Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours (HTA programme project no. 08/236/01)

	Consultation comment	Assessment Group response
	AMGEN	
	Executive summary	
1.1	***Comparator selection and relevant patient populations in prostate cancer (p3)*** In prostate cancer, NICE CG58 and CG75 recommend the use of bisphosphonates in a subgroup of patients who have painful bone metastases and history of a prior SRE.	NICE CG58 (prostate cancer) states: 1.7.18 Bisphosphonates for pain relief may be considered for men with hormone-refractory prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. NICE CG75 (metastatic spinal cord compression) states: 1.5.1.4 Offer patients with vertebral metastases from prostate cancer bisphosphonates to reduce pain only if conventional analgesia fails to control pain. The guidelines (CG58 or CG75) do not specifically recommend bisphosphonates based on SRE history. SRE is a composite term used in research and licensing but not routine clinical practice. The specific group of patients for whom the guidelines recommend bisphosphonates - patients with uncontrolled bone pain, despite treatment with analgesics or palliative radiotherapy – is not necessarily synonymous with the subgroup considered by the manufacturer - patients who have painful bone metastases and history of prior SRE.
1.2	***Population vs subgroup treatment effects used in the economic model (p3)*** We believe that parameter estimates of comparative efficacy used in the economic analysis for the prior SRE history subgroup should be derived from the overall (pooled) treatment effect in each study, not from underpowered subgroup analyses.	The base case of the economic modelling does use the pooled treatment effect. The NICE scope states that “If the evidence allows, a subgroup based on prior history of skeletal events should be considered”. Our view is that these are reasonable sensitivity analyses to have

		undertaken.
1.3	***Zoledronic acid patent expiry (p4)*** Consideration of potential future price changes of zoledronic acid following patent expiry in mid-2013 does not adhere with the Institute's *Guide to the methods of technology appraisal* with respect to acquisition prices of resources.	See response to 1.7 below.
1.4	***Potential for perverse inequity in the bisphosphonate-contraindicated population (p4)*** The relevant comparator in the bisphosphonate contraindicated population should be based on clinician treatment intent (i.e. what the clinician would prescribe were the patient not contraindicated or intolerant). This eliminates the potential for perverse inequity in access to an effective treatment in a patient group with a higher unmet need.	See response to 1.9 below.
1.5	***Comparative efficacy used in the economic model (p4)*** In line with the Institute's *Guide to the methods of technology appraisal*, data from RCTs comparing denosumab with zoledronic acid should be used in the reference-case economic analysis in preference to evidence synthesised using NMA methods.	See response to 1.10 below
	Key assumptions and supporting information	
1.6	***In prostate cancer, NICE CG58 and CG75 recommend the use of bisphosphonates in a subgroup of patients who have painful bone metastases and history of a prior SRE (p6)*** NICE clinical guideline for prostate cancer (CG58) recommends that bisphosphonates should be considered when other treatments, including analgesics and palliative radiotherapy (itself a frequently observed SRE) have failed.	See response to 1.1 above
1.7	***Zoledronic acid patent expiry (p10)*** The TAR states, *"To what extent should zoledronic acid coming off patient in 2013 be considered?"* [page xxvii]. Consideration of potential future price changes of zoledronic acid	The Assessment Group used the appropriate BNF62 list price for zoledronic acid in the base case analysis. Section 5.5.2 of the Guide to the methods of technology appraisal (June 2008) states "*When the acquisition price paid for a resource*

	following patent expiry in mid-2013 does not adhere with the Institute's *Guide to the methods of technology appraisal*[i] *(sections 5.5.1-5.5.2)* with respect to acquisition prices of resources. We kindly request that the Institute adhere to its published methods.	*differs from the public list price (for example, pharmaceuticals and medical devices sold at reduced prices to NHS institutions), the public list price should be used in the reference-case analysis. Sensitivity analysis should assess the implications of variations from this price.*"
1.8	***Efficacy of denosumab in reducing pain (p11)*** The TAR states, *"Evidence for the effectiveness of denosumab compared with zoledronic acid in reducing pain and improving relative quality of life is less evident"* [Pages xxviii, 220, 222 and 223]. The phase III studies were designed to evaluate the efficacy of denosumab versus zoledronic acid in preventing SREs and were powered to detect both non-inferiority and superiority with respect to the primary end point of time to first composite SRE. Pain is a clinically important outcome which was assessed rigorously within the phase III studies using a range of pre-specified, exploratory endpoints including; median time to moderate or severe pain; proportion of patients with moderate or severe pain by visit; and median time to worsening pain. As exploratory endpoints, the studies were not individually powered to evaluate relative effectiveness of denosumab versus zoledronic acid in reducing pain. However the results for each of the studies and for the integrated analysis for the main pain endpoints show a consistent benefit for denosumab over zoledronic acid in reducing pain (Manufacturer Submission, Section 5.3.6.1 and Appendix IV).	Data reported by the denosumab studies for the effectiveness of denosumab compared with zoledronic acid in reducing pain are given in the assessment group report, for breast cancer (section 6.2.7), prostate cancer (section 7.2.7) and other solid tumours including non-small cell lung cancer (section 10.2.7).
1.9	***Bisphosphonate contraindicated or intolerant population (p11)*** The TAR states, *"For those patients for whom bisphosphonates are not currently recommended or are not used possibly due to contraindications, both the manufacturer and the Assessment Group conclude that denosumab is not cost-effective compared to*	The protocol for the review noted that not all patients tolerate or are indicated for bisphosphonates, with BSC taken to be the comparator where bisphosphonates are not considered appropriate. The assessment report noted that, as patients with poor renal function were excluded from the denosumab RCTs due to being contra-indicated for zoledronic acid, this meant that there was a

