

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Romosozumab for treating severe osteoporosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using romosozumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using romosozumab in the NHS in England.

For further details, see [NICE's guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 16 December 2021

Next appraisal committee meeting: 17 February 2022

Details of membership of the appraisal committee are given in section 5

## 1 Recommendations

- 1.1 Romosozumab is not recommended, within its marketing authorisation, for treating severe osteoporosis after menopause in people at high risk of fracture.
- 1.2 This recommendation is not intended to affect treatment with romosozumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

### Why the committee made these recommendations

Current treatments for people with severe osteoporosis after menopause include bisphosphonates, such as alendronic acid, and other types of medicine, such as denosumab or teriparatide. The company proposes that romosozumab would only be used when there is an imminent fracture risk. It defines this as when there is severe osteoporosis and the person has had a major fracture in the past 24 months. This is narrower than the marketing authorisation.

Clinical trial evidence suggests that romosozumab followed by alendronic acid is more effective at reducing the risk of fractures than alendronic acid alone. But there is uncertainty because the population in the clinical trial is different to the proposed population. Comparing romosozumab indirectly with other bisphosphonates and other medicines for this condition suggests that it is likely to be at least as effective at reducing the risk of fractures in people with osteoporosis after menopause. But the extent of the benefit is uncertain because of differences between the trial populations in the indirect comparisons. Also, the company did not present clinical-effectiveness evidence for people at imminent fracture risk.

The most likely cost-effectiveness estimates for romosozumab followed by alendronic acid compared with alendronic acid alone are higher than what NICE

normally considers an acceptable use of NHS resources. Also, the company's economic model could not be fully reviewed by the ERG and may not be suitable for decision making. So, romosozumab is not recommended.

## 2 Information about romosozumab

### Marketing authorisation indication

2.1 Romosozumab (EVENTITY, UCB) is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.

### Dosage in the marketing authorisation

2.2 The dosage schedule is available in the [summary of product characteristics](#).

### Price

2.3 The price for romosozumab is £427.75 for 2 pre-filled pens administered subcutaneously as a single monthly dose (BNF online, October 2021). The company has a commercial arrangement. This will make romosozumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

## 3 Committee discussion

The [appraisal committee](#) considered evidence submitted by UCB, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

## The condition

### Severe osteoporosis can have a substantial effect on quality of life

3.1 Osteoporosis is a progressive skeletal disorder. It is characterised by low bone mass and deterioration of the structure of bone tissue leading to an increase in bone fragility and risk of fracture. The patient experts explained that osteoporosis affects all aspects of daily life, including walking, eating and breathing. People with the disease often have difficulty doing day-to-day tasks. Fractures can be painful and have a substantial effect on a person's independence and are also associated with increased mortality. Because of this, people with osteoporosis live in fear of having another fracture. The patient experts explained how the physical changes from osteoporosis, such as loss of height or a stooped posture, can cause feelings of shame. The clinical experts explained that it is important to build bone strength and prevent fragility fractures, particularly in people at the highest risk of fracture. The committee concluded that severe osteoporosis can have a substantial effect on quality of life, and that this would be improved by preventing fragility fractures.

## Treatment pathway and comparators

### People with severe osteoporosis would welcome a new treatment option

3.2 The clinical experts explained that several treatment options are available for severe osteoporosis. These are chosen depending on fracture risk, the presence of previous fractures, and response to or tolerance of other treatments. These treatments can be broadly divided into 2 classes: anabolic (bone-forming) agents and anti-resorptive agents. For people at high risk of fracture, first-line treatment is usually oral bisphosphonates such as alendronic acid or risedronate sodium. However oral bisphosphonates are either not tolerated or contraindicated in many people with osteoporosis, or the disease does not respond well to them. In

