs were undertaken using the deterministic version of the model. Probabilistic ICERs were also generated using the EAG's preferred analysis. All analyses were undertaken by one modeller and checked by a second modeller. All analyses presented in this section reflect the PAS price of abaloparatide. The results of the analyses are provided in Section 4.4.3. The results of the analyses including price discounts for comparator therapies are provided in a separate confidential appendix to this report.

4.4.2 EAG's exploratory analyses – methods

4.4.2.1 Correction of errors (EAG EA 1)

The following corrections were applied to the company's model:

a) The company's model uses the binomial distribution to sample heterogeneity for parameters such as prior fracture, current smoking, glucocorticoid steroid use, rheumatoid arthritis, alcohol use of ≥ 3 units per day (see Issue 2a). Because these are not continuous but discrete variables in terms of an individual patient, the EAG modified the way to sample those characteristics with probability. For example, as the proportion with a prior fracture from the ACTIVE trial is 59%, the EAG allocated the patient to having a prior fracture at baseline if a random number drawn from a uniform (0,1) distribution was under 0.59.

b) When running the PSA, the company's model does not use random number control to ensure that the same parameter sample is applied to each patient in the cohort (see Issue 2b). The EAG has adapted the model to fix this by making the samples in column P of the parameter sheet dependent on an array of random numbers that updates once for each PSA run.

c) In the company's model, RR_{frax_fx} is only applied when an incident fracture occurs in the model and is not applied for patients with a prior fracture at baseline (see Issue 2c). The EAG adapted the formulas which apply the maximum of RR_{frax_fx} and $RR_{imminent}$ in columns BH to BJ of each simulation sheet to apply RR_{frax_fx} when there is a prior fracture at baseline but no incident fracture has yet occurred.

d) The EAG adopted an approach to reduce utility with subsequent fractures, regardless of the fracture site. Therefore, in the EAG's correction, when an incident fracture is experienced, the utility for the first year after fracture for the incident fracture is multiplied by any subsequent year utility multipliers for fractures previously experienced (see Issue 2d).

e) The EAG has corrected the model to assume drug acquisition costs for abaloparatide are based on 18 pre-filled pens over 18 months (12 per annum), instead of the 19 assumed by the company (see Issue 2e). In addition, the drug cost for alendronate was based on its eMIT price (£0.18) and the drug costs for teriparatide was based on the lowest cost biosimilar (Movymia, £235).

f) The EAG used the cost estimates for acute care in the first and subsequent years post-fracture using the values uplifted to 2022 by EAG using NHSCII (Issue 2f). In this analysis, the EAG applied the costs per annum shown in Table 49.

g) The EAG fixed the formulas in column DT of each simulation sheet to look at the age of the first hip fracture (cell AU3) instead of the age of a fracture of any type (cell AT3) to refer to the probability of being admitted at a long-term care facility (see issue 2g).

h) The cost associated with teaching patients to self-administer should be applied as a one-off cost for all patients, regardless of whether they discontinue treatment within six months (see Issue 2h). The EAG has removed the dependence on treatment persistence so the cost is applied to all patients in the first cycle by adapting cell CZ7 in each of the simulation sheets.

i) The EAG fixed the formulas in columns AV, AY and BB of each simulation sheet where the time since last fracture was being used instead of the number of prior fracture to determine the HRs following an incident hip fracture (see Issue 2i).

j) The total cycles on treatment (including both anabolic and alendronate) was adjusted to ensure a maximum of 12, 13, and 14 cycles for romosozumab, abaloparatide and teriparatide respectively (see Issue 2j).

k) The EAG has corrected the transition matrix to apply the same formulae in row 7 as applied in row 8. The row 7 transition probabilities are then applied to estimate the events occurring in the first cycle rather than assuming no events in the first cycle (see Issue 2k).

l) The EAG corrected the BMD decline per annum to match the value reported by Stevenson et al (0.0512 instead of 0.0419) .[66]

As these were considered to be error corrections, these changes were maintained in all subsequent EAG analyses.

4.4.2.2 Choice of HRs and use of CODA samples in PSA (EAG EA2)

The EAG has chosen to use alternative HRs for abaloparatide for the outcomes of hip fracture an NHNV fracture due to substantial uncertainty in the NMA HRs for hip fracture and inconsistency in the direction of effect for the median HR for NHNV fractures when comparing the NMA results to the RWE (see Issue 4). The HRs applied have been previously summarised in

Table **52**.

In addition, the EAG incorporated the CODA samples for the HRs versus placebo directly into the PSA. For each iteration of the PSA, a single CODA sample (which includes the HRs for all three drugs) is randomly selected and assigned to a simulated cohort. This approach maintains the correlation between the HRs from the NMA and also ensures that the same set of sampled HRs are applied to every patient in the cohort (see Issue 3). This change was only applied when the EAG ran the PSA for its preferred base case scenario.

4.4.2.3 The persistence rate of romosozumab at 6 months (EAG EA3)

The EAG assumed a linear reduction in persistence from baseline to 1 year for romosozumab in line with the approach taken for teriparatide by the company. Given the company's assumed 80% persistence at 1 year, the EAG approach provided a persistence at 6 months of 90% instead of the company's approach of applying 80% at both 6 months and 12 months (see Issue 5).

4.4.2.4 Long-term costs simulated individually (EAG EA4)

Long-term care fracture costs are estimated using an individual approach, rather than a cohort approach of the company (see Issue 6). This is achieved by comparing the risk of admission to long-term care against a number drawn from a uniform(0,1) distribution and applying the whole cost of long-term care admission where the number drawn is less than the risk of admission. This is different to the company's approach where a proportion of the long-term care costs, equivalent to the risk of long-term care admission, are applied to every patient having a hip fracture.

4.4.2.5 Resource use for disease management (EAG EA5)

As described in Issue 8, the EAG used different estimates of resource use and unit costs for disease management costs, to reflect their preferences for unit costs and advice from their clinical experts regarding likely resource use. The values preferred by the EAG and included in their EA5 analysis have been previously provided in Table 53.

4.4.2.6 EAG's preferred base case scenario

The EAG's preferred base case scenario incorporates all changes in EAG EA 1 to 5 for the deterministic analysis. The incorporation of the CODA samples within EAG EA 2 was also included in the EAG's preferred base case scenario but it only affects the probabilistic sensitivity analysis.

4.4.2.7 Additional sensitivity analyses

The following additional sensitivity analyses were conducted using the deterministic version of the EAG's preferred base case scenario as the starting point.

EAG SA 1: Use of persistence rates from trials

In this scenario analysis, the persistence rates for patients receiving abaloparatide and teriparatide are based on the completion rates at 18 months from the ACTIVE study,[5] whilst using the completion rate of 89.3% at 12 months for romosozumab from the ARCH trial.[87] The data used in the EAG's scenario analysis are shown in

Table 56**Error! Reference source not found.**.

Table 56: Persistence data applied in the EAG's scenario analysis using trial-based persistence data (*italics* show persistence for the alendronate part of the treatment sequence)

Time, years	Abaloparatide [a]	Romosozumab	Teriparatide [a]
0.5	[redacted]	94.7%	[redacted]
1.0	[redacted]	89.3%	[redacted]
1.5	[redacted]	[redacted]	[redacted]
2.0	[redacted]	[redacted]	[redacted]
2.5	[redacted]	[redacted]	[redacted]
3.0	[redacted]	[redacted]	[redacted]
3.5	[redacted]	[redacted]	[redacted]
4.0	[redacted]	[redacted]	[redacted]
4.5	[redacted]	[redacted]	[redacted]
5.0	[redacted]	[redacted]	[redacted]
5.5	[redacted]	[redacted]	[redacted]
6.0	[redacted]	[redacted]	[redacted]
6.5	[redacted]	-	[redacted]
7.0	[redacted]	-	[redacted]

[a] *same as company scenario analysis as shown in Table 38*

EAG SA 2: Use of HRs from trials

In this scenario, the EAG applied the treatment efficacy directly from trials, by using the HRs versus placebo from the ACTIVE (teriparatide and abaloparatide) and ARCH trials (romosozumab), as implemented in the company's scenario analysis (Scenario 1 in Table 47**Error! Reference source not found.**).

EAG SA 3: NHNV subsequent year cost

In this scenario, the EAG included the cost of acute care in subsequent years after fracture for NHNV fractures from Gutierrez *et al.* 2012 (uplifted by the EAG to 2022 values using HCHS and NHSCII indices, £94.26 see Table 49).

