National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Romosozumab for treating severe osteoporosis
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Cleveland Clinic Foundation	-In the first sentence, it should read “bone” instead of “bone tissue”. -In the second paragraph of the background should read, “oestrogen levels after menopause accelerate bone loss,..” instead of “after the menopause” -In the second-to-last sentence of the second paragraph of the background, the “mostly as a result of low bone strength” should be further clarified whether the authors mean “osteoporosis” or not.	Thank you, Background section has been amended.
	Bone Research Society	The remit is appropriately worded	Thank you. No action required.
	Royal Osteoporosis Society	Yes, but is somewhat misleading to describe the population as “adults” in view of market authorisation specifically for postmenopausal women	Thank you. We acknowledge that the license is in postmenopausal women. NICE will consider its equality obligations.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Physicians FLSDB	The remit matches the licensed indication	Thank you. No action required.
	UCB Pharma	UCB do not agree with the current remit wording. Romosozumab is indicated in treatment of severe osteoporosis in postmenopausal women at high risk of fracture.	Thank you. We acknowledge that the license is in postmenopausal women. NICE will consider its equality obligations. considerations.
	Society for Endocrinology	Yes	Thank you. No action required.
Timing Issues	Cleveland Clinic Foundation	This is a relatively fundamental medication for treating severe osteoporosis that should be considered rather urgently.	Thank you. In agreement with the company, the STA process has been expedited where possible.
	Bone Research Society	Patients at very high risk of fracture remain at high risk even with the most effective of our current therapies. Additional alternative options with greater efficacy are long overdue to optimise clinical management.	Thank you. In agreement with the company, the STA process has been expedited where possible.

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	Royal Osteoporosis Society	Urgent – romososumab was given market authorisation by EMA in Dec 2019 and is already approved for use in Scotland and N. Ireland	Thank you. In agreement with the company, the STA process has been expedited where possible.
	Royal College of Physicians FLSDB	Current treatments for osteoporosis prevent less than 40% of fractures after an index fracture. The needs of patients at very high risk in particular have been inadequately addressed. The technology provides a life-line for these patients in terms of rapid and sustained reduction in fracture risk. The appraisal for the technology had its final scope in January 2019 and has been met with repeated delays. In October 2020, the Scottish Medicines Consortium gave positive advice on the technology (SMC2280), followed by integration into Scottish Guidelines in January 2021 (SIGN142). Given the delays and substantial number of high risk women who are continuing to fracture despite current approved treatments, we consider this appraisal should be rapidly processes.	Thank you. In agreement with the company, the STA process has been expedited where possible.
	UCB Pharma	UCB believe that there is an urgency for Romosozumab to be recommended by NICE for the following reasons: • The existing unmet need for postmenopausal women with severe osteoporosis who have experienced a fragility fracture in the last 24 months • UCB is aware that the clinical community is seeking for alternative access solutions i.e. Individual Funding Requests (IFRs) and private practice to be able to prescribe romosozumab • Finally, more than two years have been passed since EMA granted Market Authorisation for romosozumab • The availability of romosozumab in Scotland to treat postmenopausal women who have experienced a fragility fracture and who are at imminent risk of	Thank you. In agreement with the company, the STA process has been expedited where possible.