this situation, another anti-resorptive treatment can be offered. This includes intravenous bisphosphonates, or a non-bisphosphonate such as denosumab or raloxifene. An anabolic non-bisphosphonate, teriparatide, is another option for people with a higher fracture risk. However, non-bisphosphonates can be difficult to administer and can have other limitations. The clinical experts also noted that evidence suggests that giving teriparatide as the first treatment before oral bisphosphonates may be more effective at reducing fracture risk, but [NICE's technology appraisal guidance raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women](#) only recommends teriparatide for the secondary prevention of osteoporotic fractures. There is an unmet need for people with very high fracture risk for whom current drugs are not suitable, or for those at particularly high risk of vertebral or hip fractures. Romosozumab is the only drug with both anabolic and anti-resorptive properties, and is the first new treatment option for osteoporosis in several years. The patient experts agreed that romosozumab offered hope as an additional treatment option. The committee concluded that both patients and clinicians would welcome a new treatment option for severe osteoporosis.

### **The company's decision problem population is narrower than the NICE scope and ARCH trial population**

3.3 The population in the NICE scope was people after menopause who have severe osteoporosis and are at high risk of fracture (high risk of fracture was not further defined). The committee noted that the population in the company's main clinical trial (ARCH) was women with severe osteoporosis after menopause who are at high risk of fracture (high risk of fracture was defined as having had a major osteoporotic fracture (see section 3.6)). The company's decision problem population was women with severe osteoporosis after menopause who were at high risk of fracture (high risk of fracture' was defined as having had a major osteoporotic fracture in the last 24 months). This will be referred to as imminent

fracture risk. The committee concluded that the company's imminent risk population was narrower than both the NICE scope and ARCH trial.

### **Romozosumab would be used in people who have had a major osteoporotic fracture within 2 years, regardless of previous treatment**

3.4 The company explained that it had positioned romozosumab in the imminent fracture risk population because these people are at much higher risk of another fracture compared with those who had had a fracture less recently. The company also clarified that the imminent fracture risk population in its submission was regardless of previous treatment. The clinical experts agreed that the risk of fracture is highest soon after a fracture. But they noted that duration of increased fracture risk can vary based on factors such as age and previous fracture location, and so the company's 2-year cut off was somewhat arbitrary. The clinical experts also explained that the date of the previous fracture may not be known, particularly for vertebral fractures. So, the company's decision problem population may be difficult to implement in clinical practice. Both clinical and patient experts agreed that romozosumab should be positioned regardless of previous treatment, and that not doing this would represent a missed opportunity. The committee acknowledged that the company's population represents people with a high risk of fracture. However, it noted that most people in ARCH had not previously had treatment for osteoporosis, so there was uncertainty around the efficacy of romozosumab in later lines of therapy. The committee concluded that it would appraise romozosumab according to the company's proposed population that is, people with severe osteoporosis after menopause who are at imminent fracture risk, regardless of previous treatment.

### **Bisphosphonates and non-bisphosphonates are relevant comparators for romozosumab**

3.5 The committee recalled that it would appraise romozosumab regardless of previous treatment (see section 3.4). All of the comparators in the NICE

scope are used for treating severe osteoporosis, with non-bisphosphonates largely offered after bisphosphonates (see section 3.2). As such, the committee concluded that both bisphosphonates and non-bisphosphonates are relevant comparators for romosozumab.

## **Clinical evidence**

### **ARCH is broadly generalisable to UK clinical practice**

3.6 The main source of clinical-effectiveness evidence for romosozumab was the ARCH trial. ARCH was a randomised, double-blind, multicentre trial comparing romosozumab followed by oral alendronic acid (n=2,046) with oral alendronic acid alone (n=2,047). People were randomised to have either romosozumab or alendronic acid for 12 months, followed by open-label oral alendronic acid for at least another 12 months in both arms. ARCH included ambulatory women after menopause aged 55 to 90 if they met at least 1 of the following criteria:

- A T-score of -2.5 or less at the total hip or femoral neck and either 1 or more moderate or severe vertebral fracture, or 2 or more mild vertebral fractures
- A T-score of -2.0 or less at the total hip or femoral neck and either 2 or more moderate or severe vertebral fractures, or a fracture of the proximal femur 3 to 24 months before randomisation.