EAG SA 4: Higher risk subgroup using characteristics from ARCH trial

In this scenario, the EAG has used the patient characteristics from the ARCH trial to represent a population more closely aligned to the group likely to receive romosozumab in clinical practice. The population of the ARCH trial was considered suitable because all patients enrolled in ARCH had a prior fracture at baseline and a previous fracture is a requirement for both teriparatide and romosozumab

under current NICE guidance (see Box 1). The characteristics assumed in this scenario analysis are provided in Table 57.

Table 57: Patient characteristics used in the company's base-case and the EAG's scenario analysis for higher risk patients

Patient characteristic	Company's base-case	EAG scenario analysis for higher risk subgroup
Age	69.5	74.0[a]
Prior fracture (%)	58.50	100.00[b]
Current smoking (%)	12.10	18.00[b]
Glucocorticoid use(%)	1.30	5.00[b]
Rheumatoid arthritis (%)	0.30	3.00 [b]
Alcohol (≥ 3 units/day, %)	0.10	1.00[b]
Femoral neck T-Score	-2.19	-2.90[a]
Source	ACTIVE trial[5]	[a] TA791[3] [b] Söreskog *et al.* (2021)[56]

EAG SA 5: Apply utility for nursing home admission

In this scenario analysis, the EAG applied a utility multiplier (0.625) for new admission to long-term care to patients having this outcome after hip fracture. This was only possible due to the EAG's adaptation of the model to allow an individual approach for long-term care costs.

EAG SA 6: Use of same HRs for abaloparatide, teriparatide and romosozumab for hip, vertebral and NHNV

In this scenario analysis, the EAG wished to explore the impact on the cost-effectiveness estimates of assuming equivalent efficacy between all three anabolic therapies. To implement this, the HRs versus placebo for teriparatide were applied to the abaloparatide and romosozumab arms as these were populated by a greater number of studies. In this scenario analysis, the only differences in fracture outcomes occur due to differences in the planned duration of treatment (12 months for romosozumab, 18 months for abaloparatide and 24 months for teriparatide) or differences in treatment persistence. As discussed previously (see Issue 4), this is equivalent to a cost-comparison scenario and the HRs applied have been previously summarised in see

Table **52**.

EAG SA 7: Use of HRs for hip and NHNV from the NMA for abaloparatide

This scenario uses the HRs for hip and NHNV fractures from the NMA for abaloparatide as assumed in the company's base case. It is equivalent to removing EA2 from the EAG's preferred base case but keeping all other changes (EA1 & EA3 to EA5)

4.4.3 Results of the EAG's exploratory analyses

The results of the EAG's preferred analyses are shown in

Table **58**, which provides the impact of each individual change and the results for the EAG's preferred base case. Scenario analyses exploring individual changes using the EAG preferred base case as the starting point are shown in Table 59. As the ICERs shown in this report will not be used for decision making, because they do not include the comparator PAS or other confidential prices, the EAG's discussion of these results will focus on identifying the changes that have the largest impact on the ICER rather than on the numerical estimates of incremental costs and QALYs.

4.4.3.1 Impact of individual changes

The EAG's exploratory analysis which included all the model corrections made by the EAG (EA1) provides incremental costs and QALYs, for each pair wise comparison, which are numerically smaller than in the company's base case but are in the same direction. Therefore the differences between the treatments are reduced in the EAG's corrected model compared with the company's base case model. The impact of each individual correction within EAG1 is provided in Appendix 4 for reference. The correction to the sampling of baseline characteristics appears to have the largest impact out of all of the corrections included within EA1.

In the scenario analysis in which the treatment efficacy for teriparatide has been applied to abaloparatide for the outcomes of hip and NHNV fracture (EA2) the incremental QALYs versus teriparatide is in the opposite direction to the results for the EAG corrected model (EA1). This is because in this scenario abaloparatide has the same HRs as teriparatide but a shorter treatment duration. In the comparison against romosozumab for this scenario, the incremental QALY gains are in the same direction but are smaller as in this scenario abaloparatide has a higher HRs (i.e. worse efficacy) for hip fracture compared to romosozumab.

In the scenario incorporating higher persistence for romosozumab at 6 months (EA3), the incremental QALYs are in the same direction, but are numerically smaller than in EA1, whilst the incremental costs are in the same direction and are numerically [redacted], due to the longer time spent on romosozumab. Using an individual approach to simulating long-term care costs after hip fracture (EA4) results in incremental costs that are in the same direction, but which are numerically [redacted] compared to EA1. Using the EAG's preferred assumptions for resource use related to disease management (EA5) provides minimal change in the incremental costs.

Overall, the decision around whether to apply the HRs from teriparatide to abaloparatide for the hip and NHNV fracture outcomes, instead of using the estimates from the NMA, is having the largest impact out of all of the EAG exploratory analyses, although for the comparison against romosozumab the treatment persistence data are also having an important impact.

4.4.3.2 The EAG's estimate of the ICER (deterministic)

In the comparison against teriparatide, the EAG's preferred base case, which combines EA1 to EA5, provides incremental QALYs that are smaller and in the opposite direction to those estimated in the company's base case and the incremental costs are in the same direction but are numerically [redacted]. This is because the differences between abaloparatide and teriparatide are reduced by the assumptions made in the EAG' preferred base case, in particular the assumption of equal treatment effectiveness for hip and NHNV fractures.

In the comparison against romosozumab, the EAG's preferred base case, which combines EA1 to EA5, provides incremental QALYs that are in the same direction, but are numerically smaller but those estimated in the company's base case. The incremental costs are in the same direction and are numerically [redacted]. This is because the differences between abaloparatide and teriparatide are reduced by the assumptions made in the EAG' preferred base case, in particular the assumption of equal treatment effectiveness versus teriparatide for hip and NHNV fractures and the improved treatment persistence at 6 months for romosozumab.

The EAG re-ran its preferred base case deterministically 10 times using different sets of random number seeds to check that the results presented in

Table **58** are not outliers due to the choice of random number seeds. There was some variation in the QALY gains which varied from -0.008 to -0.001 for abaloparatide versus teriparatide and 0.001 to 0.018 for abaloparatide versus romosozumab. As the PSA used a different set of random number seeds for each PSA run, the EAG considers that the PSA results are likely to be a more robust estimate of the incremental costs and QALYs because they average over 200 sets of random number seeds as well as averaging over parameter uncertainty.

Table 58: EAG exploratory analysis results (pairwise against each of the comparators)

Option	Absolute outcomes by treatment arm			Incremental outcomes for abaloparatide versus comparator			Cost per QALY (£)
	LYGs*	QALYs	Costs	LYGs	QALYs	costs	
Company's base case, deterministic							
Abaloparatide	[redacted]	[redacted]	[redacted]				
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.013	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.031	[redacted]	[redacted]
EAG EA1: Correction of model errors, deterministic							
Abaloparatide	[redacted]	[redacted]	[redacted]				
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.024	[redacted]	[redacted]
EAG EA2: EA1+ Use of same HRs for abaloparatide and teriparatide for hip and NHNV, deterministic							
Abaloparatide	[redacted]	[redacted]	[redacted]				
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	-0.005	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.010	[redacted]	[redacted]
EAG EA3: EA1+The persistence rate of romosozumab at 6 months, deterministic							
Abaloparatide	[redacted]	[redacted]	[redacted]				
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.016	[redacted]	[redacted]
EAG EA4: EA1+Long-term costs simulated individually, deterministic							
Abaloparatide	[redacted]	[redacted]	[redacted]				
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.024	[redacted]	[redacted]
EAG EA5: EA1+ Resource use for disease management, deterministic							
Abaloparatide	[redacted]	[redacted]	[redacted]				
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.024	[redacted]	[redacted]
EAG-preferred base case (EAG EA1-5 combined), deterministic							
Abaloparatide	[redacted]	[redacted]	[redacted]				
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	-0.005	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.002	[redacted]	[redacted]
EAG-preferred base case (EAG EA1-5 combined), probabilistic							
Abaloparatide	[redacted]	[redacted]	[redacted]				
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	-0.005	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.015	[redacted]	[redacted]

**Undiscounted*
LYG - life year gained; QALY - quality-adjusted life year

4.4.3.3 The EAG's estimate of the ICER (probabilistic)

The results for the EAG's preferred base case when using the mean outcomes across 200 PSA runs provides incremental costs and QALYs that are in the same direction as the deterministic results. For the comparison against romosozumab, both incremental cost and QALYs are numerically [redacted]. For the comparison against teriparatide, incremental QALYs are similar but incremental costs are numerically [redacted]. The spread of incremental cost and QALY estimates on the cost-effectiveness plane is shown in Figure 20. It can be seen that these are much more broadly spread than in the company's PSA (

Figure 19), reflecting the EAG's preference to use the CODA samples to incorporate the uncertainty around the HRs.