	best supportive care" [page xxix]. We recognise that bisphosphonates are not recommended in specific patient groups on the basis of the existing evidence regarding their clinical effectiveness (e.g. NICE CG58 in prostate cancer for patients with no pain or pain with no history of a prior SRE) and compared denosumab to best supportive care in such patient populations accordingly for both clinical- and cost-effectiveness. We wish to highlight the potential for perverse inequity that may arise for patients requiring management of bone metastases who are currently recommended treatment with a bisphosphonate in accordance with NICE guidelines (i.e. with painful bone metastases and prior SRE), but are not able to be treated with bisphosphonates due to contraindication or intolerance. If the Institute deemed denosumab to be a cost-effective use of NHS resources in a specific solid tumour population currently recommended and treated with a bisphosphonate (e.g. all breast cancer patients and prostate cancer or OST patients with painful bone metastases and prior SRE), then the appropriate comparator in that population should be based on treatment intent (i.e. what the clinician would prescribe were the patient not contraindicated or intolerant). In the interests of eliminating perverse inequity of access to an effective treatment in a patient group with a higher unmet need (no current treatment option), we recommend that treatment intent regardless of underlying individual patient characteristics (potentially precluding treatment with bisphosphonates) is considered as the basis for comparator selection by the Institute rather a patient's ability be treated with a bisphosphonate.	lack of evidence for the efficacy of denosumab in this group of patients. The likely proportion(s) of patients for whom bisphosphonates are recommended but for whom they are contraindicated will affect the overall average cost effectiveness of denosumab across the patient group under consideration. However based on expert opinion (RT and RJ) the AG note that it is relatively rare for renal impairment to be such that it would prevent bisphosphonate administration. If the patient groups who were indicated and contra-indicated were considered together for equity reasons, the overall cost effectiveness of denosumab across this group would be the weighted average net cost divided by the weighted average net QALY, i.e. • 1-X% appropriate comparator = zoledronic acid • X% appropriate comparator = BSC as bisphosphonates contraindicated • Net cost = $(1-X\%)(£_{DENO}-£_{ZOLA})+X\%(£_{DENO}-£_{BSC})$ • Net QALY = $(1-X\%)(Q_{DENO}-Q_{ZOLA})+X\%(Q_{DENO}-Q_{BSC})$
1.10	***Comparative efficacy for economic modelling (p12)*** We recommend that in the presence of head-to-head RCTs for denosumab compared to zoledronic acid, direct efficacy data from	The head to head results were considered within a sensitivity analysis for all the comparisons undertaken within the AG report. However they were not considered as the base case within the AG

	these RCTs should be used in the reference-case economic analysis in preference to the NMA (in adherence with the Institute's *Guide to the methods of technology appraisal,*[i] *sections 5.3.13-22*).	report, and also were not modelled probabilistically. The main differences in terms of the effectiveness of denosumab compared with zoledronic acid arose within the other solid tumours modelling. For the comparisons where the main comparator is zoledronic acid there is still a requirement for an estimate of the relative effectiveness of BSC for both the denosumab arm of the model and the zoledronic acid arm of the model in order to allow for discontinuations: these estimates can only come from an NMA. These analyses also considered BSC as a comparator for those contraindicated to bisphosphonates. As a consequence the AG report concentrated upon the results of the NMA rather than the stand alone results of the RCTs in order to maintain consistency both within and across these analyses. The revised fixed effects AG NMA estimates for denosumab compared with zoledronic acid are the same as the published RCT head to head results. In the light of this the revised fixed effects AG NMA has been retained for the re-estimation of the cost effectiveness estimates. See the errata to the report prepared for the appraisal committee meeting
1.11	***Comparative efficacy for economic modelling (p12)*** There are several examples where the Academic Group NMA lacks consistency with the head-to-head denosumab RCTs. In prostate cancer the comparative efficacy of denosumab versus zoledronic is estimated by the Academic Group in their NMA for time-to-first on-study SRE to be HR=0.57 (95% CI; 0.54 to 0.59), although the head-to-head phase III RCT results demonstrated a HR=0.82 (95% CI; 0.72 to 0.95). Further inconsistencies are highlighted in bold font in Table 3 and Table 4. It should be noted that the NMA included in our evidence submission yielded comparative efficacy outputs that were identical to the results of the head-to-head phase III RCTs comparing denosumab with zoledronic acid (see Table 3 and	The assessment group report included results from a random effects NMA model that was misspecified for the time to event analyses. A revised analysis has been conducted for time to first on-study SRE and risk of first-and-subsequent SREs with fixed effects models. Details are given in the errata to the assessment report prepared for the appraisal committee meeting.

	Table 4). Due to the lack of consistency of the Academic Group's NMA estimates compared with the head-to-head phase III RCTs, we have attempted to replicate the Academic Group NMA using the information provided in the TAR and the published methods (Woods 2010[ii]*)* used by the Academic Group. We were unable to reproduce NMA estimates consistent with those synthesised by the Academic Group. Indeed, our estimates using the same data and methods as employed by the Academic Group yielded results that were more consistent with the head-to-head RCTs than the Academic Group. Given the lack of consistency with the head-to-head RCTs and our inability to replicate the Academic Group NMA estimates, we are concerned that there may be an error in the Academic Group NMA.	
1.12	***Comparative efficacy for economic modelling (p13)*** The denosumab phase III studies represent the largest and most robust evidence package constructed to-date in SRE prevention in patients with bone metastases. We recommend that the utilisation of NMA for comparative efficacy in the reference-case economic analysis should be limited to comparisons with denosumab where no direct head-to-head evidence is currently available (e.g. denosumab versus best supportive care in prostate cancer or OST in patients without pain or with pain and without a prior SRE). We request that the TAR indicates the source of efficacy data for each relevant comparator in the reference-case economic analysis for transparency and that the TAR is updated with any relevant cost-effectiveness re-analysis to adhere with the Institute's reference-case (i.e. using direct head-to-head RCTs data were available).	See response to 1.10 above.
	Detailed technical clarifications	
1.13	***Selection of SRE within the 21-day window (p15)*** The TAR states, *"However it was unclear whether, when more than one SRE occurred within a 21 day period, the SRE that was taken to represent the event was the first SRE that occurred or the*	Thank you for clarifying that when more than one SRE occurred within a 21 day period, the SRE that was taken to represent the event was the first SRE that occurred within that period.

	SRE that was considered to be the most serious within the 21-day period' [page 229]. As described within our manufacturer submission (Appendix III – Methods), the 21-day window was used to ensure that linked events (e.g. surgery to repair a fracture or multiple doses of radiation during a course of treatment) were not counted as separate SREs. To be considered as a subsequent SRE, the ensuing event must have occurred at least 21 days after the previous SRE. If more than 1 SRE occurred in a 21 day window, then the first was counted as the 'index' SRE. This approach is consistent with that used for the registrational studies supporting the approval of the active comparator, zoledronic acid, for this indication.	
1.14	***Patients with renal impairment (p16)*** The TAR states, *"Suggested Research - Evidence for safety and efficacy of denosumab in patients with severe renal impairment"* [page 236]. Patients with severe renal impairment were excluded from the denosumab phase III studies since the comparator - zoledronic acid is not recommended in this population. Therefore it was not possible to assess the efficacy and safety of denosumab in this distinct population compared to bisphosphonates. However denosumab has no known role in kidney function and no adverse renal effects have been associated with denosumab use in nonclinical or clinical studies; thus, no adverse effects on renal function were expected or observed with denosumab administration in the phase III studies. In addition there were no denosumab dose adjustments for on-study deterioration in renal function. The denosumab Summary of Product Characteristics[iii] states that "*in a study of 55 patients without advanced cancer but with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab. There is no need for renal*	Patients with renal impairment were excluded from the denosumab phase III studies because zoledronic acid is contra-indicated in this group of patients. The assessment report noted that, consequently, there was a lack of evidence for the efficacy of denosumab in such patients. However the AG accepts that this research recommendation may not be a high research priority.