A T-score relates to the measurement of bone mineral density (BMD) using central dual-energy X-ray (DXA) scanning and is expressed as the number of standard deviations below peak BMD. ARCH was an event-driven trial. The primary analysis was done after all people had completed their month 24 visit and at least 330 people had a confirmed clinical fracture (median follow up was 33 months). The clinical experts explained that the baseline characteristics from ARCH suggested that the results would be generalisable to NHS clinical practice. The committee noted that only around 10% of people having romosozumab in ARCH had previously



had treatment, so there was uncertainty around the effectiveness of romosozumab given after previous osteoporosis therapies. The committee concluded that ARCH was broadly generalisable to people who had not previously had treatment who had a high fracture risk and would have romosozumab in the NHS.

### **Romosozumab followed by alendronic acid is more effective than alendronic acid alone based on ARCH, but the company did not provide evidence for the imminent fracture risk population**

3.7 In ARCH, the primary outcomes were the cumulative incidence of new vertebral fracture at month 24, and the cumulative incidence of clinical fracture at the time of primary analysis. Key secondary outcomes included the incidence of the following fracture types: non-vertebral, all fractures, new or worsening vertebral, major non-vertebral, hip and, major osteoporotic. Percentage change in BMD at the lumbar spine, total hip and femoral neck were other secondary outcomes. People randomised to the romosozumab arm in ARCH had a 50% lower relative risk of vertebral fractures over 24 months than people having alendronic acid alone (relative risk 0.50, 95% confidence interval [CI] 0.38 to 0.66). A lower proportion of people having romosozumab (9.7%) had a clinical fracture compared with people having alendronic acid alone (13%), and this difference was statistically significant (hazard ratio [HR] 0.73, 95% CI 0.61 to 0.88). At the primary analysis there were also fewer people having romosozumab who had non-vertebral fractures (HR 0.81, 95% CI 0.66 to 0.99) or hip fractures (HR 0.62, 95% CI 0.42 to 0.92) compared with those having alendronic acid alone. People treated with romosozumab had a greater increase in BMD from baseline compared with people having alendronic acid alone, and this difference was statistically significant (adjusted  $p < 0.001$ ). The committee recalled that the company's decision problem population was narrower than ARCH (see section 3.3). The company stated that around 40% of the ARCH population had a fracture within 24 months and would be eligible for romosozumab according to the

company's decision problem population. The company stated that a post-hoc analysis of ARCH showed that the imminent fracture risk population had similar outcomes to the overall study population but had not presented this evidence in its submission. The committee concluded that romosozumab followed by alendronic acid is more effective than alendronic acid alone in the ARCH population, but that the company had not provided evidence of the effectiveness of romosozumab in the imminent fracture risk population.

**The company's indirect treatment comparisons with other comparators are uncertain, and should be adjusted for the imminent fracture risk population**

3.8 There is no head-to-head evidence comparing romosozumab followed by alendronic acid against the other comparators in the NICE scope: risedronate sodium, ibandronic acid, zoledronic acid, denosumab, raloxifene and teriparatide. Therefore, the company did network meta-analyses (NMAs) to allow for indirect treatment comparisons with these comparators. The company could not include ibandronic acid in the NMAs because there were no trials at the licensed dose reporting fracture outcomes. The results of the company's NMAs showed that romosozumab followed by alendronic acid is significantly better than or at least as good as most comparators for most fracture outcomes at various time points. The results are academic-in-confidence and cannot be presented here. The ERG explained that these results were uncertain because of the differences between the study populations in the NMAs. Most studies included had differences in mean age, ethnicity, or the rate of prevalent vertebral fractures. The ERG noted that the company's NMAs were based on the ARCH trial population rather than the imminent fracture risk population in the company's decision problem (see section 3.3). The ERG also noted that there was little direct evidence with which to assess inconsistency in the networks, and that the studies in the NMAs did not provide data consistently across timepoints. The ERG