Figure 20: Cost-effectiveness plane for the EAG's preferred model (combining EA1 to EA5)

4.4.3.4 The EAG's sensitivity analyses

The EAG's sensitivity analyses show that the scenario analysis using treatment persistent data from the trials (SA1) has an important impact on the cost-effectiveness estimates for romosozumab, with incremental QALYs in the opposite direction the EAG's preferred base case. This suggests that much of the difference between romosozumab and abaloparatide in the EAG's base case is being driven by the company's decision to assume 80% persistence at 1 year for romosozumab rather than assuming equivalent persistence to teriparatide as it assumed for abaloparatide.

The scenario analysis using HRs from the trials (SA2) shows incremental costs and QALYs that are in the same direction as for the EAG's preferred base case, but the differences in QALYs are numerically larger when using the efficacy data directly from the trials. However, the EAG notes that the comparison against romosozumab in this scenario is a completely unadjusted indirect comparison and should therefore be viewed with a high degree of caution.

The sensitivity analysis in which all HRs are set equal for all three treatment strategies (SA6) shows that the duration of time on treatment is having a large impact on the cost-effectiveness estimates, with the incremental QALYs for abaloparatide versus romosozumab being numerically greater when treatment duration is the only difference between these treatments, due to the additional 6 months on treatment for abaloparatide versus romosozumab.

The results for the higher risk subgroup (SA4) suggests that the company's decision to use the patient characteristics from the ACTIVE study, which recruited a lower risk cohort than the ARCH study, may have meant that differences between the treatments are potentially underestimated as the incremental costs and QALYs are in the same direction but are numerically [redacted] when modelling a higher risk patient cohort in which all patients had a prior fracture at baseline.

The EAG's sensitivity analyses show that the cost-effectiveness estimates are not particularly sensitive to whether there is an ongoing cost assumed beyond the first year in patients having NHNV fractures (SA3) or whether a utility multiplier is applied to those patients admitted to long-term care after a hip fracture (SA5).

The results for the sensitivity analysis using the NMA HRs for abaloparatide for the hip and NHNV outcomes (SA7) are much more favourable to abaloparatide because the median HR from the NMA for abaloparatide versus placebo provides a reduced hip fracture risk relative to both teriparatide and romosozumab. However, these results should be interpreted with caution given the wide credible intervals in the hip fracture NMA for abaloparatide which is not captured in this deterministic analysis and the fact that few events were observed in the ACTIVE study.

Table 59: EAG sensitivity analysis results (pairwise comparisons, deterministic unless stated otherwise)

Option	Absolute outcomes by treatment arm			Incremental outcomes for abaloparatide versus comparator			Cost per QALY (£)
	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	
EAG-preferred base-case, deterministic							
Abaloparatide	[redacted]						
Teriparatide					-0.005		
Romosozumab					0.002		
EAG SA1: Use of persistence rates from trials, deterministic							
Abaloparatide	[redacted]						
Teriparatide					-0.004		
Romosozumab					-0.010		
EAG SA2: Use of HRs from trials, deterministic							
Abaloparatide	[redacted]						
Teriparatide					-0.010		
Romosozumab					0.011		
EAG SA3: NHNV cost in subsequent years = £94.26, deterministic							
Abaloparatide	[redacted]						
Teriparatide					-0.005		
Romosozumab					0.002		
EAG SA4: Higher risk subgroup using characteristics from romosozumab studies, deterministic							
Abaloparatide	[redacted]						
Teriparatide					-0.016		
Romosozumab					0.027		
EAG SA5: Applying utility multiplier for nursing home admission, deterministic							
Abaloparatide	[redacted]						
Teriparatide					-0.005		
Romosozumab					0.002		
EAG SA6: Use of same HRs for abaloparatide, teriparatide and romosozumab for hip, vertebral and NHNV (cost-comparison scenario), deterministic							
Abaloparatide	[redacted]						
Teriparatide					-0.005		
Romosozumab					0.012		
EAG SA7: Use of HRs for hip and NHNV from the NMA for abaloparatide, deterministic							
Abaloparatide	[redacted]						
Teriparatide					0.008		
Romosozumab					0.016		

**Undiscounted*

LYG - life year gained; QALY - quality-adjusted life year; HR – hazard ratio; SW – ICER in South-West quadrant.

5 OTHER FACTORS

The company has not submitted any evidence to support the implementation of a severity modifier in this appraisal. Although the company has not presented estimates of the absolute and proportional QALY losses required to evaluate whether a severity modifier should be applied in this case, the EAG does not believe that it is likely that the requirements would be met in this appraisal. A managed access scheme has not been proposed.

6 OVERALL CONCLUSIONS

The pivotal trial for abaloparatide (ACTIVE) found that abaloparatide significantly reduced the risk of new vertebral fractures compared with placebo at 18 months, but a significant reduction was not demonstrated for non-vertebral fractures. Whilst the ACTIVE study provides a direct comparison against teriparatide, it was not sufficiently powered to detect a difference in fracture outcomes between abaloparatide and teriparatide. However, there is supportive evidence from a non-randomised RWE study that reported noninferiority of abaloparatide versus teriparatide for the endpoints of new non-vertebral fracture rate and time to first non-vertebral fracture.

There are no studies comparing abaloparatide directly to romosozumab and therefore the comparison against romosozumab is informed by an NMA. Abaloparatide was associated with a greater reduction in new vertebral fractures in the NMA (lowest median HR versus placebo), but the HRs for abaloparatide versus teriparatide and romosozumab cross 1, indicating uncertainty over which treatment has the greatest effect on vertebral fractures. Results for the hip fracture NMA for abaloparatide versus romosozumab and teriparatide are extremely uncertain due to the low number of events in the ACTIVE study. The difference in non-vertebral fractures between abaloparatide and teriparatide was not statistically significant when using the NMA, and the direction of treatment effect was inconsistent with the findings of the RWE study.

The EAG had concerns regarding the generalisability of the findings from the ACTIVE study to the patient group likely to be offered either teriparatide or romosozumab in current clinical practice. The main concern was the inclusion of patients without a prior fracture. This is important as the company's cost-effectiveness analysis includes only teriparatide and romosozumab as comparators but both teriparatide and romosozumab are restricted under current NICE guidance to patients who have had previous a fracture. The patient characteristics in the model are also based on the patients enrolled in ACTIVE, which means that the model results may not be generalisable to patients currently likely to be offered teriparatide or romosozumab in current practice. The CS also provides no information on the likely cost-effectiveness of abaloparatide in patients who are at high or increased risk of fracture and who are not eligible for treatment with teriparatide or romosozumab but who may be treated with either IV zoledronate or denosumab in current practice.

The company's base case cost effectiveness analysis estimates that abaloparatide is expected to provide more QALYs than either teriparatide or romosozumab, whilst having a [redacted] expected cost. However, this conclusion is being driven by the use of the median HR from the hip fracture NMA in the deterministic analysis and a failure to use the CODA samples to properly reflect the uncertainty in the HR estimates in the probabilistic analysis. In the EAG's preferred analysis, abaloparatide is estimated

to generate lower QALYs than teriparatide, because the EAG prefers to assume that abaloparatide has the same efficacy as teriparatide for hip fracture, given the uncertainty in the hip fracture NMA. In the EAG's preferred analysis, abaloparatide is estimated to have [redacted] costs and greater QALY gains compared to romosozumab, but the size of the incremental QALYs is smaller for the same reason.

The results of the sensitivity analysis using trial-based estimates of treatment efficacy were more consistent with the EAG's base case scenario than the company's base case scenario. Although the comparison against romosozumab using trial-based estimates is an unadjusted indirect comparison and should therefore be viewed with a high degree of caution.

The cost-effectiveness estimates are also sensitive to the estimates of treatment persistence. The company assumed equivalent treatment persistence for teriparatide and abaloparatide but not for romosozumab, which may have overestimated the difference in outcomes between abaloparatide and romosozumab. The EAG's 'cost-comparison scenario' in which the HRs were set equal for all treatments demonstrates that the additional 6 months of treatment duration for abaloparatide versus romosozumab is an important driver of cost-effectiveness.

