**National Institute for Health and Care Excellence**

**Multiple Technology Appraisal (MTA)**

**Non-bisphosphonates for treating 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 |
| --- | --- | --- | --- |
| Appropriateness | Amgen | Amgen believes this topic is unlikely to lead to timely and relevant guidance for the NHS and is therefore not appropriate for a NICE appraisal for the following reasons:   1. **Proposed MTA is highly complex and likely to cause uncertainty rather than adding value to the NHS**   The proposed MTA is highly complex as it aims to assess non-bisphosphonate osteoporotic treatments of different classes and treatment durations that are used to treat patients in differing treatment contexts: bone-forming agents, that have limited duration of use, as acute treatment for patients at high imminent risk of fracture; antiresorptives as chronic therapy for long term treatment and in some cases following the use of bone-forming agents.  Specifically:   * There is a lack of robust clinical data to allow for meaningful and consistent clinical comparisons within a single network meta-analysis as bone forming agents and anti-resorptives are distinct treatment classes with distinct treatment durations used in different treatment contexts * Bone forming agents are often used with the expectation of sequencing with anti-resorptives for the management of osteoporosis patients given their limited treatment duration. There is a paucity of robust, sequential data to include such comparisons in a network meta-analysis and allow for evidenced based clinical comparisons between potential sequences * These clinical data limitations would result in considerable uncertainty being introduced into cost-effectiveness analyses and results that are not robust to inform decision making   The MTA is therefore likely to cause confusion among treating clinicians rather than inform clinical decision making and add value to the NHS.   1. **The proposed MTA will not result in timely access to newer treatments to the detriment of patients**   NICE recently published guidance for the use of bisphosphonates (anti-resorptive agents) for the treatment of osteoporosis (TA464). The development of final guidance for TA464, which considered osteoporotic therapies within the same class and made significant simplifying assumptions around class efficacy, took over 3 years to be published. Due to the data issues identified above, the proposed MTA will likely be more complex and lengthy to conduct, may be difficult to interpret in conjunction with TA464 and will most likely result in delayed guidance on the use of new bone forming agents, which are currently without guidance, to the detriment of patients.   1. **There is therefore little value for the NHS in conducting an MTA and it would be more appropriate to undertake STAs for the new interventions**   The majority of osteoporotic patients are treated with BPs in the UK (>90% of the osteoporosis market). The recent publication of TA464 therefore addresses the needs of the vast majority of osteoporosis patients, reducing the urgency for a MTA to the NHS, clinicians, and patients. In addition, current guidance related to the use of Prolia (denosumab; TA204) in primary care for the treatment of patients with osteoporosis who are unable to comply with the special instructions for oral BPs, or have an intolerance of, or a contraindication to them, remains relevant in the context of TA464 and its reconsideration through a MTA is unnecessary.  Amgen therefore proposes that NICE does not undertake this MTA and that it would be more appropriate to update clinical guideline CG146. STAs could be undertaken for the new interventions which currently do not have guidance. This would ensure clarity for the NHS and that clinicians and patients have access to the most appropriate treatments in the timeliest manner. | Comment noted.  After consideration of all of the comments from a written consultation and stakeholder workshop on the review proposal for TA160, TA161 and TA204, the Institute’s Guidance Executive has decided to appraise all non-bisphosphonates licensed for the prevention of osteoporotic fragility fractures in women and men as an MTA which will be scheduled to begin when the MTA on bisphosphonates has published its final appraisal determination. For further details, please see the Guidance Executive decision paper for this review [here.](https://www.nice.org.uk/guidance/ta204/resources/ta204-osteoporotic-fractures-denosumab-appendix-b-ge-decision-paper-march-20142)  The background section has been amended to capture the different classes of treatment available (bone-forming and anti-resorptive).  The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered.  The scope has been amended so that treatment sequences will be considered if the evidence allows. |
| British Geriatrics Society | Yes the topic is appropriate and timely, but please see some concerns outlined below in the additional comments section | Comment noted. No action required. |
| British Society for Rheumatology | It would be important to ensure that inclusion of romosozumab and abaloparatide in this MTA does not compromise their evaluation given they have been developed considerably more recently than other technologies being considered, and are yet to receive UK marketing authorisation. For example, some of the evidence base supporting their use may not yet be in the public domain. In addition, prescribing costs and whether these include funding of eg Healthcare at home are currently unknown. | Comment noted. The MTA would not compromise the evaluation of romosozumab and abaloparatide as suggested. No action required. |
| Eli Lilly | This topic is appropriate for a NICE appraisal. | Comment noted. No action required. |
| MSD | Yes | Comment noted. No action required. |
| National Osteoporosis Society (on behalf of others) | The National Osteoporosis Society, the National Osteoporosis Guideline Group, The Bone Research Society and the Society for Endocrinology welcome the current MTA proposal on non-bisphosphonate therapies for osteoporosis, which will provide guidance to health professionals and the public to help raise awareness and improve the bone health of the population as well as improving quality of life for those people living with osteoporosis. The remit to proceed to a technology appraisal for non -bisphosphonates is timely following on, as it does, from TA464 that provided evidence on the cost effectiveness of bisphosphonate drugs. However, two of the proposed treatment options for the appraisal are not yet available for use within the NHS and are awaiting market authorisation. Although there is evidence of the efficacy of these drugs, no information is available on their potentials costs within the NHS. The proposed MTA is therefore immediately complicated by the decision to include two potential therapies that do not yet have marketing authorisation (MA). Guidance is urgently required on the non-bisphosphonate therapies that already exist for the treatment of osteoporosis; by including unlicensed therapies, the analysis is automatically going to be delayed.  NICE’s own information states that “Suggestions for technology appraisal guidance on a new medicinal product (that has not yet received a marketing authorisation) should be made by the relevant company through UKPharmaScan.”  It would suggest that both therapies need to pass the MA hurdle before the proposed technology appraisal could be published. Does this not go against NICE’s aim to produce guidance on the use of a new technology as soon as possible after receipt of the marketing authorisation and/or its introduction into the UK. We suggest that abaloparatide and/or romosozumab would be more efficiently handled by separate STAs, if and when they become available. Any delay in either’s availability should not delay guidance for existing therapies.  