therefore considered only the comparisons between romosozumab, alendronic acid and placebo to have a low risk of bias, while all other comparisons had a high risk of bias. The committee agreed that the NMAs may be biased because of differences between the ARCH population and imminent fracture risk population, and the heterogeneity between the studies. The committee questioned if the company had explored adjusting for baseline risk in the NMAs, because different rates of baseline fractures were seen in the placebo arms of the included studies. The company explained that previously published NMAs identified no baseline characteristics to be effect modifiers, so the company assumed the same conclusion would be applicable in its submission. It decided not to replicate the same analysis, instead focusing its NMAs as being time-point specific. The committee agreed that the NMAs should be time-point specific. However, it concluded that results of the company's NMAs were highly uncertain given the differences in baseline risk between studies and the lack of evidence for the imminent fracture risk population. The committee would have preferred to see NMAs adjusted for baseline risk, and treatment effect estimates centred around the imminent fracture risk population in the company submission.

### **More people having romosozumab had serious cardiovascular events in ARCH, but there was no difference compared with placebo in FRAME**

3.9 An imbalance in adjudicated serious cardiovascular events between treatment arms was seen in ARCH. In the romosozumab arm of ARCH, 16 people (0.8%) reported cardiac ischaemic events compared with 6 people (0.3%) in the alendronic acid arm in ARCH (odds ratio [OR] 2.65; 95% CI 1.03 to 6.77) after 12 months. Cerebrovascular events were reported by 16 people (0.8%) in the romosozumab arm and 7 people (0.3%) in the alendronic acid arm (OR 2.27; 95% CI 0.93 to 5.22). However, there was no difference in adjudicated serious cardiovascular events in the FRAME trial for people having romosozumab compared with placebo at 12 months. FRAME was a randomised, double-blind study in

women after menopause with osteoporosis, providing data on romosozumab followed by denosumab compared with placebo followed by denosumab. The committee was aware that romosozumab is contraindicated for people with previous myocardial infarction or stroke. The committee understood that there may be multiple reasons why ARCH showed an increased risk of cardiovascular events for people having romosozumab. These included romosozumab increasing the risk, or alendronic acid reducing the risk or that this was a chance finding. The committee also understood that romosozumab should only be prescribed if the clinician and person at high risk of fracture agreed that the benefit outweighed these risks. The committee concluded that there was a concern that people having romosozumab were more likely to experience cardiovascular events than those having alendronic acid alone, and that balancing the benefit and risks before starting romosozumab was essential.

## **Economic model**

### **Issues with the company's model must be resolved before it can be considered robust for decision making**

3.10 The company used a Markov microsimulation model to estimate the cost effectiveness of romosozumab compared with alendronic acid, risedronate sodium, zoledronic acid, denosumab, raloxifene and teriparatide. The model included 5 health states: at risk, hip fracture, vertebral fracture, other fracture (non-hip, non-vertebral) and death. In the company's model, the risk of having a fracture was based on a combination of 4 components: the general population risk of fracture, the increased fracture risk associated with osteoporosis relative to the general population, the increased fracture risk because of having a recent fracture (the imminent fracture risk), and the reduction in risk from osteoporosis treatment. The treatment effect of romosozumab compared with alendronic acid on fracture risk was calculated by fitting parametric

distributions to the Kaplan–Meier curves from ARCH to calculate time-dependent hazard rates. The ERG agreed that the company’s model structure was appropriate for osteoporosis. The ERG noted that it could not fully evaluate the model because it could not access all of the Visual Basic for Applications (VBA) code, in which the model calculations were done. This was because the confidential FRAX algorithm was implemented within the code. The ERG was unable to assess the functionality of the model or to make changes to assumptions beyond simple input parameters. It identified some issues with the model outputs that it could not explain without having full access to the model calculations. This includes the fact that in the model some people had a second non-hip, non-vertebral fracture over the model lifetime, while none had a first, which was counterintuitive. The ERG also noted that the company had not presented information on how the parametric distributions had been fitted to the data from ARCH. It could therefore not assess if the distributions had been properly fitted or explore the effect of using alternative distributions. The committee understood that providing full access to the VBA code would be challenging. The committee concluded that any identified issues with the model should be resolved as far as possible before it can be considered robust for decision making. It also concluded that it would have liked to see further information on how the parametric distributions had been fitted to the data from ARCH.