The EAG also notes that differences between the treatments may have been underestimated by the company's decision to the use the ACTIVE trial population to specify patient characteristics rather than a population restricted to higher risk patients with a prior fracture. This is because any QALY gains (or QALY losses) will be greater in a higher risk population.

Finally, the EAG notes that all results presented in this report use the lists price for romosozumab and teriparatide and it refers the committee to the confidential appendix which includes results incorporating confidential prices for both comparators.

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8 APPENDICES

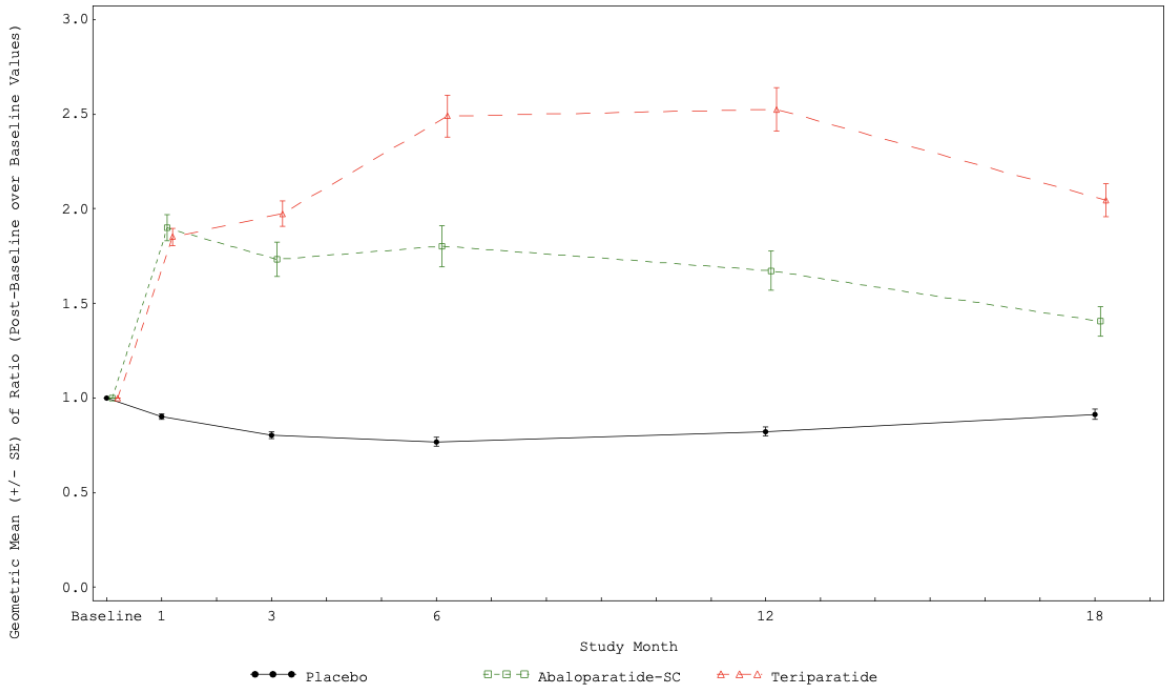
Appendix 1: Bone turnover marker endpoints in ACTIVE and ACTIVExtend

The CS reported that changes in the bone turnover markers s-P1NP (a bone formation marker) and s-CTX (a bone resorption marker) correlated with BMD data (Section 2.6.3).[1] The ACTIVE trial bone turnover marker population comprised 156 patients in the placebo group, 164 patients in the abaloparatide group and 180 patients in the teriparatide group. In ACTIVE, the bone formation marker s-P1NP showed significant increases among abaloparatide-treated participants compared with placebo at all time points ($p<0.001$) (Figure 21A). The increase in s-P1NP was similar for abaloparatide versus teriparatide at 1 month but the trend became higher for teriparatide at 3, 6, 12 and 18 months ($p<0.001$).

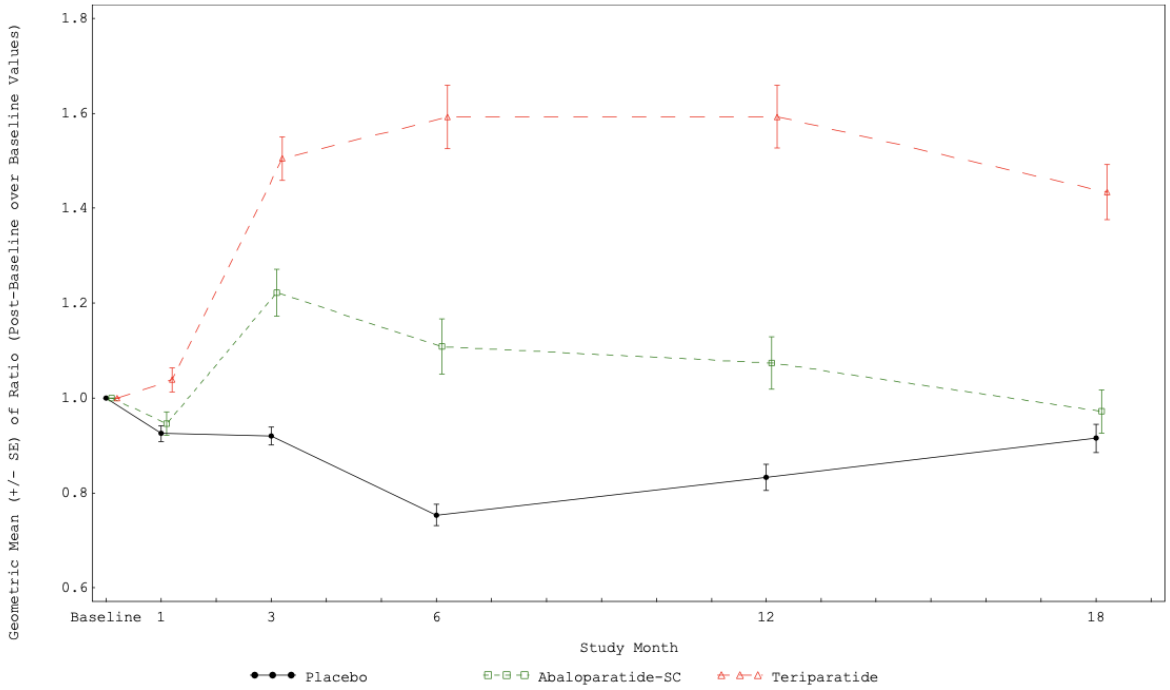
Abaloparatide treatment resulted in a transient increase in the resorption marker s-CTX vs placebo ($p<0.001$) at 3, 6 and 12 months but not at 1 month or 18 months (Figure 21B). Increases in s-CTX were greatest with teriparatide and remained elevated throughout the 18-month treatment period.

Figure 21: ACTIVE | Geometric mean (+/- SE) of ratio (post-baseline over baseline values) in serum bone metabolism markers through Month 18 (excluding Sites 131 and 132; BTM population, CS B.2.6.3, Figure 14[1])

