

Romosozumab for treating severe osteoporosis

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

- 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](#).
- 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 medicines, 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 a person has severe osteoporosis and has had a major osteoporotic fracture within 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. Comparing romosozumab indirectly with other bisphosphonates and other medicines for this condition suggests that romosozumab 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.

The most likely cost-effectiveness estimates for romosozumab followed by alendronic acid, compared with alendronic acid alone, are within what NICE normally considers an acceptable use of NHS resources. So, romosozumab is 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 for romosozumab](#).

Price

- 2.3 The price for romosozumab is £427.75 for 2 pre-filled pens administered subcutaneously as a single monthly dose (BNF online, accessed October 2021). The company has a commercial arrangement. This makes romosozumab available to the NHS with a discount. 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 not everyone can have them. The clinical experts 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 on raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women](#) only recommends teriparatide for the secondary prevention of osteoporotic fractures. Also, people can only have teriparatide once during their lifetime. 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 has 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 population in which the company positioned romosozumab is narrower than the NICE scope and ARCH trial population

- 3.3 The population in the NICE scope and the marketing authorisation 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, where high risk of fracture was defined as having had a major osteoporotic fracture within 24 months. A major osteoporotic fracture was defined as a clinical spine, hip, forearm or humerus fracture. The company's decision problem population will be referred to as imminent fracture risk. The committee was aware that defining fracture risk can be complex and there are different ways and different factors that contribute to the definition of high risk. The committee concluded that for this evaluation it would use the ARCH trial definition of high risk (see

section 3.6). It also concluded that the company's imminent fracture risk population was narrower than the NICE scope, the marketing authorisation and the ARCH trial.

Romosozumab would be used in people at imminent fracture risk, regardless of previous treatment

3.4 The company explained that it had positioned romosozumab 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 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. The clinical experts also explained that the date of the previous fracture may not always 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 romosozumab should be positioned regardless of previous treatment, but that ideally it should be available as a first-line treatment. The committee acknowledged that the company's imminent fracture risk population represents people with a high risk of fracture. However, it noted that most people in ARCH had not previously had treatment for osteoporosis (see [section 3.6](#)), so there was uncertainty around the efficacy of romosozumab in later lines of therapy. A response to consultation highlighted that in the STRUCTURE trial, romosozumab had a greater effect on bone mineral density (BMD) than teriparatide in people who had previously had bisphosphonates. STRUCTURE was a randomised, double-blind study in women after menopause with osteoporosis, providing data on romosozumab (n=218) compared with teriparatide (n=218). This gave some reassurance as to the efficacy of romosozumab regardless of previous treatment. The committee concluded that it would appraise romosozumab 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 romosozumab

3.5 The committee recalled that it would appraise romosozumab 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 fractures, 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 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

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. In the ARCH intention-to-treat (ITT) population, people randomised to the romosozumab arm 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 having 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 a post-hoc analysis of ARCH showed that the imminent fracture risk population had similar outcomes to the ITT population, but had not presented this evidence in its submission. At the first meeting, the committee concluded that romosozumab followed by alendronic acid is more effective than alendronic acid alone in the ARCH ITT population, but that the company had not provided evidence in the imminent fracture risk population. In response to consultation, the company presented a post-hoc analysis of ARCH comparing the results for people whose last major osteoporotic fracture was recent (less than 24 months) or not recent (more than 24 months). The recent fracture group corresponded to the company's imminent fracture risk population. The results showed that there were no statistically significant differences between the 2 groups for any of the primary or key secondary end points in ARCH. The company therefore considered that it was appropriate to generalise the results from the ARCH ITT population to the imminent fracture risk population. The ERG noted that there were considerable differences in the effectiveness results between the recent and not recent groups from ARCH for some end points, even though the results

were not statistically significant. The clinical experts stated that the post-hoc analysis raised questions about the company's imminent fracture risk population. This was because people in ARCH whose last fracture was not recent had similar outcomes to people whose last fracture was recent. They considered that the ARCH ITT population may better represent the population that romosozumab should be used in. The committee noted that the post-hoc analysis should be interpreted with caution. However, it concluded that the results provided reassurance that romosozumab was similarly effective in the imminent fracture risk population as in the ARCH ITT population.