### **How long people continue to have alendronic acid after romosozumab is uncertain and the company should explore further scenarios**

3.11 The length of osteoporosis treatment in clinical practice, particularly for oral bisphosphonates, is often shorter than intended. This was reflected in the company’s model using rates of persistence. The company derived persistence rates for the various treatments in its model from different sources. It used persistence rates for alendronic acid alone, risedronate sodium and raloxifene from a paper by Li et al. 2012, which was based on data from the UK General Practice Research Database (GPRD) from

1995 to 2008. The company derived persistence rates for denosumab from the Swedish Prescribed Drug Register, and assumed that the persistence for alendronic acid after romosozumab would be 85% of the rates for denosumab. This was higher than the persistence for alendronic acid alone derived from Li et al.. The company explained that people having alendronic acid after romosozumab would likely have higher persistence because their disease would be more severe than people in Li et al.. For persistence on teriparatide and zoledronic acid, the company used data from a Swedish osteoporosis database. The company explained that it preferred to use data from observational studies to model persistence, as persistence in clinical trials is likely to be higher than in clinical practice. However, because of a lack of real-world data on romosozumab persistence, it assumed that 90% of people would complete the 12-month treatment period based on the persistence rates seen in the clinical trials. The ERG noted that the company's approach was inconsistent and likely biased, because it had used clinical trial data to model persistence for romosozumab but not the comparators. It considered that real-world persistence with romosozumab would likely be lower than in the clinical trials, so it preferred to use a lower value of 80% for its base case. This was based on an assumption in a Swedish cost-effectiveness analysis by Söreskog et al. 2021. The ERG preferred to use data from a study by Morley et al. 2020 rather than Li et al. to inform persistence rates for alendronic acid, risendronate sodium and raloxifene. This was because Morley et al. used more recent data from the UK Clinical Practice Research Datalink (CPRD). Morley et al. provided persistence rates for treatments split by whether people had a previous treatment. The ERG used persistence rates for people having oral bisphosphonates after a previous treatment to model persistence for alendronic acid after romosozumab. This gave a much lower persistence at 6 months (31%) compared with the company base case (85%). Clinical experts broadly agreed with the ERG's preference for using persistence rates from Morley et al. rather than Li et al.. However, they explained that

persistence on alendronic acid after romosozumab would likely be higher than alendronic acid alone, and that 31% persistence at 6 months was too low. They suggested that people having romosozumab would likely have more severe osteoporosis than those in the CPRD or GPRD datasets, and would be more motivated to continue with treatment. The committee was aware that the company had not provided a scenario using persistence data from ARCH for alendronic acid, either after romosozumab or as a comparator. The committee considered that this scenario would support its decision making. It noted that the choice of persistence rates for alendronic acid after romosozumab had a major effect on the cost-effectiveness results. This was because once alendronic acid treatment is stopped, its effect is assumed to decrease to zero over time. So, a reduced persistence for alendronic acid after romosozumab compared with alendronic acid alone reduces the associated quality-adjusted life year (QALY) gains. The committee understood that in the ERG base case, people having alendronic acid after romosozumab had a lower persistence at 6 months than people having alendronic acid alone after 24 months. It considered that this lacked face validity. It concluded that there was uncertainty about persistence on alendronic acid after romosozumab. The committee would prefer to see a scenario with persistence rates for people having first-line oral bisphosphonates in Morley et al. also applied for alendronic acid after romosozumab, adjusted according to the total length of time after starting treatment, including romosozumab. This would mean that the same source of data is used for alendronic acid both as a comparator and after romosozumab, for consistency.