	monitoring when receiving denosumab." [Section 5.2 Pharmacokinetic properties] Some clinical data do exist from the denosumab program in patients with renal impairment, including severe renal impairment and provides an evaluation of denosumab in patients with renal impairment, including a total of 317 subjects with creatinine clearance (CrCl) <30 mL/min and a total of 4742 subjects with CrCl 30 to 60 mL/min across the program. The only unique finding in these patients is that patients with severe renal impairment (CrCl <30 ml/min) or receiving dialysis had a greater risk of developing hypocalcaemia; this information is provided in the Summary of Product Characteristics[iii]	
1.15	***Efficacy in patients with non-small cell lung cancer (NSCLC) (p16)*** *The TAR states, "Efficacy for time to first on-study SRE favoured denosumab without being statistically significant'* [pages xx and 221]. We wish to highlight the Study 244 evaluated a range of tumour types and was not powered to evaluated efficacy in individual tumour types such as NSCLC or other solid tumours excluding NSCLC.	In the assessment group report we stated (section 8.3) that the Henry study was not powered to detect either non-inferiority or superiority for time to first on-study SRE or risk of first-and-subsequent on-study SREs for the NSCLC subgroup alone.
1.16	***Breast cancer network meta-analysis (p17)*** The TAR states, *"It is unclear what the precise method was that was used by the manufacturer to calculate the HR for the Rosen study"* [page 92, paragraph 1]. We wish to clarify that the FDA Statistical Review and Evaluation of Zometa, 2002[iv] was used as a supplementary data source for the Novartis 010 Study (Rosen 2003)[v] since no HR or 95% CI was reported for time to first on-study SRE. The FDA evaluation provides relevant efficacy estimates for zoledronic acid compared to disodium pamidronate in this RCT (Novartis 010 Study) in subjects receiving chemotherapy (HR 0.96, 95% CI 0.70 to 1.32) and those receiving hormone therapies	The estimate used in the manufacturer's NMA appears to be a pooled estimate from the hormone and chemotherapy groups (Table 17, Appendix VI of the manufacturer submission). Although Table 2.3.8 of the FDA report quotes separate HRs for chemotherapy 0.96 (0.70, 1.32) and hormone therapy 0.83 (0.62, 1.12), neither the source of the manufacturer's pooled estimate nor the method for combining the results is clear. The AG therefore has no evidence that the AG estimate is less robust than the estimate suggested by the manufacturer.

	(HR 0.83, 95% CI 0.62 to 1.12). We acknowledge that the Academic Group estimated a HR of 0.97 (95% CI 0.78 to 1.20) based on combining the lytic and non-lytic subgroup Kaplan-Meier curves from the primary publication (Rosen 2003)[v] using methods proposed by Tierney 2007[vi]. We recommend that the HR reported in the FDA Statistical Review and Evaluation of Zometa[iv] are utilised instead for zoledronic acid versus disodium pamidronate in accordance with recommendations cited by Tierney[vi] (*the direct methods make no assumptions and are preferable, followed by the various indirect methods based on reported statistics. The curve methods are likely to be the least reliable and it is not yet clear which method of adjusting for censoring is most reliable)* and included as the data source for the basis of the NMA in breast cancer.	
1.17	***Drug administration and staffing costs (micro-costing study) (p17)*** We wish to highlight the following factual inaccuracies concerning the micro-costing study and methodology in the AG report. Firstly, the TAR states that "*The manufacturer estimates through a survey of oncology doctors and nurses...*" [page xxi, paragraph 3] We wish to clarify that the structured questionnaire surveys were conducted with oncology nurses and pharmacists, as these are the healthcare professionals typically involved in drug administration.	Thank you for this clarification.
1.18	Secondly, the TAR states that "*...the micro-costing study did not estimate the additional nursing time associated with different infusion durations. Infusion was apparently estimated from the products' SPCs and subsequently confirmed by respondents...*" [page xxi, paragraph 3 and page 152, paragraph 2]. We wish to clarify that the infusion times associated with each of the intravenous bisphosphonates were captured in the one-off administration of the structured questionnaire to each of the relevant healthcare professionals (in this instance, the oncology	Thank you for this clarification. We will amend "*...the micro-costing study did not estimate the additional nursing time associated with different infusion durations. Infusion was apparently estimated from the products' SPCs and subsequently confirmed by respondents...*" To "*…the micro-costing study prompted respondents about the administration times associated with different infusion durations:*

	nurse specific questionnaire). This element was captured during the drug administration phase questions to specifically quantify the infusion time and healthcare professional (*Question: It is assumed that an infusion of IV X would typically occur over a minimum of X minutes according to the Summary of Product Characteristics. Is this correct for your centre? If not, please specify the infusion time.*) alongside the other additional activities which occur sequentially during this administration phase, such as: nursing clinical check prior to administration, infusion line preparation, preparation/hanging of the infusion bag, connecting tubing, saline infusion and post bisphosphonate saline flush.	*"Question: It is assumed that an infusion of IV X would typically occur over a minimum of X minutes according to the Summary of Product Characteristics. Is this correct for your centre? If not, please specify the infusion time." This wording may have framed responses to the question. It also does not appear to ask whether the duration of the IV infusion involved any additional nursing time…."*
1.19	***Doses withheld (p18)*** The TAR states that, *"However, there is a suggestion that there may be slightly fewer zoledronic acid administrations per annum than denosumab administrations. This triangulates with the higher proportion of zoledronic acid patients within the prostate cancer trial having doses withheld for creatinine clearance"* [page xxiii] and with respect to drug acquisition costs, *"These costs do not include withheld doses due to poor renal function"* [page xxii]. We wish to confirm that there were slightly fewer doses of zoledronic acid and that these doses were withheld due to increased levels of serum creatinine (in accordance with the zoledronic acid SPC)[vii]. The impact of a reduced number of zoledronic acid doses was not explicitly included within the direct drug and administration costs for simplicity and we wish to highlight that this simplification will have a negligible impact on the cost-effectiveness and likely to be conservative in favour of bisphosphonates. During the development of the manufacturer evidence submission, independent clinical experts had indicated that in instances of increased serum creatinine, the scheduled dose of bisphosphonate would be withheld and patients are subsequently required to undergo more frequent attendance (every two weeks)	These costs do not include withheld doses due to poor renal function, or any patient management costs due to poor renal function. But Assessment Group clinical expert opinion suggests that patients would only be monitored every four weeks for reduced creatinine clearance. The resource use associated with this has to be weighed against that associated with an IV administration of zoledronic acid."