The currently available non-bisphosphonate therapies that are listed as comparators all have different modes of action and cover different patient groups. We would ask NICE to consider how the cost effectiveness modelling and comparison will be undertaken to take in to account these differences in action, duration of therapy and also potential lack of data to help with this. We would welcome a definition of the stated "pragmatic and simplifying approach" to the analysis to ensure that this accommodates current practice, for example, the limited use of anabolic therapies, under the direction of secondary care physicians, in a subset of osteoporotic patients at very high risk of fracture, particularly vertebral fractures.  We have concerns that the disparities in absolute risk between the two risk assessment tools (FRAX and QFracture) may be greater in those at the upper end of the risk distribution, where the more expensive non-bisphosphonate therapies likely have a role, thus not lending the analysis to a simple conclusion (e.g. 1% threshold) as used in TA464. | Comment noted. The suggestion for technology appraisal guidance on romosozumab has followed due process for consideration of new medicinal products. However, including romosozumab in this MTA was considered more appropriate than a separate single technology appraisal.The inclusion of the currently unlicensed treatments will not significantly delay guidance on non-bisphosphonates. Furthermore, the current appraisal committee schedule is such that an MTA is expected to provide more timely guidance on these treatments than separate single technology appraisals of them.The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered.The disparities in absolute risk between the 2 risk assessment tools (FRAX and QFracture) and their implications on establishing when these treatments are cost effective are matters for the committee to discuss. |
| UCB | It is appropriate that NICE provide timely guidance on alternative treatments to bisphosphonates (BP) where there’s uncertainty around treatments and that this guidance address treatments of osteoporosis in men as well as women.  In line with the ongoing NICE STA consultation ‘Consultation on proposed changes to the technology appraisals programme’, and the ambition to align with the regulatory process, UCB supports the aspiration to speed up access for NHS patients to clinically and cost effective innovations. We have concerns on delay to access caused by the MTA process, both for the UK & globally.  UCB feel that an STA is a more resource-efficient approach to understand the innovation romosozumab will bring. This could then set the basis for an MTA when there is better view on the specificities and intended positioning of each of the new entrants via individual STA processes. Nevertheless, we have provided our views for the MTA scoping exercise.  UCB believe that the categorisation of the technologies into a class of non-bisphosphonates (non-BP) is inappropriate. We feel it is inappropriate to define a drug by what it is not (non-BP) and ask that the scoping more explicitly separates “anti-resorptives” and “bone forming agents”. It is important to understand that romosozumab is a bone forming agent with both bone building and anti-resorptive attributes and not as a” non-BP”.  In addition to the acknowledgement by NICE of the complexity of evaluating technologies within osteoporosis as part of the original scoping discussions when considering the evaluation of BPs and non-BPs. UCB believe there are multiple factors that will contribute to delays throughout an MTA not least the differences in terms of target populations, mode of action, clinical trial design, treatment outcomes: fracture type and time to gain outcomes. These differences can be identified between bone forming agents as well as anti-resorptives. All of these elements contribute to clinical decision-making for optimising patient outcomes and add to the complexity of evaluating all these technologies at the same time.  *Cosman, Journal of Bone and Mineral Research, Vol. 32, No. 2, February 2017, pp 198–202*  TA161 & TA204 position non-bisphosphonates later in the treatment pathway and therefore a relatively small population. UCB would like clarification from NICE regarding the urgency for updated guidance on all appropriate non-bisphosphonates as an MTA in a market where their current use is well understood, have already been reviewed by NICE, and are already well outlined by the NICE accredited NOGG group.  UCB suggest it will be important to incorporate and consider the differences and clinical impact of primary versus secondary fracture prevention as well as the now recognised imminent risk element to accurately assess when it is most cost-effective to treat and in which patients. A general wide approach to “patients with osteoporosis” may prevent recognition of how best to use new technologies to improve health outcomes. | Comment noted.  The Institute’s Guidance Executive has decided to appraise all non-bisphosphonates licensed for the prevention of osteoporotic fragility fractures in women and men as an MTA. For further details, please see the Guidance Executive decision paper for this review [here](https://www.nice.org.uk/guidance/ta204/resources/ta204-osteoporotic-fractures-denosumab-appendix-b-ge-decision-paper-march-20142).  The background section has been amended to capture the different classes of treatment available (bone-forming and anti-resorptive).  The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered. The current appraisal committee schedule is such that an MTA is expected to provide more timely guidance on romosozumab than a single technology appraisal.You are encouraged to describe in your submission to NICE the differences in benefit between primary and secondary prevention of fractures.No action required. |
| Wording | Amgen | The remit does not accurately reflect the issues given the different treatment contexts associated with the differing classes of medicines in the scope (anti-resorptives and bone forming agents - both with varied mechanisms of action within these ‘classes’). As such the remit is an oversimplification of a very complex area. | Comment noted.  The remit is broad to allow for any variation in the use of treatments, which would be taken into account in the assessment of clinical and cost-effectiveness.  The background section has been amended to capture the different classes of treatment available (bone-forming and anti-resorptive).  The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered. |
| British Geriatrics Society | Generally the wording reflects the important issues, but again please see the comments below in the additional comments section | Comment noted. No action required. |
| British Society for Rheumatology | Yes | Comment noted. No action required. |
| Eli Lilly | Yes, no further comments. | Comment noted. No action required. |
| MSD | Yes | Comment noted. No action required. |
| National Osteoporosis Society (on behalf of others) | The remit specifies “all non-bisphosphonates licensed for the prevention of osteoporotic fragility fractures in women and men…….”. As noted above, the inclusion in the scope of non-licensed therapies is at odds with the remit. Otherwise, the remit is entirely appropriate. | Comment noted. NICE will only issue guidance for technologies that are licensed for this indication. No action required. |
| UCB | Yes, and as per comments throughout this response | Comment noted. No action required. |
| Timing Issues | Amgen | As the majority of osteoporotic patients are treated with BPs (>90% of the osteoporosis market) in the UK the recent publication of TA464 significantly reduces the urgency for a MTA to the NHS. Updating the current clinical guideline and undertaking STAs for interventions currently without guidance would provide greatest clarity to the NHS and timeliest access for patients and clinicians to newer bone forming (anabolic) agents. | Comment noted. Please see previous response. |