### **It is uncertain if the company's approach to modelling the effect of fractures on quality of life is appropriate**

3.12 In ARCH, health-related quality of life was assessed at pre-determined time points. The company noted that ARCH did not provide robust utility values sensitive to the effect of fractures, so it considered it inappropriate

to use the quality of life data from ARCH in its model. Instead, it used the utility multipliers for fractures from the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS), combined with the UK general population values from Szende et al. 2014 in line with the approach in [NICE's technology appraisal guidance on bisphosphonates for treating osteoporosis](#). The utility multiplier values are academic-in-confidence and cannot be reported here. The ERG agreed with the company's approach of using fracture utility multiplier from the ICUROS study. However, the ERG noted that the values differed from NICE's guidance on bisphosphonates, and that the approach for modelling the effect of multiple fractures was also different. The ERG explained that it could not test the potential effect of different approaches as it could not change the VBA code in the model (see section 3.10). The committee concluded that it is uncertain if the company's approach to modelling the effect of fractures on quality of life was appropriate.

### **Excess mortality should be modelled after hip and vertebral fractures**

3.13 The company modelled the mortality risk of fractures by applying an increased relative mortality risk to the general population all-cause mortality risk. It took the all-cause mortality risks from the UK Life Tables from 2012 to 2014. The company reduced the relative risk of mortality associated with fractures to 30% to account for the higher mortality risk associated with general frailty in the fractured population. This was in line with recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and International Osteoporosis Foundation (IOF). The company assumed that hip, vertebral and other (non-hip, non-vertebral) fractures have a mortality risk. The ERG preferred to use more recent values for all-cause mortality from the UK Life Tables from 2017 to 2019, and was unclear why the company used UK Life Tables from 2012 to 2014. The ERG explained that the ESCEO and IOF did not recommend modelling excess mortality for 'other' fractures. Because of a lack of clinical consensus on including excess



mortality after vertebral fractures, it preferred to include excess mortality after hip fractures only. The clinical experts noted that early mortality may be higher after hip fractures, but that overall long-term mortality is similar after both hip and vertebral fractures. The committee agreed, concluding that excess mortality should be modelled after hip and vertebral fractures.

## **Costs in the economic model**

### **Incremental fracture costs are more appropriate than total costs, but should also include rehabilitation costs**

3.14 The company estimated the costs of hip (£13,293), vertebral (£2,897) and other (£2,131) fractures during the first year based on a UK study by Gutiérrez et al. 2011 and 2012 (updated using the Consumer Price Index [CPI]). The company estimated the costs of fractures in subsequent years based on Davies et al. 2016 (updated using the CPI), but only applied these costs to hip and vertebral fractures. These costs were £115 and £361 respectively. The ERG noted that the company had taken the total fracture costs from Gutiérrez et al. but these studies also provided the incremental costs of people with fractures relative to matched controls. The ERG considered that incremental costs would be more specific to the fracture than total costs. It preferred to use these incremental cost estimates for hip (£5,369), vertebral (£1,465) and other (£877) fractures for its base case. The ERG noted that a similar approach was used in [NICE's technology appraisal guidance on bisphosphonates for treating osteoporosis](#), but acknowledged that the incremental costs from Gutiérrez et al. did not include rehabilitation costs. The company responded that its fracture cost estimates from Gutiérrez et al. were already case controlled. The committee noted that using total or incremental costs had a relatively minor impact on the cost-effectiveness results. However, it noted that rehabilitation costs were likely to be large and omitting them may be inappropriate. The committee concluded that incremental fracture costs

were more appropriate than total costs, but that they should also include rehabilitation costs.

### **The costs associated with long-term care are uncertain**

3.15 The company explained that hip fractures are associated with increased admission to long-term care facilities. To account for this, the company applied daily long-term costs based on ESCEO and IOF guidelines and in line with [NICE's technology appraisal guidance on bisphosphonates for treating osteoporosis](#). It applied a daily long-term nursing home care cost of £112 based on an EU study, updated using the CPI and calculated based on the probability of being discharged to institutional care. The ERG preferred to use a daily long-term care cost of £67 for its base case based on unit costs from the Personal Social Services Research Unit (PSSRU) 2020, derived using a similar approach to NICE's guidance on bisphosphonates. The committee concluded the costs associated with long-term care were uncertain.