Despite uncertainty, the indirect comparisons with other comparators are suitable for decision making

3.8 There is no head-to-head evidence comparing romosozumab followed by alendronic acid with 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 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 ITT population rather than the imminent fracture risk population (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. At its first meeting, the committee considered that it would like to see NMAs adjusted for baseline risk, and treatment effect estimates centred around the imminent fracture risk population. In response to consultation, the company updated its NMAs to include the results from the post-hoc analysis for the recent fracture group (see [section 3.7](#)) as a scenario analysis. The results were

consistent with the company's original NMAs using the ARCH ITT population. The company noted that this scenario analysis was likely to be more uncertain because it could not adjust the comparator trials to the imminent fracture risk population. The company also did meta-regressions to explore if baseline risk or any other covariates impacted the estimated treatment effects in the NMAs. The company used 2 approaches:

- adjusting for the rate of people with a history of vertebral fracture at baseline, and
- reducing the network to include trials with a placebo comparator and adjusting for the fracture rates in the placebo arm.

With the exception of new vertebral fractures at 12 months, the results of the company's meta-regressions showed that neither vertebral fractures at baseline nor baseline risk significantly affected the treatment effects in the NMAs. So, the company considered that its original NMAs remained the most appropriate for decision making. The committee noted that the results of the baseline risk meta-regression had wide credible intervals, indicating a high level of uncertainty. The committee considered that both the company's original and updated NMAs had considerable uncertainty. Despite this, the updated NMAs provided reassurance that the relative efficacy of romosozumab compared with current standard care was likely to be similar in the imminent fracture risk and ARCH ITT populations. The committee therefore concluded that the results of the original NMAs using the full ARCH ITT population data were appropriate for decision making.

More people having romosozumab had serious cardiovascular events in ARCH, but no imbalance was seen in another larger romosozumab study

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 (n=3,589) compared with placebo followed by denosumab (n=3,591). The committee noted that FRAME had a larger population than ARCH. In response to consultation, the company also noted that no imbalance in cardiovascular events had been seen in STRUCTURE (compared with teriparatide) and in a phase 2 trial compared with placebo. 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 of cardiovascular events, or alendronic acid reducing the risk of cardiovascular events, or that this was a chance finding. The committee also understood that romosozumab should only be prescribed if the clinician and the 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 benefits and risks before starting romosozumab was essential.

Economic model

The company's economic model is suitable 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. It 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. In response to consultation, the company explained that parametric curves were fitted to the hip fracture and non-vertebral fracture data from ARCH. It used an exponential model for romosozumab followed by alendronic acid and a log-normal model for alendronic acid alone to model hip fractures. For non-vertebral fractures, the company used a log-normal model for both treatment arms. The ERG noted that the company had not provided graphs comparing different parameterisations to the observed data, or tables detailing statistical fit. The committee concluded that the company's model was suitable for decision making but there was still some uncertainty about how the parametric distributions had been fitted to the data from the ARCH.

How long people continue to have romosozumab is uncertain

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. In its original base case, because of a lack of real-world data on romosozumab persistence, the company 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 the company had used clinical trial data to model persistence for romosozumab but not the comparators. It considered that real-world persistence on romosozumab would likely be lower than in the clinical trials, so it preferred to use a value of 80% for its base case. This was based on an assumption in a Swedish cost-effectiveness analysis by Söreskog et al. (2021). In response to consultation, the company did a Delphi panel with 18 clinical experts in the UK. The Delphi panel explored persistence on different osteoporosis treatments, and persistence on alendronic acid specifically as a follow-on treatment. The experts' consensus was that a slightly lower proportion of people would complete the 12-month romosozumab treatment period than in the persistence rates seen in ARCH. The outputs of the Delphi panel are academic in confidence and cannot be reported here. The company considered that the true persistence rate estimates on romosozumab would likely be slightly higher in UK clinical practice than the Delphi panel estimates. Therefore, it continued to assume a 90% persistence on romosozumab at 12 months for its revised base case. The ERG reiterated that it was inconsistent to use real-world evidence to model persistence for the comparators, and clinical trial data to model persistence for romosozumab.

Therefore, the ERG preferred to use a lower estimate of persistence on romosozumab in line with the Delphi panel for its revised base case. The company noted that the ERG's position was also inconsistent, in that it used different types of data to model persistence on romosozumab and alendronic acid. The committee was aware that the choice of persistence rates for romosozumab had a major effect on the cost-effectiveness results. The committee concluded that persistence on romosozumab was highly uncertain, and that it would consider cost-effectiveness scenarios using both the company's and ERG's preferred assumptions.