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		another fragility fracture (within 24 months) following the Scottish Medicines Consortium positive advice in November 2020, and availability of romosozumab for eligible patients in Northern Ireland (January 2021). • UCB and Amgen have been engaging with NICE since the appraisal process began in 2018. NICE have determined that the Multiple Technology Appraisal (MTA) model they have been using to assess romosozumab is no longer appropriate, which has led to a significant delay that impacts patients with severe osteoporosis.	
	Thornton & Ross	Any resulting guidance from this STA will need to be integrated into CG146. Since the withdrawal of ID901, this pathway should be reviewed and updated considering existing technologies and sequential treatment of bone forming agents and anti-resorptives in certain patient populations.	Thank you. CG146 has been recommended for a full update
	Society for Endocrinology	There are clearly a proportion of patients with severe osteoporosis who would benefit significantly if this anabolic agent were available. This is a relatively fundamental medication for treating severe osteoporosis that should be considered rather urgently.	Thank you. In agreement with the company, the STA process has been expedited where possible.
Additional comments on the draft remit	Society for Endocrinology	The once monthly administration is likely to result in greater uptake and better compliance when compared to daily administration of teriparatide.	Thank you. Your comment has been noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Cleveland Clinic Foundation	-In the first sentence, it should read “bone” instead of “bone tissue”. -In the second paragraph of the background should read, “oestrogen levels after menopause accelerate bone loss,..” instead of “after the menopause” -In the second-to-last sentence of the second paragraph of the background, the “mostly as a result of low bone strength” should be further clarified whether the authors mean “osteoporosis” or not. -The authors should include the mortality rate associated with osteoporotic or fragility fractures.	Thank you, Background section has been amended.
	Bone Research Society	The information provided is largely accurate but limited in extent (e.g. it does not really describe or characterise severe osteoporosis at high risk of fracture and how this might arise) and repeats statements that are questionable (e.g. it suggests that outputs from the two fracture risk assessment tools are comparable and interchangeable).	Thank you. The full context of the assessment tools will be explored in the appraisal.
	Royal Osteoporosis Society	No comments	Thank you. No action required.
	Royal College of Physicians FLSDB	The background is brief and accurate. While corticosteroids are mentioned, other commorbidties, medications are not. Also, it is important to note the risk of subsequent fracture depends on fracture site and recency, neither are included in risk assessment tools in NICE CG 146	Thank you. No action required.
	UCB Pharma	The background information is accurate and complete.	Thank you. No action required.
	Society for Endocrinology	-In the first sentence, it should read “bone” instead of “bone tissue”. -In the second paragraph of the background should read, “oestrogen levels after menopause accelerate bone loss,..” instead of “after the menopause”	Thank you, Background section has been amended.

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		-In the second-to-last sentence of the second paragraph of the background, the “mostly as a result of low bone strength” should be further clarified whether the authors mean “osteoporosis” or not. -The authors should include the mortality rate associated with osteoporotic or fragility fractures.	
The technology/ intervention	Cleveland Clinic Foundation	The technology is described appropriately and accurately.	Thank you. No action required.
	Bone Research Society	No. The intervention is romosozumab for one year followed by anti-resorptive treatment (alendronate or denosumab in clinical trials to date). This is covered within the posology section of the marketing authorisation (Following completion of romosozumab therapy, transition to antiresorptive therapy is recommended in order to extend the benefit achieved with romosozumab beyond 12 months).	Thank you. The committee will consider the intervention within its marketing authorisation. No action required.
	Royal Osteoporosis Society	No comment	Thank you. No action required.
	Royal College of Physicians FLSDB	The intervention is a Romosozumab as part of a sequence of therapy. In ARCH fracture rates in the Alendronate treated patients are lower if they are pre-treated with Romosozumab. This illustrates the sequence of therapy has greater benefits than the component drugs. A typical sequence would be Romosozumab followed by bisphosphonates or denosumab.	Thank you. The intervention section ahs been amended.
	UCB Pharma	The description of the technology is accurate.	Thank you. No action required.

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	Society for Endocrinology	Could include the frequency of administration	Thank you. The committee will consider the intervention within its marketing authorisation. No action required.
Population	Cleveland Clinic Foundation	The population is defined appropriately.	Thank you. No action required.
	Bone Research Society	The population is defined appropriately (Adults with severe osteoporosis at high risk of fracture) but the source of this population in the analysis is of major concern given recent analyses by the Technology Assessment Group. These have focussed on a derived population which contains a marked under-representation of patients at high risk of fracture. The question that the clinician needs to know is 'at what level of fracture risk or probability does romozosumab followed by antiresorptive become cost-effective, if ever'? If this level of risk does not exist in the modelled population, the question cannot be answered, or more likely, will be answered negatively and incorrectly. It should be noted that a difference in calibration between the two fracture risk assessment tools is even more marked at higher levels of fracture risk. We would suggest that to avoid confusion only one tool (the FRAX tool) be included in the approach.	Thank you. The full context of the assessment tools will be explored in the appraisal.
	Royal Osteoporosis Society	• As above, it is misleading to describe the population as "adults" in view of market authorisation being specifically for postmenopausal women. • It is disappointing that NICE will not consider use of romosozumab in men within this STA as there are data demonstrating efficacy (J Clin	Thank you. We acknowledge that the license is in postmenopausal women. NICE will