### **The company's proposed patient support programme should not be considered**

3.16 The company applied no drug administration costs for romosozumab in its model. The company explained that it plans to set up a patient support programme which will include a homecare service, an adherence support program and training on delivering injections. The company also did not apply any administration costs for alendronic acid since it is taken orally. The company applied administration costs for denosumab and zoledronic acid in its model based on the PSSRU 2020. At clarification, the ERG requested the company include administration costs for romosozumab and all relevant comparators. The company provided scenario analyses that included the following additional administration costs: 12 nurse visits per year for romosozumab, and 365 nurse visits per year for teriparatide. The ERG preferred not to consider the proposed patient support programme in its base case, and therefore included the romosozumab

administration costs. The committee understood from NICE that the proposed patient support programme could not be considered within the appraisal of romosozumab. It noted that the patient support programme had little impact on the cost-effectiveness results but concluded that it should not be considered, in line with the guidance from NICE.

### **It is uncertain if the treatment effect of romosozumab wanes over time**

3.17 In its model, the company assumed that the duration of the treatment effect of romosozumab is maintained for 5 years. After this, a dynamic offset (linear waning) of the treatment effect is assumed for another 5 years. At year 11, the company assumed there would be no treatment effect. The ERG explained that the Kaplan–Meier curves for time to first clinical fracture and time to first non-vertebral fracture show that there is a visible separation for romosozumab followed by alendronic acid compared with alendronic acid alone. However, the ERG also noted that the curves seem to converge from month 42 to month 48, and so questioned if the treatment effect of romosozumab may wane over time. The committee noted that the curves by month 48 were based on very small numbers of people having treatment and considered that it would be difficult to make any firm conclusions about treatment waning. It concluded that because of the small numbers of people having treatment towards the end of the curves, it was uncertain if the treatment effect of romosozumab wanes over time.

### **The cost and quality of life effect of cardiovascular events should be included in the model**

3.18 The company's model only included gastrointestinal adverse events that are associated with oral bisphosphonates. It excluded all other adverse events because of a lack of evidence and in line with [NICE's technology appraisal guidance for raloxifene for the primary prevention of osteoporotic fragility fractures in postmenopausal women](#) and [raloxifene and teriparatide for the secondary prevention of osteoporotic fragility](#)

[fractures in postmenopausal women](#). The ERG noted that more people having romosozumab had serious cardiovascular events in ARCH than those having alendronic acid alone (see section 3.9). Although romosozumab is contraindicated for people with previous myocardial infarction or stroke (see section 3.9), the ERG was unclear if all cardiovascular events in ARCH happened in people with a history of myocardial infarction or stroke. The ERG explained that excluding events which happened in people who would not be contraindicated was inappropriate. Therefore, the ERG considered it was appropriate to include the costs and quality of life effect of serious cardiovascular events in its base case. The committee questioned if ARCH showed whether people for whom romosozumab was contraindicated had cardiovascular events. But the company responded that cardiovascular risk factors had not been collected at baseline. The clinical experts explained that in clinical practice it can be challenging for rheumatologists to evaluate cardiovascular risk, and so referral costs to cardiologists should be included in the model. The committee was aware that [NICE's clinical guideline on osteoarthritis care and management in adults](#) considered cardiovascular adverse events associated with non-steroidal anti-inflammatory drugs. The committee concluded that, because of the uncertainty in identifying cardiovascular risk, cardiovascular adverse events should be included in the model.