| British Geriatrics Society | It is timely and urgent given that two new drugs are imminently in the process of being licensed. | Comment noted. No action required. |
| British Society for Rheumatology | 1. It’s important to ensure that NICE guidance for non bisphosphonates to treat osteoporosis complements guidance recently issued for bisphosphonates under TAG 464 2. Two new non-bisphosphonate treatments for osteoporosis are likely to receive marketing authorisation in the foreseeable future | Comment noted. No action required. |
| Eli Lilly | Given additional data disclosures and new treatments entering this space a review now, is appropriate. Furthermore, given two of the proposed comparators have yet to receive a marketing authorisation, any regulatory delay with respect to these comparators should not further delay the issue of guidance from this MTA. | Comment noted. The inclusion of the currently unlicensed treatments will not significantly delay guidance on non-bisphosphonates. No action required. |
| National Osteoporosis Society (on behalf of others) | There is an urgent need, following TA464 in 2017, to conduct an appraisal of non bisphosphonates. While oral bisphosphonates remain the mainstay of treatment in the osteoporosis pathway, with intravenous bisphosphonates as alternatives, renal function impairment and other clinical scenarios (e.g. bisphosphonate contraindication and/or intolerance) require the use of non-bisphosphonate therapies such as raloxifene and denosumab. In patients at high risk, particularly with vertebral fractures, earlier treatment with teriparatide may be preferable rather than waiting for “treatment failure” under current guidance. An economic update is urgently required, particularly given recent data from head to head trials of bisphosphonate and teriparatide. | Comment noted. No action required. |
| UCB | There are several new treatments that are in the EMA review cycle with anticipated CHMP opinions expected at the end of 2018. With this we see the emergence of head to head studies versus bisphosphonates suggesting an ongoing unmet medical need.  UCB have concerns on the impact this MTA would have for achieving timely access of the new treatments to patients. Past MTAs have demonstrated that complexity introduced by the consideration of many technologies in one review and the complexity of ensuring that any new guidance will be consistent with established guidance.  *https://www.ohe.org/system/files/private/publications*  */NICE%20HTA%20methods%20RP%20FINAL.pdf*  As such it will bring significant increase in duration to the MTA process, e.g.   * TA 464 (Bisphosphonates for treating osteoporosis)   *Scoped Sept 2014 & published Aug ‘17*   * TA375 (Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed)   *Scoped Nov’12 & published Jan ‘16.*   * A 2013 study suggested that from 116 MTAs, the median time for evaluation was 74 weeks with all medians exceeding published timelines (even after adjusting for appeals). Only about 20% of all guidance published on time. In comparison 80 STAs produced a median of just 48 weeks.   *Ruiz, Casson, Miners (2013) A retrospective study to estimate predictors of time to guidance. BMJ Open;3: e001870*  UCB suggest that the value of existing non- bisphosphonates is well understood both by NICE and within the NHS. We suggest that an STA would be a more efficient way to establish the place of romosozumab within this therapeutic area.  In addition to the duration of the BP MTA, it is important to recognise there was existing guidance on BP usage while the revision was undertaken. As such clinical decision-making was not impacted whilst the review was undertaken. It is UCB’s experience that while a product is under review by NICE where no prior guidance exists, the NHS ‘waits’ before allowing access to patients for new medicines. It is also important to consider that for this non-BP MTA no prior guidance would exist for the new treatments effectively preventing their usage from a clinical and patient perspective. | Comment noted.  The current appraisal committee schedule is such that an MTA is expected to provide more timely guidance on romosozumab than a single technology appraisal.  No action required. |
| Additional comments on the draft remit | British Society for Rheumatology | N/A | No action required. |
| Eli Lilly | No additional comments. | No action required. |

Comment 2: the draft scope

| Section | Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- | --- |
| Background information | Amgen | Please note that to more accurately reflect NICE TA204 the wording for primary prevention should be:  *for the primary prevention of fragility fractures in postmenopausal women at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture, who have osteoporosis and who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments* | Comment noted. The scope has been amended as suggested. |
| British Geriatrics Society | Background information is generally accurate | Comment noted. No action required. |
| British Society for Rheumatology | It may be worth mentioning limitations in bisphosphonate efficacy, safety and tolerability leading to the consideration of alternative treatments | Comment noted. This scope only focuses on treatment with non-bisphosphonates. No action required. |
| Eli Lilly | The background information is deemed accurate and complete. | Comment noted. No action required. |
| MSD | Yes | Comment noted. No action required. |
| National Osteoporosis Society (on behalf of others) | The information in the background is an accurate description of osteoporosis as a condition and sets out the consequences to people living with osteoporosis. There is no mention of the costs to health and social care as highlighted in the background to the MTA of bisphosphonate drugs, which helps set the context to the NHS: | Comment noted. This information is not considered necessary to give an overview of the condition and its management. No action required. |
| UCB | UCB request that the population heterogeneity be acknowledged within the background information particularly as it relates to risk for fracture characteristics/determinants, to help ensure the disease complexity and ongoing unmet need is understood accurately. | Comment noted. The background section has been amended to capture the different classes of treatment available (bone-forming and anti-resorptive). |
| The technology/ intervention | Amgen | Please note that:   * Denosumba (Prolia) is administered as a single subcutaneous injection once every 6 months   For romosuzumab (Evenity) the statement that it has been studied in a clinical trial compared with alendronate for treating osteoporosis in postmenopausal women is technically incorrect. The ARCH study alluded to is more accurately described as 12 months of romosozumab followed by at least 12 months of alendronate, compared to at least 24 months of alendronate alone (Sagg, 2017) | Comment noted. This scope has been amended to reflect this comment. |
| British Geriatrics Society | Yes | Comment noted. No action required. |
| British Society for Rheumatology | It should be clarified that if and when romosozumab receives marketing authorisation, this is likely to be for a maximum treatment duration of 12 months (in contrast with other osteoporosis therapies which are given for a minimum of two years) | Comment noted. The scope has been updated to reflect the treatment duration in the trial. |
| Eli Lilly | Forsteo (teriparatide) also has the following licensed indication: treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture. | Comment noted. This scope has been amended to reflect this comment. |