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		Endocrinol Metab 103: 3183–3193, 2018). We trust this will be promptly re-visited with any subsequent change to the MA. • It will be critical to define the subgroup of individuals at "high risk of fracture" appropriately in order to evaluate the group in whom romososumab is likely to be most clinically- and cost-effective: • In defining "high fracture risk" the ARCH study is highly relevant and the inclusion criteria for that study were *a bone mineral density T score of –2.5 or less at the total hip or femoral neck and either one or more moderate or severe vertebral fractures or two or more mild vertebral fractures; or a bone mineral density T score of –2.0 or less at the total hip or femoral neck and either two or more moderate or severe vertebral fractures or a fracture of the proximal femur sustained 3 to 24 months before randomization*. It should be noted that nearly all women in the study had at least 1 vertebral fracture, and many had multiple vertebral fractures whilst ≤10% had a recent hip fracture. It should also be noted that spine BMD can be unreliable (over-estimate) in the presence of vertebral fractures but also that there may be discordance between spine and hip BMD in vertebral fracture patients (with disproportionately low spine BMD compared to hip). We therefore recommend the definition is reworded with an emphasis on vertebral fracture, particularly if multiple, and suggest that **"osteoporosis and vertebral fracture, and/or multiple vertebral fractures" would be the best definition.** • Economic models tend to under-estimate the cost effectiveness of drugs for preventing vertebral fractures, as the true socio-economic costs are difficult to define. For this reason, cost effectiveness models used by NICE are largely driven by preventing hip fractures. This would be a justification for defining a further high risk target population based on FRAX, such as those at "**high risk of imminent fracture"** https://pubmed.ncbi.nlm.nih.gov/33409591/	consider its equality obligations.

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	Royal College of Physicians FLSDB	The population is defined as adults with severe osteoporosis at high risk of fracture without defining any thresholds. A sub-group at high imminent fracture risk are women after a hip, spine, humeral, femur or pelvis fracture. The other risk groups are those with multiple fractures and those with a fracture while on treatment. While NICE CG 146 recommends both QFracture and FRAX, these tools are not interchangeable and neither adequately takes into account imminent fracture risk following a major fragility fracture.	Thank you. We acknowledge that the license is in postmenopausal women. NICE will consider its equality obligations.
	UCB Pharma	UCB do not agree with the current description, as the population is not defined appropriately. Romosozumab is indicated in treatment of severe osteoporosis in postmenopausal women at high risk of fracture.	Thank you. We acknowledge that the license is in postmenopausal women. NICE will consider its equality obligations.
	Society for Endocrinology	Appropriate	Thank you. No action required.
Comparators	Cleveland Clinic Foundation	The comparators should also include anabolic agents as a separate group (abaloparatide, teriparatide). Abaloparatide is an important medication that was not included in the comparator group, and certainly should be.	Thank you, Amended to note anabolic agents, however abaloparatide does not hold a license in the UK.
	Bone Research Society	Yes, but as stated above, the technology is sequential therapy with romosozumab followed by antiresorptives, compared with other available (largely antiresorptive) comparators. The comparison to no active treatment	Thank you. No action required.

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		is essential as some patients are intolerant of, or have contraindications to, current therapies.	
	Thornton & Ross	Sequential treatment of bone forming agents and anti-resorptives should be considered, rather than a single technology comparator. This should then be reflected in an updated CG146 with all existing technologies to ensure clarity for clinicians when treating patients.	Thank you. The committee will consider if the model reflects the current practice in the NHS. CG146 has been recommended for a full update
	Royal Osteoporosis Society	• The comparators are appropriate in that they are all used in management of osteoporosis. • Caution is advised to ensure that any network meta-analysis conducted fulfils the assumption of transitivity: which in this context means taking great care to compare only those trials with matching severity of osteoporosis/fracture burden to those in the romosozumab ARCH trial, which reflects clinical practice, the principles of personalised medicine and the exact scenario in which an 'anabolic first' strategy would be selected over alendronate. For non-romosozumab medications, the severity of osteoporosis in those studies (based on inclusion criteria and demographic tables) must closely match those patients in the ARCH trial of romosozumab versus alendronate, where romosozumab was superior. That is not the case for inclusion/demographics of some of the comparator drugs; RCT's containing lower clinical severity patients should not have their effects compared against romosozumab's target population of "Adults with severe osteoporosis at high risk of fracture". • The treatment which best fulfils the description of "best alternative care" would be teriparatide as the only other agent with an anabolic	Thank you. Your comment around NMA's is noted. No action required.