	to monitor renal function. Our submission only included the costs associated with the management of serious renal adverse events. However additional costs associated with the management of non-serious renal adverse events (e.g. raised serum creatinine triggering renal ultrasounds) were not included. These investigations as well as additional consultant led follow-up appointments (and serum creatinine or renal function monitoring) were not included. The costs associated with instances of increased serum creatinine are anticipated to be at least equivalent and likely more than that of drug acquisition and administration of bisphosphonate. We recommend the wording in the TAR [page xxiii] to be amended to *"These costs do not include the impact of withheld doses on drug costs. Additional patient management costs due to poor renal function have also not been included"* to provide a balanced view on the impact of withheld doses on both drug acquisition and patient management costs.	
1.20	***The cost of skeletal-related events (p19)*** The TAR [page 155, Section: trim point and manufacturer costings] describes the SRE costing methodology and source of unit costs employed in our submission. The TAR states that "*...it is questionable whether any allowance for excess bed day costs should have been made by the manufacturer*." [page 155, paragraph 4] given the Payment by Results national tariff (2010/11)[viii] trim points for some SREs exceeds the observed mean length of stay for SRE management observed in STARS and our costing methodology employing retrospective NHS reference costs (2009/10)[ix]. This adaptation results in a reduction in the mean SRE management costs. We wish to raise technical concerns with the proposed costing approach in the TAR. This is a due to a merging of activity costs from retrospective NHS reference costs (i.e. actual costs to the NHS) with trim points from prospective Payment by Results for reimbursement (i.e. not actual costs to the NHS) and the	The general point made remains valid and it is not appropriate to cost durations of stay above the average HRG inpatient length of stay using the excess bed day cost. The reference cost trimpoint is not the average HRG length of stay. 1. "National Schedule of Reference Costs 29. All inpatient elective and non-elective schedules are based on the established statistical technique known as data truncation. This truncated data is derived by excluding bed days that fall outside nationally set lengths of stay (trimpoints). The costs of any days beyond these trimpoints are separately identified in the schedules. This assists in giving a like-for-like comparison of activity and costs." 2. "Q2. How are the Reference Costs trimpoints calculated? The trimpoints used for the 2008-09 Reference Costs are calculated

	consequential removal of excess bed day costs resulting in an underestimation in the costs of SRE management to the NHS.	by using 2007-08 Hospital Episode Statistics (HES) data. The trimpoints are calculated as follows: Trimpoint = Upper Quartile + (1.5 * Inter Quartile Range) The trimpoints are calculated on a FCE basis and there is one trimpoint for both elective and non-elective long stay. The trimpoints used for the PbR tariff are different to those used for Reference Costs. Tariff trimpoint are calculated on a spell level and reflect the structure of the tariff." 3. "Trimpoints are used by NHS providers when preparing Reference Cost submissions, where excess bed day unit costs and activity are reported separately by HRG. The NHS Information Centre (NHS IC) publishes trimpoints on its website and includes them in its HRG Reference Costs Grouper software. For further information about the Reference Costs exercise please go to the Department of Health website www.dh.gov.uk/pbr." 1 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_118338.pdf 2 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_118330.pdf 3 www.ic.nhs.uk/webfiles/.../RC0910%20Trimpoints%20v1.0.xls
1.21	***Quality of life based on the denosumab phase III studies (p19)*** TAR: *"There may be some concerns around not having included two indicator variables for SRE experience: one which is turned on from T(0) to P(5) for an SRE naïve patient experiencing their first SRE, and another which is turned on from M(5) to P(5) for patients who have experienced an SRE other than the one being assessed*	Thank you for this clarification.

	at T(0)" [page 162] We wish to confirm that the M5 to P5 covariates flag whether a particular EQ-5D measurement may be affected by being within a particular proximity to an SRE (with the proximity graded into monthly intervals). All SREs experienced by the subject are considered, so an EQ-5D is flagged for its proximity to all SREs within +/- 5 months of the EQ5D assessment and several of the M5 to P5 variables may be simultaneously flagged accordingly. Hence, the model recognises that multiple SREs may be influencing the EQ-5D simultaneously.	
1.22	***Discounting of QALYs (p21)*** The TAR states: *"The total QALY decrements associated with SREs as presented by the manufacturer are summarised below. For the SRE naïve patient experiencing an SRE there is a permanent loss from the first SRE that is experienced. This accounts for much of the difference in the SRE QALY impacts between SRE naïve and SRE experienced patients. It is not clear that the full discounted impact of this is within the figures below."* [page 161, paragraph 1]. We wish to confirm that the QALYs for SREs (SRE naive and experienced health states) and QALYs for AEs were appropriately discounted in the cost-effectiveness analysis. This is detailed in columns EK:EL and EX:EY in the "ZOL" and "Comp*n*" worksheets of the economic model.	The AG is of the view that these have not been discounted to the baseline T(0), although the impact of this would in all probability be limited given that the monthly decrements straddle T(0) by 5 months either side and the overall period is of only 11 months duration. Given the overall maximum duration it could be argued that these quantities should not be discounted to T(0) as appears to be the case within the electronic model; e.g. the antecedents to D37 of the Utility SRE worksheet, such as F419-F429. This does not imply that within the electronic copy of the model the QALY decrements are incorrectly discounted.
1.23	***Application of disutility prior to start of treatment (p21)*** The TAR states, *"The manufacturer model appears to attempt to correct the SRE utility decrements in order avoid projecting any effect priors to the start of treatment; i.e. during the first five cycles of the model. For instance, for the third 28 day cycle the intention appears to be not to include the impacts of the 5th and 4th months prior to an SRE. But it appears that there is an error within the*	Thank you for clarifying that there is no error in the model coding.

	model coding, such that for this example it excludes the quality of life decrements for the 4th and 5th month subsequent to the SRE. This may have quite a large impact upon modelling results, given the overall survival curves and the evolution of SRE utility decrements" [page 162, paragraph 2]. We wish to confirm that there is no error in the model coding. As per the example stated in the TAR, all QALY decrements are taken into account and placed diagonally into the model with columns relating to time points (T-5 to T+5) and rows relating to the model cycles (1-144) for patients having an SRE in the third 28 day cycle. This was adopted to ensure that the discounting was applied correctly.	
1.24	***Double counting of health benefits (p21)*** The TAR states, *"Due to the lack of detail on the manufacturer EQ-5D analysis, it is unclear whether the step change HRQoL impact of moving from being SRE naïve to SRE experienced has been double counted during the five months subsequent to an SRE within the manufacturer model. The calculation of the SRE HRQoL impact among SRE naïve patients does not include the SRE experienced parameter in the 5 months prior to the SRE, but introduces it at diagnosis and for the 5 months subsequent to diagnosis. This increases the SRE HRQoL decrement by the SRE experienced step change at diagnosis and for the 5 months subsequent to diagnosis"* [page 162, paragraph 4]. We wish to confirm that the model does not double-count health benefits. The area between the SRE baseline utility and the disutility pre- and post-SRE is estimated on the "Utility SRE" worksheet of the economic model. For time points T-5 to T-1 the baseline utility reference is the SRE naive health state and for time points beyond this (T0 to T+5) the reference utility value is that of the SRE experienced population to reflecting their new health state. In the case of SRE experienced patients, the SRE experienced reference utility values are always used.	Thank you for clarifying that the model does not double count health benefits. Note that the implementation within the AG model is quite different but results in the same overall QALY decrement, with some provisos around half cycle correction. The stated decrements within the utility worksheets do not include the decrements arising from the step change in utility at 1st SRE. This is rather modelled within the cohort flow, i.e. for the SRE naïve the 5 post diagnosis months also require the SRE naïve QoL – SRE experienced QoL decrements to be applied to arrive at the total QALY decrement over the 11 month window.