| MSD | Yes | Comment noted. No action required. |
| National Osteoporosis Society (on behalf of others) | Please note our concerns about the two unlicensed treatments as described above.  The description of the currently available technologies provides high level information about the drugs to be appraised. It is important to be clear that denosumab is administered as a course of injections not just one dose. It should also be noted that if a decision is taken to discontinue denosumab, there appears to be a rapid return to an increased risk of fracture so that a course of alternative treatment is likely required to prevent new fragility fractures. Evidence to underpin this: Cummings, S. R., Ferrari, S., Eastell, R., Gilchrist, N., Jensen, J.-E. B., McClung, M., Roux, C., Törring, O., Valter, I., Wang, A. T. and Brown, J. P. (2017), Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. J Bone Miner Res. doi:10.1002/jbmr.3337  The list of currently available and licensed technologies is incomplete. Calcitriol should be considered as a technology (evidence suggests that this is used in 0.3% of women with post-menopausal osteoporosis). Hormone replacement therapy (HRT) is also licensed, though its use is more usually restricted to younger postmenopausal women who are at increased risk of osteoporotic fracture and also have vasomotor symptoms. Both calcitriol and HRT should be included in the appraisal. | Comment noted.  The scope has been amended to clarify that denosumab is given every 6 months. Calcitriol and hormone replacement therapy are outside the remit of this MTA. |
| UCB | UCB feel the scope does not sufficiently capture the different treatment duration of each regimen. The assessment method should take this into account in terms of costs and health outcomes. UCB believe that the mode of administration along with the treatment duration impacts the way products are being used in the clinical practice. This represents an additional factor which if not considered could underestimate the potential impact of new technologies in the treatment sequence/ pathway.  In addition, there is no reference to the impact of the sequence of therapy which is established in romosozumab clinical trial program and will be part of our label.  It is important to recognise that romosozumab is a bone forming agent with both bone building and anti-resorptive attributes that may not be appropriately captured in the “non-BP” heterogenous mix. | Comment noted.  Mode of administration and where evidence allows, treatment duration will be considered. The scope has been amended so that treatment sequences will be considered if the evidence allows.The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered. |
| Population | British Geriatrics Society | It would be worth considering the following subgroups:   * Older people (eg aged 80 years and older) * Frail older population. NICE multi-morbidity guideline explicitly mentions the need to review osteoporosis treatment in this group * Older fallers (2 or more fall in the previous year) * Vertebral fracture subgroup of patients * Dementia patients * Care home residents * Possibly patients with renal disease * Glucocorticoid induced osteoporosis   Those receiving hormone deprivation treatments such as for prostate cancer | Comment noted. In line with the final scope for TA464, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes have been included. |
| British Society for Rheumatology | 1. Patients receiving glucocorticoids may respond better to treatment with anabolic therapies like teriparatide, since bone loss in this context is thought to predominantly reflect reduced bone formation 2. Patients at high risk of breast cancer may show preferential benefit to treatment with raloxifene | Comment noted. In line with the final scope for TA464, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes have been included. |
| Eli Lilly | NICE should consider sub-groups as defined by higher levels of 10-year fracture risk.  An analysis of patients with prevalent vertebral fractures (established osteoporosis) vs. pure densitometric osteoporosis (without fractures) should be in the scope of this appraisal. | Comment noted. In line with the final scope for TA464, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes have been included. |
| National Osteoporosis Society (on behalf of others) | We acknowledge that the population defined in NICE CG146 defines the majority of adults who need to be assessed for their risk of fragility fracture.  High baseline fracture risk is likely to improve the cost-effectiveness of more expensive non-bisphosphonate therapies, so this should be a focus of the MTA; several papers have examined the interaction between efficacy and risk as assessed by FRAX, including the recently published SCOOP study. There are no data on the reversibility of high risk identified by QFracture or on potential interactions with efficacy.  Data on fracture incidence show a favourable effect of switching to teriparatide from antiresorptive therapy (predominantly oral bisphosphonates) in women with postmenopausal osteoporosis and two or more moderate/severe vertebral fractures.  A clear statement about the cost-effectiveness of the use of teriparatide in men would permit more equitable access to this treatment.  Comparative studies in patients with or at risk of glucocorticoid-induced osteoporosis should be included so that specific guidance can be provided.  We note that currently there is inequity of access and funding for teriparatide for men which should be taken in to account in the technology appraisal. | Comment noted. In line with the final scope for TA464, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes have been included. |
| UCB | UCB believe that it is in the interest of the NHS to consider primary and secondary fracture prevention separately (not just as risk factors):  Patients that have had a fracture are different to those that haven’t. Experiencing a fragility fracture leads to different unmet needs and elevated humanistic and economic burden. This is mainly driven by the elevated risk of experiencing a subsequent fracture in the period immediately following a fragility fracture (the imminent risk period).    The occurrence of a fracture denotes a microstructural bone deficit which allowed the trauma to result in a fracture. If a structural deficit is present, there is a difference between what an anti-resorptive versus a bone forming technology can provide as solution to the problem; accordingly, recent studies have shown superiority between bone forming versus BPs in post fracture patients (ARCH and VERO trials)  *ARCH - Saag et al. N Engl J Med 2017; 377:1417-27.*  *Kendler et al. Lancet 2018; 391: 230-40*  In secondary prevention, the imminent risk is now being recognised as a key element that requires interventions that provide fracture reductions faster and above that which other therapies can offer.  *van Geel et al Annals of the Rheumatic Diseases 2009; 68:99-102.*  Patient characteristics that increase the risk of fracture (NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes should be considered, of which fracture and the recency of the fracture are key.  UCB suggest that non-bisphosphonates target different populations at different risk of profiles of fracture and an MTA may underestimate the need to distinguish the populations of interest that would benefit the most from each regimen when the population of interest is broadly defined.  UCB acknowledge NICE’s past recognition of constantly emerging specific risk factors (appropriateness and magnitude of influence) and the need for new insights to be incorporated within appraisals, as such we request incorporation of imminent risk and post-fracture populations. | Comment noted.  In line with the final scope for TA464, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes have been included. You are encouraged to describe in your submission to NICE the differences in benefit between primary and secondary prevention of fractures. |