## Cost-effectiveness estimates

### **The most likely cost-effectiveness estimates are higher than those normally considered an acceptable use of NHS resources**

3.19 The committee recalled that the company had not provided data on the effectiveness of romosozumab for people at imminent fracture risk (see sections 3.7 and 3.8). It would have liked to have seen the NMA adjusted for baseline risk, and treatment effect estimates adjusted for imminent fracture risk (see section 3.8). The committee also recalled that there

were issues with the company's model that needed to be resolved before it could be considered robust for decision making (see section 3.10). It was concerned that the ERG was not able to fully test the company's model because it could not change the VBA code in which the model calculations were done. This was because the confidential FRAX algorithm was implemented within the code (see section 3.10). The committee was satisfied with some of the ERG's preferred assumptions but noted that neither the company nor ERG base cases fully met its preferences. The committee conclude that it would like to see:

- evidence for the effectiveness of romosozumab for people at imminent fracture risk and the company's NMA adjusted for baseline risk, and treatment effect estimates adjusted for imminent fracture risk (see sections 3.7 and 3.8)
- issues resolved with the company's model as far as possible and satisfy the committee it is robust for decision making (see section 3.10)
- further information around how the parametric distributions had been fitted to the Kaplan–Meier data from ARCH (see section 3.10)
- a scenario including the following preferences:
  - persistence on alendronic acid (alone and after romosozumab) based on the data from people having first-line oral bisphosphonates in Morley et al. 2020. These persistence rates for alendronic acid after romosozumab should be adjusted according to the total length of time after starting treatment, including romosozumab (see section 3.11)
  - modelling excess mortality after fracture using updated UK Life Tables from 2017-2019, and after hip and vertebral fractures only (see section 3.13)
  - fracture costs based on incremental costs with rehabilitation costs from Gutiérrez et al. 2011 and 2012 (see section 3.14)
  - including cardiovascular events (section 3.18).

Because of confidential commercial arrangements for romosozumab, alendronic acid and other comparator treatments, the incremental cost-effectiveness ratio (ICERs) cannot be reported here. Taking into account all confidential discounts, the committee noted that the ERG's base-case ICER compared with alendronic acid was well above what NICE considers a cost-effective use of NHS resources. The committee acknowledged that the ICER with the committee-preferred assumption for persistence on alendronic acid after romosozumab would be lower than this. However, even if the model could be considered robust for decision making, the committee's preferred ICER would likely not be below the upper end of the range normally considered a cost-effective use of NHS resources (£30,000 per QALY gained). Therefore, romosozumab is not recommended for use in the NHS.

## Innovation

### **Romosozumab is an innovative treatment for severe osteoporosis, but all relevant benefits are reflected in the cost-effectiveness estimates**

3.20 The company considered romosozumab to be innovative because it is a unique osteoporosis therapy that stimulates bone formation and decreases bone resorption. The company explained it is the first anti-sclerostin antibody to be licensed for use in Europe and the USA. The patient experts highlighted that romosozumab is the first new treatment to be available in 10 years. Patient experts also highlighted that romosozumab will offer a step change for treating severe osteoporosis. The clinical experts explained the benefits of romosozumab dual mode of action over the current treatments. The committee acknowledged the benefits offered by romosozumab. However, it concluded that it had not been presented with evidence of any additional benefits that were not captured in the QALY measurements.

## Equalities consideration

### There are no equalities issues relevant to the recommendations

3.21 The patient experts explained that although romosozumab has a marketing authorisation for women after menopause, this should not prevent using romosozumab for men, because the benefits of treatment are likely to be similar. The committee concluded that romosozumab will be considered within its marketing authorisation. The company noted that osteoporosis is more common in women than men, and socially deprived groups have increased fracture risk, higher mortality after fracture, and longer hospital stays and risk of re-admission. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. No other equality or social value judgement issues were identified.

## 4 Review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Sanjeev Patel

Chair, appraisal committee

November 2021

## **5 Appraisal committee members and NICE project team**

### **Appraisal committee members**

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### **NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

#### **Harsimran Sarpal**

Technical lead

#### **Charlie Hewitt**

Technical adviser

#### **Shonagh D'Sylva**

Project manager

ISBN: **[to be added at publication]**