	For example, an SRE naive breast cancer patient suffering a vertebral fracture is estimated in cells F386:F399 of “Utility SRE” worksheet (noting the formula change due to a change in baseline value from T0 onwards). For this patient, the marginal utility associated with having a vertebral fracture is estimated in cells F401:F413. The utility is subsequently transformed into QALYs by multiplying by the cycle length. These 11 single cycle decrements are then used in the Markov model worksheet and applied by cycle whilst ensuring that patients are still alive when adding the QALY decrements for future cycles. The QALY decrements are small in time points T0 to T+5 due to the modeling of the reduced baseline utility. Notably, the utility decrements would have been considerably higher if patients were modeled to return to their original baseline utility.	

	The following contains the Assessment Group responses to the comments in Table 5 (pp23-24) of the Amgen document.			
	Technology Assessment report section	**Factual inaccuracy**	**Amgen recommended correction**	**Assessment group response**
2.1	Page xix, Executive Summary Page 39, Table 4	Sequence generation and allocation concealment for Stopeck 2010 were considered unclear due to insufficient information.	These details are contained in the Clinical Study Report which was provided to the Assessment Group as part of the reference package supporting the Manufacturer's Submission.	The quality assessment of the studies was based on the information reported in the published papers.
2.2	Page 15, Section 3.3.3	"The direct drug cost is £309.85 per dose."	The NHS list price of denosumab (XGEVA) is £309.86 per 120mg vial	Thank you for pointing out this typo.
2.3	Page 38, Table 3	Stopeck column - the number of patients for the ECOG status 0-1 is not included	The number of patients for the ECOG status 0-1 is available in the paper; Dmab 955 (93%) and Za 932 (91%)	Thank you for this information.
2.4	Page 41, Table 5	A footnote should be included for Stopeck	The Stopeck footnote should be "Cox proportional hazards model with treatment group as the independent variable and stratified by the randomization factors"	Thank you for this information.
2.5	Page 43	Section on Prior history of SRE - refers to Study 103 which is incorrect	Should refer to Study 136	Thank you for pointing this out.
2.6	Page 48	Section on SRE by type: Last sentence	The value 1.75 should be 0.37	Thank you for drawing this to our attention.

		"….for spinal cord compression (0.07 versus 1.75)" is incorrect.		
2.7	Page 69, Table 21	Fizazi denosumab column Ethnicity other - 121 (135) is incorrect	Should be 121 (13%) not 121 (135)	Thank you for pointing out this typo.
2.8	Page 76	"….780 SREs occurred in 1045 patient-years in the denosumab arm and 943 occurred in 996 patient-years…."	Marked as academic in confidence in the manufacturer's submission	This information is in the public domain and was reported in the Miller 2011 paper (J Urol 2011;185(Suppl):e262, reference 125 in the assessment report). The paper stated 'Seven hundred eighty SREs occurred in 1,045 patient-years in the denosumab arm; 943 SREs occurred in 996 patient-years in the ZA treatment arm.'
2.9	Page 9, Table 37:	Column headings 'dmab' and 'za' are the wrong way round 'Age median 60(19-89)' is incorrect	Henry the columns say dmab and za but the data in the dmab column refers to za and vice versa. Age, median is 60(19-89) this should be 60 (18-89)	Thank you for drawing this to our attention.
2.10	Page 97	"The study by Henry and colleagues reported a statistically significant difference in favour of denosumab for overall survival (21% risk reduction with	Need to make clear what which cancer population this refers to.	The cancer population referred to is the NSCLC subgroup.

		denosumab) but in OST not NSCLC as per Section 8",		
2.11	Page 105, Table 46:	The numbers randomized are incorrect Not clear what source reference was used for the p value for median months	Denosumab and Zoledronic acid number randomised is 886 and 890 respectively, Need to reference where the p value for median months comes from	Thank you for drawing this to our attention. The source for the p value for median months was Henry 2011.
2.12	Page 106	First paragraph: is not reported in Henry reference	Need to indicate where this information comes from	Information from the first paragraph of page 106 comes from the following abstract which was considered a secondary report to Henry 2011. We cited this as reference no 135: von Moos R, Patrick D, Fallowfield L, Cleeland CS, Henry DH, Qian Y et al. Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with advanced cancer (excluding breast and prostate) or multiple myeloma (MM): Results from a randomized phase III clinical trial. *J Clin Oncol* 2010;28(Suppl):abstr 9043." In Appendix 4 (List of included studies) von Moos 2010 is listed as a secondary report to Henry 2011.

2.13	Page 108,Table 49	The numbers randomised for denosumab and zoledronic acid are the wrong way round	Denosumab and Zoledronic acid number randomized is 886 and 890 respectively	Thank you for drawing this to our attention.
2.14	Page 113	'The risk reduction for overall survival was not statistically significant (0.92, 95% CI 0.81 to 1.05, p=0.2149). '	Clarify that this sentence refers to Study 244 excluding multiple myeloma	Yes, this sentence refers to Study 244 excluding multiple myeloma.
2.15	Page 116	'10% of denosumab treated patients' is incorrect	Should be 10.8% not 10% for the denosumab group	Thank you for pointing this out.
2.16	Page 117	Renal toxicity AEs should say Serious AEs	Clarify that the 34 patients compared with 24 patients are for those with serious renal aes. Serious not mentioned in report	Yes, these patients are those for serious renal adverse events.
2.17	Page 120	Denosumab group 10% is incorrect	Should be 10.8% not 10% for the denosumab group	Yes, agreed.
2.18	Page 145, Table 70	SRE naïve for OST is incorrect	SRE naïve for OST is 51% or 49% for OST excluding MM	Thank you for drawing this to our attention. We will revise the model accordingly.
2.19	Page 213, Table 118	The table states incremental costs and effects for denosumab versus best supportive care. The table incorrectly states that the manufacturer modelling was based on the SRE	Amgen modelled the SRE naive subgroup for comparisons with best supportive care	Thank you for drawing this to our attention.

		experienced subgroup for this comparison.		
2.20	Page 231	“One phase II study is currently evaluating denosumab for prolonging bone metastasis-free survival in hormone refractory prostate cancer.”	The study evaluating denosumab for prolonging bone metastasis-free survival in hormone refractory prostate cancer is a phase III study.	Thank you for pointing this out.