| Comparators | Amgen | Please also refer to the ‘*Appropriateness*’ Section.  Anti-resorptive and bone forming agents are distinct classes of osteoporotic treatment and cannot be legitimately compared because of the distinct treatment durations associated with them. There is therefore a lack of robust clinical data to allow for meaningful and consistent comparisons within a single network meta-analysis in this proposed MTA between these distinct treatment classes used in different treatment contexts; specifically anti-resorptive agents used in a ‘chronic use’ setting with bone forming agents that have limited duration of use (Cosman, 2017; Roux, 2017):   * The proposed MTA of non-BPs includes bone forming agents (e.g. anabolic agents such as abaloparatide, romosozumab and teriparatide) and anti-resorptives (e.g. bisphosphonates, denosumab and raloxifene) which are two distinct drug classes that have different treatment durations, and are therefore used by clinicians to treat different patients in differing treatment contexts * Bone forming agents and anti-resorptives demonstrate distinct, non-overlapping time to peak fracture reduction efficacy in the clinical trials supporting their marketing authorisations. Bone forming agents are only used for 12-24 months and reach peak fracture effects by 12-18 months. Peak effects are, however, reached at 3-4 years with anti-resorptives (Black,1996; Black, 2000; Cosman, 2016; Cummings,1998; Cummings, 2009; Ettinger,1999; Gallagher, 2005; Liberman, 1995; Miller, 2016; Neer, 2001; Pols, 1999) * This will lead to issues with clinical data synthesis, making appropriate direct comparisons difficult due to non-comparable time frames to reach peak effect. Any network combining clinical data on these agents would therefore be invalid due to insufficient evidence, non-overlapping time periods and disconnected data being inserted into a homogenized analysis * Efficacy estimates (relative risks and hazard ratios) required for cost-effectiveness analyses would therefore be non-comparable and attempts to do so would lead to inappropriate clinical comparisons   Given the relatively limited treatment duration of bone forming agents they are often used with the expectation of sequencing with anti-resorptives for management of osteoporosis patients when the proper treatment context dictates (Cosman, 2017):   * Sequenced data must be comparable with respect to time to peak efficacy and the choice of sequenced agent in order to enable similar time periods to peak efficacy to be compared. In any bone forming agent review a common anti-resorptive sequencing agent must therefore be used to compare one bone forming agent to another * Furthermore, the choice of sequenced anti-resorptive agent must be consistent for the bone-forming agents included in a network, and the sequence of bone-forming agent followed by anti-resorptive must be consistently compared to the same anti-resorptive agent * Sequenced data is, however, lacking for an analysis of common comparisons * This paucity of data will create significant technical challenges in constructing a valid NMA given treatment sequencing time-dependent effects and thus not allow for valid, evidenced based clinical comparisons between potential sequences of the osteoporosis therapies proposed      * Efficacy estimates (relative risks and hazard ratios) required for cost-effectiveness analyses would therefore be confounded by incorporation of inadequate additive sequenced affects   Application of time dependent effects is critical with any bone forming agent (O’Hanlon, 2017). However, as discussed, the challenges associated with combining these effects across multiple therapies of different classes, including a large number of potential combinations of therapies, would result in significant complexity and likely heavily confounded results in any clinical evidence synthesis. This would lead to potentially inappropriate clinical comparisons or those based on very limited data. The resulting significant and potentially inappropriate assumptions that would need to be made would therefore introduce considerable uncertainty into any cost-effectiveness analyses. This in turn would result in cost effectiveness results that are not robust to inform clinical decision making. | Comment noted.  The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered.  The scope has been amended so that treatment sequences will be considered if the evidence allows. |
| British Geriatrics Society | As outlined we are concerned that the anabolics should not be considered necessarily as alternatives to anti-resorptives, but rather should be considered as sequential treatment in some situations | Comment noted. The scope has been amended so that treatment sequences will be considered if the evidence allows. |
| British Society for Rheumatology | Combination therapy could also be considered. For example, BMD gains are greater in patients receiving combination therapy with denosumab and teriparatide, as compared with treatment with either agent alone (though no fracture data is available as far as I am aware) | Comment noted. The appraisal of combination therapy is outside the remit of this MTA. |
| Eli Lilly | The bisphosphonates have been assessed in a separate TA and have been included as comparators in this MTA. It should therefore be made clear to the NHS and patients how the guidance issued in this MTA should be interpreted in the context of TA464.  It is noted that abaloparatide and romosozumab do not yet have marketing authorisation in the UK. It should be clarified that guidance for these treatments will not be issued until marketing authorisation has been granted and that the MTA should proceed with no further delay with respect to the other comparators (see comment on timing above). | Comment noted. NICE will only issue guidance for technologies that have a marketing authorisation. No action required. |
| National Osteoporosis Society (on behalf of others) | We agree that the comparators are those that are currently used within the NHS. The technologies that are presented for appraisal would be described as alternatives to the bisphosphonates. However, there is real complexity in the comparison between the non-bisphosphonates and bisphosphonates due to their different mode of action, the relative lack of head-to-head data and differing durations of therapy. In addition, sequential therapy is the norm in clinical practice with teriparatide treatment, which is restricted to a duration of two years and is necessarily followed by anti-resorptive agents. | Comment noted.  The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered.  The scope has been amended so that treatment sequences will be considered if the evidence allows. |