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		mode of action although it should be noted that romosozumab has the additional benefit of anti-resorptive properties. • In evaluating romosozumab it will be important to acknowledge that the treatment period is for 12 months with the intention in clinical practice that the patient is subsequently treated with an anti-resorptive agent to maximise and maintain the treatment response. The use of the follow-on anti-resorptive agent should be incorporated within longer term models. • However, many high-risk patients have contraindications to bisphosphonates (e.g. renal impairment), so it is appropriate to include no treatment as a comparator.	
	Royal College of Physicians FLSDB	The comparators are appropriate.	Thank you. No action required.
	UCB Pharma	UCB agree with the proposed comparators.	Thank you. No action required.
	Society for Endocrinology	The comparators could also include anabolic agents as a separate group (abaloparatide, teriparatide). Abaloparatide is an important medication that was not included in the comparator group, and probably should be.	Thank you. No action required.
Outcomes	Cleveland Clinic Foundation	Risk of cardiovascular morbidity and mortality should be included in this section, in addition to bone mineral density expressed as T-score and g/cm^2	Thank you for your comment. BMD, and mortality have been included as outcomes. We have chosen not ot include Risk of cardiovascular

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			morbidity as an outcome.
	Bone Research Society	The outcomes are important and appropriate.	Thank you. No action required.
	Royal Osteoporosis Society	The outcome measures are appropriate. In examining outcomes relating to osteoporotic fractures, it will be particularly important to focus on the occurrence of vertebral fractures, and specifically multiple vertebral fractures	Thank you. No action required.
	Royal College of Physicians FLSDB	The outcomes are appropriate. Loss of independence and care home admission are two key outcomes for patients.	Thank you. No action required.
	UCB Pharma	UCB agree with the proposed outcomes.	Thank you. No action required.
	Society for Endocrinology	Risk of cardiovascular morbidity and mortality should be included in this section, in addition to bone mineral density expressed as T-score and g/cm^2	Thank you for your comment. BMD, and mortality have been included as outcomes. We have chosen not ot include Risk of cardiovascular morbidity as an outcome.
Economic analysis	Cleveland Clinic Foundation	This study describes an appropriate time horizon.	Thank you. No action required.

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	Bone Research Society	The time horizon should be remaining lifetime with at least a 10-year treatment or intervention period. While romosozumab is only administered for the first year, the fracture incidences during subsequent treatment with anti-resorptives are lower than those observed during anti-resorptive therapy initiated from the beginning (i.e. the trajectory of fracture incidence is altered/lowered in the longer term by the prior treatment with romosozumab). This has important implications for the total number of fractures prevented over the longer term.	Thank you. No action required.
	Royal Osteoporosis Society	Although romosozumab is administered for a treatment period of 12 months, in clinical practice romosozumab will be followed by anti-resoprtive treatment as in the clinical trials. Effectiveness should therefore be modelled at 12, 24 and 36 months to identify the beneficial effects of early fracture prevention on multiple health outcomes and in acknowledgement of the greatly increased fracture risk in-year following an incident fracture, where romosozumab has been shown to have rapid effects compared head-to-head with alendronate.	Thank you. No action required.
	Royal College of Physicians FLSDB	The time horizon should reflect the Romosozumab sequence duration of at least 5 years.	Thank you. No action required.
	Thornton & Ross	As detailed in 'Costs used in Health Technology Assessment' July 2020, it is important to ensure this STA considers the current prices available for other technologies. Biosimilars of Teriparatide are now offered to the NHS under hospital contract across England, and this cost should be considered when assessing cost effectiveness in this STA, and any resulting integration and update of CG146	Current prices available within the NHS will be considered.