	Consultation comment	Assessment Group response
	Royal College of Physicians	
3.1	We note that the only large-scale head-to-head of oral ibandronate and IV zoledronate is the NCRI ZICE trial which is still in follow-up and has not yet reported. Similarly, the limitations due to the lack of direct comparisons between denosumab and bisphosphonates are noted.	No response required.
3.2	Given the lack of head-to-head data, assumptions on efficacy may not be valid and at the very least our experts believe that a sensitivity analysis should be completed.	The sensitivity analyses around the clinical effectiveness estimates are limited to those which apply the results of the manufacturer NMA and those that apply the SRE naïve subgroup results and SRE experienced subgroup results for the comparison of denosumab with zoledronic acid. In addition, NMA analyses for 1) NSCLC, 2) OST excluding NSCLC and 3) OST including NSCLC, are presented within the AG report. These results act as a sensitivity analysis of the NMA. The analyses are consistent with each other and further improve the validity. To some extent additional sensitivity analyses would be arbitrary and the values which should be chosen for these are not immediately obvious. The AG is of the opinion that the SRE naïve and SRE experienced subgroup sensitivity analyses provide a reasonable insight into how changes to the central effectiveness estimates alter the results, while also having the advantage of being grounded in trial data.
3.3	The validity, accuracy and source of the QALY effects of a skeletal complication seemed very arbitrary but are a major driver of the cost effectiveness analyses. For some of the reasons given below this is a major cause for concern.	While there is a lack of detail on the Amgen quality of life estimates and functional forms tested as outlined in the AG report, it should be borne in mind that these are time limited, based upon RCT EQ-5D data, and derived using the UK social tariff. The AG does accept that further sensitivity analyses could have been undertaken around the quality of life decrements based upon the published studies. However the values within

		the literature are probably subject to greater uncertainties than those drawn from the RCTs.
3.4	The amalgamation of skeletal complications within a 21 day window as a single event, as required by the regulators, leads to a significant underestimate of the real effects of treatment on the number of events and healthcare resource use. Clearly this is not a reflection of the real world, even where multiple events may be linked, from the patient's perspective or from a healthcare resource standpoint, as all such events are individually of relevance. Since the total number of events may not be apparent from the published trials, the effects and benefits of treatment may be significantly underestimated.	Thank you for this comment. No response required. .
3.5	There is the opportunity for service redesign and the delivery of treatment close to home given that a subcutaneous injection provides potentially a great reduction in patient burden over the long time period compared with 3 to 4 weekly visits for IV therapy. There is some data available suggesting that quality-of-life was better for patients receiving home therapy rather than hospital use (Wardley et al British Journal of Cancer 2005). Unfortunately, this paper is listed as 'no relevant intervention' but is the sole study comparing the quality-of-life for patients with bone metastasis according to where they received the treatment.	Thank you for this comment. The paper by Wardley and colleagues failed to meet the inclusion criteria for the clinical effectiveness part of our review because it reported only zoledronic acid and did not compare it with another intervention. It is listed in Appendix 5 of our report (List of Excluded studies) under the section 'No relevant interventions'.
3.6	One of the key studies cited comparing pamidronate to placebo (Lipton et al 2000) is not the original trial report but an amalgam of the registration studies by Hortobagyi et al and Theriault et al. As such it misses out on key data including effects on quality of life contained in those original reports.	Studies by Hortobagyi et al and Theriault et al are referenced as secondary reports in Appendix 4. Both of these studies had the same design and recruitment, but one recruited patients treated with hormones and the other patients treated with chemotherapy. Data from Lipton was used to provide a representative group of patients treated with hormones and chemotherapy. The additional quality of life data were unsuitable because they did not include direct evidence on denosumab or were unsuitable for the NMA.
3.7	Radiotherapy for metastatic disease in current UK practice is a single fraction except for spinal cord metastasis in contrast to statements	We accept that this is the case for the majority of patients, although clinical expert opinion (RJ) also suggests that a

	made in the report.	number of patients receive fractionated therapy for bone metastases. Changing the number of radiotherapy fractions to 1 would have minimal impact on the cost-effectiveness. This has been tested for in further sensitivity analyses and has minimal impact on the ICER (<1%).
3.8	The issue of waiting for results as a time factor may not be relevant in UK clinical practice where GP surgeries perform pre- treatment blood tests.	Based on clinical expert (RJ and RT) opinion, we agree that GP surgeries generally undertake pre-treatment blood tests; however to some extent this may be offset by the inconvenience of an otherwise unnecessary visit to the GP surgery or nurse visit to the patient's home.
3.9	In calculating costs does treating hypercalcaemia cost the same as an orthopaedic operation?	No. The cost of treating hypercalcaemia is based upon the value calculated within the Ross HTA Monograph, while the cost of orthopaedic operations is the average of reference costs HR04B, HR04C and HR05Z.
3.10	The use of arbitrary thresholds of time to first SRE is seemingly based on single clinician's judgement. For patients who live 5 to 10 years with metastatic disease a three-month difference may not be significant. However, it is very different from those who live 5 to 10 months.	We accept that the three month difference may considered a rather arbitrary time threshold. This probably applies to many statements about minimum 'clinically significant' impact. Emphasis should probably be placed more on the hazard ratio reduction than the time threshold.
3.11	The question of how progression is taken into account (page 128) is a matter for concern since while progression may lead to a change of therapy it is unlikely to change the bisphosphonate use or approach.	This comment relates to the section of our report that reports the published cost-effectiveness studies identified from our literature search, and specifically the paper by Botteman and colleagues (Ann Oncol 2006;17:1072-82), where we state that it was not obvious how progression was included in the modelling. Within the manufacturer and AG modelling progression is not assumed to affect the use of bisphosphonates or denosumab.

3.12	Our experts were puzzled by the quotation of median survival with metastatic disease of 14 months. Certainly for postmenopausal ER positive women the figure is over three years.	We did not quote a figure of 14 months in our report. We stated (section 3.1.2, Overview of types of cancer commonly spreading to bone, Breast cancer, page 1) that 'Bone metastases are associated with reduced median survival of approximately 24 months and five year survival of 20%.'
3.13	Is there any data to support the statement that 'the risk of an SRE among those discontinuing is assumed to be equal to that for BSC' given that a bisphosphonate will be in the bone for years following administration whereas denosumab may not be?	No, this is an assumption that was required for the economic modelling.
3.14	With reference to blacked out table 77, our experts consider that most discontinuation of bisphosphonate is either for toxicity or proximity to death and not related to SAE's.	Thank you for this comment. No response required.
3.15	The assumption that loss of quality-of-life with an SRE starts five months before is considered strange.	The AG also queried this in our report (chapter 11 – Assessment design and results) section 11.2.5 Quality of life, p158, where we stated: 'The other key assumption is that the most appropriate functional form is to estimate the HRQoL impact of an SRE from 5 months before its diagnosis through diagnosis and on through to 5 months subsequent to its diagnosis: 11 months in total. For fractures, it is not obvious why the extended period of time prior to the fracture being identified is required.' In their consultation comments on our assessment report the manufacturer stated (pp19-20) in relation to this issue: 'We wish to highlight the bone metastases result in a progressive deterioration in bone health. This results in a locally increased pathological rate of remodelling and the development of bone lesions. Lesions are characterised by painful bone destruction and/or chaotic bone formation, resulting in weak and fragile bone tissue with a propensity to fracture. Therefore, a pathological fracture is the end result of this gradual progressive deterioration (and associated disutility) rather in comparison to a spontaneous fracture that may occur

		in other disease areas such as osteoporosis that is otherwise asymptomatic prior to the event.' It should be noted that the functional form assumed permits the impact of an SRE to straddle the SRE incidence from 5 months prior to 5 months post. It does not imply that large quality of life impacts are estimated 5 months prior to the SRE. This comment needs to be read in conjunction with Appendix 13 of the assessment report which unfortunately was classed as academic in confidence. Typically, this suggests a somewhat lesser quality of life impact in the 5 months prior to the SRE diagnosis than might be inferred from the text of the assessment report.