A) s-P1NP



B) s-CTX

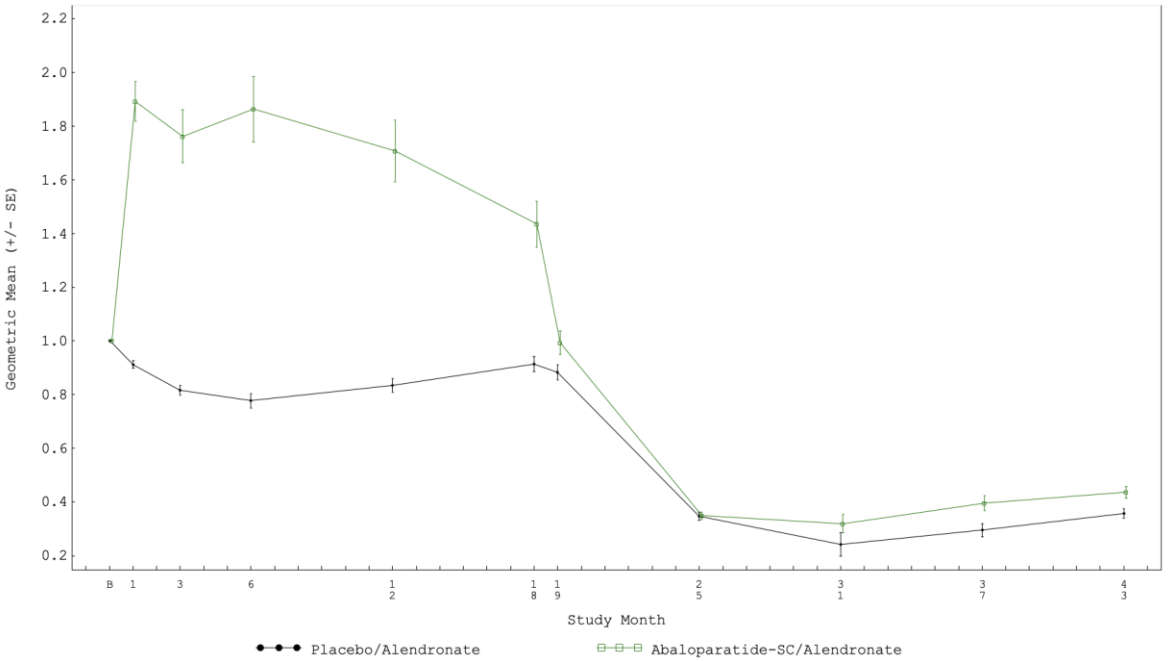


Levels indicate geometric mean (+/- SE) of ratio (post-baseline over baseline values change from baseline for a bone turnover marker population subset (n=156 placebo, n=164 abaloparatide, and n =180 teriparatide for change from baseline at Months 6, 12 and 18 for both s-P1NP and s-CTX)
Abbreviations: BTM, bone turnover marker; s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; SC, subcutaneous; SE, standard error; s-P1NP, serum procollagen type I N-terminal pro-peptide

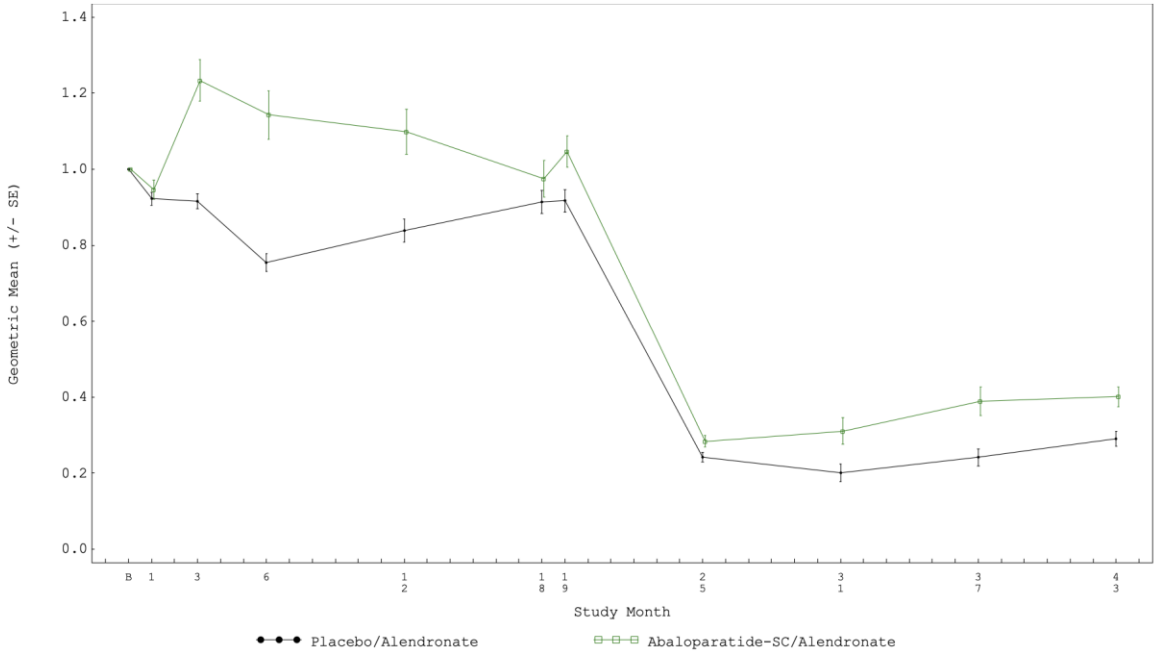
The ACTIVExtend bone turnover marker population comprised 140 patients in the placebo/alendronate group and 148 patients in the abaloparatide/alendronate group. Levels of both s-P1NP and s-CTX decreased well below ACTIVE baseline levels during treatment with alendronate (Months 19 to 43) and remained suppressed through Month 43 in both treatment groups (Figure 22A & B). At Month 43, the difference between the groups was not clinically meaningful because the changes for both groups indicated a decrease for s-CTX.

Figure 22: ACTIVExtend | Secondary endpoints | Changes in bone turnover markers from ACTIVE baseline to end of ACTIVExtend (through Month 43) (excluding Sites 131 and 132; BTM population, CS B.2.6.3, Figure 15[1])

A) s-P1NP



B) s-CTX



Alendronate monotherapy started at 19 months
Levels indicate geometric mean (+/- SE) of ratio (post-baseline over baseline values change from ACTIVE baseline for a bone turnover marker population subset (n=140 placebo/alendronate, n=148 abaloparatide/alendronate for change from baseline at Months 6, 12, 18, 19, 25; n=87 placebo/alendronate, n=96 abaloparatide/alendronate for change from baseline at Month 43 for both s-P1NP and s-CTX)
Abbreviations: BTM, bone turnover marker; SC, subcutaneous; s-CTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; SE, standard error; s-P1NP, serum procollagen type I N-terminal pro-peptide

Appendix 2: Results of the EAGs NMA

Table 60: Summary of EAGs NMA and comparison to company's analyses

Outcome	New vertebral fracture (S=20)			Hip (S=17)			Non-vertebral fracture (S=18)		
Comparator	EAG RE model		CRCQ2 RE model	EAG RE model		CRCQ2 RE model	EAG RE model		CRCQ2 RE model
	HR (95% CrI)	(95% PrI)	HR (95% CrI)	HR (95% CrI)	(95% PrI)	HR (95% CrI)	HR (95% CrI)	(95% PrI)	HR (95% CrI)
Abaloparatide	[redacted]								
Romosozumab									
Teriparatide									
Alendronate									
Denosumab									
Ibandronate									
Raloxifene									
Risedronate									
Zolendronate									
Model fit									
DIC									
Residual deviance									
datapoints									
Between study SD									

FE: fixed effect, RE: random effect, HR: hazard ratio (median) , CrI: credible interval, PrI: prediction interval, NR: not relevant

Appendix 3: EAG's additional validation analysis

As part of the approaches adopted by the EAG to investigate and critically appraise the company's health economic model, the EAG undertook additional sensitivity analyses using the CRCQ2 version of the model provided, as part of its activities to check the model validation and the face validity of the results generated by the model.

The EAG ran three scenarios using the deterministic version of the company's base-case analysis, where:

- Validation scenario 1: The EAG changed the seed values used to generate the random numbers used to sampling data for each patient in the model cohort to random numbers between 1 and 1.0E+30;
- Validation scenario 2: The EAG set the random numbers in the company's base case to match those applied in the EAG model
- Validation scenario 3: The hip and NHNV HRs for patients receiving abaloparatide were set equal to those for patients receiving teriparatide (as assumed in EAG preferred base case, see

- Table **52**).
- Validation scenario 4: The HRs for all three fracture outcomes (hip, vertebral and NHNV) for patients receiving both abaloparatide and romosozumab were set equal to those for patients receiving teriparatide. This is equivalent to the EAG's cost-comparison scenario (see

- Table **52**) in which any differences in fractures between abaloparatide and teriparatide are driven solely by differences in time on treatment.

All the remaining parameters in the model remained the same as in the company's base-case, and all analyses presented in this section reflect the PAS price of abaloparatide and list price for other drugs. The results of the scenarios are presented in Table 61.

[redacted] across all of the validation scenarios. In the comparison against teriparatide, [redacted] in the scenario where there was a change of the seed values (validation scenario 1). However, in the scenario where the random numbers were set equal to those applied in the EAG model (validation scenario 2), abaloparatide resulted in lower QALY gains than teriparatide [redacted] This suggests that the results are sensitive to the random numbers used to determine the patient flow through the model. The EAG would therefore urge caution in interpreting the results for scenarios which generate small differences in QALYs.

In the scenarios which involved assuming the HRs for abaloparatide to be equivalent to those for teriparatide (validation scenarios 3 and 4), abaloparatide generates lower QALYs and [redacted] costs compared to teriparatide, with ICERs of [redacted] and [redacted] per QALY gained ([redacted]) for scenarios 3 and 4, respectively.