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	UCB Pharma	UCB agree with the proposed economic analysis.	Thank you. No action required.
	Society for Endocrinology	This study describes an appropriate time horizon.	Thank you. No action required.
Equality and Diversity	Cleveland Clinic Foundation	This proposal does not seem to violate any ethical or legal codes of conduct with regards to equality, discrimination or persons with protected characteristics or disabilities.	Thank you. No action required.
	Bone Research Society	Two particular issues have been identified. The first is the real danger that an inappropriate analysis in an inappropriate population will lead to discrimination by excluding patients at high or very high risk of fracture from more effective therapies. Secondly, much recent evidence has demonstrated the impact of recency of fracture on subsequent fracture risk (so called imminent risk but associated with a longer term increase in fracture risk). Failure to include adjustments for recency of fracture in the model will, as outlined in the paragraph above, disenfranchise those at highest risk of fracture from more effective treatment strategies. A final comment would be whether the considerations of high risk would be independent of gender so that men are included in the outputs from the analyses.	NICE will consider its equality obligations. Equality issues are recorded in the equality impact assessment form. Particular attention will be given to any issue that has a potential discriminatory impact on a protected group.
	Royal Osteoporosis Society	No comments	Thank you. No action required.

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	Royal College of Physicians FLSDB	Many patients at high risk of fracture will be elderly with reduced survival. However, when risk factor assessment tools apply a 10 year mortality risk to understand the 10 year fracture risk, this may discriminate against older adults who may be at high risk of fracture in the next 2 years but survive only 5 years, thereby attenuating a 10 year risk of fracture. The intervention is not licenced in men.	Equality issues will be recorded in the equality impact assessment forms. Particular attention will be given to any issue that has a potential discriminatory impact on a protected group.
	UCB Pharma	No comment	Thank you. No action required.
	Society for Endocrinology	This proposal does not seem to violate any ethical or legal codes of conduct with regards to equality, discrimination or persons with protected characteristics or disabilities.	Thank you. No action required.
Other considerations	Cleveland Clinic Foundation	None.	Thank you. No action required.
	Bone Research Society	None	Thank you. No action required.
	Royal Osteoporosis Society	No comments	Thank you. No action required.
	Royal College of Physicians FLSDB	The expected fracture rate is a key driver for the benefits from the technology. One sub-group are women with a recent major fracture. It is critical the assessment process takes into account the early time dependent increase in	Thank you. This subgroup will be considered.

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		fracture risk for the first 2 years, now the NHS has implemented a number of specialised services, fracture liaison services, that can rapidly identify and manage these high risk patients as part of routine practice.	
	UCB Pharma	No comment	Thank you. No action required.
	Society for Endocrinology	None	Thank you. No action required.
Innovation	Cleveland Clinic Foundation	Yes, this technology is innovative and this proposal is appropriate and accurate.	Thank you. No action required.
	Bone Research Society	We regard the technology as a potential step-change in the management of osteoporosis that brings to clinical practice a therapeutic option that has a faster and greater reduction in fracture risk than currently used/available treatments. The speed of fracture reduction and the lowered fracture incidence trajectory will have a significant impact in those at the highest risk of fracture, regardless of how this risk id determined (recent fracture, multiple fractures, multiple risk factors etc). These benefits should be captured within well-conducted analyses with appropriate QALY calculations.	Thank you for your comment. The committee will consider innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	Royal Osteoporosis Society	Romosozumab is highly innovative in that it is the first agent to be licensed in the management of osteoporosis that has clear potential to increase bone formation whilst simultaneously reducing bone resorption. It therefore	Thank you for your comment. The committee will consider

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		represents a step change in the management of people at high risk of fracture. We strongly recommend that NICE considers use of romosozumab as a first line agent in this subgroup of people at very high fracture risk in order to take full advantage of its novel mechanism of action.	innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	Royal College of Physicians FLSDB	The technology provides a step change in the management of osteoporosis by rapidly de-risking patients within months of treatment onset. As evidenced by both the ARCH trial and the FRAME rest of the world analysis, the technology enables rapid risk reduction of both hip, spine and other fracture sites within 12 months of initiation. This is particularly relevant for the post fracture care setting. The increases in hip areal bone mineral density are relevant given the substantial body of evidence relating changes in hip density and fracture risk reduction.	Thank you for your comment. The committee will consider innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	UCB Pharma	UCB consider romosozumab to be an innovative technology due to its rapid onset and unique mechanism of action:	Thank you for your comment. The committee will consider innovative nature of the