	Consultation comment	Assessment Group response
	Healthcare Improvement Scotland	
4.1	I am not sure if there has been an assessment made of the cost of ambulance transport for those patients living some distance away from hospital. Savings on transport costs for denosumab given at GP practice rather than hospital appointments for zoledronic acid may shift the balance more in favour of denosumab in those requiring transport for longer journeys.	This, and the percentage of patients requiring ambulance transport, was not addressed in the assessment report.
4.2	Agree that the balance may change completely with Zoledronic acid coming off patent next year. Is there a threshold cost for this that would shift the balance and if so would it be detailed in the report?	A range of sensitivity analyses on this point is presented in the assessment report, but due to the with Patient Access Scheme (PAS) price for denosumab being commercial in confidence (CIC) these have also been marked up as CIC in order to avoid the possibility of back calculating the with PAS price for denosumab.
4.3	Patients being treated in the community rather than in hospital day units which administer chemotherapy will 'free up' chemotherapy slots which may have an impact in waiting times for chemotherapy commencement, potential to reduce number of patients breaching target waiting times in busy units.	Thank you for this comment. No response required.

	Consultation comment	Assessment Group response
	National Collaborating Centre for Cancer	
5.1	Although the report does not quote the comparison of zoledronate with best supportive care (BSC), from your data our health economist estimates that zoledronate is not cost effective compared to BSC with an ICER of £316,714 in breast cancer and an ICER of £293,900 in prostate cancer. Can you confirm that these figures are correct using your model? If so, it would appear that your baseline comparator, zoledronate, is not cost effective in the prevention of skeletal related events in breast and prostate cancer.	Since estimating the cost-effectiveness of zoledronic acid compared with best supportive care is outwith the scope of our report, the AG is not in a position to confirm the figures calculated by your health economist.
5.2	The NICE prostate cancer guideline (CG58) does not recommend bisphosphonates for the prevention of skeletal related events but the advanced breast cancer guideline (CG81) does. CG81 concludes that bisphosphonates are probably cost effective in breast cancer but this was based on a review of published health economics not a de-novo model. If your model shows that zoledronate is not cost effective in breast cancer we may need to update this area of our guideline. It would also be odd for a NICE Technology Appraisal to use a baseline comparator that was not cost effective.	The NICE Guide to the methods of technology appraisal (June 2008) states that: “Relevant comparators for the technology being appraised are those routinely used in the NHS, and therapies regarded as best practice when this differs from routine practice.” This is not necessarily synonymous with the comparators themselves being cost effective.

	Consultation comment	Assessment Group response
	Novartis	
6.1	***Summary of main points*** The Assessment Group (AG) analysis did not fully incorporate the effect of generic price of zoledronic acid on the cost effectiveness (CE) of denosumab for all cancers considered. Novartis believes the impact could be significant given the small QALY gain attributed to denosumab.	This is correct, and is related to the more detailed consideration of the future price of zoledronic acid as in the AG response to the Amgen comment on the price of zoledronic acid, 1.7.
6.2	It is not clear why other oral bisphosphonates such as clodronate and ibandronate were excluded from the analysis yet they were included in the NICE scope. The impact of including oral bisphosphonates in the economic analysis is likely to be significant because there are no administration costs associated with these treatments.	Ibandronic acid and clodronate are only licensed for use in breast cancer. Based on advice from clinical experts (RJ and RT) they are not routinely used in breast cancer or used as an unlicensed medication in other cancers. The AG attempted to indirectly assesses these drugs through NMA. However studies were judged to be too heterogeneous for analysis. The main reason for heterogeneity was a difference in reported outcome. This criterion was described in the agreed protocol (p8). Characteristics and results of studies assessing ibandronic acid and clodronate are presented in the AG report (Appendices 6 and 7).
6.3	The economic analysis by the AG did not incorporate the reduced dosing frequency of zoledronic acid due to renal toxicity.	See AG response above to similar point made by Amgen, 1.19.
6.4	The economic analysis by the AG has overestimated the staff and administration time savings for denosumab.	The AG accepts that administration costs could have been more fully and more explicitly examined. This mainly relates to the comparison with zoledronic acid. The range of sensitivity analyses undertaken with respect to the list price of zoledronic acid was viewed by the AG as a reasonable proxy by which other cost sensitivities could be assessed.
6.5	The price for pamidronate applied in the model does not reflect the lower generic cost for the drug.	BNF62 suggests 90 mg every 4 weeks (or every 3 weeks to coincide with chemotherapy in breast cancer) and gives a list price for non-proprietary disodium pamidronate of £165 per 10-mL vial at 9 mg/mL. The AG report applies this cost.

		See the AG response to the Amgen comment, 1.7.
6.6	All these factors are likely to have a huge impact on the cost effectiveness of denosumab and Novartis recommends that the AG conduct additional analyses incorporating the above points in the base case analysis. This will enable the Appraisal Committee to make an informed decision on the true cost effectiveness of denosumab compared with zoledronic acid and other bisphosphonates.	Thank you for this comment. No response required
6.7	***Detailed discussion of key points*** The future generic price of zoledronic acid Zoledronic acid will be going off patent (generic) in early 2013 and therefore its price is going to significantly go down after this date. The AG's base case analyses for all the different cancers has shown that the QALY gain for denosumab compared with zoledronic acid is very small ranging from 0.013 in breast cancer, 0.006 in prostate cancer, to as low as 0.003 in lung cancer. This implies that any slight changes in the incremental costs results in a significant change in the incremental cost effectiveness ratio (ICER). It is therefore not surprising that the ICER for denosumab compared with zoledronic acid changes significantly (from denosumab not cost effective to denosumab dominating) when changes to the cost inputs are made. The economic model adopts a lifetime horizon and therefore the full time horizon includes a significant period when zoledronic acid will be generic and hence far cheaper than the current price applied in the AG model. Given that the QALY gain is so small, the price of generic zoledronic acid will have a massive impact on whether denosumab is cost effective or not. Evidence based on other generic bisphosphonates (ibandronate and pamidronate) shows that at the point of going generic the price could go down by as much as 50% and within six months the price could go down by as much as 80%. The AG acknowledges the impact of zoledronic acid going generic and poses the same question as Novartis by stating the following: *To what extent should zoledronic acid coming off patent in 2013 be considered? The anticipated patient benefits from denosumab over zoledronic acid are small. Only a relatively small drop in the price of*	See the AG response to comments on this subject by Amgen, 1.7.