The cost-comparison scenario (validation scenario 4) demonstrates that approximately 0.01 QALYs is gained by the additional 6 months of abaloparatide treatment compared to romosozumab treatment and by the additional 6 months of teriparatide treatment compared to abaloparatide. This is 26% of the QALY achieved for abaloparatide versus romosozumab in the company's base case, and is of a similar magnitude to the QALY gains for abaloparatide versus teriparatide in the company's base case.

The EAG notes that the results for validation scenario 3 are identical to two other scenarios presented by the company in which they used less favourable HRs for abaloparatide (company scenario 7 using trial-based HRs and company scenario 11 in which alendronate efficacy was applied for the subsequent therapy). The EAG has been unable to explain why these scenarios should produce identical results, but it suspects that it is related to the fact that for a fracture to be prevented, a difference in HR needs to combine with a random number that means that a fracture occurs in one arm and not the other and these occurrences are rare in scenarios where similar HRs are applied for abaloparatide and teriparatide. This means that whilst the absolute costs and QALYs may change when including different HRs, the incremental costs and QALYs may be identical if the HRs versus placebo are similar between treatment

arms. The EAG would therefore urge caution in interpreting the results for scenarios which generate small differences in QALYs.

Table 61: EAG validation scenario analysis using the company's model - abaloparatide versus romosozumab and teriparatide (generated by the EAG based on the CRCQ2 version of the model, pairwise against each of the comparators), deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Company's base-case							
Abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.013	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.031	[redacted]	[redacted]
Validation scenario 1 – use of new random seeds							
Abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.012	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.026	[redacted]	[redacted]
Validation scenario 2 – use of random numbers matched to those used in EAG model							
Abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	-0.008	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.009	[redacted]	[redacted]
Validation scenario 3 – use of same HRs for abaloparatide and teriparatide for hip and NHNV							
Abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	-0.003	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.015	[redacted]	[redacted]
Validation scenario 4 – use of same HRs for abaloparatide, teriparatide and romosozumab for hip, vertebral and NHNV (equivalent to a cost-comparison)							
Abaloparatide	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	-0.010	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]

**Undiscounted*

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year

Appendix 4: Cumulative changes for individual corrections within EA1

Table 62 below shows the results of each correction applied within EA1. The first row is the 'EAG base model' which is the EAG model will all EAG switches turned off or set to match the company's base case. It differs from the company's submitted model at CRCQ2 because the EAG made some simplifications to the formulae used to convert from rates to probabilities. It also includes corrections for Issues 2(j) and 2(k) which cannot be switched off in the EAG base model. The modifications made by the EAG also resulted in the random numbers being allocated differently within the model despite the random number seeds being set for each patient, due to the addition and removal of columns from the array used to store the random numbers for each patient (sheet called 'Random Numbers' in the company model and 'Random Numbers_live' in the EAG model). This change was found to have an important impact on the cost-effectiveness estimates in validation scenario 2 in Appendix 3. This led the EAG to conclude that caution should be exercised in interpreting the results for scenarios which generate small differences in QALYs.

Table 62: Deterministic results using the EAG's model (each change is applied cumulatively)

Scenario	Option	Absolute outcomes by treatment arm			Incremental outcomes for abaloparatide versus comparator			Cost per QALY (£)
		LYGs*	QALYs	Costs	LYGs	QALYs	costs	
Correcting Issue 2(j) and 2(k), and formulas of rate/probability based on the company model: the EAG base model	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.000	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.016	[redacted]	[redacted]
Correcting Issue 2(a)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.007	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.020	[redacted]	[redacted]
Correcting Issue 2(c)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.020	[redacted]	[redacted]
Correcting Issue 2(d)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.019	[redacted]	[redacted]
Correcting Issue 2(e)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.019	[redacted]	[redacted]
Correcting Issue 2(f)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.019	[redacted]	[redacted]
Correcting Issue 2(g)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.019	[redacted]	[redacted]
Correcting Issue 2(h)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.019	[redacted]	[redacted]
Correcting Issue 2(i)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.019	[redacted]	[redacted]
Correcting Issue 2(l)	Abaloparatide	[redacted]	[redacted]	[redacted]				
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.024	[redacted]	[redacted]

Scenario	Option	Absolute outcomes by treatment arm			Incremental outcomes for abaloparatide versus comparator			Cost per QALY (£)
		LYGs*	QALYs	Costs	LYGs	QALYs	costs	
EAG EA1: Correction of model errors (correcting Issue 2(a)-2(l))	Abaloparatide	[redacted]	[redacted]	[redacted]				[redacted]
	Teriparatide	[redacted]	[redacted]	[redacted]	[redacted]	0.008	[redacted]	[redacted]
	Romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	0.024	[redacted]	[redacted]

**Undiscounted*
LYG - life year gained; QALY - quality-adjusted life year

Single Technology Appraisal

Abaloparatide for treating osteoporosis in postmenopausal women [882]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 14th March 2024.** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Additional actions to address uncertainties raised by the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1; page 13 *"The EAG has assumed that abaloparatide has the same efficacy as teriparatide for preventing non-hip non-vertebral (NHNV) fractures because the HRs from the NMA suggest a direction of treatment effect that is inconsistent with direction of treatment effect from the real-world evidence (RWE) study"*	To support the NMA efficacy estimates, the Company propose to supplement the current evidence with emerging data; The latest real-world evidence (RWE) for abaloparatide, updated as of July 2023. This data offers fresh insights into treatment effectiveness and patient outcomes, particularly regarding hip and non-hip, non-vertebral (NHNV) fracture outcomes when compared to teriparatide.	The RWE update provides more current and comprehensive data, essential for addressing the uncertainties noted by the EAG. This evidence is key for refining the cost-effectiveness analysis to reflect true clinical effectiveness.	This is not a factual inaccuracy issue. The company's comment suggests that additional evidence on teriparatide efficacy would be sent; however no new evidence was presented at the FACT check stage; therefore, no amendments were made by the EAG.
Section 4.3.4.2; page 146 *"Generalisability of the model to the population likely to receive anabolic therapy in current practice"*	The Company propose to refine the analysis, focusing specifically on subgroups within the ACTIVE trial's population that directly correspond to NICE's very high-risk categories.	By conducting targeted post-hoc analyses on these subgroups, the Company aim to demonstrate the efficacy and safety of abaloparatide within the specific patient populations identified by NICE.	No new evidence or subgroups analyses were presented by the company at the FACT check stage; therefore, no amendments were made by the EAG.

Issue 2 Missing or incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1; page 38 *"No additional search methods (e.g. reference checking) were performed."*	*"In addition to these sources, the reference lists of eligible articles and SLRs were scanned to identify any additional, relevant articles."*	A revision is requested to align with the process followed as per the protocol for the systematic literature review.	The EAG has removed the sentence "*"No additional search methods (e.g. reference checking) were performed."* from the EAG report.
Section 4.3.4.3; page 163; Table 54 *'Urinary tract infection' for abaloparatide is [redacted]%'*	The incidence of 'Urinary tract infection' for abaloparatide is [redacted]%	A revision is requested to align with the CSR addendum Table 18	The EAG has already spotted the issue related to the incidence of urinary tract infection AE reported in the model, and had added a footnote to Table 54 which says '*The EAG believes this is a typo and it should be [redacted] according to CSR addendum table 18.'* Therefore, no further amendments

			were made to the EAG report.

Issue 3 Requests to clarify ambiguous wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.4.2; Issue 2; page 149 *"(e) Drug acquisition costs per course: The EAG also noted that the company was basing the cost for teriparatide on the list price for the original branded formulation (Forsteo, £272) rather than the list price for the lowest cost biosimilar (Movymia, £235)."*	*"(e) Drug acquisition costs per course: The EAG also noted that the company was basing the cost for teriparatide on the list price for the original branded formulation (Forsteo, £272) rather than the list price for the lowest cost biosimilar (Movymia, £235).* ***However, the model includes the functionality to select teriparatide biosimilars—Movymia, Sondelbay, and Terrosa—with their respective list prices.***"	The Company cost-effectiveness model allows the option for further analyses using biosimilar pricing.	The EAG agrees partially with the proposed amendments, since the results presented by the company in the CS, clarification response appendix 1 or clarification response 2 did not include results using any of the biosimilar options for teriparatide. The text in the EAG report has been amended to '*The EAG also noted that the company was*

			basing the cost for teriparatide on the list price for the original branded formulation (Forsteo, £272) rather than the list price for the lowest cost biosimilar (Movymia, £235). The model presented by the company includes the functionality to use list prices for each of the teriparatide biosimilars (Movymia, Sondelbay, and Terrosa). However, the EAG notes that results using any of these options for teriparatide have not been presented at CS, CRCQ1 or CRCQ2."