| UCB | UCB is of the view that it is inappropriate to pre-determine the position of newer non-bisphosphonates relative to other, previously reviewed and well established, technologies. We ask that the committee do not underestimate the need to compare these regimens in the right sequence to gain the most value for appropriate patients and the NHS. It is also important to recognise the limited sequential data at this time to enable such comparisons with any level of certainty to bring value to patients and the NHS.  Clinical comparison of the trials will bring issues of increasing heterogeneity and uncertainty. In addition, there is the challenge of how much the trials reflect how products are being used in clinical practice and for which patients. UCB ask that NICE consider these challenges and bring assurance that these issues will not create a lengthening of the review process.  UCB agrees that a comparison against no active treatment, other non- BP & BP is appropriate, if not complex. It has been acknowledged as part of the discussions leading up to the BP MTA that the original osteoporosis technology evaluation decision problem was unmanageable and as a result it was decided to split the reviews into the BP and non-BP MTAs. This MTA’s suggested comparators will bring NICE back to the larger complex decision problem. Again, UCB has concerns about the feasibility of this and the impact on duration, outcome and value of the assessment.  An STA is a more resource-efficient approach to understand the innovation romosozumab will bring initially and then set the basis for an MTA when there is better view on the specificities and intended positioning of each of the new entrants via individual STA processes. | Comment noted.  The scope has been amended so that treatment sequences will be considered if the evidence allows.  The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered. You are encouraged to describe in your submission to NICE the innovative nature of romosozumab. The committee would normally consider this information in its deliberations. |
| Outcomes | British Geriatrics Society | * Within osteoporotic fractures, specifically vertebral fractures, hip fractures, then “major osteoporotic fractures” * Adherence to treatment eg injection versus oral * Measurement of bone quality/strength eg QCT techniques * Quality of life * Longer term harm events such as atypical femoral fractures should be considered | Comment noted. In line with the final scope for TA464, the outcomes remain unchanged. No action required. |
| British Society for Rheumatology | Osteoporotic fragility fracture should be separated into vertebral fractures and non vertebral fractures for the following reasons:-   1. The relative efficacy of different technologies for vertebral fractures and non vertebral fractures differs significantly 2. The impact of vertebral fractures on health-related quality of life differs significantly compared to that of non vertebral fractures 3. Conventional fracture risk calculators such as FRAX have limited predictive value for vertebral fractures 4. Patients at high risk of vertebral fractures are readily identifiable using alternative methods to FRAX (eg using a combination of prevalent vertebral fractures and spinal BMD) | Comment noted. In line with the final scope for TA464, the outcomes remain unchanged. No action required. |
| Eli Lilly | Osteoporotic fragility fracture: Fragility fractures would need to be split by vertebral, clinical vertebral and clinical non-vertebral in order to account for the differing resource use and quality of life impact  Bone mineral density: We suggest excluding bone mineral density. The mechanism for an increase in BMD is different between anti-resorptive and anabolic treatments. With antiresorptives BMD increases through increased mineralisation of existing bone whereas with anabolics BMD increases as a result of new bone formation. Comparing anti-resorptive and anabolic bone therapies and drawing conclusions about likely fracture risk reduction based on changes in BMD is misleading. Direct evidence of fracture risk reduction should be utilised. | Comment noted. In line with the final scope for TA464, the outcomes remain unchanged. No action required. |
| National Osteoporosis Society (on behalf of others) | The outcomes listed will capture the most important health related benefits. Hip, vertebral and osteoporotic fractures should be considered separately; special consideration should be given to the use of vertebral fracture as a specific outcome as patients at high risk of such events are particular beneficiaries of anabolic therapy.  Treatment adherence should be included.  It would also be important to capture and model the side effects related to the therapies such as atypical fractures and osteonecrosis of the jaw.  Additional benefits should also be included in the primary models including for example the effect of raloxifene on breast cancer incidence. | Comment noted. In line with the final scope for TA464, the outcomes remain unchanged. No action required. |
| UCB | Yes | Comment noted. No action required. |
| Economic analysis | British Geriatrics Society | No comment | No action required. |
| British Society for Rheumatology | In phase 3 trials, romosozumab was given for 12 months followed by 12 months treatment with alendronate or denosumab. To provide fair comparison with other technologies, will results be assessed for 24 months treatment (as in the majority of other anti-fracture trials), despite romosozumab only being given for 12 months? | Comment noted. All technologies will be appraised within their marketing authorisation over a lifetime time horizon. No action required. |
| Eli Lilly | The economic model should consider a lifetime horizon. The model should capture adverse events and their consequences that account for the differing side-effect profiles e.g. osteonecrosis of the jaw. | Comment noted. No action required. |
| National Osteoporosis Society (on behalf of others) | An economic evaluation will be complex due to the different modes of action, diversity of use and patient groups and different durations of therapy. Costs of health and social care should be taken into account along with costs for home delivery of medication and training patients with injections, secondary care follow-up for injectable therapies, and the need for sequential therapies. A remaining lifetime horizon (or to the age of 100 as in TA464) should be used.  Costs associated with adverse events should, if possible, be taken into account within the economic modelling - such as atypical fractures and ONJ. | Comment noted. The scope has been amended so that treatment sequences will be considered if the evidence allows. |
| UCB | UCB recognises the importance of maintaining a consistent approach towards the development of multiple pieces of guidance in a similar topic area.  We believe that clinical and economic elements have evolved over time and one economic model may not fit all technologies due to the different attributes of the products and therefore the optimal sequence. The complexities of modelling how to obtain maximum value to the NHS is likely to bring:   * variation in models submitted from consultees and commentators and; * the need to simplify the methods to fit all attributes in one assessment tool.   Evaluation of multiple models would lead to a delay, which would impact the time to access for romosozumab.  There is also the risk of limiting the potential of new technologies when applying existing techniques. UCB request that NICE consider the time for review brought by the impact of models which may bring a departure from current practice.  Romosozumab is intended to be followed by an anti-resorptive treatment as established in the clinical trial program. Although romosozumab is a 12-month treatment the benefits on fracture reduction are maintained when patients are transitioned to an antiresorptive treatment. The modelling horizon needs to be sufficiently long to account for such benefits.  It should be noted that romosozumab has a rapid effect on bone-formation, a differentiation from other products which leads to relative costs and health consequences. UCB request that NICE consider to incorporate time-dependent efficacy data into the economic evaluation to capture the rapid effect of certain products that translates into long-term consequences for the patient and the NHS.  UCB went through a review process with PRIMA/NICE team for the preparations of our economic model that would be used in the evaluation of romosozumab. Elements mentioned here and in the population section have been endorsed as unique to romosozumab and it is critical these are acknowledged during the assessment. Something that an MTA might miss due to the desire for consistency in addition to the complexity of evidence and multiple stakeholders and approaches that will be presented.  