	zoledronic acid would be sufficient to make denosumab not cost effective when judged by conventional thresholds (page 217 of the AR) We fully agree with the AG's statement and we are requesting the AG to incorporate a higher reduction in the price of zoledronic acid in the model after a year to reflect the likely price of the drug when it goes generic. The AG should consider a zoledronic price reduction of at least 50% which we believe will be conservative given the percentage fall in price of other generic bisphosphonates when they went off patent. Novartis believes that applying such a discount is crucial because the NHS will not be paying the list price of zoledronic acid from next year and more importantly ignoring this significant generic price drop produces results that might not reflect the true CE of denosumab when compared with zoledronic acid in this setting. As mentioned earlier, the economic analyses both from the manufacturer and the AG have shown that denosumab offers marginal benefit (if any) over and above zoledronic acid. Novartis views it as inappropriate for the economic analysis to consider the list price of zoledronic acid for the lifetime given that the drug will be far cheaper and offering the same benefit as denosumab. Novartis reiterates that the AG incorporates a higher percentage drop in price in the base case analyses.	
6.8	Exclusion of some comparators from the analysis The inclusion and exclusion of some comparators in the analysis is not clear. The final scope of this appraisal specified that all bisphosphonates including oral versions were appropriate comparators. The analysis from the manufacturer and the AG seems not to have fully considered oral ibandronate and clodronate. Novartis market share data shows that oral ibandronate and clodronate have significant market share to warrant consideration as 'stand alone' comparators in the health economics analysis. The market share data further shows that infusional ibandronate is rarely used in clinical practice yet it was considered as part of the comparators. Thus the analysis seems to have broadly excluded oral comparators for inclusion (oral clodronate and ibandronate studies) and concentrated more on infusional or intravenous options some of which	See response to 6.2.

	are not usual clinical practice in this setting. The NICE scope for the appraisal specifies these as comparators and their inclusion might have an effect on the cost effectiveness analysis (CEA) given that there are no administration costs associated with the oral treatments. Novartis therefore believes that the true cost effectiveness of denosumab can be established when all the appropriate comparators (both oral and infusional or intravenous bisphosphonates) as per the NICE scope are considered in the analysis. Novartis reiterates that the cost effectiveness of denosumab could easily change given the small QALY gain predicted in both the manufacturer's model and the AG's model and therefore suggests that the AG analyses is updated with oral bisphosphonates as 'stand alone' comparators where appropriate.	
6.9	Zoledronic acid dosing frequency Within the denosumab trials intravenous therapy could be withheld due to elevated creatinine. This affects the average dose received within the zoledronic acid arm. It appears possible that since exposure to zoledronic acid could only be resumed once creatine levels had returned to acceptable levels, some of these incident patients may have had more than one dose withheld. The AG reports that there was no attempt to correct for doses of zoledronic acid being withheld due to renal toxicity (page 181 of the AR). It is clear that the number of doses of zoledronic acid withheld can have an impact on cost of treatment. The zoledronic acid SPC lists both renal impairment and raised blood creatinine as common side effects, defined as an incidence of between greater than 1 in 100 and less than 1 in 10. It is therefore surprising that the AG have decided to exclude the reduced dose of zoledronic acid in a proportion of patients in calculating the costs of treatment. This is more so when you consider the fact that the adverse event costs associated with renal toxicity were included in the AG model. The impact of this approach is to favour denosumab at the expense of zoledronic acid. Novartis suggests that the AG incorporates the reduced doses of zoledronic acid in its base case analyses to be consistent with the inclusion of renal toxicity AE costs and more importantly to reflect the actual costs of zoledronic acid treatment. Novartis considers that this update to the analysis will have a	See AG response to Amgen comment on this point, 1.19.

	significant impact on the ICER for denosumab.	
6.10	Staff time and drug administration costs The manufacturer of denosumab used median instead of mean in estimating the costs of staff time and drug administrations from the micro-costing study. We agree with the AG's conclusions that the requirement to make this adjustment might suggest that the micro-costing study that was used to inform the estimates was not reliable. In addition, we do not believe that denosumab will result in staff time savings and administration cost savings as implied in the micro-costing study. Section 6.6 of the denosumab SPC states that when taken from the fridge, the denosumab vial should reach room temperature before use, while zoledronic acid can be used straight from the fridge. In addition denosumab requires special storage conditions of between 2 and 8 degrees, i.e. refrigeration (section 6.4 of SPC), while zoledronic acid requires no special precautions for storage (section 6.4 of SPC). This extra preparation time for denosumab needs to be taken into account when estimating the staff time saving and administration time saving. Furthermore zoledronic acid has recently been launched as a new Ready to Use (RTU) formulation which means there is no drug preparation time, compared to the previous concentrate formulation which had to be added to a 100ml bag dilutent before being administered intravenously. We therefore suggest that the AG updates its base case analysis and assume no staff time and pre-administration time saving for denosumab. Novartis considers this to be a conservative assumption because it is more likely that zoledronic acid will result in staff and administration time savings if the points discussed above are considered.	See above response to Amgen comment on this point, 1.18. However we would also note that the AG was not aware of and has not considered the impact of Ready to Use zoledronic acid.
6.11	Price for pamidronate The AG has applied the list price for pamidronate for the purposes of the economic analyses. Novartis is of the opinion that relying on the BNF for the cost of a drug that is generic is misleading and will not reflect the actual cost effectiveness of new compounds such as denosumab. There is evidence showing that the actual reference price of pamidronate is far lower than the BNF list price. Novartis contacted three major generic	This is governed by the NICE Guide to the methods of technology appraisal (June 2008), as considered in greater detail in the responses to Amgen's comments on the price of zoledronic acid above.

	manufacturers of pamidronate and the average price was approximately more than 50% lower than the list price. In addition Novartis' market research showed that the NHS is paying as low as £20 for a 28 tablet pack of pamidronate and in other NHS organisations, the price is even lower. The pamidronate price is therefore inflated and using a lower price (reflecting the price the NHS is paying for the drug) may have a huge impact on the final results given the small QALY gain associated with denosumab.	
6.12	***Conclusion*** The AG economic analysis excluded some factors (discussed earlier) that are likely to have a significant impact on the cost effectiveness of denosumab. These factors are very important given that the QALY gain for denosumab is very small and any slight changes to the cost inputs could render denosumab cost ineffective. It should be borne in mind that the main motivation for conducting cost effectiveness analysis in this instance is to establish whether denosumab is a cost effective use of NHS resources. This notion is not reflected in the current economic analysis where several important factors have not been fully taken into account. Novartis suggests that the AG update its analyses to incorporate the points discussed in this document in order to reflect the true cost effectiveness of denosumab compared with zoledronic acid and other bisphosphonates.	Thank you for this comment. However in line with our responses to the above points we do not feel that we require to update our analyses.