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		Patients are at imminent risk of re-fracture in the 24 months following a fracture.[1] These patients require treatment that reduces subsequent fracture risk throughout this high risk period. The imminent risk currently represents a high unmet clinical need as current therapies only reach their optimal risk reduction by 36 months of treatment initiation.[2-5] Romosozumab is a one-year treatment, discovered and developed here in the UK. It is a bone-forming monoclonal antibody treatment that rapidly increases bone formation and decreases bone resorption (a 'dual' effect), addressing the imminent risk of subsequent fractures. Romosozumab increased bone mineral density (BMD) as early as 6 months (ARCH[6]; STRUCTURE[7]) and significantly reduced vertebral and clinical fracture risk over 12 months compared to alendronate (ARCH).[6] Benefits of romosozumab are thus achieved within one year and only 12 subcutaneous injections. The reduction in fracture risk is maintained beyond 12 months when romosozumab is followed by an anti-resorptive therapy, maximising the benefit of Romosozumab.[8] [1]Pinedo-Villanueva R, Charokopou M, Toth E, et al. Imminent Fracture Risk Assessments in the UK FLS Setting: Implications and Challenges. Archives of Osteoporosis 2019;14:12. [2]Black DM, Cummings SR, Karpf DB, et al. Randomised Trial of Effect of Alendronate on Risk of Fracture in Women with Existing Vertebral Fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535–1541. [3]Cummings SR, Black DM, Thompson DE, et al. Effect of Alendronate on Risk of Fracture in Women with Low Bone Density but Without Vertebral Fractures: Results from the Fracture Intervention Trial. Jama 1998;280:2077–2082. [4]Harris ST, Watts NB, Genant HK, et al. Effects of Risedronate Treatment on Vertebral and Nonvertebral Fractures in Women with Postmenopausal Osteoporosis: A Randomised	technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.

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		Controlled Trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. Jama 1999;282:1344–1352. [5]Reginster J, Minne HW, Sorensen OH, et al. Randomised Trial of the Effects of Risedronate on Vertebral Fractures in Women with Established Postmenopausal Osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83–91. [6]Saag KG, Petersen J, Brandi ML, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *N Engl J Med*. 2017;377(15):1417-1427. doi:10.1056/NEJMoa1708322. [7]Langdahl BL, Libanati C, Crittenden DB, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet*. 2017;390(10102):1585-1594. doi:10.1016/S0140-6736(17)31613-6. **[8]EVENITY®(romosozumab), Summary of Product Characteristics, UCB Pharma S.A., Brussels, Belgium. Last updated: December 2019.**	
	Society for Endocrinology	This is a highly innovative technology targeted specifically at enhancing osteoblastic bone formation via the Wnt pathway. Anabolic agents are currently critically needed for the treatment of osteoporosis and this sclerostin inhibitor represents a step change in osteoporosis management. Its once a month administration will improve patient acceptability and compliance. N Engl J Med 2016;375:1532-43 N Engl J Med 2017;377:1417-27 Lancet 2017 390:1585- 94 Given then need to treat with an antiresorptive agent, such as denosumab, after 12 months therapy, a direct comparison with other agents is therefore problematical.	Thank you for your comment. The committee will consider innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.

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Questions for consultation	Cleveland Clinic Foundation	Have all relevant comparators for romosozumab been included in the scope? No. Abaloparatide should be included as well. Which treatments are considered to be established clinical practice in the NHS for severe osteoporosis? The authors include the treatments that are established clinical practice for severe osteoporosis. **Are the outcomes listed appropriate? Yes.** **Are there any subgroups of people in whom romosozumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Romosozumab is particularly beneficial in reducing vertebral and clinical fracture risk. This has been demonstrated in comparison to placebo and alendronate in prior clinical trials (FRAME and ARCH trial). Where do you consider romosozumab will fit into the existing NICE pathway, osteoporosis? I believe it will be helpful in preventing vertebral fractures and clinical fractures in patients with severe osteoporosis, and additionally in preventing the recurrence of vertebral and clinical fractures in those with prior fractures. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which romosozumab is licensed. No.**	Thank you, your comments have been noted

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		• **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology. No.** • **could have any adverse impact on people with a particular disability or disabilities. No.** **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** Do you consider romosozumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, I truly believe that this medication is a viable therapeutic option for reducing clinical fractures and vertebral compression fractures. Do you consider that the use of romosozumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. The following trials should be taken into consideration: 1. Cosman F, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Engl J Med. 2016; 375:1532-1543. 2. Cosman F, et al. FRAME Study: The Foundation Effect of Building Bone with 1 Year of Romosozumab Leads to Continued Lower	