A major component of the costs related to osteoporosis and fragility fractures are social care costs particularly with patients who lose mobility and have increased disabilities due to hip, spine and other fractures. These costs should be incorporated in any evaluation.  UCB ask that NICE confirm whether the committee will use the economic model developed for the bisphosphonates MTA. If so, when will this be shared with consultees and commentators? | Comment noted.  The scope has been amended so that treatment sequences will be considered if the evidence allows. The current appraisal committee schedule is such that an MTA is expected to provide more timely guidance on romosozumab than a single technology appraisal. You are encouraged to describe in your submission to NICE the innovative nature of romosozumab. The committee would normally consider this information in its deliberations.  The committee will consider economic cases made by companies alongside the assessment group’s evaluation.  The economic model used by the assessment group for this MTA will be shared with consultees and commentators during consultation on the assessment report, before the first committee discussion. In addition the economic model used by the Assessment Group for TA464 will be offered for information at the start of the appraisal. |
| Equality and Diversity | British Geriatrics Society | * See section on population above. Older frailer people and including those in care homes need to be considered. As an example there may be situations where getting a DXA scan prior to denosumab may not always be practical in frail less mobile patients, but who very much need bone strengthening medication. | Comment noted. The potential equality issues raised during consultation on this scope will be presented to the committee. |
| British Society for Rheumatology | Osteoporosis therapies exert equivalent effects in men and women as judged by intermediary endpoints such as bone mineral density. However, the great majority of clinical trials with fractures as end points just included females, and many of the therapies available for osteoporosis are just licensed in females. As a consequence, previous NICE recommendations for osteoporosis precluded the use of teriparatide in men, meaning that rare cases of severely affected men with osteoporosis have been denied access to this treatment. | Comment noted. The potential equality issues raised during consultation on this scope will be presented to the committee. |
| Eli Lilly | Any advice issued should take into account license differences with the comparators between men and women with osteoporosis. | Comment noted. The potential equality issues raised during consultation on this scope will be presented to the committee. |
| National Osteoporosis Society (on behalf of others) | Both adult women and men are covered within the remit of the guidance.  However, at present there are issues with access to one of the technologies, teriparatide, for men so the guidance should provide clarity and equilibrate practice by ensuring that there are no barriers to groups of the population at risk of fragility fractures receiving therapeutic interventions that have been appraised for their cost and clinical effectiveness. | Comment noted. The potential equality issues raised during consultation on this scope will be presented to the committee. |
| UCB | UCB is supportive that the evaluation doesn’t discriminate against the male population in recognition of limited evidence, especially for new treatments that are not introduced to the market yet. | Comment noted. The potential equality issues raised during consultation on this scope will be presented to the committee. |
| Other considerations | British Geriatrics Society | * There is a need to specify whether these medications are to be prescribed in primary or secondary care, as there is currently a CCG postcode lottery over whether denosumab is “green” or “amber” or “red” which is leading in some areas to reduced use in those who may benefit from it. We should try and avoid the same situation happening with the new non-bisphosphonates aboutt be marketed and make the position clearer for the use of denosumab * Guidance on a sequential approach to treatments (as above) should be considered * The NOGG guidance was NICE endorsed but has not been mentioned * Injectables need to have consideration of costs associated with hospital visits and delivery | Comment noted.  The clinical setting in which these technologies should be prescribed is not a matter for NICE to determine.  The scope has been amended so that treatment sequences will be considered if the evidence allows. |
| British Society for Rheumatology | Anabolic agents (ie all those included in the scope apart from denosumab) are considered to have significantly greater skeletal safety compared to bisphosphonates as a consequence of their different mode of action, which may offer important advantages. | Comment noted. The scope has been amended so that comparisons within classes of treatment (bone forming or anti-resorptives agents) may be considered. |
| Eli Lilly | No further comments. | No action required. |
| UCB | UCB has engaged fully with the NICE teams throughout the milestones of bringing romosozumab to patients including early scientific advice and PRIMA. Each engagement has supported the UCB approach and the methodologies to best evaluate romosozumab for use in patients. NICE has already agreed on the validity of the UCB approach to modelling osteoporosis and romosozumab.  We recognise the desire to consistently evaluate the so called ‘non-BPs’. However, we believe it is not possible, necessary or appropriate to evaluate the BP and non-BPs consistently with acceptable levels of certainty at this time.  UCB strongly recommend the MTA either progress without the forthcoming non-BP technologies or wait until an STA that identifies an efficient way to navigate new models has been completed to avoid unnecessary delay of access to medicines for patients in line with the life science strategy. | Comment noted. The suggestion for technology appraisal guidance on romosozumab has followed due process for consideration of new medicinal products. However, including romosozumab in this MTA was considered more appropriate than a separate single technology appraisal. |
| Innovation | British Geriatrics Society | No comment | No action required. |
| British Society for Rheumatology | There is good RCT evidence that these technologies reduce vertebral fracture risk relative to patients taking oral bisphosphonates, suggesting they have a significant health benefit over and above first line osteoporosis treatment  In contrast to bisphosphonates included in TAG 464, with the exception of denosumab, the technologies included in this guidance are not expected to have adverse effects associated with prolonged suppression of bone resorption, namely atypical femoral fractures and osteonecrosis of the jaw. Since these are relatively rare events, they may have relatively little impact on QALY calculations, despite the fact that concern about them creates a lot of anxiety amongst both patients and health professionals, and has led to recommendations of drug holidays in which treatment is withdrawn after five years with possible adverse consequences for fracture prevention.  Published phase three trials with fracture endpoints are available to enable the appraisal committee to take account of these benefits. | Comment noted. You are encouraged to describe in your submission to NICE the innovative nature of the technologies. |
| Eli Lilly | No further comments. | No action required. |