Issue 4 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Abbreviations; page 10 *"Summary of Product Characteristic"*	*"Summary of Product Characteristic**s**"*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 1, page 12 *"This External Assessment Group (EAG) report assess abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture."*	*"This External Assessment Group (EAG) report assess**es** abaloparatide for the treatment of osteoporosis in postmenopausal women at increased risk of fracture."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 1.1, page 12 *"Each to these anabolic therapies should be followed by an antiresorptive therapy and the company assumes that alendronate will be used for this purpose."*	*"Each **of** these anabolic therapies should be followed by an antiresorptive therapy and the company assumes that alendronate will be used for this purpose."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 1.1, page 13 *"The EAG adapted the model to simulate whether a new admission to long-term*	*"The EAG adapted the model to simulate whether a new admission to long-term care occurred for each patient having a hip fracture, whereas*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.

care occurred for each patient having a hip fracture, whereas the company used a cohort-level approximation for long-term care cost in which is applied a proportion of the costs for long-term care to every patient experiencing a hip fracture."	*the company used a cohort-level approximation for long-term care cost in which* ***~~is applied~~*** *a proportion of the costs for long-term care to every patient experiencing a hip fracture* ***is applied****."*		
Section 1.4, page 13 *"The EAG was not able to assesses the impact of these uncertainties on the ICER"*	*"The EAG was not able to assess****~~es~~*** *the impact of these uncertainties on the ICER"*	To correct a typographical error.	The EAG notes that the issue was in page 15 of the report instead of 13. Nonetheless, the EAG agrees and has amended the text in the EAG report.
Section 1.1, page 13 *"The EAG was not able to assesses the impact of this high risk of bias on the ICER"*	*"The EAG was not able to assess****~~es~~*** *the impact of this high risk of bias on the ICER"*	To correct a typographical error.	The EAG notes that this issue relates to section 1.4 and was located in page 15 of the report instead of 13. Nonetheless, the EAG agrees and has amended the text in the EAG report.

Section 1.5, page 13 *"In addition, the company has presented a scenario analysis incorporating trial-based estimate of treatment persistence rather that RWE for abaloparatide and teriparatide"*	*"In addition, the company has presented a scenario analysis incorporating **a** trial-based estimate of treatment persistence rather **than** RWE for abaloparatide and teriparatide"*	To correct a typographical error.	The EAG notes that this issue was located in page 19 of the report instead of 13. Nonetheless, the EAG agrees and has amended the text in the EAG report.
Section 1.5, page 20 *"Using an individual rather than a cohort-level approached resulted in incremental costs that were in the same direction but were numerically [redacted] in both pairwise comparisons."*	*"Using an individual rather than a cohort-level approach~~**ed**~~ resulted in incremental costs that were in the same direction but were numerically [redacted] in both pairwise comparisons."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 2.1, page 24 ***"…**so the EAG had difficultly identifying the exact sources and assessing the validity of these estimates."*	***"…**so the EAG had **difficulty** identifying the exact sources and assessing the validity of these estimates."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 2.1, page 24 ***"**The EAG notes that the National Hip Fracture Database reported an national average*	***"**The EAG notes that the National Hip Fracture Database reported a~~**n**~~ national average 30-day mortality rate following hip*	To correct a typographical error.	This amendment has been made in the EAG report.

30-day mortality rate following hip fracture ranging from 6.4% to 6.9% across 2022"	*fracture ranging from 6.4% to 6.9% across 2022"*		
Section 2.1, page 24 *"…but this is based on estimate from a 1989 publication and is therefore unlikely to reflect current risks"*	*"…but this is based on **an** estimate from a 1989 publication and is therefore unlikely to reflect current risks"*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 2.3; page 8 and 26 *"Box 1: Summary of NICE guidance for romosozumab and teriparatidea"*	*"Box 1: Summary of NICE guidance for romosozumab and teriparatide[a]"*	To correct a typographical error.	The EAG notes Box 1 is located in page 30 of the report instead of 26. This amendment has been made in the EAG report.
Section 2.3.3; page 30 *"In terms of the population specified in the ACTIVE study, the EAG's clinical experts considered that the group who were enrolled in ACTIVE without a prior fracture, whose risks factors were being aged over 65 years"*	*"In terms of the population specified in the ACTIVE study, the EAG's clinical experts considered that the group who were enrolled in ACTIVE without a prior fracture, whose risk~~**s**~~ factors were being aged over 65 years"*	To correct a typographical error.	This amendment has been made in the EAG report.

Section 3.2.2; page 52 *"A balanced randomized block assignment will be utilized to insure that an approximately equal number of patients are assigned to each treatment group after a pre-specified block size has been achieved.'*	*"A balanced randomized block assignment will be utilized to **ensure** that an approximately equal number of patients are assigned to each treatment group after a pre-specified block size has been achieved."*	To correct a typographical error.	The text corresponds to a quote retrieved from Miller et al. 2016 (trial protocol published as a supplement with the principal manuscript). A [sic] was included to identify that the typographical error was identified but corresponds to the original source.
Section 3.2.2; page 67 *"Primary end point (mITT population)"*	*"Primary **endpoint** (mITT population)"*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report. Similar typographical errors were identified by the EAG also in pages 32 and 78, which were also fixed.
Section 3.4.1; Page 77 *"in the placebo group and 14 patients (2.0%) in the teriparatide group (CS, sSection B.2.10.1.5)."*	*"in the placebo group and 14 patients (2.0%) in the teriparatide group (CS, ~~s~~Section B.2.10.1.5)."*	To correct a typographical error.	This amendment has been made in the EAG report.

Section 3.8.1; Page 91 *"The company also chose to restrict studies to those conduced in North American or Western European populations, with the rationale being to ensure relevance and applicability to the UK"*	*"The **C**ompany also chose to restrict studies to those **conducted** in North American or Western European populations, with the rationale being to ensure relevance and applicability to the UK"*	To correct a typographical error.	The EAG disagrees with the capitalisation of the word company in this context and has not made this amendment to the text. The second amendment has been made in the EAG report.
Section 4.2.4.2, page 118 *"The excess mortality rates related to hip and vertebral fractures used in updated version of the model submitted upon CRCQ2 to estimate the RRs are presented in Table 34"*	*"The excess mortality rates related to hip and vertebral fractures used in **the** updated version of the model submitted upon CRCQ2 to estimate the RRs are presented in Table 34"*	To correct a typographical error.	This amendment has been made in the EAG report.
Section 4.2.4.6, page 134 *"this cost is applied as an one-off-cost to patients that have persisted with treatment in the first 6 months (see Section 4.3.4 for more details)."*	*"this cost is applied as **a** one-off-cost to patients that have persisted with treatment in the first 6 months (see Section 4.3.4 for more details)."*	To correct a typographical error.	This amendment has been made in the EAG report.

Section 4.2.4.6, page 134 *"…where all patients were assume to equally receive calcium and vitamin D supplementation regardless of the treatment received, so these costs were not included in the model."*	*"…where all patients were assume**d** to equally receive calcium and vitamin D supplementation regardless of the treatment received, so these costs were not included in the model."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 4.2.4.6, page 136 *"…and are applied in the model from the second year after a fracture occurring until the patient's point of death"*	*"…and are applied in the model from the second year after a fracture **occurs** until the patient's point of death"*	To correct a typographical error.	This amendment has been made in the EAG report.
Section 4.2.6.3, page 142 *"but the EAG notes that the different is small and does not change the interpretation of the results."*	*"but the EAG notes that the **difference** is small and does not change the interpretation of the results."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 4.3.4.2, page 148 *"The EAG has also allowed the random number seeds that determine the random*	*"The EAG has also allowed the random number seeds that determine the random number array for each patient to change for each PSA run to ensure that any variation due to the random*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.

number array for each patient to change for each PSA run to ensure that any variation due to the random number seeds is average out over the PSA."	*number seeds is **averaged** out over the PSA."*		
Section 4.3.4.2, page 149 *"Drug acquisiton costs per course"*	*"Drug **acquisition** costs per course"*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 4.3.4.2, page 156 *"The EAG's clinical expert agreed that based on personal experience higher persistence might be expected for patients taking alendronate therapy after an anabolic treatment than for patients staring alendronate after other therapies."*	*"The EAG's clinical expert agreed that based on personal experience higher persistence might be expected for patients taking alendronate therapy after an anabolic treatment than for patients **starting** alendronate after other therapies."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 4.3.4.2, page 158 *"The EAG's clinical advisors stated that they would usually also see patients at end of teriparatide treatment"*	*"The EAG's clinical advisors stated that they would usually also see patients at **the** end of teriparatide treatment"*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.