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		Fracture Risk After Transition to Denosumab. J Bone Miner Res. 2018; 33(7):1219-1226. 3. Lau EMC, et al. Romosozumab or alendronate for fracture prevention in East Asian patients: a subanalysis of the phase III, randomized ARCH study. Osteoporosis Int. 2020; 31(4):677-685. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. The medication can be quite costly for insurance coverage, and at times, can be a barrier. This is a significant barrier, and should be considered.	
	Royal Osteoporosis Society	No comments	Thank you, no action required
	Royal College of Physicians FLSDB	Given the sub-optimal experience of the previous MTA, it is critical the modelling takes into high imminent fracture risk and is clearly shown.	Thank you, your comments have been noted
	UCB Pharma	*Have all relevant comparators for Romosozumab been included in the scope?* • All relevant comparators have been included in the scope. *Which treatments are considered to be established clinical practice in the NHS for severe osteoporosis?* • Currently bisphosphonates are offered as a first-line treatment to people with a high risk of osteoporotic fragility fractures.[1] Denosumab can be used as a second-line treatment for patients with intolerance of or contraindications to bisphosphonates.[2] Non-bisphosphonates raloxifene and teriparatide are	Thank you, your comments have been noted

Section	Consultee/ Commentator	Comments [sic]	Action
		recommended as alternative treatment options for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.[3] *Are the outcomes listed appropriate?* • All relevant outcomes have been included in the scope *Are there any subgroups of people in whom Romosozumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?* • Romosozumab is a cost-effective option for patients who have experienced a major osteoporotic fracture (MOF) and are at imminent risk of another. This is a population of patients who have a high unmet clinical need, therefore recommendation of Romosozumab would ease the current burden of fragility fractures due to osteoporosis in the UK. *Where do you consider Romosozumab will fit into the existing NICE pathway, osteoporosis?* • Romosozumab is anticipated to be used as a first-line treatment option for postmenopausal women with severe osteoporosis who have experienced a fragility fracture and are at imminent risk of another fragility fracture. [1]'Bisphosphonates for treating osteoporosis' (2017). NICE Technology Appraisal 464. Review date 2022. [2]'Denosumab for the prevention of osteoporotic fractures in postmenopausal women' (2010). NICE Technology Appraisal 204. Reviewed 2014 **[3]'Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women' (2008, updated 2018). NICE Technology Appraisal 161**	

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	Society for Endocrinology	Have all relevant comparators for romosozumab been included in the scope? Abaloparatide could be included as well. Which treatments are considered to be established clinical practice in the NHS for severe osteoporosis? The authors include the treatments that are established clinical practice for severe osteoporosis. Are the outcomes listed appropriate? Yes. Are there any subgroups of people in whom romosozumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Romosozumab is particularly beneficial in reducing vertebral and clinical fracture risk. This has been demonstrated in comparison to placebo and alendronate in prior clinical trials (FRAME and ARCH trial). Where do you consider romosozumab will fit into the existing NICE pathway, osteoporosis? We believe it will be helpful in preventing vertebral fractures and clinical fractures in patients with severe osteoporosis, and additionally in preventing the recurrence of vertebral and clinical fractures in those with prior fractures. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:	Thank you, your comments have been noted

Section	Consultee/ Commentator	Comments [sic]	Action
		• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which romosozumab is licensed. No. • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology. No. • could have any adverse impact on people with a particular disability or disabilities. No. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Do you consider romosozumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, we believe that this medication is a viable therapeutic option for reducing clinical fractures and vertebral compression fractures. Do you consider that the use of romosozumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. The following trials should be taken into consideration:	

Section	Consultee/ Commentator	Comments [sic]	Action
		4. Cosman F, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Engl J Med. 2016; 375:1532-1543. 5. Cosman F, et al. FRAME Study: The Foundation Effect of Building Bone with 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab. J Bone Miner Res. 2018; 33(7):1219-1226. 6. Lau EMC, et al. Romosozumab or alendronate for fracture prevention in East Asian patients: a subanalysis of the phase III, randomized ARCH study. Osteoporosis Int. 2020; 31(4):677-685. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. The medication can be quite costly for insurance coverage, and at times, can be a barrier. This is a significant barrier, and should be considered.	
Additional comments on the draft scope	Bone Research Society	Will details of the proposed approach to identification of the population at risk be made available prior to any further analysis?	Thank you, your comments have been noted
	Society for Endocrinology	None	Thank you, no action required

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None