More people are likely to continue having alendronic acid after romosozumab than having alendronic acid alone

3.12 In its original base case, the company assumed that persistence on alendronic acid after romosozumab would be 85% of that of denosumab, based on the Swedish Prescribed Drug Register. These persistence rates were higher than what the company assumed persistence would be for alendronic acid alone, which it took from a different source. The ERG preferred to use data from the same study to model persistence for alendronic acid after romosozumab and alendronic acid alone. It favoured a study by Morley et al. (2020), which used recent data from the UK Clinical Practice Research Datalink (CPRD). The clinical experts broadly agreed with the ERG's preference for using persistence rates from Morley et al. However, they explained that persistence on alendronic acid after romosozumab would likely be higher than on alendronic acid alone, and that the ERG's modelled persistence on alendronic acid alone was too low. People having romosozumab would likely have more severe osteoporosis than those in the CPRD dataset, and would be more motivated to continue with treatment. The committee 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. The committee understood that in the ERG's 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. At its first meeting, the committee requested to see a scenario with the same persistence rates from Morley et al. applied for alendronic acid in both arms, adjusted according to the total length of time after starting treatment, including romosozumab. In response to consultation, the company argued that assuming equal persistence

on alendronic acid after romosozumab and alendronic acid alone is extremely conservative. The Delphi panel concluded that persistence on alendronic acid after romosozumab would be higher than on alendronic acid alone. To reflect this and the feedback from the clinical experts at the first committee meeting, the company adjusted the persistence rates for alendronic acid after romosozumab to be higher than those for alendronic acid alone at the equivalent time points using the data from Morley et al. For persistence on alendronic acid alone, the company used the unadjusted data from Morley et al. The ERG accepted that persistence on alendronic acid would be higher after romosozumab and considered that the company's adjusted persistence rates from Morley et al. were plausible. However, it noted that at 24 months in ARCH the persistence in both arms was the same. The committee questioned the validity of only adjusting the persistence rates for alendronic acid after romosozumab and not adjusting those for alendronic acid alone. However, it understood that the adjustment to Morley et al. was to account for the increased persistence after romosozumab, rather than the higher risk population. The committee considered whether the Delphi panel consensus estimates were more plausible than those from Morley et al., because this approach would use the same source of data for both treatment arms. It noted that the Delphi panel consensus was that people having romosozumab after alendronic acid would have a constant persistence from 12 to 60 months, which it considered implausible. The committee also considered that physicians can tend to overestimate persistence, which made the Delphi panel uncertain. It concluded that more people are likely to continue having alendronic acid after romosozumab than having alendronic acid alone. Using persistence rates from either Morley et al. or the Delphi panel would each have flaws, but the committee concluded that it was appropriate to consider both during decision making.

The company's approach to modelling the effect of fractures on quality of life is appropriate

- 3.13 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 \(TA464\)](#). The ERG agreed with the company's approach of using fracture utility multipliers from the ICUROS study. However, the ERG noted that the values differed from TA464, and that the approach for modelling the effect of multiple fractures was also different. At its first meeting, the committee concluded that it is uncertain if the company's approach to modelling the effect of fractures on quality of life was appropriate. In response to consultation, the company presented a scenario using the fracture utility multipliers from TA464. This significantly reduced the incremental cost-effectiveness ratio (ICER), because there was a larger utility loss associated with vertebral fractures when using the TA464 fracture utility multipliers. The committee concluded that the fracture utility multipliers from ICUROS were more appropriate than TA464 because they were newer and based on a larger sample size.

Excess mortality should be modelled after hip and vertebral fractures

3.14 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, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the 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 the 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. At its first meeting, the committee concluded that excess mortality should be modelled after hip and vertebral fractures. In response to consultation, the company updated its base

case to exclude mortality linked to non-hip, non-vertebral fractures and included excess mortality after hip and vertebral fractures only. The committee was aware that the company continued to use the 2012 to 2014 UK life tables for all-cause mortality, despite the ERG's preference for using the more recent mortality rates.

Costs in the economic model

Uncertainties around fracture costs have a minor effect on the cost-effectiveness results

3.15 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, 2012; updated using the Consumer Price Index [CPI]). The company estimated the costs of fractures in subsequent years based on Davis 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 [TA464](#), but acknowledged that the incremental costs from Gutiérrez et al. did not include rehabilitation costs. 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. At its first meeting, the committee concluded that incremental fracture costs were more appropriate than total costs, but that they should also include rehabilitation costs. In response to consultation, the company updated its base case to use the fracture costs from [TA464](#). The committee concluded that using different approaches to calculate fracture costs had a minor effect on the cost-effectiveness results.