Section 4.3.4.2, page 159 *"the EAG prefers to assume that the first supervised administration occurs as an addition task within a secondary care outpatient visit rather than being delivered by a primary care nurse, as assumed by the company."*	*"the EAG prefers to assume that the first supervised administration occurs as an **additional** task within a secondary care outpatient visit rather than being delivered by a primary care nurse, as assumed by the company."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 4.3.4.3, page 164 *"…costs and QALY losses related to cardiovascular (CV) AEs were included as part of a scenario analysis for patients without a contraindicating history of prior MI or stoke."*	*"…costs and QALY losses related to cardiovascular (CV) AEs were included as part of a scenario analysis for patients without a contraindicating history of prior MI or **stroke**."*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 4.4.2.1, page 164 *"In additiontThe drug costs for alendronate was based on the eMIT price (£0.18) and the drug costs for teriparatide was based on the lowest cost biosmilar (Movymia, £235)."*	*"In **addition, the** drug cost~~**s**~~ for alendronate was based on the eMIT price (£0.18) and the drug cost~~**s**~~ for teriparatide was based on the lowest cost **biosimilar** (Movymia, £235)."*	To correct a typographical error.	The EAG agrees with the proposed amendments. The text in the EAG report has been amended to *"In addition, the drug costs for alendronate was based on its eMIT price*

			(£0.18) and the drug cost for teriparatide was based on the lowest cost biosimilar (Movymia, £235).”
Section 4.4.2.7, page 171 *“…the only differences in fracture outcomes occur due to differences in the planned duration of treatment (12 moths for romosozumab, 18 months for abaloparatide and 24 months for teriparatide)…”*	*“…the only differences in fracture outcomes occur due to differences in the planned duration of treatment (12* ***months*** *for romosozumab, 18 months for abaloparatide and 24 months for teriparatide)…”*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Section 4.4.3.4, page 176 *“…or whether a utility multiplier is applied to those patients admitted to long-erm care after a hip fracture (SA5).”*	*“…or whether a utility multiplier is applied to those patients admitted to* ***long-term*** *care after a hip fracture (SA5).”*	To correct a typographical error.	The EAG agrees. This amendment has been made in the EAG report.
Pages 77, 81, 101, 102 Capitalisation of abbreviation for adverse events “*Aes*	*“AEs”*	To correct a typographical error.	The EAG agrees. Amendments related to this issue have been made in the EAG report (in five instances in pages 77, three in page

			81 and once each in pages 4, 5, 101 and 102).

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr>
<td>Table 38, page 127</td>
<td>Persistence rates sourced from Arden et al. were redacted. These data is publicly available.</td>
<td>
<table>
<tr><th>Drug/ treatment group
Time (months)</th><th>Abalop.</th><th>Terip.</th></tr>
<tr><td>6</td><td>93.0%</td><td>93.0%</td></tr>
<tr><td>12</td><td>87.0%</td><td>87.0%</td></tr>
<tr><td>18</td><td>79.0%</td><td>79.0%</td></tr>
<tr><td>24</td><td>–</td><td>71.0%</td></tr>
<tr><td>30</td><td>–</td><td>–</td></tr>
<tr><td>36</td><td>–</td><td>–</td></tr>
<tr><td>42</td><td>–</td><td>–</td></tr>
<tr><td>48</td><td>–</td><td>–</td></tr>
<tr><td>54</td><td>–</td><td>–</td></tr>
<tr><td>60</td><td>–</td><td>–</td></tr>
<tr><td>66</td><td>–</td><td>–</td></tr>
<tr><td>72</td><td>–</td><td>–</td></tr>
<tr><td>78</td><td>–</td><td>–</td></tr>
<tr><td>84</td><td>–</td><td>–</td></tr>
<tr><td>Source</td><td colspan="2">Arden et al.[62]</td></tr>
</table>
</td>
<td>This amendment has been made in the EAG report.

The EAG notes they have now also added CIC marking to the persistence data from the ACTIVE trial in Tables 38 and 56 to make this consistent with the CIC marking in the CRCQ2 NMA and model Appendix, Table 26.</td>
</tr>
</table>

<table>
<tr>
<td>Table 51, page 153</td>
<td>Network meta-analysis credible intervals for HRs</td>
<td>
Table 51: Credible intervals (95%) for the HRs versus placebo for the company's NMA (REM) and the gamma distributions used to sample the HRs versus placebo in the PSA
<table>
<tr><td>Outcome</td><td colspan="2">Vertebral fracture</td><td colspan="2">Hip fracture</td><td colspan="2">Non-vertebral fracture</td></tr>
<tr><td>Treatment</td><td>NMA</td><td>Gamma</td><td>NMA</td><td>Gamma</td><td>NMA</td><td>Gamma</td></tr>
<tr><td>Abaloparatide</td><td colspan="6" rowspan="4">[redacted]</td></tr>
<tr><td>Romosozumab</td></tr>
<tr><td>Teriparatide</td></tr>
<tr><td>Alendronate</td></tr>
</table>
</td>
<td>This amendment has been made in the EAG report.</td>
</tr>
<tr>
<td>Section 4.4.3.3, page 172</td>
<td>Estimate of the ICER (probalistic)</td>
<td>For the comparison against romosozumab, [redacted]. For the comparison against teriparatide, incremental QALYs are similar but incremental costs are [redacted]. The spread of incremental cost and QALY estimates on the cost-effectiveness plane is shown in Error! Reference source not found.. It can be seen that these are [redacted] than in the company's PSA (Error! Reference source not found.), reflecting the EAG's preference to use the CODA samples to incorporate the uncertainty around the HRs.</td>
<td>The EAG agrees partially with the proposed amendments. The text in the EAG report has been amended to:

"For the comparison against romosozumab, both incremental cost and QALYs are numerically [redacted]. For the comparison against teriparatide, incremental QALYs are similar but incremental costs are numerically [redacted]. The spread of incremental cost and QALY estimates on the cost-effectiveness plane is shown in Error! Reference source not found.. It can be seen that these are much more broadly spread than in the company's PSA (Error! Reference source not found.), reflecting the EAG's preference to use the CODA samples to incorporate the uncertainty around the HRs."</td>
</tr>
</table>

Section 4.4.3.4, page 176	The EAG's sensitivity analyses	The scenario analysis using HRs from the trials (SA2) shows incremental costs and QALYs that are in the same direction as for the EAG's preferred base case, but the differences in [redacted] when using the efficacy data directly from the trials. However, the EAG notes that the comparison against romosozumab in this scenario is a completely unadjusted indirect comparison and should therefore be viewed with a high degree of caution. The sensitivity analysis in which all HRs are set equal for all three treatment strategies (SA6) shows that the duration of time on treatment is having a large impact on the cost-effectiveness estimates, with the incremental QALYs for abaloparatide versus romosozumab being [redacted] when treatment duration is the only difference between these treatments, due to the additional 6 months on treatment for abaloparatide versus romosozumab. The results for the higher risk subgroup (SA4) suggests that the company's decision to use the patient characteristics from the ACTIVE study, which recruited a lower risk cohort than the ARCH study, may have meant that differences between the treatments are potentially underestimated as the incremental costs and QALYs are in the same direction but are [redacted] when modelling a higher risk patient cohort in which all patients had a prior fracture at baseline.	The EAG agrees partially with the proposed amendments, but notes that the company has since confirmed that incremental QALYs do not need to be marked CIC. The text in the EAG report has been amended to: "The results for the higher risk subgroup (SA4) suggests that the company's decision to use the patient characteristics from the ACTIVE study, which recruited a lower risk cohort than the ARCH study, may have meant that differences between the treatments are potentially underestimated as the incremental costs and QALYs are in the same direction but are numerically [redacted] when modelling a higher risk patient cohort in which all patients had a prior fracture at baseline." The other suggested changes have not been implemented.