| National Osteoporosis Society (on behalf of others) | The technologies that should be included in this MTA are well established but the MTA provide a ‘step-change’ in access to appropriate treatment in high risk individuals.  For example, recent data from comparator studies with fracture outcomes have demonstrated that individuals at very high risk of fracture show greater benefit from anabolic followed by anti-resorptive therapy than from than anti-resorptive therapy alone, providing support for a new treatment paradigm in these high-risk individuals. | Comment noted. You are encouraged to describe in your submission to NICE the innovative nature of the technologies. |
| UCB | It is important to understand that romosozumab is a bone forming agent with both bone building and anti-resorptive attributes and not as a” non-BP”.  Romosozumab is intended to be followed with anti-resorptive treatment. Although the treatment is a 12-month treatment the benefits on fracture reduction are extended when patients are transitioned to antiresorptive treatment. Clinical data show clear benefits of using 12 months of romosozumab prior to anti-resorptive treatment to reduce clinical fractures. There are increasing evidence and literature supporting reconsideration of sequence of therapy for appropriate patients.  *http://www.nejm.org/doi/full/10.1056/NEJMoa1607948*  *http://www.nejm.org/doi/full/10.1056/NEJMoa1708322*  There are elements of innovation in romosozumab (e.g. short treatment duration, route of administration and posology, sequential approach along with the dual effect of romosozumab) that do not allow a clinical and economic assessment that fits all products of consideration. Individual assessments better reflect the nature of each technology and allows for room to demonstrate additional value created for the patient. An MTA runs the risk of misinterpreting the products being evaluated as direct alternatives. Such assumptions of similarity may underestimate the value new technologies bring to the patient and market landscape. | Comment noted.  The scope has been amended so that treatment sequences will be considered if the evidence allows. The committee may consider any potential health-related benefits that are unlikely to be included in the QALY calculation. You are encouraged to describe any such benefits in your submission to NICE. |
| NICE Pathways | British Society for Rheumatology | Treatments under this appraisal include second line options in those unable to tolerate oral bisphosphonates prescribed according to NICE TAG 464, or who are unresponsive to these agents. In addition, specific groups of patients may exist in whom alternatives to bisphosphonates should be considered as first line on the basis of (i) superior efficacy in reducing risk of vertebral fractures (eg those at very high risk of vertebral fracture), (ii) contraindications to bisphosphonate treatment initiation (eg impaired renal function, reflux oesophagitis) or continuation (osteonecrosis of the jaw, atypical femoral fractures). | Thank you for your comment. |
| Eli Lilly | All technologies will be options in patients alongside or following bisphosphonate treatment depending on 10 year fracture risk and tolerability, patient preference etc. | Thank you for your comment. |
| Questions for consultation | British Society for Rheumatology | *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of these technologies into practice? If yes, please describe briefly.*  For those agents given by injection, costs and feasibility of administration represent potential barriers to adoption. Most GP practices agree to administer six monthly denosumab, but in the absence of funding this is not uniform. In the case of teriparatide, the company funds Healthcare At Home to supply the drug directly to patients and train patients in self-administration. Equivalent arrangements may be in place when abaloparatide and romosozumab are marketed. | Comment noted. The potential equality issues raised during consultation on this scope will be presented to the committee. |
| Eli Lilly | **Have all relevant comparators for the technologies been included in the scope?**  No further comments  **Are the outcomes listed appropriate?**  No further comments  **Are there any subgroups in whom the technologies are expected to be more clinically effective and cost-effective or other groups that should be examined separately?**  Consideration of patients with higher levels of 10 year fracture risk who would benefit from anabolic treatments  **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of these technologies into practice? If yes, please describe briefly.**  There are no technical adoption barriers as such, but any differences in guidance from TA161 should be clearly outlined in order to allow smooth adoption and amendment to current NHS practise. | Comment noted.  In line with the final scope for TA464, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes have been included. |
| UCB | *Do you consider the technologies to be innovative in their 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, as per previous comments regarding patient heterogeneity. Further to this, existing treatments are aimed at reducing fracture risk often over the longer term without the benefit of achieving their optimal goal for the patient at imminent risk. Identifying patients at imminent risk of another fracture is crucial for the benefit of the patient.  *“Do you consider that the use of the technologies can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation”.*  Yes, the significant BMD reductions over a short period is an element that cannot be directly captured in the QALY calculation due to the lack of technique to indirectly compare technologies on this surrogate endpoint and eventually incorporate it into the economic model | Comment noted.  You are encouraged to describe in your submission to NICE the innovative nature of romosozumab. The committee would normally consider this information in its deliberations. The committee may consider any potential health-related benefits that are unlikely to be included in the QALY calculation. You are encouraged to describe any such benefits in your submission to NICE. |
| Additional comments on the draft scope | British Geriatrics Society | * This TA must make reference to the bisphosphonate TA and how these should link with one another | Comment noted. Bisphosphonates are included as comparators in the scope.The economic model used for TA464 will be the basis for the model in this appraisal, so a similar modelling approach will be used. . |
| British Society for Rheumatology | N/A | No action required. |
| Eli Lilly | NA. | No action required. |
| UCB | UCB asks that if this is to continue as a full non-BP MTA, a public scoping meeting be arranged in light of recent changes to guidance and the introduction of new entities since the last scoping meeting 4 years ago.  UCB would also like to understand whether access will be granted to the DES model used as part of the BP MTA.  We highlight that this model is developed for BP which have different attributes and are targeted to different populations versus the bone builders, anti-resorptives, and is not appropriate for the decision problem. A recent NICE PRIMA evaluation recognised the appropriateness of a different model for romosozumab. | Comment noted. A further scoping workshop is not deemed necessary for this MTA. A stakeholder information meeting will be held approximately 6 weeks after the start of the appraisal. The economic model used by the assessment group for this MTA will be shared with consultees and commentators during consultation on the assessment report, before the first committee discussion. In addition the economic model used by the Assessment Group for TA464 will be offered for information at the start of the appraisal. |

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

# Daiichi-Sankyo