The ERG's average cost associated with long-term care is appropriate for decision making

3.16 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 [TA464](#). 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 TA464. At its first meeting, the committee concluded the costs associated with long-term care were uncertain. In response to consultation, the company explained that the ERG's assumption that 36% of people moving into long-term care are self-funded and do not incur any costs contrasts with NICE guidance which recommends that only those moving to residential care are self-funded. It explained the proportion of people moving to nursing homes is likely to increase with age, while the proportion of people who are self-funded is likely to decrease. Therefore, the company retained its original base case assumption. Because of the uncertainty, the ERG preferred to use an average of its original estimate and that of the company for its revised base case (£90 per day). The committee concluded that the ERG's revised average long-term care costs were appropriate for decision making.

Romosozumab administration costs should be limited to a single nurse visit

3.17 The company applied no drug administration costs for romosozumab in its original 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 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. 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. In response to consultation, the company explained that romosozumab will be self-administered like other biologics already used in the NHS. In rare circumstances, NHS resource may be used only to provide the first administration of romosozumab, in line with clinical practice in NHS Scotland. To

reflect this, the company updated its base case with 1 nurse visit only and assumed that the 11 remaining doses will be self-administered. The committee agreed that the company's updated base case was appropriate.

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

- 3.18 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.

It is appropriate to consider cost-effectiveness results both with and without the inclusion of cardiovascular adverse events

- 3.19 The company's original 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 on 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 committee was aware that [NICE's guideline on osteoarthritis: care and management](#) considered cardiovascular adverse events associated with non-steroidal anti-inflammatory drugs. Therefore, it was appropriate to consider them within the model. In response to consultation, the company updated its base case model to include cardiovascular events based on the rates in ARCH. It explained that the other romosozumab studies (see section 3.9) did not show any imbalances in cardiovascular events. Therefore, the inclusion of cardiovascular events based only on ARCH represented a conservative approach. The ERG agreed, noting that the company could have pooled cardiovascular events across the romosozumab studies. The committee noted there was still uncertainty around the inclusion of cardiovascular events in the model. The committee concluded it would consider results both with and without cardiovascular events in its decision making.

Cost-effectiveness estimates

Romosozumab is cost effective for treating severe osteoporosis after menopause in people at imminent fracture risk

3.20 The committee focused on the pairwise ICERs for romosozumab followed by alendronic acid compared with alendronic acid alone. The company's and ERG's deterministic base cases included the confidential Commercial Medicines Unit price for alendronic acid, which means they cannot be reported here. The committee recalled that there were several uncertainties in the modelling, specifically:

- the efficacy of romosozumab in the imminent fracture risk population (see [section 3.7](#))
- the results of the NMAs (see [section 3.8](#))
- the persistence on romosozumab (see [section 3.11](#)) and alendronic acid after romosozumab (see [section 3.12](#))
- the fracture utility multipliers (see [section 3.13](#))

- the effect of cardiovascular adverse events (see [section 3.19](#)).

It understood that the key difference between the company and ERG base cases was the romosozumab persistence assumption, although the ERG had also made several other changes that had a small effect on the cost-effectiveness results. Because of the uncertainty around the following assumptions, the committee considered both the company and ERG base cases:

- with and without cardiovascular events
- with persistence rates based on the Delphi panel
- with the fracture utility multipliers from [TA464](#).

The committee noted that although the ERG base case was above the range NICE normally considers an acceptable use of NHS resources (that is, £20,000 to £30,000 per quality-adjusted life year [QALY] gained), if the Delphi panel persistence rates were applied then the ICER would fall within an acceptable range. It noted that excluding cardiovascular events from the model would further reduce the ICER. The committee therefore considered that the most plausible ICER for romosozumab followed by alendronic acid compared with alendronic acid alone was likely to be below £30,000 per QALY gained. It concluded that romosozumab followed by alendronic acid is a cost-effective use of NHS resources.

Innovation

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

- 3.21 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's 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

3.22 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 noted that there may be some people who have been through the menopause but do not identify as a woman. The committee concluded that romosozumab will be considered within its marketing authorisation but that the recommendation need not specify sex. The company noted that osteoporosis is more common in women than men, and people of low socioeconomic status have increased fracture risk, higher mortality after fracture, longer hospital stays and greater risk of re-admission. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. In response to consultation, a consultee highlighted that rare types of osteoporosis had not been considered. However, the committee did not consider this an equality issue that could be resolved by this appraisal. The committee concluded that no other equality issues raised were relevant since romosozumab is recommended.

4 Implementation

- 4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has severe osteoporosis and the doctor responsible for their care thinks that romosozumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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Accreditation

